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T.L. Lavy
2208 Sweetbriar
Fayetteville, AR 72701
December 3, 1984

Dr. Barclay Shephard
Office of Env. Medicine
Veterans Administration
810 Vermont Ave.
Washington, D.C. 20420

Dear Barclay:

I am pleased to send you this final copy of my monograph "Human Exposure to Phenoxy Herbicides." I hope you are able to get this published as soon as possible since some of the information is already becoming outdated.

At times it seemed like this was a never ending task. Recapping for you - in July 1983 I completed the first draft of the entire monograph. It was returned to me for revisions about January 1, 1984 after Dr. Shelden Wagner edited it. I made many of the changes suggested and then returned it to the V.A. around April 1, 1984. After that time I'm not exactly sure what happened at the V.A.; why it happened and why it took so long. After finally receiving Alan Fitzgibbens comments and suggestions I was shocked and disappointed at the revisions he was demanding. In all of that confusion somehow the incorrect, unrevised version of Chapter 5 kept getting into your hands. As I indicated to you following my trip to Florida in February, major revisions were made, but somehow they didn't get to you.

A significant step forward occurred when I learned I no longer had to interact with Mr. Alan Fitzgibbens. I labored extensively over his reactions, comments, suggestions, and threats. Since my April revision I have put in 96 dedicated hours to completing this monograph. Conservatively, I can truthfully say that Fitzgibbens diversions have cost me at least 60 hours of work. Originally I tried hard to attempt to revise it in the manner he was requesting. After his dismissal I was able to concentrate on completing my task.

If further revisions are required I will be able to work on it further at an additional expense to the Veterans Administration.

Please call me if you have any questions or if I can be of assistance in getting this published.

Truly yours,

T.L. Lavy
Professor

TLL/jlu
cc: Dr. Al Young
Dr. Layne Dresh

T.L. Lavy
2208 Sweetbriar
Fayetteville, AR 72701
December 3, 1984

Dr. Al Young
1498B
Edwards Place
Bolling Air Force Base
Washington, D.C. 20336

Dear Al:

Please give me your opinion on the following:

1) At one time you indicated that we needed to indicate why I was selected to write the monograph. I am not sure it is appropriate or necessary.

2) Is the Table of Contents too detailed? I do not object to drastically cutting the Table of Contents for Chapters 1-5, but for the Appendix I would like to preserve the entire list of questions as currently listed in the Table of Contents. Note that I have also listed them at the beginning of the Appendix. Perhaps this is too redundant. Should I omit them from the beginning of the Appendix?

3) Especially look at: My interpretations of the controversy Chapter 1, Chapter 5, Appendix A-54.

Thanks for your assistance.

Truly yours,

T.L. Lavy
Professor

TLL/jlu
Enclosure
P.S. I wish to thank you for your part in getting me geared up to write the monograph, your suggestions, and encouragement.

HUMAN EXPOSURE TO PHENOXY HERBICIDES

T.L. Lavy

Professor of Agronomy
University of Arkansas

PREFACE

The primary intent of this monograph is not to present new information in a manner which will stimulate the scientific community but rather to communicate with those in other disciplines who have an interest in or concern for those who have been or believed to have been exposed to phenoxy compounds or the associated dioxin contaminants.

The goal of this monograph is to provide information to the reader which will allow him to better evaluate the facts and fiction which surround the use of phenoxy herbicides employed in crop production. The reader will have a better understanding of the toxicity associated with these compounds after considering some of the physical and chemical properties of the phenoxy herbicides, taking an in-depth look at their fate in the environment, and evaluating animal feeding trials in which the phenoxys make up a portion of the food supply.

Since the phenoxy herbicides have been used by agriculture for nearly 40 years, volumes of research projects have been completed. An evaluation of animal feeding studies and discussion of industrial exposure accidents accompanied by over 15 years of historical follow-up of those humans who have inadvertently been exposed to high levels of dioxin provide an extraordinary opportunity to view the effects of phenoxy compounds and their contaminants on man and other animals.

Emphasis is placed on evaluating the kinds and amounts of exposure received by pesticide applicators. By thoroughly measuring the levels of exposure being received by this group of workers, who routinely apply phenoxy herbicide for their means of livlihood, we are examining

those most likely to receive health threatening levels. Others not associated with phenoxy spraying would be expected to receive much less exposure. In this monograph special effort is devoted to differentiating between exposure and dose. Clarity regarding these concepts will provide us a better opportunity to assess the potential health effects of phenoxy herbicides on the human body.

Personnel involved with the manufacture of the compounds, herbicide applicators, and others in and around the agriculture community, the Vietnamese people and veterans serving the military during the Vietnam conflict deserve to have the facts on exposure, dose and risk presented to them in a manner they can understand.

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Phenoxy Herbicides, Their Use, Their Controversies

Phenoxy herbicides as weed control chemicals

Weeds have presented serious problems to human food production for centuries. They infest home lawns and gardens and cause, among others, the human allergies of poison ivy and hay fever. Commmonly, weeds invade man's recreation areas and interfere with his fishing, boating, golf courses, or parks. Rights-of-way for telephone and electrical power lines, railways, highway systems in addition to navigational waterways and irrigation systems could be drastically affected if weed growth was allowed total freedom.

In recent time, we have learned to successfully control many serious weed problems with chemical control measures. Among these chemicals are phenoxy herbicides which are very effective and economical control agents.

The first of the phenoxy herbicides to be discovered was 2,4-dichlorophenoxyacetic acid (2,4-D) whose synthesis was described by Pokorny in 1941. Ahlgren et al. (1951) described a series of alkaline reactions which lead to the production of 2,4-D.

Use of 2,4-D as a plant growth regulator was shown in 1942. Removal of dandelion, plantain and other broadleaved plants from a bluegrass lawn following an application of 2,4-D was first reported in 1944 (Marth and Mitchell, 1944). Discovery of this concept of selectivity and its potential for enhancing farm productivity through weed control was a key motivating factor which prompted scientists in academia and several chemical manufacturers to initiate new research

efforts. This series of events has played a vital role in helping the U.S. build a sound economic foundation. The American farmer's output has steadily risen as shown by the fact that one U.S. farm worker fed 16 people in 1950, 26 people in 1960, 47 people in 1970, and in 1978 fed 65 people (Farmline, 1980). The use of organic chemicals for weed control and other pests has played a major role in this marked increase in agricultural production. As shown in Table 1.1, the tonnage of phenoxy herbicides used has continued to rise (Bovey and Young, 1980).

The ability of the formulation chemist to adapt the phenoxy molecule to different field applications has added to the popularity of the herbicides.

For a pesticide to have an optimum biological effect on its target it must be permitted an opportunity to make contact with the organism. Some of the formulations employed to put pure chemical pesticides into a form facilitating field use include: wettable powders, emulsifiable concentrates, dusts, granules, water-soluble concentrates, flowables and aerosols (Van Valkenburg, 1967). The formulation chemist is interested in achieving several goals. Assuming he has found a compatible mix that will readily pass through the applicating equipment, he is interested in creating a spray solution with viscosity properties which will allow it to be retained on the foliage of the target plant, to penetrate the tissues and to translocate within the plant. Pesticide formulations and surfactants have primarily been designed to provide a high level of biological activity on plants or other pests. Most of the research which has been completed on the phenoxy

Table 1.1. Production of 2,4-D and 2,4,5-T (Acid Basis), United States 1951-1971. Modified from Bovey and Young (1980).

	Produced	
Year	2,4-D x 10^6 kg	2,4,5-T x 10^6 kg
1951	9.4	1.1
1958	14.0	1.7
1959	13.3	2.5
1960	16.5	2.9
1961	19.7	3.1
1962	19.5	3.8
1963	21.0	4.1
1964	24.3	5.2
1965	28.7	5.3
1966	30.9	7.0
1967	35.0	6.6
1968	36.0	7.9
1969	21.4	2.3
1970	19.8	N.A.
1971[a]	N.A.	N.A.

[a]Production data for 2,4-D and 2,4,5-T not available after 1970 to avoid disclosure of individual company data.

Source. The Pesticide Review; 1969, 1970, 1971, 1972, and 1975, U.S. Department of Agriculture, Agricultural Stabilization and Conservation Service.

herbicides has centered around determining how much to use, what plants are most easily controlled, which are not affected, and how long they remain active in the soil-plant-water environment. Extensive information on the effects of phenoxy herbicides on mammals in animal feeding studies has been gathered. Extrapolation of these data from sensitive experimental animals provides much information which can add to our understanding of their effects on humans.

Prior to 1978 only a few studies have been devoted to measuring the exposure received by people who apply phenoxy compounds in the field. As a result, little information is readily available to the field applicator about which formulations are most likely to penetrate skin or those most likely to be present in the air.

Chemical properties of phenoxys

Although all compounds are volatile to some extent, in the case of pesticides this property may represent a significant mechanism for permitting the active component to penetrate at a biologically active concentration to the most susceptible layer of the target organism.

Table 1.2. Vapor pressures of esters of some phenoxyacetic acid herbicides.

	C	mm Hg
2,4-D methyl ester	25	3.5×10^{-4}
	35	1.1×10^{-3}
2,4-D n-butyl ester	25	9.6×10^{-6}
	35	2.6×10^{-5}
2,4-D Methyl Amine	38	8.9×10^{-10}
2,4,5-T n-propyl ester	25	7.5×10^{-5}
	35	1.2×10^{-4}

Vapor pressure of pesticides determines the maximum vapor concentration at the target site and also governs the rate the compound may diffuse (Hamaker and Kerlinger, 1967). Volatile compounds with relatively high vapor pressures, may be more efficacious in their plant killing properties; thus, coverage within a canopy could be supplemented as the compound vaporizes.

As shown in Table 1.2, the ester formulations of some of the phenoxy herbicides are markedly more volatile than amine salt formulations. Movement of phytotoxic vapors away from the site of application can damage crops and irritate neighbors, especially in areas where several different kinds of crops are grown in close proximity. Formulation of long chain ester herbicides has decreased the volatility of the compound but still facilitates the entry of the herbicide

into the plant tissues.

Formulations of the phenoxys include emulsifiable acid, amine salts, mineral salts and esters. The concentration of these materials are expressed on the basis of acid equivalents, i.e. that portion that could be converted to the acid. Since the acid form is only slightly soluble in water and the emulsifiable concentrate is relatively expensive, only limited amounts of this formulation are used (Klingman and Ashton, 1982). The most commonly used of the phenoxys are the amine salts. Characteristically these materials are white crystalline solids that are readily soluble in water and present essentially no volatility problem. As a contrast, phenoxy esters are essentially insoluble in water but dissolve in petroleum oils. Esters made by using alcohols with one to four carbons are no longer used due to the high volatility of the phenoxy moiety. Today more expensive, long chain alcohols with an ether linkages (-O-) are used in the formulations to lower the volatility hazard (Klingman and Ashton, 1982). The ester forms are often preferred over the amines since the esters are much more effective on some species - especially woody plants. It should be emphasized that the high molecular weight alcohols are now used to make phenoxy esters with reduced volatility; although these esters are low volatile they may, under hot, humid conditions, still volatilize enough to injury highly susceptible plants (Klingman and Ashton, 1982). Since esters are more phytotoxic, more caution is required to ascertain that excessive levels are not used, killing susceptible plants where specificity is desired. Three possible explanations for the enhanced toxicity to plants from ester for-

mulations include: (1) volatility permits absorption of the gases through leaf stomates, (2) wetting action of the oil-like ester and the oil carrier may aid penetration and (3) ester forms, with their low polarity, are compatible with the cuticle and aid penetration through it (Klingman and Ashton, 1982). Thus, it seems likely that man's skin surfaces would also be more susceptible to penetration of the phenoxy compounds when formulated as the ester form.

When the ester and amine formulations are compared with respect to potential for exposure to man, the more volatile ester formulations are more likely to be present in the air of man's breathing zone. If skin contact occurs, the more soluble compounds will be more likely to be absorbed. Polar perspiration would aid in solubilizing the amine salt phenoxy formulations. However, oily skin surfaces of humans would tend to solubilize ester formulations of the phenoxy compounds.

Surfactants are classified as cationic, anionic or ionic. In general, they consist of a hydrophobic and hydrophilic section. This unique combination of polar and non-polar properties provide surfactants with the ability to emulsify, disperse, spread, wet, or solubilize, thus enhancing herbicidal action through increased foliar penetration (Foy and Smith, 1967). Freed and Witt (1967), in Table 3, present data showing that the energy required for plants to absorb herbicide is reduced in the presence of surfactants.

Table 1.3. Effect of surfactant on absorption energy. (Freed and Witt, 1967).

	E_a(kcal/mole)	
Herbicide	Without surfactant	With surfactant
Picloram	18.9	-
Dicamba	12.0	10.4
2,4-D	6.5	3.0

Considerable time and study have been devoted to evaluating enhanced herbicidal action due to surfactants, however, little is known with regard to any inadvertent exposure man may receive during application processes or other times he comes into contact with surfactant-phenoxy herbicide mixtures. Since Smith and Bayer (1966) have shown that diuron leaching in a soil column can be increased or decreased by the kind and rate of surfactant added, several interactions are possible. Thus, theoretically someday it may be conceivable that phenoxy herbicides or other pesticides could be optimized for penetrating plant tissues and minimized for passing man's skin.

Commercial uses of phenoxy herbicides in the United States

Annual and perennial broadleaf weeds in non-cropped areas, as well as in tolerant crops, are routinely controlled using 2,4-D formulations. This compound is used extensively in the cornbelt and for small grain production. Much of the cropland acreage is treated with 2,4-D as a postemergence application after the weeds are rapidly

growing. Postemergence application rates are routinely 0.5 lb/acre or less; at rates above 1 lb/acre this compound will serve as a preemergence herbicide, thus killing weeds as they germinate. A drawback to this means of application is the relatively short residual life of 2,4-D in the soil.

The forest industry has relied heavily on the use of 2,4,5-T for vegetation control. Bans on the use of this material for forestry applications has had a negative impact on timber production. Of the nearly 500 million acres of commercial forest land in the United States less than half of this is available for timber production. In 1972 the U.S. imported 11% of the U.S. consumption of wood (USDA, 1982).

As a consequence of the ban of 2,4,5-T use in forestry and accompanying problems associated with aerial spraying of U.S. forest lands, vast acreages of potentially excellent production sites became overgrown by undesirable, much less productive woody vegetation. On these sites eighteen inch tall, 4-year-old pine seedlings that could have attained heights of 5 to 7 feet or more are pressed to compete for sunlight, water, and fertility. Newer, more expensive compounds and other application means are being used to remedy the problems in some of these areas. In many cases mechanical means such as chain saws or machetes have been used in an attempt to eliminate undesirable species. In addition to this being an extremely costly and dangerous task for man, the competitive advantages seldom lasts for more than one growing season.

Table 1.4 (USDA, 1982) shows aerial application if possible, would

be the primary tool for utilizing 2,4,5-T in the South, Rocky Mountains, and Pacific Coast while in the North individual stem treatment (hand applied) would be the preferred application method.

Table 1.4. Estimated annual potential use of 2,4,5-T on commercial forest land by section, application purpose, and application method. (USDA, 1982).

Purpose and application method	North			South		
	Present	Potential	Application rate	Present	Potential	Application rate
	(Acres)		(lb ae/acre)	(Acres)		(lb ae/acre)
Site preparation and rehabilitation						
Aerial application	1,500	40,600	2-3	200,000	585,700	2-4
Broadcast ground	1,200	5,400	3-4	131,050	336,500	2-4
Individual stem	30,000	89,400	1-3	19,300	65,100	4-6
Total	32,700	135,400	--	350,350	987,300	--
Release and TSI						
Aerial application	0	32,200	1-2	414,000	1,083,100	2
Broadcast ground	1,650	9,300	2	17,000	42,600	2-4
Individual stem	62,200	256,500	1/4-2	8,250	31,900	2-6
Total	63,850	298,000	--	439,250	1,083,100	--
Fuel breaks						
Aerial application	0	0	--	0	0	--
Broadcast ground	200	700	2	0	0	--
Individual stem	0	10	2	0	0	--
All purposes						
Aerial application	1,500	72,800	--	614,000	1,594,300	--
Broadcast ground	3,050	15,400	--	148,050	379,100	--
Individual stem	92,200	345,910	--	27,550	97,000	--
Total	96,750	434,110	--	789,600	2,070,400	--
	Rocky Mountains			Pacific Coast		
Site preparation and rehabilitation						
Aerial application	20	4,400	2-3	29,142	57,184	2-4
Broadcast ground	0	800	2	1,369	3,670	3-4
Individual stem	0	0	2	489	3,746	2-3
Total	20	5,200	--	31,000	64,600	--

Purpose and application method	North			South		
	Present	Potential	Application rate	Present	Potential	Application rate
Release and TSI						
Aerial application	220	13,400	1-2	231,872	500,330	2
Broadcast ground	0	2,400	2	9,519	21,126	2
Individual stem	0	0	1-2	4,609	15,844	1-3
Total	220	15,800	--	246,000	537,300	--
Fuel breaks						
Aerial application	0	0	--	0	6,000	2-4
Broadcast ground	0	0	--	800	3,700	2-4
Individual stem	0	0	--	70	400	4
All purposes						
Aerial application	240	17,800	--	261,014	563,514	--
Broadcast ground	0	3,200	--	11,688	28,496	--
Individual stem	0	0	--	5,168	19,990	--
Total	130	1,000	--	277,870	612,000	--

[1]ae = acid equivalent.

Pastures and rangelands. Grazing lands are a vital natural resource of the U.S. They are used not only for forage production but also for watersheds, soil and water conservation, lumber, medicinal compounds, mining and recreational purposes. This land is often used only for grazing since it is too steep, too wet, too shallow, too cold, too dry, or too acid to be important for growing other crops. The relatively low cost of the phenoxy herbicides and the wide spectrum of broadleaved weed control have contributed significantly to the popularity of this group of chemicals for forage and pasture weed control. Pastures are subject to being invaded by many different species of woody plants. If an extensive woody plant problem was present on a minimum acreage ground application, equipment could be used to

apply a broadcast treatment. More commonly, land owners spot treat woody plants in cultivated pastures as they appear, thus minimizing the amount of 2,4,5-T required (USDA, 1982).

Rice production. Rice production has relied heavily on the use of 2,4,5-T for weed control. The 2.5 million acres of rice the U.S. located primarily in Arkansas, Louisiana, Texas, Mississippi, and California. Broadleaf aquatic weeds have been effectively controlled by this compound; 28 percent of the rice acres in this four-state area has relied on the use of 2,4,5-T. A rate of 1 lb/acre is commonly used for weed control, resulting in an annual application of 300,000 pounds 2,4,5-T. Silvex, another chlorinated phenoxy herbicide, is also effective in controlling this broadleaf aquatic weed complex (USDA, 1982).

In 1983 rice was the only U.S. produced commodity for human consumption that could legally be sprayed with 2,4,5-T during its production. However, all routine domestic uses of this compound was ceased in September, 1984.

Phenoxy herbicide use in rights-of-way management in the United States. Good vegetation management programs are critical to the nation as they ensure the safety, security, and reliability of our rights-of-way systems. Major rights-of-way types include railroads, highways, pipelines, and electrical transmission lines. They supply our needs for food, fuel, communication, energy, and many other items.

Estimated rights-of-way acreage in each of the major categories are listed: Railroads - 2.4 million acres; highways - 21.7 million

acres; pipelines - 2.2 million acres; and electrical utilities - 5 million acres; this makes up 31.3 million acres or nearly 1 percent of the total U.S. acreage (USDA, 1979). Annual treatment with 2,4,5-T occurred on more than 680,000 acres annually.

Ground application equipment was usually used when 2,4,5-T was applied to highways and railway rights-of-way areas while electrical and pipeline utilities relied more heavily on aerial means of application.

Use of 2,4,5-T resulted in decreased soil erosion since little soil erosion or compaction occurs due to a lack of site disturbance. If bulldozers or other large land clearing devices were required to clear the vegetation soil erosion would be increased markedly. Use of 2,4,5-T and other phenoxy compounds for vegetation management has generally enhanced wildlife activity in treated areas (USDA, 1982).

Other uses. Other extensive areas of phenoxy herbicide use include drainage ditches, canals, channels, recreational areas, and other waterways where brush control is important.

Selectivity

The selectivity of phenoxy herbicides to control broadleaf plants in the presence of grasses or grain crops is one of the important reasons they phenoxy herbicides have gained in popularity.

Ashton and Harvey (1971) suggested that a herbicide is selective to a particular crop only within certain limits. These limits are the result of an interaction between plants, herbicides, and the environment. Significant factors affecting plant responses to a chemical include: rate of plant growth, shape and characteristics of leaf sur-

faces, amount of chemical taken up by the plant, how it moves in the plant, and deactivation in the plant.

The molecular configuration of the herbicide and its concentration are important factors governing the ability of the compound to kill the desired plant.

How do phenoxy herbicides kill plants?

When these compounds kill plants they penetrate into leaves, stems, or roots; are absorbed into the plant's living protoplasm; migrate across surrounding tissues to the vascular channels; and trasnlocate from the point of entry to the actively growing portion where plant death beings. Ashton and Crafts noted that

> Final death of plant tissues may result from contact action; most characteristic of the 2,4-D light ester or amine formulations on foliage. It may result from extreme hormone-like response giving rise to tumorous tissues, excessive production of buds or root initials, softening of root cortex and general degeneration where concentrations are not sufficient to cause direct death, crushing and plugging of vascular tissues may result in a slower death from lack of nutrients normally supplied via these tissues (Ashton and Crafts, 1973).

Although phenoxy compounds are also effective as weed killers after they have been applied to the soil, the mode of action associated with their removal from the soil-solution complex, translocation through root systems, and subsequent plant killing steps are less well understood.

Advantages of using phenoxy herbicides

The family of chlorophenoxy herbicides has gained worldwide acceptance for several reasons. Among these reasons are 1) low rates are effective in killing a wide spectrum of broadleaf plants, 2) they

are readily adaptable for many different formulations, 3) they degrade rapidly in the environment and 4) the vast quantities used and the advances in technology have allowed the phenoxy compounds to compete favorably from an economical standpoint.

Controversies associated with the phenoxy herbicides

In view of the positive aspects of the phenoxy compounds, why is there any controversy? Confusion abounds and misinformation is common with regard to this subject. One of the goals of this book is to present facts and allow the reader to place them in their proper perspective.

During production of 2,4,5-trichlorophenol which is used to make some of the chlorophenoxy herbicides an undesirable by product is formed. As a group these compounds are commonly referred to as dioxins. Often the term dioxin, TCDD and 2,3,7,8-tetrachlorodibenzo-p-dioxin are used interchangeably as synonyms. Since there are eight possible locations for chlorine atoms on the dioxin molecule there is the possibility of 75 different dioxin isomers being formed and 22 of these could contain 4 chlorine atoms and be labeled as tetrachlorinated dioxins (Halperin et al., 1982). The tetrachlorinated dioxin molecule with chlorine atoms in the 2,3,7, and 8 positions is the most toxic of the known dioxin members.

Any of the dioxins containing four chlorine atoms can correctly be called TCDD. The 1,2,3,4 TCDD is only 1/50,000th as toxic as its 2,3,7,8 relative which appears from animal studies to be the most toxic of the dioxin isomers studied to date (International Agency for Research on Cancer, 1978). Costly special mass spectrophotometers are

required to quantify and differentiate between the different TCDDs. For further discussion in this monograph the term TCDD will be reservesed specifically for the 2,3,7,8 isomer.

By proper regulation of pressure, temperature and solvent conditions the level of TCDD contamination in 2,4,5-T can be minimized. In 1964 the Dow Chemical Company became aware of TCDD contamination in 2,4,5-T. At that time they closed their production facilities and made major modifications in the reaction conditions for synthesis of trichlorophenol and by late 1965 Dow Chemical had developed technology that permitted production of 2,4,5-T containing 1 ppm or less TCDD (Young et al, 1978).

Dioxins also result from sources other than phenoxy herbicides. Recent research conducted at the University of Amsterdam and in the U.S. has shown that chlorinated dibenzodioxins, which includes TCDD, can be formed on combustion in municipal incinerators and by heating chlorophenols (Rappe et al. 1979).

Pentachlorophenol, a commonly used preservative for wood products, is contaminated during manufacturing processes with hexa, hepta, octa, and possible tetra-chlorinated dioxins (Plimmer, 1973, Buser and Bosshardt, 1976).

TCDD and phenoxy herbicide news items

Following is a list of items concerning the phenoxy and associated dioxins which have caught public attention during the past 30 years:

Chick Edema Disease, 1955

Bionetics Institute's Report on 2,4,5-T teratogenicity

Use of 2,4,5-T and TCDD in Vietnam

Claims of Vietnamese Birth Defects

Swedish Lapland

Globe, Arizona

EPA Alsea II

Missouri Horse Arena

Seveso, Italy Explosion and Other Accidents

On Going Concerns for Veterans

Chick edema disease. Sanger et al. (1958) reported a new (undiagnosed) disease responsible for killing millions of chickens in 1957. Only a few similar problems were described until 1969. At that time soapstock, a by product from refining crude vegetable oil, was the source of the toxic substance. Firestone et al (1971) found that chlorophenols used in antimicrobial water treatment had contaminated the feed fat. Research stimulated by these findings now allows commercial vegetable oils to be filtered through activated carbon filters to remove any dioxins which may be formed as a by product from refining crude vegetable oil (Mounts, 1976).

Findings of bionetics research laboratories. Studies conducted for the National Cancer Institute by the Bionetics Research Laboratories in 1969 revealed that rats or mice given relatively large oral doses of 2,4,5-T during the early stages of pregnancy showed a higher than average number of deformed offspring (Allen et al., 1977). This research triggered Dr. Lee A. DuBridge, Science Advisor to the President and Executive Secretary of the President's Environmental Quality Council, to state that the "Department of Agriculture will cancel registration of 2,4,5-T for use on food crops effective January

1, 1970, unless by that time the Food and Drug Administration has found a basis for establishing a safe, legal tolerance in and on foods" (Bovey and Young, 1980). Immediately after this announcement of 2,4,5-T registration cancellation, the Department of Defense suspended the use of Herbicide Orange in Vietnam (Anonymous, 1977; Bovey and Young, 1980).

Following this announcement and restrictions on 2,4,5-T a close evaluation was made of the Bionetic's findings, since 2,4,5-T had had an excellent health record. It had been used in agriculture for over 20 years with no claims of human or other animal problems. Close scrutiny of the Bionetics Research Laboratory findings showed that the 2,4,5-T used was an old sample from a company no longer producing 2,4,5-T. The compound used contained 27 $\pm$8 ppm TCDD. This level was well in excess of the TCDD levels occurring in 2,4,5-T being produced by other companies at that time. In an attempt to reproduce results to those reported, the Dow Chemical Company conducted a study in consultation with scientists at the National Institute of Environmental Health Science Laboratires at Research Triangle, North Carolina. The only planned deviation in the study was to substitute regular production grade 2,4,5-T. Results of these studies showed that 2,4,5-T of regular production grade did not cause birth defects in rats at 24 mg/kg/day administered orally on days 6 through 15 of gestation (Bovey and Young, 1980).

Claims of Vietnamese health problems. The reports from the Bionetics Research Laboratories, Dr. Lee DuBridges' consequent actions, the fact that 2,4,5-T used in the U.S. war effort contained

low levels of the TCDD contaminant caused concern in Vietnam for the possibility of increased birth defects due to exposure to 2,4,5-T. Independent surveys were conducted by Cutting et al. (1970) and Meselson et al. (1971). In 1971 an Advisory Committee on 2,4,5-T evaluated the two studies mentioned above for U.S. Environmental Protection Agency (Advisory Committee, 1971). A summary of the evaluation follows:

Summarizing the Vietnam data on human embryotoxicity, it said that (1) the sample of births surveyed was from year to year a variable but usually very small fraction of the total number, (2) it was quite unrepresentative of the geographic and ethnic distributions, (3) the heavily sprayed and otherwise exposed areas were greatly underrepresented, and (4) the birth records were not trustworthy and, therefore, the rates of stillbirth, and especially of congenital malformation, derived from them were equally unreliable. For example, the overall congenital malformation rate found in South Vietnam, 4.91 per 1000 live births, is about half of what was reported in other studies in various parts of Asia, and possible a quarter of what might actually exist at term. A further indication that the newborn children were not carefully examined is the absence of Down's syndrome in the list of specific malformations compiled by the Army survey (Cutting et al., 1970) despite the fact that some Oriental populations have been reported to have an incidence of this condition not unlike that in Western populations.

There is, and can be, no precise knowledge of the exposure to 2,4,5-T (and hence, TCDD) experienced by pregnant South Vietnamese

women, including what amounts they ingested or absorbed and when this may have occurred during pregnancy. Consequently, attempts to accurately relate birth defects or stillbirths to herbicide exposure can not be made. The detailed searches reported by Cutting et al. (1970) almost certainly would have shown any marked increase in the incidence of birth defects if they had occurred.

The incident at Globe, Arizona. Soon after the U.S. Forest Service applied 1670 kg Silvex and 54 kg 2,4,5-T in the Kellner-Canyon Gulch Spray Project near Glove, Arizona reports of harmful effects on human and other animals were made (Tschirley et al., 1970). These claims were investigated by the U.S. Forest Service, but many of the local residents did not agree with the report of the investigation and in February, 1970 the incident attracted national attention. Television coverage showed deformities in animals which allegedly had been caused by the herbicides. A public hearing was held on February 13, 1970. An account by Time Magazine (Anonymous, 1970) indicated that the local veterinarian insisted that he had noticed nothing out of the ordinary in local animals. Local medical doctors could find no relationship between the spraying and the illnesses. Time also reported that the investigators holding the public hearing ended up perplexed. The investigators were accused by some local townspeople of being imposters, really representatives of chemical companies.

The Office of Science and Education, USDA further investigated the charges. Results of this investigation were published by Tschirley et al. (1970). Roan and Morgan (1972) in a subsequent report of the investigation concluded:

> We cannot find any evidence that there was long term exposure of resident of the Globe, Arizona area to chlorophenoxy herbicides, or significant contamination of water supplies in this area with 2,4-D, 2,4,5-T, silvex, or metabolites of these herbicides. Nor have we found contaminants such as TCDD that may be associated with one or more of the above technical grade products. Statistics on reproductive mortality and morbidity for the period 1960 through the first six months of 1970, from one hospital serving this area do not indicate any trends that are suggestive of adverse influences on human reproductive function that might be associated with herbicide use during the years 1965, 1966, 1968, and 1969.

Reindeer in Swedish Lapland. Sudden deaths of reindeer grazing on 2,4,5-T treated vegetation was reported in the Swedish Lapland during the spring of 1970. Within a week of a heavy snowfall approximately 30 reindeer died without any previous signs of illness; also it was reported that about 10 reindeer cows aborted their fetuses. Veterinarian examination of the dead animals revealed empty stomachs. When food was given to the surviving reindeer the deaths stopped. To more fully evaluate the possibility that 2,4,5-T may have been the culprit, Erne (1973) conducted a controlled experiment by feeding 2,4,5-T to female reindeer. From results of his study he concluded that any toxic problems associated with the reindeer deaths were probably not caused by ingestion of 2,4,5-T.

Alsea II Report. The EPA issued an order for the emergency suspension of 2,4,5-T on the last day of February, 1979. They had found it to be an imminent threat to human health and had it immediately removed from the market. The public had expressed concern over miscarriages and other adverse health effects.

In the fall of 1978, the EPA began a search for answers in three areas - an area where 2,4,5-T was used in the forest in Oregon, and

two Oregon areas where it was not used. This study followed an earlier study of the circumstances in which nine women in the area suffered miscarriages in which the women could reach no conclusion as to the cause. Upon the completion of the second study (in February of 1979), known colloquially as "Alsea II", the EPA suspended 2,4,5-T for forestry, pasture, and right-of-way uses, but not for rice or range, or for a variety of trivial uses such as industrial or vacant lots.

Witt (1980) in reviewing world-wide assessment of the EPA Alsea II Report found 18 reports, assessments or reviews on the subject. Every one of these evaluations found that the EPA data in the reports did not support the EPA conclusions. The most detailed accounting of Alsea II was prepared by Wagner et al. (1979).

Following are statements prepared by the Advisory Committee on Pesticides for the United Kingdom (Kilpatrick, 1980).

> In essence we concluded that the data reported were not valid in either scientific or statistical terms and did not provide an adequate basis on which to compare abortion rates in women exposed and not exposed to 2,4,5-T; that evidence of relevant exposure to 2,4,5-T was lacking; and that a correlation had not been established between the abortion rates and the usage of material.

The on-going Missouri horse arena (Times Beach) Episode. Several of the alledged TCDD "incidents" reported in this chapter have been of the "suspected" exposure nature. The report of TCDD poisoning in this episode have been confirmed both by effects on animal health and by sound analytical determinations.

In 1972, following the spraying of horse arenas with salvage oil for dust control, 54 of 57 horses exposed to the arena died. In a report by the Missouri Division of Health and the Center for Disease

Control (CDC), Atlanta, Georgia (Anonymous, 1974) extensive investigations were completed. Symptoms of the illness of the horses were skin lesions, severe weight loss and heptotoxicity. Birds, cats, dogs, insects and rodents were also found dead in the arena. An exposed 6-year-old girl developed hemorrhagic cystitis (characterized by blood in the urine). Other horse arenas sprayed with the similar salvage oil reported horse deaths occurring. The three arenas were sprayed within a month of each other. According to CDC testing, the original soil in the arena contained 33,000 ppb of the dioxin. The problem was supposedly solved by removing the treated soil from the arenas.

The report of this incident was misquoted by several newspapers across the country which implied that the herbicide 2,4,5-T was responsible for the problem (Anonymous, 1974b).

Published facts (Carter et al, 1975, Kimbrough, 1977) reveal that a factory in southwestern Missouri, while producing hexachlorophene, had accumulated by-product distillate containing up to 356 ppm TCDD. Episodes such as this, vividly point out our past inadequacies for properly disposing of toxic wastes. Whether the blame should lie with the manufacturer of the toxin or with the poor judgement of the licensed vendor for proper disposal is debateable.

Unfortunately the episode is not complete. The top several inches of soil from the arenas were excavated and disposed of in several places. Soil from one arena was dumped along the highway front of the arena where human exposure would be minimal. Soil from another stable was dumped in a sanitary landfill. Soil from the third arena was used as landfill for two homes located in Imperial, a small town near St.

Louis. As of January, 1983 families in these two homes along with four other families had been allocated Superfund money for temporary relocation (Sun, 1983). A considerable expansion in use of Superfund dollars has more recently been appropriated for relocation, etc. for families and businesses in Times Beach, Missouri where similar TCDD materials have been found.

A re-examination of the young girl who had been exposed in one of the horse arenas conducted 5 years later revealed that the patient had grown normally. Detailed physical, chemical and neurological examinations were also conducted and found to be normal. The researchers concluded:

> Our experience demonstrates that people exposed to dioxin can recover completely with no apparent sequels from the toxin. It remains to be determined whether the exposure to dioxin in these children will result in abnormal pregnancies or affect their offspring" (Anonymous, 1974).

An additional 4600 gallons of salvage oil from the hexachlorophene producing plant was located in the mid 1970's. Six years later, in 1980, the material was degraded using photodegradation techniques.

Up to 100 sites in the state may have been contaminated with the TCDD twelve years ago. For some of the sites the kind and amount of TCDD have been well established. The important item, its availability to man, has not been demonstrated but its water solubility and other properties indicate it is not readily available for man to receive an absorbed dose.

Assume 1) that the 2,4,5-T contained 0.1 ppm TCDD (the highest allowable level) and 2) that 2,4,5-T is applied at a rate of 2 lb per acre, 3) that an acre 6 inch slice of soil weighs 2,000,000 lbs. If

the 2,4,5-T was incorporated to a depth of 3 inches then 1,000,000 lbs of soil would contain 2 lbs 2,4,5-T. If TCDD was present in the 2,4,5-T at a 0.1 ppm level then in 2 lb of 2,4,5-T 2×10^{-7} lb TCDD would be present. Dispersing this 2×10^{-7} lb TCDD in the top 3 inches of soil gives a concentration of 0.2 ppt or 2×10^{-4} ppb. Comparing this amount to the 33,000 ppb TCDD present in the horse arena

$$\frac{\text{33,000 ppb in horse arena}}{\text{0.002 ppb in normal use}} = 165 \text{ million}$$

The important findings are: 1) that the dioxin concentration in soil from the horse arena was 165 million times greater than the concentration of dioxin in a soil normally treated with 2,4,5-T, and 2) no major health problems to residents of the affected areas have been reported other than those of the young girl described above.

Seveso, Italy and other explosions. Since 2,4,5-T has come into commercial production in 1946, several industrial accidents have occurred resulting in human exposure to 2,3,7,8 tetrachlorodibenzo-p-dioxin and/or other chlorinated dibenzo-p-dioxins. The most common method of human exposure occurred during handling of contaminated intermediate products (e.g. trichlorophenol, TCP). Young (1978) reported 23 industrial exposure episodes; eight of these occurred during an explosion or clean-up after the accident occurred. At least 740 people have been exposed during these episodes.

Although accidents involving toxic dioxins and subsequent exposure to humans are highly undesirable they do afford us with an opportunity to evaluate the health of humans who have received massive TCDD doses. By detailed investigations of the accidents and extensive record

keeping of the victims scientists have been able to follow the health patterns of humans who have inadvertently received documented exposure to the tetrachlorinated dioxins. A combination of any or all trichlorophenol (TCP), pentachlorophenol (PCP), or 2,4,5-T may have been involved with these exposures. The most consistent disease exhibited by the victims was a skin disease called chloracne. Crow (1979) indicates that men are more likely than women to be afflicted by chloracne.

The most publicized chemical accident in modern times occurred in Seveso, Italy. Hundreds of physicians, scientists and veterinarians have been involved in either on-site inspections, conferences or consultations involving the accident. This accident did not involve 2,4,5-T, but was associated with the production of trichlorophenol. Details of this TCDD episode follow: The episode of TCDD poisoning occurred on 10 July 1976 in Seveso, Italy, a small town 40 kilometers (km) north of Milan (Forth, 1977; Hay, 1977). The source of the TCDD was a chemical factory that produced trichlorophenol through the alkaline hydrolysis of tetrachlorobenzene. When the temperature in a steam-heated reaction vessel rapidly increased, a safety disk ruptured sending a plume of trichlorophenol, TCDD and other products 30 to 50 meters (m) high above the factory. The cloud apparently rose into the air, cooled and came down over a cone-shaped area about 2 km long and 700 m wide.

It was estimated that 650 to 1700 grams of "TCDD was discharged into the environment (Reggiani, 1978). The escaped product had a TCDD concentration of 35,000 ppm (Anonymmous, 1977). Measurements of TCDD

on vegetation in the immediate vicinity ranged from 1 to 50 ppm. Reggiani (1978) also reported that birds, rabbits and chickens began to die 2-3 days after the accident. A few children and some adults who had been exposed to cloud of TCDD dust complained of nausea and different kinds of skin lesions. Wagner (1981) reported that families were not evacuated from the area until 17 to 38 days after the explosion.

Within the next 6 weeks (by late August, 1976) an extensive system for monitoring the health of people in the vicinity was established to cover the acute as well as the long-term effects. The most complete analysis of health data was published by Reggiani in 1978. He concluded that the Seveso accident did not reveal toxic effects in humans, which had not been observed in other episodes. Chloracne, the typical skin lesion, has occurred in children with tendency to spontaneous and rapid healing. None of the exposed children showed clinical signs of pathology other than chloracne during these years.

Chapter 1
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CHAPTER 2

Factors Influencing Man's Exposure to Phenoxy Compounds

Chapter 1 pointed out that the phenoxy compounds have been widely used for several purposes. Their use has not been confined to sparsely populated forests or prairies: they have also been used on or in croplands, rights-of-way, railroads, public utilities, and national parks.

This chapter will attempt to clarify the fate and distribution of the phenoxy herbicides in use. If people are exposed, what factors determine what their exposure level will be?

The continued development of more sensitive analytical instruments allow us a new perspective in looking for and locating trace levels of contaminants in our environment. From one standpoint these new analytic tools should enable us to be "safer" because we can locate and identify much smaller amounts of toxic compounds than we could 10 years ago. Because of these advances, we must better understand the language used to describe the new trace levels.

The term "milligrams per kilogram" (mg/kg) is commonly used to denote the weight in milligrams of the compound of interest, while the kilogram figure represents the weight of the test organism in kilograms. This ratio is useful in extrapolating data from an animal of one size to another.

Sometimes large numbers with small units tend to be confusing. We could call the distance across the crater of a volcano 804,672 millimeters or equally as true we could call the distance one-half mile.

Measurement terms commonly encountered when reading about con-

taminants in the environment are parts-per-million (ppm) (10^{-6}), parts-per-billion (ppb) (10^{-9}), and parts-per-trillion (ppt)(10^{-12}). To gain a better concept of what 1 ppm represents imagine a full railroad box car that contains 240,000,000 soybeans; if 240 of these soybeans were somehow different (let's assume they have a different odor), then the concentration of these different soybeans would be 240 in 240,000,000 or one in every million or 1 ppm. If we were searching for 1 ppb level, this would be equivalent to finding one of these soybeans with a different odor in 4.18 full box cars; if we are looking for a 1 ppt level we must look through all of the soybeans in 4180 box cars (or a train 39.5 miles long). This example may sound somewhat absurd but we have sensitive mass spectrometers capable of identifying and quantifying dioxins down to the ppt range. The terminology ppm is correctly interchanged with micrograms per gram (ug/g) or milligrams per kilogram (mg/kg).

The ultimate question remains: will trace levels of a chemical cause harm to a human? This monograph will address several of the factors necessary before one can make a valid answer.

How long do phenoxy compounds persist in the environment?

Phenoxys are usually applied in postemergence treatment of growing vegetation and directly to soil as a preemergence treatment to control weeds during the germination or small seedling stage. The special structure of many herbicide molecules gives them excellent specificity properties, i.e., they will kill a target weed species without harming the surrounding cash crop. Under some conditions these very specific molecules are also easily destroyed. Their biologic activity is often

greatly affected by a very simple change in molecular structure. The herbicide is ordinarily at its optimal plant-killing capability (bioactivity) when it is applied in the field. Almost all environmental alterations that occur in the phenoxy compounds result in their loss of bioactivity.

The following discussion is designed to illustrate the persistence of phenoxy compounds in the environment. As they degrade or are removed from the environment, the changes of human exposure to them as dislodgeable residues from leaf surfaces or through food uptake also decrease.

Since the soil acts as an intermediary between application of the phenoxy herbicides and their potential uptake in human food, knowledge of the factors that affect their fate in soil is important. Those factors include adsorption, leaching, runoff, plant uptake, non-biologic chemical reactions, microbial decomposition, volatilization, and photodecomposition.

Adsorption. This factor keys the importance of most of the other dissipating factors. If the compound is tightly bound, only a small fraction of the total applied material is available for the other modes of dissipation. For the phenoxy compounds, adsorption to soil colloids does not tie up a large percentage of the soil-applied material. Although both clay and organic components of soil are effective in binding phenoxys, the bond is not strong when compared to many other families of pesticides. Adsorption may be thought of as a reservoir in an equilibrium process. One of the primary reasons for the phenoxys' rapid degradation is the relatively weak bonds between

them and soil colloids.

Leaching. Since the phenoxys are not tightly bound in soil, their ability to leach throughout soil is relatively high. Comparing their mobility with other herbicide families, Helling (1971) found them moderately mobile to mobile. The amount of downward movement in a soil profile depends on several factors, among which are the compounds' water solubility, a property which varies greatly depending on the formulation; the amount and intensity of rainfall; and the physical and chemical composition of the soil. Relatively mobile compounds such as 2,4-D and 2,4,5-T are also able to move upward in soil. This can happen as a wick action which allows the wetting front to move downward or upward in a soil profile.

Runoff. Because of the phenoxys' low adsorption and relatively high water solubility, runoff may occur, especially when applied to very sloping land. Several factors, such as rapid herbicide breakdown, can prevent excessive runoff. For runoff to be of major importance, rainfall or irrigation must occur within the first week after application.

Plant uptake. Although this is the primary reason soil-applied herbicides are used, it is surprising that seldom is more than 5% of the herbicide taken up by plants. In silty clay loams, 2% is more common. The amount of plant uptake is often related to the amount of herbicide in the soil solution; thus, any factor limiting this value will also decrease the amount the plant takes up (Lavy et al., 1968). Once inside the plant the herbicide may be degraded or it may remain as an intact molecule. Plants are able to degrade phenoxys by several

pathways, as reported by Kearney and Kaufman (1975).

Chemical decomposition. Several chemical reactions routinely occur in higher plants as the phenoxy acetic acid compounds degrade. Among these reactions are side-chain degradation, ring hydroxylation, and beta oxidation (Kearney and Kaufman, 1975). These reactions may become important if other factors do not readily dissipate the compounds.

Microbial decomposition. This breakdown mode appears to be the major one for the phenoxy compounds. Experiments with sterile and nonsterile soils produce marked differences in the rate of loss of phenoxy herbicide phytotoxicity. An interesting phenomenon occurs when one retreats soil which had earlier been treated with phenoxy compounds. The half-life of a phenoxy in previously untreated soil may be in the vicinity of one to four weeks (Klingman, 1961), but when the same soil is retreated with a similar compound the half-life may be 3 to 15 days. Walker and Smith (1979) conducted a laboratory study to evaluate rates of 2,4,5-T degradation in soil. Degradation approximated first-order kinetics and the half-life varied from four days at 35°C and 34% moisture to 60 days at 10°C and 20% moisture.

Soil microorganisms are quite adaptable. They live in a variety of climates and can devise ways to detoxify compounds they have not encountered before. We are indeed indebted to this mass of active biologic material.

Volatilization. Compounds with high vapor pressures are more volatile. Their phytotoxic properties remain with them as they escape from the soil into the air. Once the farmer applies herbicides to the

soil, he often incorporates his herbicide in it; i.e., turns the soil over and thus covers the treated layer with an untreated portion, thereby preserving the phenoxys' plant-killing properties for their intended purpose. Before a properly incorporated herbicide is free to leave the soil through volatilization, it must first escape the binding capacity of the adsorptive soil complex.

Loss of a herbicide through volatilization is often underestimated. EPTC, not a phenoxy but one of the more volatile herbicides, was lost from a free-liquid surface at a rate of about 5 lb/A/h (Ashton and Sheets, 1959). Even herbicides with relatively low vapor pressures may be lost from a surface in significant quantities over an extended period, especially if exposed to high temperature. Soil temperatures as high as 180°F have been measured (Klingman and Ashton, 1982).

Photodecomposition. Photodecomposition commonly degrades many herbicides. Like volatilization, it is often thought of as a surface reaction which can be prevented by proper incorporation techniques. On soil and leaf surfaces it represents a major avenue of loss.

Pesticide transformation in sunlight plays an increasingly significant role in our environment (Crosby, 1976). The photo-oxidation of phenoxy acid herbicides results in rapid deactivation and low persistence. This process also limits the phenoxys' usefulness since they degrade so easily.

Other important factors

Adequate moisture and a temperature range of 20°C to 35°C greatly enhance the dissipation of most soil-borne phenoxy compounds. The

chemistry of 2,4-D and 2,4,5-T is very similar in many respects. Studies have shown that 2,4-D is somewhat more rapidly biodegradable, but the two herbicides' mobility factors are quite similar. Another difference is that no TCDD affiliation has been shown for 2,4-D. Because of their striking number of similarities, 2,4-D and 2,4,5-T will be exemplified interchangeably herein.

One study showed that shortly after 2,4-D was sprayed on growing vegetation, the leaves contained residues of 200 to 500 ppm, but 10 weeks later this decreased to 20 to 50 ppm (Ramel, 1977). In a British review of U.S. research, 2,4-D was shown to be nonpersistent in plant tissues (Turner, 1977). When 2,4-D was applied to cucumbers in a sublethal dose, more than 75% of the herbicide disappeared within 13 days. Thus, if people are to be exposed to dislodgeable residues on sprayed leaf surfaces to any appreciable extent, they must make contact with the treated plants shortly after application.

Photodegradation, rainfall washoff, volatilization, and plant uptake all play roles as these 2,4-D losses from leaf surfaces occur.

Persistence of phenoxy herbicides in soil

Initial levels of 2,4,5-T in soils are usually low and disappear relatively rapidly. In field studies, DeRose and Newman (1947) found that 2,4,5-T at 10 pounds per acre persisted 93 days after application. The investigators concluded that persistence was determined by soil microbial activity since 2,4,5-T persisted longer in autoclaved soil than in nonautoclaved soil. Other factors affecting disappearance of 2,4,5-T in soil include soil temperature, leaching, and soil organic matter. Generally, those conditions that favor microbial

activity will favor more rapid decomposition of 2,4,5-T.

In 1954, Warren (1954) studied the leaching and rate of breakdown of several phenoxy herbicides in a fine sand and silt loam, using crabgrass as a bioassay species. He found that 2,4-D ester, 2,4,5-T amine, and silvex amine moved readily in sandy soil but moved little in mineral soils or mucks. Esters of silvex and 2,4,5-T were resistant to leaching in all soils, with some movement in sand only. The amine formulation decomposed in the soil faster than the ester formulation. Silvex tended to be more persistent than 2,4-D and 2,4,5-T.

More recent research, using gas chromatographic analytical techniques, has generally confirmed the results of earlier investigators. Altom and Stritzke (1973) reported that the average half-life of the diethanolamine salts of 2,4-D, dichlorprop, silvex, and 2,4,5-T were 4, 10, 17, and 20 days, respectively, in three soils. Except for 2,4-D, the rate of disappearance of the other phenoxys was faster in soil from Oklahoma grasslands than in soil from forests. Lutz and others (1973) studied the movement and persistence of picloram and 2,4,5-T (2 and 4 lb/acre) on a North Carolina watershed that averaged a 27-percent slope. Approximately 60 percent of the picloram and 90 percent of the 2,4,5-T disappeared in 15 days. Most of the 2,4,5-T was found in the top 3 inches of soil, with no movement of 2,4,5-T beyond 12 inches downslope. In Texas, Bovey and Baur (1972) applied an ester of 2,4,5-T at 0.5 and 1 pound per acre to soils at five locations. Soils were sampled to a depth of 3 feet. Similar results were obtained at other geographical locations (Norris et al. 1977).

Plumb et al. (1977) and others reported on the persistence characteristics of 2,4,5-T applied at 3 pounds per acre to a chamise site in southern California. Residue levels immediately after application were not determined, but based on residues present 14 days after application (0.9 ppm), 2,4,5-T showed a half-life of about 19 days for the period 14 to 29 days after application. The rate of degradation changes with time, however. Approximately 1 year after application, the residue level was about 0.05 ppm.

Norris et al. (1977) determined 2,4,5-T residues in forest floor and soil after two successive annual applications of herbicide at 2 pounds per acre (ae) applied as the isooctyl ester in diesel oil by helicopter in March. The study area was a cool, moist site in western Oregon. The rate of decline in 2,4,5-T levels in forest floor after the first application at this site was slower than at the hot, dry site in southern California (Plumb et al., 1977), which may reflect the importance of volatilization and photodecomposition on the loss of phenoxy herbicides from exposed soil surfaces. The rate of loss of 2,4,5-T was quite rapid the first 30 days after the second application, which indicates good adaptation of the microorganisms after the first application. One year after application, residue levels in forest floor were about 0.75 percent of the amount of herb-icide originally applied. These data show the strong tendency of forest sites to dissipate 2,4,5-T. Residues were largely confined to the top 6 inches of soil.

Effects of high rates of application or persistence

Some people are concerned that residues of 2,4-D and 2,4,5-T left

in soils in Vietnam might destroy subsequent crops. Early work by Craft (1949) DeRose and Newman (1944), and many others indicated that 2,4-D and 2,4,5-T, when applied even at high rates, usually do not persist from one growing season to another, due largely to microbial decomposition of the herbicides. Work by Bovey and others (1968) in Puerto Rico indicated that corn, sorghum, wheat, rice, soybeans, and cotton could be grown in soils without reduction in fresh weight of the crops 3 months after the application of a 1:1 mixture of the n-butyl esters of 2,4-D + 2,4,5-T at 24 pounds per acre. Similar results were obtained for a 2:2:1 mixture of 2,4-D + 2,4,5-T + picloram at 15 pounds per acre (except for soybeans, which required 6 months for the phytotoxic effect to disappear). The longer residual effect on soybeans is prob-ably due to picloram, because of its greater persistence in soils.

Blackman et al. (1974) reported on recent studies in Vietnam, which indicate that sensitive crops can be safely grown 4 to 6 months after single applications of the n-butyl esters of 2,4-D and 2,4,5-T at rates up to 12 pounds per acre. The authors indicate that the dosage of herbicides in their experiments was considerably higher than would occur in spraying forests or mangroves since their materials were applied directly to bare soil and were not intercepted by herbaceous and woody vegetation. Young and others (1974) incorporated a 50:50 mixture of the n-butyl ester of 2,4-D and 2,4,5-T into a soil trench in Utah at the rate of 1,000, 2,000, and 4,000 pounds per acre. After 440 days, 89 percent of the herbicide was degraded at the 1,000-lb rate, 85 percent was degraded at the 2,000-lb rate, and 83

percent was degraded at the 4,000-lb rate. The rate of loss of the herbicide was rapid considering the low temperatures that prevailed for 7 months during the experiments.

In another study, Young and others (1974) reported on the effect of massive doses of 2,4-D and 2,4,5-T sprayed on an area at Eglin Air Force Base in Florida. About 92 acres received 1,900 pounds per acre 2,4-D and 2,4,5-T in 1962 to 1964; a second area received 1,200 pounds per acre in 1964 to 1966; and a third area received 340 pounds per acre of 2,4-D and 2,4,5-T from 1966 to 1970. Chemical analyses of soil cores collected in 1970 from the treated areas showed a maximum concentration, 8.7 ppb of either herbicide, indicating that the herbicide had essentially disappeared.

Factors affecting phenoxy vapors in air

A human's absorbed dose of any compound will be due to inhalation of airborne materials, ingestion of food or water, and absorption through the skin. Tobacco use many contribute to the ingested portion. Human applicator exposure studies will be addressed in detail in Chapter 3.

Some of the factors that affect the amount of inhalation are the compound's vapor pressure, the particle size produced during application, and the amount of protective equipment used.

Vapor pressure

The vapor pressure of the phenoxy compounds is markedly affected by the chemical make-up of their formulation. Since the esters are more toxic to plants than acid or salt formulations, this is the preferred form for many of the use areas. These more phytotoxic forms

have a higher vapor pressure and are thus more volatile. This property of volatility nearly eliminated the use of the phenoxy compounds in agricultural areas where crop rotations are common since broadleaf plants, be they weed or cash crop, are indiscriminately killed by this family of compounds. Formulation chemists have greatly widened the scope of their use by linking longer chain esters with the active plant killing component. This lower vapor pressure, less volatile material, allows the compound to be used in the near proximity to susceptible crops. Thus, when correctly applied placed in the field, it is expected that they will not move in the vapor state but will remain on the target area. The necessity of decreasing the vapor pressure of the phenoxys to allow their acceptance in the agricultural community has at the same time, markedly reduced the levels of the phenoxy vapors in the air that man breathes. A factor that has led man to be wary of pesticides in general, and the phenoxys specifically is the fact that the human nose is sensitive to low levels of these chemicals and/or their carriers.

Another factor contributing to man's concern over the use of phenoxys is the fact that visible symptoms of extremely low levels of airborne phenoxys are sometimes shown by off-site broadleaf green plants. Some chemicals that are not acutely toxic to plants or animals may contaminate an area without anyone suspecting their presence, however, even the presence of trace levels of phenoxy herbicides becomes quite obvious. Phytotoxic symptoms such as leaf curling or twisting for sensitive species such as cotton, tomato, potato, grapes, peas, beans, and many broadleaf weeds readily reveal the presence of

these compounds.

In an analytical laboratory this property of vapor pressure among the esters of the phenoxys can be seen quite easily. In a gas chromatographic determination of a mixture of the compounds, the more volatile short chained esters are eluted before the high molecular weight long-chained materials. Use of formulations containing these low volatile esters and even lower vapor pressure amines greatly lowers the probabilities of phenoxy vapors becoming airborne.

Particle size

Once the herbicide has been formulated in a manner that its vapor pressure does not significantly contribute to it being present in the air there is still another factor that can cause it to be airborne and that is particle size of the spray material. Larger particles would be expected to fall faster and smaller particles to remain suspended for a longer time period.

A modification of Stokes Law (Hansen, 1965) which can be used to calculate how far a compound may drift is:

$$D = \frac{1.49\ 10^4\ V \cdot H}{r^2} \qquad D = 1.49\frac{10^4}{r^2}\ V \cdot H$$

where: D = drift in feet, H = height above ground in feet, V = crosswind velocity in mi/h, r = droplet diameter in m

The drift of spray droplets in a 5 mi/h crosswind from a height of 100 feet would be as shown in Table 2-1. The drift distances resulting from other crosswind velocities or other release heights can be determined by applying an appropriate factor to the distances given or by calculation using the modified Stokes' equation. Thus, droplet

size is the critical factor determining spray drift since halving the droplet diameter results in a fourfold increase of drift distance.

A spray droplet is also subject to evaporation while falling. A very small droplet can evaporate completely before reaching the ground or a leaf surface (USDA, 1982). Assuming an air temperature of 86°F, relative humidity of 50 percent, and still air, the approximate lifetime and distance of fall for water droplets would be as shown in Table 2-2. The tabulation shows that water droplets less than 100 um in diameter would probably never reach the ground or a leaf surface when applied from a height of 10 feet, which is nearly a minimum for aerial application.

Table 2-1. Theoretical drift of spray droplets released 100 feet above ground in a 5-mi/h crosswind (USDA, 1982).

Droplet size, diameter (um)	Theoretical drift (feet)
50	298.0
100	74.0
200	19.0
400	4.6
600	2.0
800	1.2
1,000	.7
1,500	.3

The lifetimes and fall distances for herbicide spray droplets would vary from the figures given above. The kind of carrier (oil or water), vapor pressure of the carrier and the herbicide, and the kind of emulsion (oil in water or water in oil) would all influence droplet lifetime. Air turbulence causes major deviations from calculated fallout rates.

Table 2-2. Lifetime and fall distance of water droplets in air at 86 F and 50% relative humidity (USDA, 1982).

Droplet size, diameter (um)	Lifetime (seconds)	Fall distance (inches)
200	56.0	1,678
100	14.0	151
80	9.5	36
50	3.5	11
40	2.4	2
20	.6	<1
10	.2	<1
2	.1	<1

[1]86°F, 50 pct relative humidity, still air.

Most of the application equipment in use today produces a range of droplet sizes. The greater the volume of spray solution found in

small droplets (less than 100 um), the greater the drift; however, there is an upper range of droplet sizes beyond which biological effect of a herbicide is reduced. Thus, herbicide applications should have the goal of achieving a range of droplet sizes that minimizes drift without unduly sacrificing biological effectiveness.

Under field conditions the effective fall distance is the vertical distance moved relative to the surrounding air. In turbulent air this may be several times the height at which the spray is released. Knowledge of the in-flight behavior of selected droplet sizes and of the micrometereological factors should allow us to make significant improvements in predicting drift potential from agricultural spray operations (Seymour, 1967).

Since it has been established that use of larger droplet sizes will reduce the amount of particle potentially available to drift let us examine means of selecting the desirable particle size. Stewart and Gratkowski (1976) present five factors of importance. (1) Increasing airspeed results in smaller droplets because of the greater shear forces imposed on the spray solution as it leaves the nozzle. (2) Pressure in the spray system also affects droplet size. Higher pressure increases turbulence in the nozzle, which in turn increases shear forces at the nozzle orifice, resulting in smaller droplets being formed. (3) Orifice diameter of nozzles is directly related to droplet size. A larger orifice will reduce shear forces caused by turbulence in the nozzle, and produce larger droplets. (4) The kind of nozzle also affects droplet size. Nozzles producing narrow, cylindrical patterns form fewer small drops; thus, they are better for

reducing drift. (5) Nozzle orientation is a major factor affecting droplet size. The smallest range of droplet sizes and the lowest volume of spray solution in small droplets is obtained when nozzles are oriented parallel to the airstream and discharge downwind to the direction of airflow.

Equipment is available that will provide droplet sizes of 300 to 400 vmd (volume median diameter in m) with 70 to 90 percent recovery in a 500-foot width; 400 to 600 vmd with 85 to 95 percent recovery; 800 to 1000 vmd with 95 to 98 percent recovery; and 800 to 1000 vmd with 99 or more percent recovery (Akeson et al., 1978).

Temperature and relative humidity influence drift through evaporation, which reduces droplet size and results in more drift. In practice, many States impose limitations to herbicide application based upon these two factors. Limitations are also imposed in terms of maximum permissible windspeed at the time of application. A maximum windspeed of 5 mi/h is common, although up to 10 mi/h is permitted in areas where there is less hazard to sensitive vegetation.

A critical atmospheric factor is the temperature gradient with height, specifically the occurrence of warm air overhead, usually referred to as an inversion condition (Akeson et al., 1978). An inversion limits vertical air circulation and acts to concentrate fumes and small particles in a cloud under the inversion ceiling, relatively close to the ground. The material thus entrapped may be transported long distances in amounts sufficient to cause damage to sensitive crops.

Spray solutions can be modified to reduce the number of small

droplets and thereby reduce drift. The principles involved are the increase of viscosity or of surface tension, each of which tends to reduce the number of small droplets. The types of preparations available to reduce drift may be classified as invert emulsions, thickeners, particulating agents, and foaming agents (Gratkowski, 1973).

Although many variables affect spray drift, it is clear that elimination of small droplets, especially those less than 100 m in diameter, is the fundamental solution to the drift problem; however, the biological effectiveness of the phenoxy herbicides decreases as droplet size increases and droplet density decreases. For example, McKinlay et al (1972) found that increasing droplet size from 100 to 200 um, with volume kept constant, required three times as much active ingredient, and when size was increased to 400 um, six times as much herbicide was needed to give equivalent biological effects. There are two factors that tend to make smaller droplets more effective. First, the leaf area contacted by a given volume of spray solution is greater when droplets are smaller. That may enhance absorption. Second, high herbicide concentrations localized in larger droplets may so damage the underlying cells that translocation to other tissues is reduced. In practice, the lower effectiveness of larger droplets can be offset by increasing herbicide concentration of the spray solution or by increasing the total volume. Both increase costs.

Drift can be reduced when conventional application equipment is used, by taking advantage of the best combination of nozzle type and

orientation, orifice size, pressure, and spray mixture. In addition, modern engineering developments permit reduction of droplets below 100 m diameter to near zero. The microfoil boom, for example, has nozzles placed in a boom shaped like an airfoil, which minimizes turbulence at the point where droplets are formed. Primary droplets from microfoil nozzles are about twice the size of the orifice. Smaller satellite droplets are formed from thin filaments of spray between the primary droplets, but proper nozzle orientation will result in the capture of small droplets by large droplets in the smooth air behind each nozzle.

The microfoil boom provides many of the desirable qualities in droplet size. However, the microfoil boom is expensive to buy and is subject to clogging and other problems if it is not properly maintained. Nevertheless, it provides the best drift control available at this time. Other application systems are in the process of development (Stewart, Gratkowski, 1976).

Protective equipment

Although much can and has been done to limit the number of respirable particles it is not always possible or practical to eliminate all of them. Many kinds of masks and filters have been devised to remove respirable size pesticide particles.

Although it may be recommended that a mask be worn the human element plays an important role in determining whether it actually will be. If the compound of concern is known to be highly hazardous the worker is more likely to use the protective mask. Since most woody vegetation growth occurs during the warm and hot months of the year that is also when much of the phenoxy herbicide use occurs. Both the

heat and the humidity add to the discomfort of man using the protective devices. When men engage in strenuous physical activity in the hot summer months such as during phenoxy herbicide application masks are seldom used. Many of these workers have been using phenoxy herbicides for over 25 years with no known ill effects. In spite of the fact the label on the phenoxy herbicides container indicates that masks be used, they seldom are.

Possibilities of human exposure via phenoxy components in air

Most dependable inhalation data are achieved by trapping exposure levels via air. Bamesberger and Adams (1966) indicated that 2,4,5-T was found infrequently and in low concentrations in air-sampling studies in Washington state. In high use areas, however, one might expect concentrations similar to 2,4-D as reported by Adams and others (1974). Average concentrations of ester of 2,4-D in air in Washington during the spraying season was 0.1 ug/m^3. Assuming that a person would inhale 30 cubic meters of air per day, the exposure would be 0.003 mg per day. The threshold limit values in air adopted by the American Conference of Government and Industrial Hygienists in 1977 were 10 mg/m^3 for 2,4-D or 2,4,5-T.

The highest concentration of phenoxy herbicides in the air probably occurs during application. Russian workers (Fetison, 1966) reported concentrations of the sodium salt of 2,4-D up to 22.4 mg/m^3 after spraying. Akesson, 1978 (communication to USDA, 1982) however, has shown a maximum of 20 ug/m^3 of herbicides downwind from typical aerial application sprays. TCDD has not been measured in the air in spray areas, but possible levels can be calculated based on an assumed

2,4,5-T:TCDD ratio of $1:1x10^{-7}$ and the levels of herbicide above (this assumes TCDD to be present at 0.1 ppm level).

In a national air monitoring pesticide program there were 2,479 samples taken in 14 to 16 different states (Kutz et al.). The sampling sites for 1970 and 1972 were selected for being potentially areas with a high concentration of pesticides. The analytical method had a sensitivity of 1-10 nanograms per cubic meter. It is evident that most samples were analyzed at the lower limit of the method's capability. There is no established concentration in the air for 2,4-D that is considered to be safe or unsafe for the general population. The TLV of 2,4-D for a normal working eight-hour day without adverse effect is 10 mg/m^3.

Table 2-3. Three-Year Summary of 2,4-D in Ambient Air in U.S.A. in Nanograms[a] per Cubic Meter from 1970-1972 (Kutz et al. 1976).

	Total 3-yr Average
Percent positive samples	5.64
Average values	1.54
Average values of positive samples	18.33
Maximum values	68.17

[a]A nanogram is 1×10^{-9} grams = 1×10^{-6} mg, 68.17 nanograms = 0.000,068,17 mg.

Table 2-3 shows that the maximum value found was 68.17 nanograms which is 0.00006817 mg. This amounts to a safety factor of 146,700

before reaching the TLV value considered to be a safe exposure for a 40-hour working week. Again it should be remembered that over the three-year period covered by this report 2,4-D occurred in the air on the average only 5.64% of the time and the sites were potentially the worst possible situations. Thus, practically speaking, the general public is not exposed to 2,4-D in the air.

Man's potential for exposure to phenoxy herbicides in drinking water and other water sources

As discussed under photodecomposition of phenoxy herbicides in soil, UV light is effective in degrading many herbicides including the phenoxy compounds. Microbial action and other chemical reactions may also occur to rid water of trace levels of herbicide.

The Water Resources Division (WRD) of the U.S. Geological Survey reported a study on 12 pesticides occurring in 11 western streams (Brown and Nishloka, 1967). The three herbicides 2,4-D, 2,4,5-T and silvex were included but none was found. The sensitivity of the method was given as 100 parts trillion (ppt) for 2,4-D and 5 ppt for 2,4,5-T and silvex. The survey was made over approximately one year.

The WRD reported on the incidence of pesticides in selected western streams (Mangold and Schulze, 1969). This report covered a three-year period, 1966-1968. Samples were taken from 20 locations over 15 western states. The highest amount of 2,4-D found was 0.35 g/liter (0.35 ppb) in James River at Huron, S.D. (According to this report, the Committee on Water Quality Criteria has established a standard of 100 ug/liter (100 ppb, 0.1 ppm or 0.1 mg/liter) for all the phenoxy herbicides.) There were 321 samples analyzed for 2,4-D.

Eighty-seven percent of the samples tested had no 2,4-D. Of the 41 samples containing 2,4-D, 29, or 70%, had less than 0.15 parts per billion (ppb). Table 3 gives a detailed breakdown of the quantities of 2,4-D found in these samples that occurred only 13% of the time.

Table 2-4. Occurrence of 2,4-D in ppb in selected Western streams over a three-year period (Mangold and Schulze, 1969).

ppb	0.01-0.05	0.06-0.10	0.11-0.15	0.16-0.20	0.21-0.25	0.26-0.30	0.31-0.35
No. of occurrences[a]	13	13	6	2	3	2	2

[a]Remember that this is only in the samples containing 2,4-D and 87% of the samples had none.

A monitoring program on water has also been conducted by the Federal Water Quality Administration of the U.S. Department of Interior (Lictenberg et al., 1970). In their five-year survey of water in the major river systems in the U.S.A., no mention is made of the phenoxy herbicides. Analyses were not made for them presumably because based on the earlier studies (Brown and Nishloka, 1967; Mangold et al., 1969) they were thought not to be of sufficient concern to warrant analysis.

The U.S. government has established an acceptable level of 0.1 ppm 2,4-D as a contaminant in what they call community water systems. This information was published in the Federal Register (Anonymous,

1975) in 1975. A tolerance of 0.1 ppm of 2,4-D in potable water has also been established by EPA. EPA published in 1980 a list of 64 toxic pollutants classified under the Clean Water Act. As would be expected from the foregoing, 2,4-D is not included on this list.

Since residues of phenoxy herbicides tend to remain in upper soil layers, they are rapidly degraded. It is unlikely that ground water would be polluted from current registered uses of phenoxy herbicides, and thus exposure is considered to be zero.

Surveys by the U.S. Geological Survey program of the surface waters of major rivers in the Western United States over a period of years indicated that the highest concentration of a phenoxy herbicide was 0.97 ppb of 2,4-D. Researchers have found that even in streams adjacent to aerial spraying operations in the forest, concentrations of 2,4-D, 2,4,5-T, or other herbicides seldom exceed 0.01 ppm. After application, concentrations of the herbicide rapidly diminish by dilution. The preponderance of streamwater samples from operational monitoring programs in forest land has not contained detectasble residues of 2,4,5-T. Even when ditchbanks were sprayed directly, so that spray fell into the stream, the maximum 2,4,5-T found after applications at 2 pounds per acre was 0.04 ppm. Herbicide could be found only in the treated area, but none could be found one mile downstream.

Therefore, considering that only small and intermittent portions of the total land area are treated, the risk of exposure of the general population in the United States to significant levels of the phenoxy herbicides in water is remote. The greatest potential for

exposure occurs if domestic water is taken from very small streams in, or immediately downstream from, treated areas. An extensive research base shows: (1) Such exposure would be infrequent because most small watersheds are never treated and those that are treated seldom yield water contaminated with herbicides; and (2) when contamination does occur, it is low (less than 0.1 ppm, usually less than 0.01 ppm 2,4,5-T) and remains for only one hour to a few days.

Sugarbeets, soybeans and dwarf corn crops were irrigated with phenoxy treated water at concentrations of 0.02, 1.1 and 5.5 ppm in 2 acre in. of water by both furrow irrigation and sprinkler irrigation (Bruns et al., 1973). These levels added to the water were much higher than those found in monitoring studies. At the two highest concentrations 2,4-D residues were detected in roots only. Sugarbeet roots contained 0.01 ppm or less. The concentrations of the residues in the crops even from this height concentration treated irrigation water, were many times below the tolerance in effect in 1972 for certain food and forages for human and livestock consumption (Bovey and Young, 1980).

Averitt (1967) studied the persistence of 2,4-D amine in a bayou in Louisiana after application for control of water hyacinth. Application of 2,4-D was made as a coarse wet stream at 4.48 kg/ha by wetting the leaves with little or no runoff into the water.

An evaluation of the persistence of 2,4-D amine in a bayou for water hyacinth control in Louisiana was made (Averett, 1967). He applied 2,4-D as a coarse wet stream with little run-off occurring from the leaves.

Water samples taken below depths of 13.5 in one location indicated residues of 153, 37, 727, 38, 12, and 0.6 ppb for 1 hr, 24 hrs, 1, 2, 3, and 20 weeks, respectively, after application. Residues at a deeper depth were similar. The high concentration of 2,4-D after 1 hr is attributed to direct spraying of the water and/or "roll-off" of spray droplets from hyacinth leaves. The increased concentration at 1 week compared to the level at 24 hr was attributed to loss of chemical from the plants into the water. Three weeks after treatment the 2,4-D levels diminished considerably to 12 ppb. The body of water was relatively stagnant with somme flow from upstream, however, the banks of the bayou upstream had been treated so an influx of water should have also contained 2,4-D. Small plastic lined boxes, 60 x 120 x 30 cm deep, filled with lake or bayou water and supporting stands of water hyacinths were treated with rates of 4.5 or 5.6 kg/ha of 2,4-D amine. Loss of 2,4-D from the boxes was similar to loss in tha natural bayou. The 2,4-D had essentially disappeared in 27 days (4 and 15 ppb for 4.5 and 5.6 kg/ha application). Two lagoons chosen for study gave similar results to earlier studies.

Man's exposure to phenoxy herbicides through the food he eats

Evaluation of market basket surveys provide us with the best criteria for quantifying the levels man is ingesting. For definition purposes a "market basket" represents the amount of food consumed by a 16-19 year old male in a basic two-week diet. This amount represents almost twice the food intake for the average individual.

Pesticide residue studies of our food has been conducted by the U.S. Food and Drug Administration since 1964. Seventeen classes of

food are sampled: dairy products; meat; shellfish, fish; eggs and poultry; grain and cereals; potatoes; leaf and stem vegetables; beans; vine and ear vegetables; root vegetables; garden fruits large and small; oils; fats and shortening; tree nuts; infant and junior foods. There are 82 individual food items in these "market baskets". Thirty markets are sampled in 28 different cities.

In a report by Corneliussen (1972) which covers the period from June 1969 to April 1970, 2,4-D was analyzed using a test method with a sensitivity of 0.02 ppm. Some trace residues were reported which were below the sensitivity level of analysis. Such low values are only estimates. Chlorophenoxy acids were found four times during this reporting period. However, 2,4-D is listed as occurring only twice with the highest value being 0.125 ppm in the June, 1969 to April, 1970 reporting period. For earlier periods they report phenoxy herbicides were found seven times in 1967-1968, eight times in 1966-1967, and 13 times in 1965-1966.

Shown in a series of reports (Corneliussen, 1972; Johnson et al., 1976; Manske et al., 1975; Manske et al., 1974) covering the period of June, 1970 through July, 1973 2,4-D was present only infrequently (once or twice in all the yearly samples) and in low amounts (about 0.01 ppm). From August, 1973 through July, 1975, no 2,4-D was found in any of the samples (Johnson et al., 1977; Manske et al., 1977). A summary report (Duggan et al., 1969) for the period July 1963 to July 1970 indicates the maximum possible amount of 2,4-D a person might have ingested during this six-year period (1964-1970) is given. These amounts are well below the daily intake quantity regarded as safe by

the FAO-WHO Expert Committee and even further below the "no-effect-level" established by the World Health Organization. An expert group on pesticide residues working for FAO-WHO has established an acceptable daily intake of 2,4-D for humans of 0.3 mg/kg (Anonymous, 1972). For a 132 lb person this would amount to 18 mg per day. Taking a maximum daily intake of 0.005 mg as calculated from market basket surveys would give a 3600 safety factor before the acceptable daily intake was even reached. This same international group (Anonymous, 1972) has also accepted 31 mg/kg/day of body weight in the rat as being a dose level that causes no toxicological effect. The use of this figure of course would result in an even larger safety factor. When considering this point, it should be noted that the Environmental Protection Agency (EPA) has issued a number of tolerances for 2,4-D. These tolerances are permissible residues of 2,4-D in our food and water that EPA considers would not be harmful to human health.

Following are printed notices EPA has presented as guidelines. This was taken from the Code of Federal Regulations Title 40 Protection of Environmental Parts 100 to 399 revised as of July 1, 1979 p. 489 Section 180.142 2,4-D: tolerances for residues. (a) Tolerances are established for residues of the herbicide plant regulator and fungicide 2,4-D (2,4-dichlorophenoxyacetic acid) in or on raw agricultural commodities as follows:

5 parts per million in or on apples, citrus fruits, pears and quinces. The tolerance on citrus fruits also includes residues of 2,4-D (2,4-dichlorophenoxyacetic acid) from the preharvest application

of 2,4-D isopropyl ester and 2,4-D butoxyethyl ester and from the postharvest application of 2,4-D alkanolamine salts to citrus fruits, and from the postharvest application of the 2,4-D isopropyl ester to lemons.

0.2 part per million in or on potatoes.

(b) Tolerances are established for residues of 2,4-D (2,4-dichlorophenoxyacetic acid) at:

1000 parts per million in or on grasses (pasture and rangeland):

300 parts per million in or on grass hay:

20 parts per million in or on the forage of barley, oats, rye, and wheat, corn fodder and forage, rice straw, sorghum fodder and forage, and sugar cane forage:

2 parts per million in or on sugarcane:

0.5 part per million in or on the grain of barley, oats, rye, and wheat, corn grain and fresh corn including sweet corn (kernels plus cob with husks removed), cranberries, grapes, and sorghum:

0.1 part per million in or on blueberries and rice from application of 2,4-D in acid form, or in the form several salts or esters.

The FDA, according to Pesticide and Toxic Chemical News (Anonymous, 1979), list 2,4-D as being found twice in its food monitoring programs in fiscal 1978 and zero in fiscal 1979. To put this in perspective the insecticides malathion and captan were found 329 and 305 times; and 141 and 185 respectively in the same time period. Thus, it may be concluded that from a health standpoint there is essentially no 2,4-D in our food supply.

Measurable amounts of 2,4,5-T were found only in two food samples

in FDA market basket surveys in 1966-67 and in one sample in 1967-68. No 2,4,5-T has been found in food since 1968 in the FDA studies. A total of over 2,000 samples was collected and analyzed. The highest 2,4,5-T concentration in the 1966-67 samples was 0.19 ppm. Only two residues of silvex were found. These occurred in dairy products collected in 1965-66 and were 0.018 ppm and 0.029 ppm (Environmental Protection Agency, 1978). Therefore, based on FDA market basket surveys, the amount of phenoxy herbicides in food is virtually undetectable.

The most direct exposure of humans to 2,4,5-T through food products is probably via plants; however, research has shown that phenoxy residues in forage and agronomic crops usually disappear rapidly. Since most weeds in crops are treated in early spring, residues disappear by harvest time. Devine (1970) analyzed 27 samples of rough rice fromm Texas, Arkansas, and Louisiana for residues of 2,4,5-T at intervals from 50 to 84 days after application of 2,4,5-T for weed control. No detectable residues (0.01 ppm) were found. Rice straw contained residues that varied from <0.01 ppm to 1 ppm. In the case of pasture and rangeland plants, which may intercept relatively high amounts of phenoxy herbicides (up to 200 ppm), residues can be avoided in meat and milk products by deferring grazing for milk cows on the treated area a few days to a few weeks and removing meat animals from treated pastures 2 weeks before slaughter. These restrictions appear on current product labels.

Will the meat from slaughtered animals which had been bean fed 2,4-D or 2,4,5-T for four weeks contain residues? Negligible levels

(less than 0.1 ppm in muscle and fat) were found when no withdrawal time was employed. If the animals were fed a regular diet for 1 week after the 2,4-D or 2,4,5-T feeding occurred, no detectable phenoxys were found in fat or muscle tissue (Leng, 1972).

Even when wildlife species or livestock graze on pastures immediately after spraying, only small amounts of phenoxy herbicide may appear in meat or milk. They disappear after a few days due to rapid loss of the herbicides from forage and by normally rapid excretion from the grazing animal. Klingman et al. (1966), in actual field grazing trials with cattle, found 0.01 ppm to 0.09 ppm of 2,4-D in milk the first 2 days after spraying 2,4-D at 2 pounds per acre, and lower amounts thereafter. No residues of 2,4,5-T were found in milk from cows put into pastures 4 days after spraying. Bjerke et al. (1972) found no residues of 2,4-D, 2,4,5-T, or MCPA, or their corresponding phenols, greater than 0.05 ppm in milk from cows exposed to 30, 300, or 1,000 pm 2,4,5-T in their feed level. Residues of silvex were found only at the 1,000 ppm feeding level. Clark et al. (1975) concluded that residues of phenoxy herbicides or phenolic metabolites in meat of sheep or cattle are unlikely under normal patterns of 2,4,5-T use.

In field studies, Newton and Norris (1968) found that blacktail deer did not accummulate large amounts of 2,4,5-T when they grazed browse that had been treated with 2 pounds per acre. Concentrations in tissue rarely reached detectable levels, and the ruminant was able to degrade and eliminate the herbicide soon after ingestion. Obviously, game animals may graze in treated areas immediately after

spraying, but in most cases spray areas are substantially smaller than the home range of large game animals, and thus exposure is not continuous. Game animals are likely to constitute a vanishing small proportion of the average human diet in the United States, but they may be an important component in the diet of a few individuals.

Fish and other aquatic organisms are also important components of the diet of humans. The occurrence of significant amounts of phenoxy herbicides in the FDA market basket survey in fish products was not indicated. Research shows that most fish do not accumulate large amounts of the phenoxy herbicides (<1 ppm), even when the herbicide is applied directly to water surrounding the fish. The degradation rate of phenoxys in surface water is quite rapid. Fish also have the capability of eliminating and degrading the phenoxys.

None of these reports show food to be a major source of human exposure.

Assessment of human exposure to the phenoxy herbicides

Man's potential exposure to phenoxy herbicides through the air he breathes, water he drinks or food he eats has been shown to be minimal. Levels that his skin may absorb by coming into casual contact with sprayed vegetation would probably be low since these compounds degrade rapidly on both leaf surfaces and soil.

Although much of phenoxy applied to vegetation may find its way to the soil or run-off into water the degradation rate is so rapid that no buildup occurs. Thus, all of avenues for human exposure examined so far have indicated that humans are receiving non-existant to minimal levels. In the next chapter an in-depth look into exposure levels

received by those who apply herbicides for their livelihood will be made.

It is important to differentiate between man's exposure and his absorbed dose. It was pointed out that humans may be exposed via inhalation, dermal depositions or ingestion. An important item which dictates the degree of risk man encounters is his absorbed dose or how much of the chemical actually enters the body fluids. The rate and amount excreted from the body is also important.

The absorbed dose resulting from inhalation must take into consideration how much was present in the air a man breathes in and also how much is in the air he exhaled. The difference would conceivably be the absorbed dose unless a fraction of this was expelled as sputum. Absorbed dose resulting from dermal exposure is that amount penetrating man's dermal membranes. Herbicide contacting the skin does not necessarily penetrate the surface. In the case of water soluble phenoxy compounds a considerable amount can be washed off using soap and water if this is done soon after contact. In the case these compounds are ingested, the opportunities for absorption are much greater. Thus, man or any other organism can <u>not</u> be injured merely by being exposed to a toxin.

CHAPTER 2
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CHAPTER 4

Pharmacokinetic Studies of the Phenoxy Herbicides in Humans and Animals

Toxicity can be defined as the ability of a material to cause injury by other than physical (mechanical) means. It can be determined by administering known doses of a test substance to laboratory animals.

A relatively simple test for acute (single dose) toxicity is the determination of a substances' acute oral median lethal dose LD_{50}. Such an LD_{50} (mg/kg) is defined as the single dosage of milligrams per kilogram body weight required to kill 50% of a test population of animals when given by mouth. The lower the number, the greater the toxicity.

Most commonly used pesticides have some degree of toxicity. Table 4-1 provides information on toxicity, terminology, LD_{50}'s and estimates for probable lethal dose for a 150 lb man if exposed to a toxic material. The toxicity ratings in this table will be used to evaluate pesticide toxicity presented in Table 4-2. Humans are seldom exposed to concentrated pesticides. Batchmen mixing chemicals for a spray operation or those in manufacturing plants are most likely to contact the concentrates. Some accidents and suicides have occurred.

Table 4-1. Ratings of toxicity, LD_{50}, and estimates of man's lethal dose. (Cleason, et al. 1957).

Toxicity rating[2]	LD_{50} (mg/kg)[1]	Probable lethal dose for 150 lb man[3]
Extremely toxic	less than 5	a taste (less than 7 drops)
Very toxic	5-49	7 drops to 1 teaspoonfull
Moderately toxic	50-499	1 teaspoon to 1 ounce
Slightly toxic	500-4,999	1 ounce to 1 pint (1 pound)
Almost non-toxic	5,000-14,999	1 pint to 1 quart
Non-toxic	15,000 and above	more than 1 quart

[1]Toxicity rating is from Clinical Toxicology of Commercial Products by Cleason, M.N., Gosselin, R.E. and Hodge, H.D., and published by Williams and Wilkins Co., Baltimore, MD, 1957.

[2]These doses refer to a 100% concentrate. Many pesticides are contained in solvents which dilute the active ingredient. (In some cases the solvent may be more toxic than the pesticide.)

Table 4-2. Relative Toxicity of Some Pesticides to Mammals. (Virginia Pest Management Guide, 1980).

Common name	Trade name	LD_{50}[1] (mg/kg)	Toxicity rating
Herbicides			
Alachlor	Lasso	1,800	slightly toxic
Amino triazole	Amitrole-T	5,000	almost non-toxic
ASPIRIN (for comparison		750	slightly toxic
Atrazine	Aatrex	3,080	slightly toxic
Bromacil	Hyvar-X	5,200	almost non-toxic
Butylate		4,659-5,431	slightly toxic
Chloramben	Amiben	3,500	slightly toxic
Cyanazine	Bladex	334	moderately toxic
Dalapon	Dowpon	7,570-9,330	almost non-toxic
Dicamba	Banvel-D	1,028	slightly toxic
Dinitramine	Cobex	3,700	slightly toxic
Dinoseb	DNBP	58	moderately toxic
Diquat	Diquat	230	moderately toxic
Diuron	Karmex	3,400	slightly toxic
Fluometuron	Cotoran	1,550	slightly toxic
Glyphosate	Round-up	4,320	slightly toxic
Linuron	Lorox	1,500	slightly toxic
MSMA	MSMA	1,800	slightly toxic
Metolachlor	Dual	4,286	slightly toxic
Metribuzin	Sencor	1,090-1,206	slightly toxic

Table 4-2 (cont.)

Common name	Trade name	LD_{50}[1] (mg/kg)	Toxicity rating
Monuron	Telvar	2,300-3,700	slightly toxic
Oxadiazon	Ronstar	30,000	non-toxic
Paraquat	Paraquat	120	moderately toxic
Pendimethalin	Prowl	3,380	slightly toxic
Picloram	Tordon	8,200	almost non-toxic
Profluralin	Tolban	2,200	slightly toxic
Propachlor	Ramrod	710	slightly toxic
Silvex	Weed-B-Gon	1,070	slightly toxic
Simazine	Princep	5,000	almost non-toxic
Sodium Chlorate	Tumbleaf	5,000	almost non-toxic
Table salt (for comparison)		3,320	slightly toxic
Terbacil	Sinbar	5,000-7,500	almost non-toxic
Trifluralin	Treflan	3,700	slightly toxic
2,4-D	2,4-D	300-1,000	moderately toxic
2,4-DB	2,4-DB	1,960	slightly toxic
2,4,5-T	2,4,5-T	300	moderately toxic
Hexazinone	Velpar	16,900	non-toxic
Insecticides			
Acephate	Orthene	866-945	slightly toxic
Aldicarb	Temik	1.0	extremely toxic
Azinphosmethyl	Guthion	13	very toxic

Table 4-2 (cont.)

Common name	Trade name	LD_{50}[1] (mg/kg)	Toxicity rating
Carbaryl	Sevin	850	slightly toxic
Carbofuran	Furadan	10	very toxic
Chlordane	Ortho-Klor Belt	335	moderately toxic
Chlordimeform	Fundal, Galecron	170-220	moderately toxic
Chlorpyrifos	Dursban,	97-276	moderately toxic
Demeton	Systox	12	very toxic
DDT	-	113-118	moderately toxic
Diazinon	AG 500 Spectracide	108	moderately toxic
Dichlorvos	Vapona, DDVP	80	moderately toxic
Dimethoate	Cygon, DeFend	215	moderately toxic
Disulfoton	Di-Syston	12	very toxic
Ethylene dibromide	Dowfume	108-70	moderately toxic
Fenthion	Baytex, Tiguvon Entex	313	moderately toxic
Lindane		88	moderately toxic
Malathion	Cythion	1,375	slightly toxic
Methiacarb	Mesurol	130-135	moderately toxic

Table 4-2 (cont.)

Common name	Trade name	LD_{50}[1] (mg/kg)	Toxicity rating
Methomyl	Lannate, Nudrin	17-24	very toxic
Methyl Parathion	Penncap-M	14	very toxic
(Microencapsulated MP)		480	moderately toxic
Parathion		13	very toxic
Pentachlorophenol		27	very toxic
Phorate	Thimet	2.3	extremely toxic
Pyrethrum		200	moderately toxic
Ronnel	Korlan, Trolene, Ronnel	906-3,025	slightly toxic
Rotenone		132	moderately toxic
Tetradifon	Tedion	14,000	almost non-toxic
Fungicides			
Benomyl	Benlate	64	almost non-toxic
Captan	Captan	9,000	almost non-toxic
Fensulfothion	Dasanit	2-10	extremely toxic
Dichlone	Dichlone	1,300	slightly toxic
Captafol	Difolantan	6,200	almost non-toxic
Oxydisulfoton	Disyston	3.5	extremely toxic
Ferbam	Ferbam	17,000	non-toxic
Carbofuran	Furadan	11	very toxic
Maneb	Maneb	6,750	almost non-toxic

Table 4-2 (cont.)

Common name	Trade name	LD_{50}[1]	Toxicity rating
Captan	Orthocide	9,000	almost non-toxic
Thiram	Thiram	780	slightly toxic
Zineb	Zineb	5,200	almost non-toxic

[1] LD_{50} (mg/kg) - The dosage of milligrams per kilogram of body weight required to kill 50% of test animals when given a single dosage by mouth. From: Herbicide Handbook of the Weed Science Society of America, 4th Edition, 1979.

A list of several pesticides grouped as families of herbicides, insecticides, or fungicides is presented in Table 4-2. This table suggests that as a family, the toxicity of herbicides presents a minimal risk to human health. Phenoxy herbicides have been specifically designed to kill broadleaf weeds; as such it is not surprising that they have relatively low capability to cause harm to animals (Vaccaro, 1983). Insecticides as a family have a higher potential for harming higher animals. It is interesting to look at information from the Poison Control Center on reported cases of poisoning. In 1979, there were over 144,000 reported cases of poisoning with 70 fatalities.

None of the 70 fatalities were due to herbicides. Of the 144,000 reported cases, 5% were attributed to all pesticides and 0.2% to herbicides.

The LD_{50} values as listed in Table 4-2 represent acute doses or the amount that an animal can tolerate if all was administered in one dose. These values from test animals are of real assistance when addressing poisoning or attempted suicide cases in humans. Since men are seldom used as guinea pigs in our society to study potential long-term (chronic) effects of repeated exposure to low levels of pesticides, animal feeding experiments are conducted. In these studies several different concentrations of pesticides are routinely incorporated into all of the food ingested by the test animal. The duration of feeding periods may range from 1 week to more than a year for many of the tests. The studies are required to include concentrations that are sufficiently high to at least cause injury to some of the test animals. No observed effect levels (NOELs) are determined by citing the highest pesticide level at which no harmful effects are detected on the test animals.

It is relatively easy for the results of this type of study to be misinterpreted since often the information is not presented in a manner that one can easily understand regarding how much of the chemical was required to cause the effect. Information derived from studies of this kind are of importance to man as he seeks to make judgements regarding any exposure to pesticides that he may receive. Conducting a well designed research study is not as difficult as effectively communicating the findings to an interested audience of

varying backgrounds.

Results from the applicator exposure studies have shown that a portion of the phenoxy herbicides as they are being applied as vegetation control do not reach their target. In fact, at times humans may be inadvertent receptors resulting in an "absorbed dose." The goal of this chapter is to investigate the fate of the phenoxy compounds after they have contacted humans, entering the body by penetrating the skin (the most common route) via the food and water consumed or in the air breathed. The most commonly used phenoxy compounds 2,4-D and 2,4,5-T will be discussed. Since the LD_{50} for 2,4-D and 2,4,5-T is "upwards of 300 mg/kg" for several animal species (CAST, 1978) it is highly likely that these compounds have some biological activity for humans also. The mere fact that a compound has some moderately toxic properties does not make it dangerous unless one receives an absorbed dose and even then the amount of the dose is the important factor.

A philosopher of the Middle Ages, Paracelsus, said "All substances are poison; there is none which is not a poison. The right dose differentiates a poison and a remedy." If the full understanding of the meaning of dose could be clearly communicated an informed U.S. public would have less trouble sleeping at night. The user needs to be aware of the toxicity of the compound he is using. As shown in Table 4-2 pesticides vary greatly in their toxicity to man and other animals.

The phenoxy compounds have an excellent human health record when considering their widespread use and the lack of complaints or health problems arising from pesticide applicators, the most exposed group.

What protective mechanism(s) does man possess which allows him to be in contact with these compounds, sometimes over an extended period, without them causing him noticeable physical harm? To gain a better understanding of how his body is able to excrete or rid itself of these compounds an evaluation of animal feeding studies with the phenoxy compounds is in order.

An indication of the extent of animal toxicological testing with the phenoxy compounds is obtained from Diaz-Colen et al. (1977) who indicate that more than 870 such studies have been completed in the past 25 years. In one study residues of the 2,4-D and its breakdown products were determined in muscle, fat, liver and kidney of cattle and sheep fed up to 2000 mg 2,4-D per kg in their feed. Muscle and fat contained the lowest levels while kidneys and liver contained the highest residue level. Withdrawal from treatment for one week resulted in a significant reduction in tissue residue levels. With the exception of the kidneys, 2,4-D residues averages less than 1 mg/kg in the tissue analyzed. The kidney tissue level averaged 7.82 mg/kg with 0.37 mg/kg present after a 7-day withdrawal period. No 2,4-D was detected in fat or muscle of any animals at a detection limit of 0.05 mg/kg. (Lack of build-up of the phenoxy herbicides in fatty tissues of animals is common; this is in sharp contrast to some of the more persistent chlorinated insecticides which are stored in fatty tissues of mammals.) All treated animals in this study showed some loss of apetite, weight loss or poor weight gain depending on the level 2,4-D present in the feed. During the 7-day withdrawal period, feed consumption in all groups returned to normal (Clark et al.,

1975). Cattle, which were fed 50 or 100 mg/kg/day phenoxy herbicide (2,4,5-T or Silvex) for as long as 1 year, suffered no ill effects. Livestock can safely eat vegetation freshly treated with phenoxy herbicides, however, milk or meat fromm these animals could contain trace levels of residue. It is recommended that 2 weeks elapse between phenoxy treatment of vegetation and slaughter of animals grazing the treated area (Leng, 1972).

One of the short-comings of some animal testing data as described by the Advisory Panel on Toxic Substances (Beljan et al., 1981) states "One of the common failings of animal toxicity assessments is the use of test doses that are much higher than those that may be encountered by humans. Such massive doses are intended to shorten the time for a response or, in the case of a carcinogenicity test, to increase the probable incidence of tumors within a sample of animals." However, much valuable information can be obtained from animal studies when realistic rates are selected properly.

A two-year study by Smith et al. (1978) of chronic toxicity and incidence of cancer among rats ingesting diets containing 2,4,5-T revealed few toxicological symptoms (loss of body weight and slight changes in the size or shape of kidneys, livers, and lungs) even at the highest does level (30 mg 2,4,5-T/kg body weight/day). This study also showed no incidence of cancer response in rats even when administration of 2,4,5-T extended over most of their life span at a dosage high enough to induce other toxicity. As for the effects of 2,4,5-T on reproduction, they found in studying three generations of rats that dose levels of 2,4,5-T high enough to cause signs of toxi-

city had no effect on the reproductive capacity of rats, except for a tendency to reduce survival of the young at dose levels of 10 and 30 mg/kg/day.

Numerous studies on the fate of 2,4-dichlorophenoxy-acetic acid (2,4-D) and related herbicides in animals have shown that these chemicals are absorbed and excreted unchanged in the urine within a week after administration (Leng, 1977). Pharmacokinetic studies with 2,4,5-T in rats and dogs (Piper et al., 1973) supported these findings (Pharmacokinetic studies show us how a chemical is treated by the body and how rapidly it is excreted).

Repeated doses of 2,4-D or 2,4,5-T in animals do not cause toxic symptoms since they continually eliminate it. This process is protective since it does not allow the concentration to build-up. The study of how animals eliminate foreign chemicals and the rate of elimination is important in understanding the fate of phenoxy compounds in humans.

Fate of phenoxy herbicides in man

In an experiment to determine the fate of ingested 2,4,5-T in man, five male volunteers (from 31 to 58 years of age) were each given a single dose of 5 mg/kg of body wt of 2,4,5-T (which contained less than 0.05 ppm of TCDD). Blood concentration of 2,4,5-T reached a maximum in 7 hours, and then declined for the following 5 days. Within 5 days, 89% of the ingested 2,4,5-T was excreted unchanged in the urine (Gehring et al., 1973). From these results the investigators predicted that an individual ingesting daily doses of 2,4,5-T would have attained his highest level after 3 days.

In related research showing 2,4-D excretion Sauerhoff (1977) showed that 2,4-D was also absorbed almost entirely and eliminated from the body in the urine - 95% within 4 days. With repeated doses, a plateau is reached and the body excretes 2,4-D as rapidly as it enters.

This research provides evidence of the fate of phenoxy herbicides that are orally ingested by humans; but, as shown in Chapter 3, forest crew members applying phenoxy herbicides appeared to receive their highest dose when these compounds penetrated their bare skin areas. Personnel associated with the "Operation Ranch Hand" program, which involved use of the phenoxy herbicides as defoliants in Vietnam would probably also have received the majority of their exposure by skin absorption. Studies by Sauerhoff et al., 1976 show that regardless of the path of entry, rapid urinary elimination of 2,4,5-T occurred in rats.

Probability of dermal absorption

Is it feasible that significant levels of an organic chemical could pass through man's skin? Baranowska-Dutkiewicz (1982) indicates that under industrial conditions the skin is the main route of aniline absorption. To obtain a measure of the absorbed dose of aniline occurring in 30 or 60 minute exposure a 24-h urine sample was analyzed for p-aminophenol. They cited other research which showed that benzene, styrene, xylene and carbon disulphide were even more readily absorbed by human skin. Hosler et al. (1980) analyzed blood plasma and urine to provide indicators for the amount of 10% lindane cream absorbed by human skin in a 12-hr exposure study. Jakobson et al.

(1982) indicates that uptake of organic solvents through the skin may pose a risk during occupational handling of these compounds. Warnings are given that considerable uptake may occur when certain solvents contact human skin. Durham et al. (1972) indicates that although absorption by the respiratory route is faster than through the skin, the opportunities for dermal exposure are often much greater.

Studies of the dermal absorption of 2,4-D applied to human forearms revealed that 6% of the applied amount was recovered in urine collected during the week after exposure (Feldman and Maibach, 1974). The findings of the applicator exposure studies presented in Chapter 3 which showed dermal absorption of phenoxys to be the major route of entry into the body are compatable with the results of the research above.

Although the odor near an application site often times is quite pronounced, it is interesting that in both of the detailed phenoxy applicator exposure studies reported here and also in other studies the amount of the compound in the air was minimal on a weight basis compared to the dermally absorbed dose.

Young et al. (1981) applied the propylene glycol butyl ether esters (PGBE) of 2,4,5-T to the shaved skin of rats. This is the same formulation of 2,4,5-T used in the 2,4,5-T applicator exposure studies described in detail in Chapter 3.

When this 2,4,5-T was absorbed through the skin only 2,4,5-T could be detected in the urine. The authors concluded that the application of PGBE ester to the skin of rats resulted in 2,4,5-T itself in the body. Therefore, exposure to esters of 2,4,5-T can be regarded as

toxicologically equivalent to the 2,4,5-T itself. Six days after application to the skin they recovered approximately 97% of the 2,4,5-T in the urine. Samples of either blood or urine from exposed individuals should provide a measure of the absorbed dose since the phenoxy compound must enter the blood stream before it is excreted in urine. Total urine collection allows the researcher to recover almost all of the phenoxy herbicide that was absorbed.

Young et al. (1981) also observed that adsorption through skin was much slower than absorption of ingested 2,4,5-T. The low rate of absorption of the ester through the skin suggests that removal of the ester from the skin by washing after exposure could substantially reduce the dose of 2,4,5-T received by this route. The relatively slow dermal absorption and excretion rate agrees with human data derived from the 2,4,5-T exposure study presented in Chapter 3.

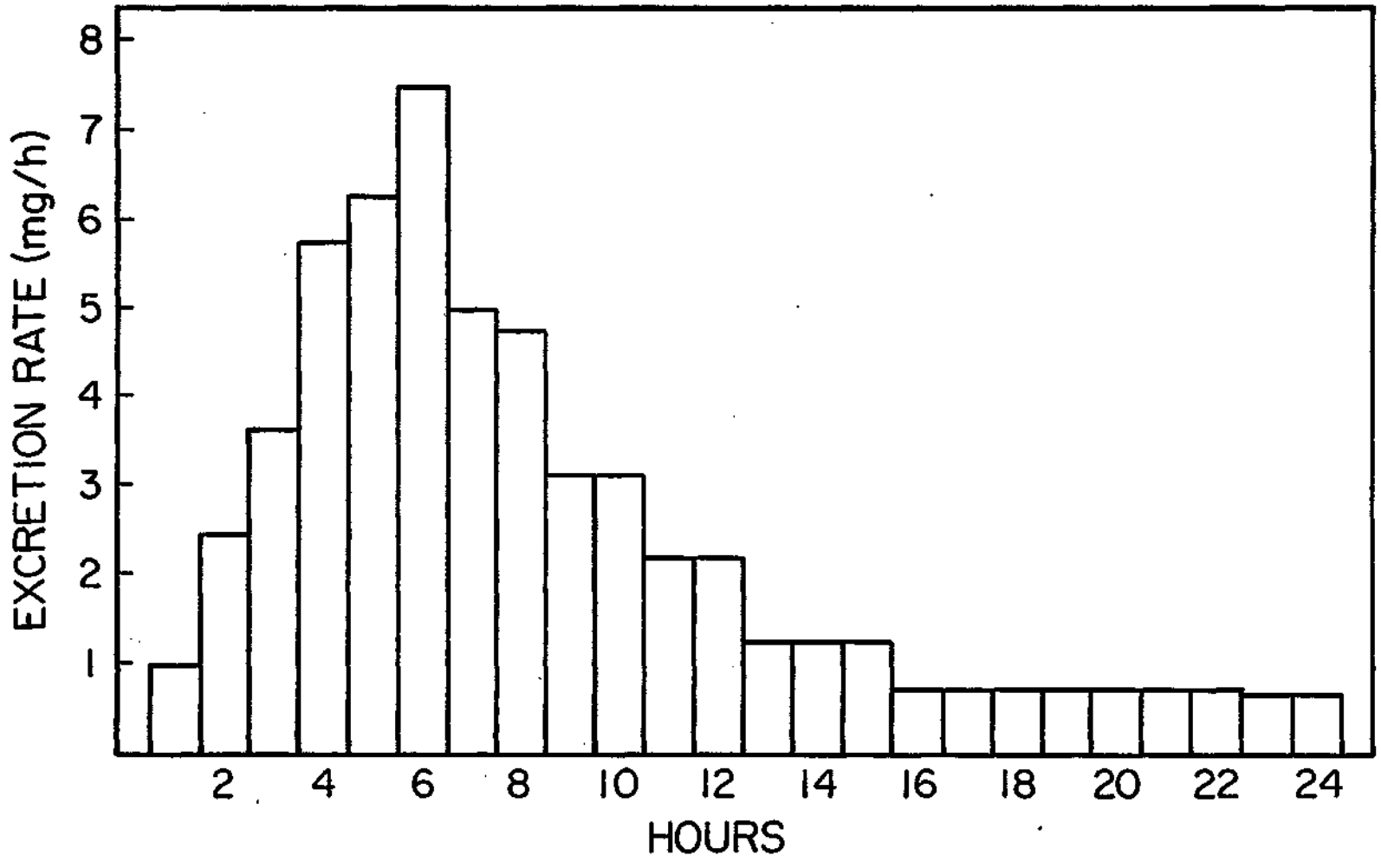
The extraordinary ability of man's body to rid himself of foreign substances and other toxins is vividly demonstrated as one scans the literature. Although the prudent man will protect himself from unnecessary exposure to toxins in the environment, it should be reassuring to him to learn that he has several built in safety devices. Perhaps in this age when the media almost monthly reveals to us the toxic effects of one of our foods or some other chemical product that we come into contact with it is reassuring to know that our kidneys or other body systems are attempting, on a full-time basis to remove both known and unknown toxins that we encounter.

Factors affecting man's absorption and excretion rates of phenoxy compounds

One of the more perplexing questions with regard to interpreting results from pesticide applicator exposure data is why the correlation is so low between the amount of pesticide deposited on patches and that excreted in urine. Data presented earlier in this chapter indicates that phenoxy herbicides are nearly quantitatively excreted in man's urine and that dermal absorption is the major avenue of entry into his body. Thus, intuition suggests that levels derived from quantitatively measuring the herbicide deposited on man's skin and the amount excreted in his urine would be highly correlated. In both the 2,4,5-T and the 2,4-D applicator exposure studies (Lavy et al., 1980; Lavy et al., 1982) poor correlation for these two measurements was found. What are some of the potential reasons for these findings?

Figure 4-1 depicts the typical excretion rate of p-aminophenol for an individual dermally exposed for 1-hr to liquid aniline (Baranowska-Dutkiewicz, 1982). When a single dermal exposure occurs over a 1-hr period for a rapidly absorbed compound a smooth uniform excretion pattern occurs. Figure 3-1 on page illustrated the excretion pattern of 2,4-D by one of the more heavily exposed crewmembers in the 2,4-D exposure study who probably did not receive all of his exposure on the day the spray was applied (Lavy, 1980). Since patches were attached to the worker's clothing only on the application day, and urine was collected over a 6-day period it is not surprising to find poor correlation between patch data and urinary excretion data if exposure was not limited to the day of application. As discovered

Figure 4-1. Excretion rate of p-aminophenol in urine in a subject exposed to 1% aniline solution for 1 h (Baranowska-Dutkiewicz, 1982).


EXCRETION RATE (mg/h)
8
7
6
5
4
3
2
1
2
4
6
8
10
12
14
16
18
20
22
24
HOURS

in post-study interviews for some workers, the opportunity for continuing exposure occurred as they cleaned equipment. Contaminated clothes could also provide prolonged exposure.

Another fact that could be contributing to the low correlation between patch and urine data is the physical location of the patches on the test subject. In the 2,4,5-T study (Lavy, 1978) 6-10 x 10 cm paper backed gauze patches were attached to clothing of the worker at the following locations: chest, back, upper arms, and upper thighs. In the 2,4-D study the denim patches were attached to worker's clothing near their bare skin areas. The calculations for predicting dermal exposure to humans are dependent on knowing: a) the area of patches retaining the chemical, b) the total weight of the pesticide deposited on the patch, c) the area of bare skin of the crewmember (this is obtained by viewing photographs of the crewmember in his work clothes and using a human area formula developed by Durham and Wolfe (1962)). Use of patches and consequent interpretation of data derived from their use is based on assumptions that pesticides 1) are uniformly deposited across all parts of the body; 2) that patches capture and retain the same amount of pesticide that the skin retains (this could hardly be true if a man were perspiring and he was wearing dry patches) and 3) that all portions of a man's skin are equally penetrable by the pesticide in use.

Data presented by Lavy et al. (1980b) showed that the range in weight of 2,4,5-T on similar sized patches on the same individual ranged from 20 to 8760 micrograms. The anatomical site of application has been shown to affect the percutaneous absorption of compounds in

humans (Maibach et al., 1971). The interaction between skin and the specific pesticide will also be important. Some will adhere strongly to the skin while others will more readily pass through.

When all of these factors are taken into consideration it is not surprising that low correlations exists between patch and urinary excretion data in phenoxy exposure studies.

Gehring et al. (1973) developed an equation to predict a per day excretion curve for humans given a single dose of phenoxy herbicide. Nash (1983) has expanded on this work and devised an equation which allows one to make an estimate of the absorbed dose which occurred on the day of exposure. He indicates that by knowing the elapsed time between the exposure day and the day a 24-hr urine sample was taken, his equation can provide a good estimate of the extent of absorption which occurred. If functional use of the above approaches could be made it would save the field research crews considerable time and the crew participants inconvenience (as contrasted to collecting every drop of urine over a 6-day period). Unfortunately as shown in Figure 3-1 on page , actual field exposure received by some workers does not occur all on the same day. Thus, if the researcher is looking for measurement of the total phenoxy exposure occurring to all crewmembers who work as a part of the field application process he will continuously monitor the phenoxy content of urine from humans during all of the time exposure is potentially occurring and for at least 5 days following the last potential exposure. Even though the exposure to humans applying the phenoxy herbicides was not all limited to the actual application day it was shown in Chapter 3 that even for the

individuals mixing the concentrate and receiving multiple exposures, natural human body processes are capable of keeping the level of the phenoxy herbicides which penetrate the body well below harmful levels.

It is vital that we not overlook the primary findings of this monograph - namely although man experiences some exposure to the phenoxy compounds the detection of this exposure is made possible only through advances in analytical equipment which allow pesticide detection capabilities in the parts per billion range. The backpack applicators and mixers (those receiving the highest absorbed dose) (Lavy, 1978) did not feel ill or exhibit any symptoms. The absorbed dose for these highest occupationally exposed individuals is 300-fold below the no-effect level. Putting this into another context - if one were dependent on surveys and results from questionnaires of workers who mix and apply the phenoxy herbicides, basically we would come to the conclusion that no exposure was occurring. These compounds have been used extensively for over 30 years with no known ill effects due to their use when used in accordance to the directions provided. Thus, other than through the use of analytical equipment capable of detecting trace levels of pesticide residues, the only evidence that exposure is occurring is by visually observing that sometimes workers get the spray materials on their skin and that a characteristic odor is often present at spray operation sites.

Effects of repeated exposures

Questions such as the following have not been addressed fully: Do repeated exposure to the phenoxy herbicides pose a threat to the health of people who work as pesticide applicators for several months

a year? How high a concentration of the phenoxy herbicides will build up in such applicators?

The exposure data presented have addressed the question: How much exposure does a human receive during a one-time exposure? Researchers are aware that normally field workers do not apply phenoxy herbicides just one time a year. However, to obtain good replicated data it is important that each of the crewmembers enter the study on an equal exposure basis. If some had been spraying continuously for a week prior to the study, others two days, and others intermitently for 3 or 4 days it would be nearly impossible to attain meaningful replicated data. If the study had been designed to measure the exposure occurring during and after 4 sequential spray days, how would one handle the data collected following a weather pattern which allowed 2 days of application before a 3-day rainstorm prevented continuation of the research? The logistic problems associated with carrying out the research would be greatly increased and the replications would be destroyed unless all workers were at the same location experiencing the identical work conditions for the same period of time. Another reason for selecting a single exposure day was the fact that single dose exposure data could be extrapolated to produce the same results that would have been attained if an individual had been exposed repeatedly.

Taking a scientific approach to answering the repeated exposure question Ramsey et al. (1978) made a pharmacokinetic analysis of the 2,4,5-T exposure study reported in Chapter 3 (Lavy, 1978). They indicate that the total amount of 2,4,5-T excreted in the urine following

exposure represents a minimum estimate of the amount of 2,4,5-T absorbed, since excretion may not be complete at termination of the experiment. However, calculation of the absorbed dose of 2,4,5-T based on pharmacokinetic analysis of urinary excretion data is not dependent on total excretion and can provide a realistic estimate of the absorbed dose.

Ramsey et al. (1978) estimated the amount of 2,4,5-T by the workers using knowledge of 2,4,5-T in humans from controlled experiments Gehring et al. (1973). Experiments in laboratory animals have shown that 2,4,5-T is excreted in the urine at the same rate regardless of how it enters the body. In other words intravenously and orally administered 2,4,5-T are excreted in the urine at the same rate. Since urinary excretion of 2,4,5-T is independent of the route of exposure (Young et al., 1981; Sauerhoff et al., 1977; Piper et al., 1973) these authors used the data of Gehring et al. (1973) to calculate the dose of 2,4,5-T absorbed by forest workers, even though most of it was absorbed through the skin.

Ramsey et al. (1978) took this information and prepared the following model for urinary excretion.

$$S(t) \xrightarrow{k_{01}} B(t) \xrightarrow{k_{ie}} E(t)$$

This is a schematic diagram of the pharmacokinetic model for the absorption of 2,4,5-T or its PGBE ester in humans, followed by urinary excretion of 2,4,5-T acid. $S(t)$ = amount of 2,4,5-T in the body at time t. $E(t)$ = amount of 2,4,5-T excreted in urine at time t, and k_{01} and k_{ie} = first order rate constants for absorption and excretion of

2,4,5-T, respectively. B(t) = amount in body at time t.

They took urinary excretion data from Lavy (1978) and employed the model. They indicated

> The amount of 2,4,5-T in the pre-exposure samples fluctuated widely with no apparent pattern, therefore no background corrections were applied. The workers employed as mixers may have been exposed on the day previous to the application date (since the formulations are usually mixed the day before the actual application), but for purposes of pharmacokinetic analysis they were considered to be exposed only at the date of application. The duration of the application procedures ranged from 55 minutes to approximately 4 hours (average 138 minutes). Since this is a short time span relative to the total duration of the experiments (up to seven days), the calculated dose was considered to be a single application to the skin at time zero.

Values listed in Table 4-3 represent the percentage of the total absorbed dose of 2,4,5-T which was excreted on each of first seven days following exposure.

Table 4-3. Cumulative fraction of the dermally absorbed dose of 2,4,5-T excreted in the urine (Ramsey et al., 1978).

Days following exposure	Cumulative fraction of dose excreted
1	0.1956
2	0.4819
3	0.6974
4	0.8326
5	0.9105
6	0.9532
7	0.9760

Ramsey et al. (1978) commented:

> The pattern of the daily amount of 2,4,5-T excreted in the urine following exposure is characterized by a maximum on day 2, followed by a steady log-linear decline thereafter. However, an examination of the data shows that, in many cases, there is a significant increase in the amount of 2,4,5-T excreted after the second day following exposure. These data are inconsistent with the excretion pattern expected from a single exposure (Gehring et al., 1973), and thus, probably indicates subsequent exposure to 2,4,5-T or to its ester after the actual application date. The speculation that such exposure might arise from the use of contaminated clothing or footgear should be verified by further experiments and observations. In each case, these increased amounts of urinary 2,4,5-T have the effect of increasing the calculated dose, and therefore result in maximized estimates of the dose absorbed on the application date.

Since the data reported by Lavy (1978) indicate clearly that the respiratory route of exposure to 2,4,5-T is virtually negligible, the major portion of the absorbed dose of 2,4,5-T was the result of dermal exposure to ESTERON 245 herbicide formulations. Methods used to calculate the absorbed dose will reflect the total amounts of 2,4,5-T absorbed by all

possible routes.

Figure 4-2 is a composite of the urine excretion curves from the 21 workers in the 2,4,5-T exposure study. The above detailed interpretation by Ramsey et al. (1978) evaluated each of the worker's excretion data individually. It is interesting that a relatively smooth pattern exists when the whole group is evaluated on a composite basis. This is in contrast to the rather marked variability from individual to individual.

The question of maximum attainable body burden is specifically addressed by Ramsey et al. (1978).

> The pharmacokinetic model describing the absorption and excretion of 2,4,5-T in humans can also be used to predict the accumulated body burden of 2,4,5-T that would result from repeated daily exposures. The results of this mathematical simulation are shown by the solid line in Figure 4-3. These simulated data predict that the maximum accumulated body burden of 2,4,5-T resulting from repeated daily exposures would be 1.4x the daily dose (D_o). In other words, if a worker absorbed a dose of 0.05 mg/kg each day, the maximum body burden attained would be 0.07 mg/kg and this maximum would be reached after approximately 7 daily exposures. However, if the 2,4,5-T remaining to be absorbed were removed 6 hr after each exposure (e.g., by washing or changing clothing), the predicted accumulated body burden would be represented by the dotted line in Figure 4-3. In this case, the maximum body burden would be 0.3x the daily dose D_o, and this maximum would be reached after approximately 3 daily exposures.
>
> In summary, the amount of 2,4,5-T absorbed by forest workers during the application of ESTERON® 245 has been shown to be generally less than 0.1 mg 2,4,5-T per kg of body weight. Since this dose level is far below the no effect level of 20 mg/kg for fetotoxic or teratogenic effects cited by EPA (1978), we conclude that under these conditions the absorption of 2,4,5-T presents a negligible toxic hazard to forest workers.

A composite of the urinary excretion of 2,4-D forestry workers is presented in Figure 4-4. Ramsey et al. (1980) attempted to use this information on their pharmacokinetic model:

Figure 4-2. Average daily excretion of 2,4,5-T in urine of forest workers applying 2,4,5-T (backpack, mist blower, and helicopter methods)(Lavy, 1978).

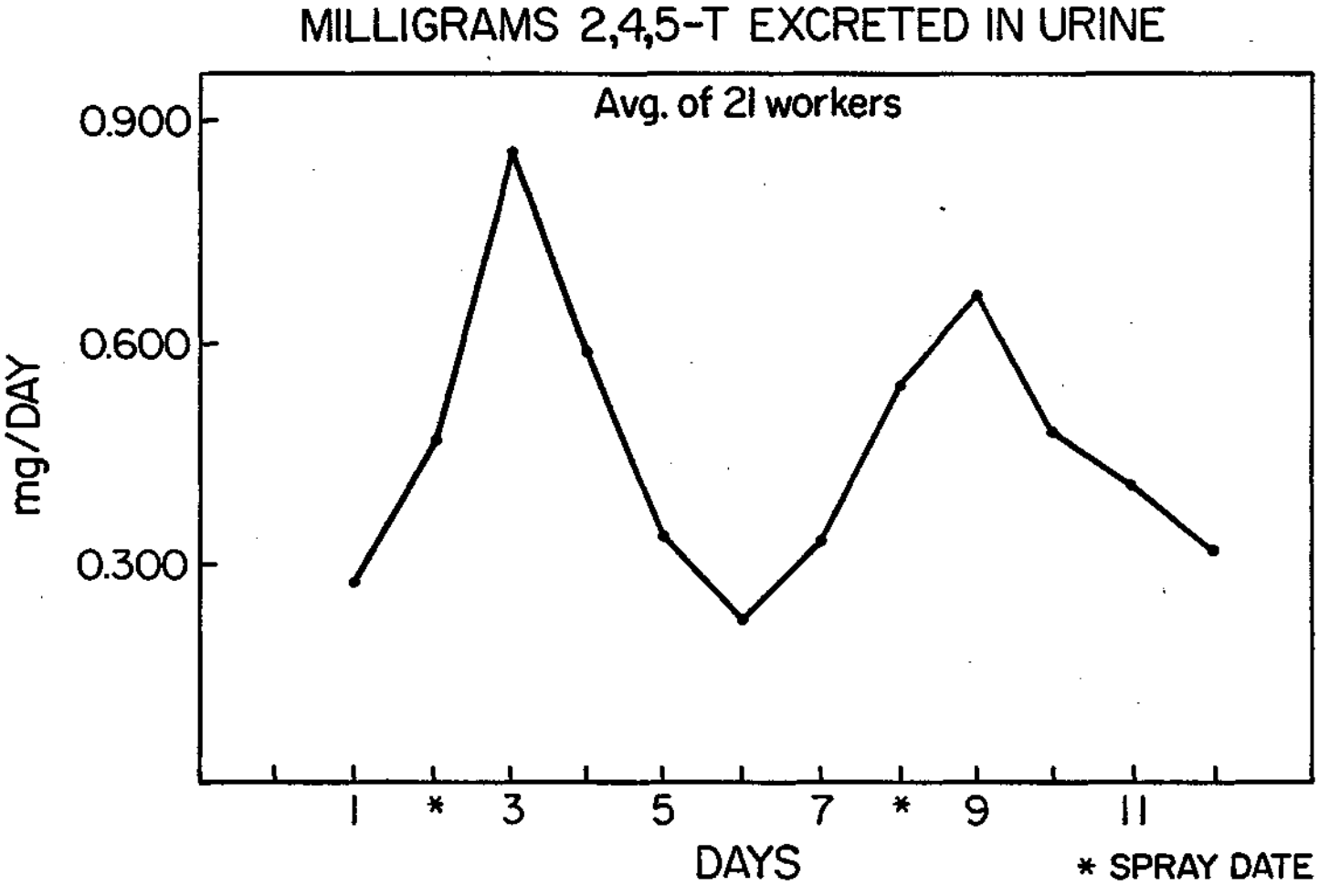
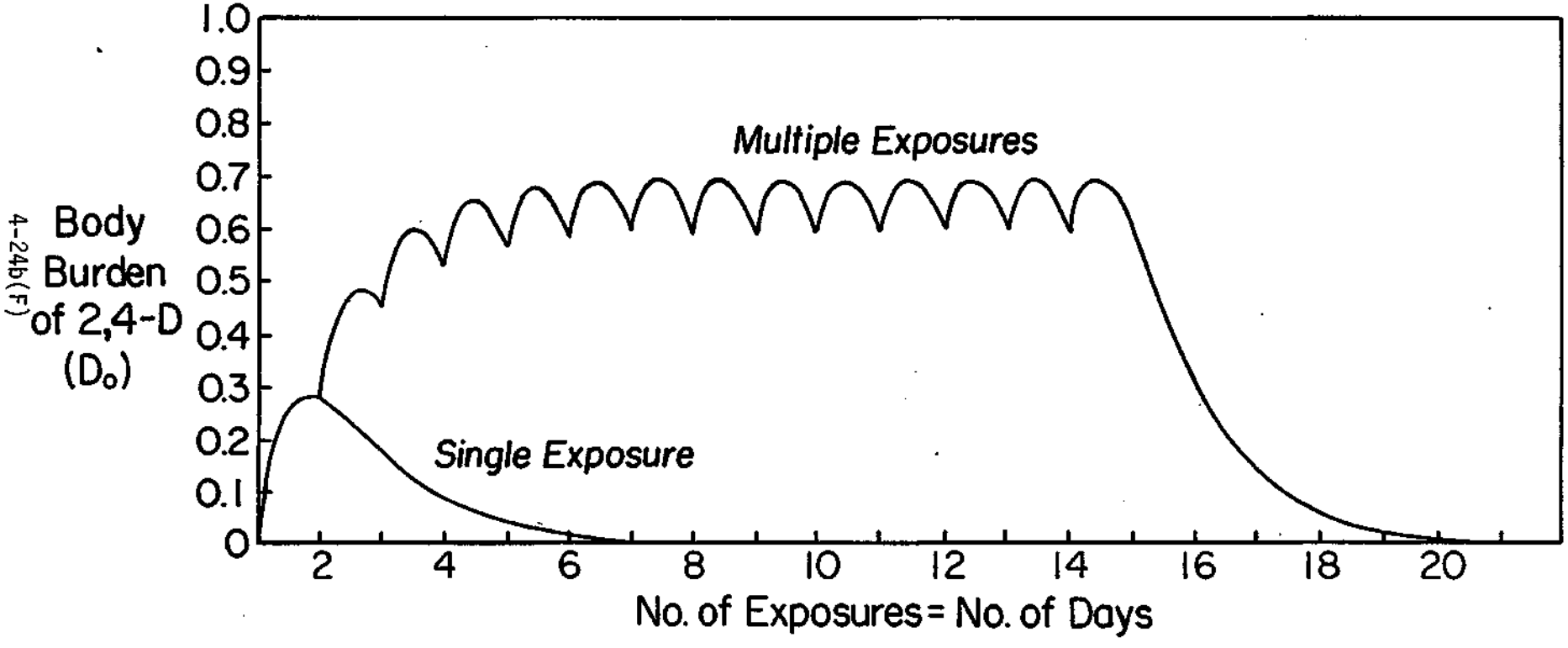
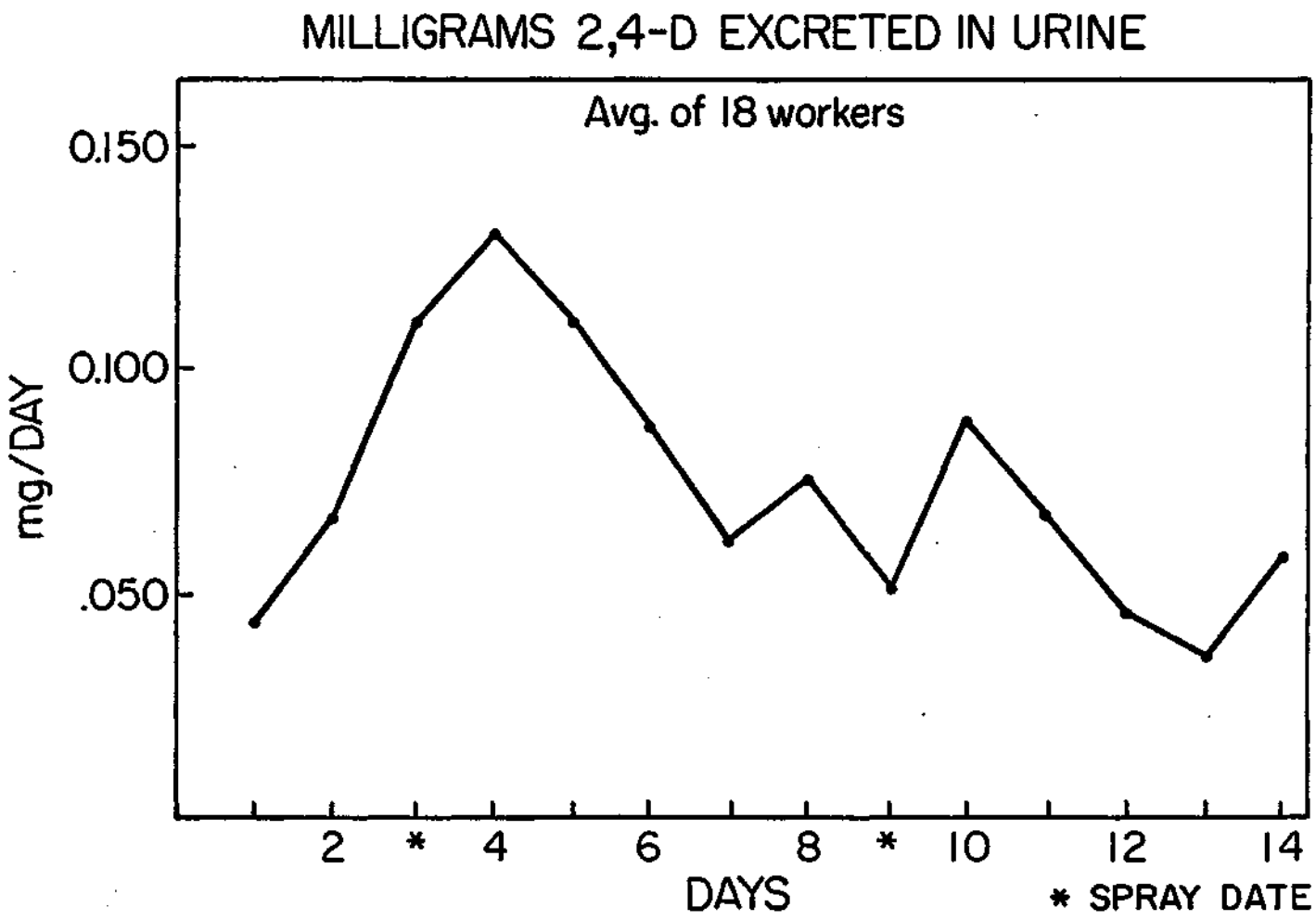

MILLIGRAMS 2,4,5-T EXCRETED IN URINE
Avg. of 21 workers
0.900
0.600
0.300
mg/DAY
1
*
3
5
7
*
9
11
DAYS
* SPRAY DATE

Figure 4-3. Simulated body burden of 2,4,5-T following 13 repeated daily exposures in units of the daily dose D_0 (Lavy, 1978).


Body Burden of 2,4-D (D_o)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Multiple Exposures
Single Exposure
2
4
6
8
10
12
14
16
18
20
No. of Exposures = No. of Days

4-24b(F)

Figure 4-4. Average daily excretion of 2,4-D in urine of forestry workers applying 2,4-D by helicopter (Lavy, 1980).


MILLIGRAMS 2,4-D EXCRETED IN URINE
Avg. of 18 workers
0.150
0.100
.050
mg/DAY
2
*
4
6
8
*
10
12
14
DAYS
* SPRAY DATE

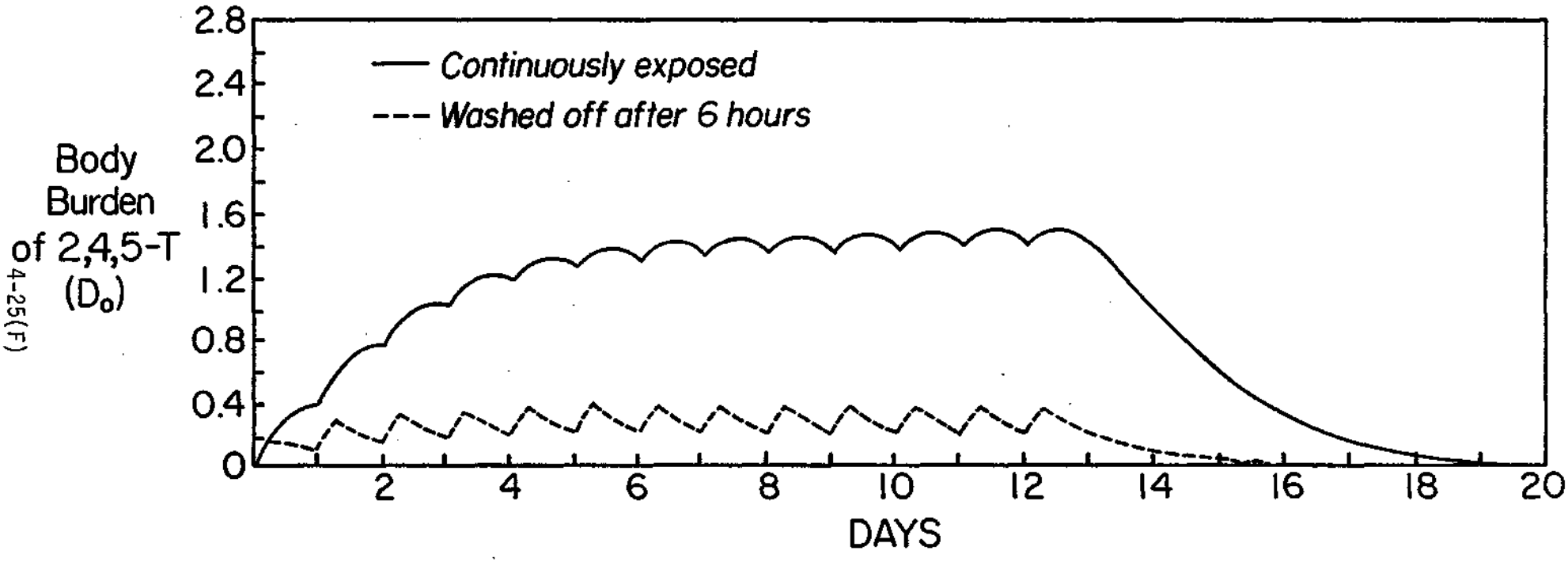
In contrast to the 2,4,5-T study cited above, the levels of urinary 2,4-D in the present study could not be measured for a sufficient length of time (because the exposure levels were so low that the concentration of urinary 2,4-D was often below the analytical detection limit) to allow direct determination of the first order rate constant for the dermal absorption of 2,4-D esters in these workers. However, because of the close similarity between the pharmacokinetic profiles of 2,4-D and 2,4,5-T, the rate of dermal absorption of 2,4-D esters in humans may be similar to that for 2,4,5-T esters. This assumption is supported by the observation that the half-life values for the dermal absorption of the PGBE esters of 2,4-D and 2,4,5-T in rats are similar, approximately 20 hours and 24 hours, respectively (Young et al., 1981).

In order to calculate the pharmacokinetic fate of dermally absorbed 2,4-D in humans, numerical values for the rate constants of absorption and elimination are required. Based on the considerations above, the dermal absorption rate constant of 2,4-D esters in humans was assigned the same value as that for 2,4,5-T esters (half-life = 18 hours) (Ramsey et al., 1980).

The urinary excretion rate constant of 2,4-D and conjugates was assigned the value previously determined in a human study (half-life = 11 hours) (Sauerhoff et al., 1977). These values then allowed the calculation of the amount of dermally absorbed 2,4-D that is excreted in the urine at any time following exposure (Ramsey et al., 1979). This calculation reveals that approximately 99% of a dermally absorbed dose of 2,4-D esters would be excreted in the urine as 2,4-D during the exposure day and for 5 days thereafter.

These values for the rate constants were also used to obtain a computer simulation of the body concentration of 2,4-D that would result from repeated daily dermal exposure to 2,4-D esters. The results of prediction are shown in Figure 4-5 in which the body burden of 2,4-D is given in units of the dose that has been absorbed thru the skin. This simulation shows that the maximum body burden attained

Figure 4-5. Simulated body burden of 2,4-D in humans after a single dermal exposure and after repeated (daily) dermal exposures. The body burden is expressed in units of the dose level applied to the skin (D_o) (Lavy, 1980).


Continuously exposed
Washed off after 6 hours
Body Burden of 2,4,5-T (D_o)
2.8
2.4
2.0
1.6
1.2
0.8
0.4
0
2
4
6
8
10
12
14
16
18
20
DAYS

4-25(F)

would be approximately 0.7 times the daily dose. In other words, if a dose of 0.050 mg 2,4-D per kg were absorbed through the skin each day the maximum concentration attained in the body after repeated daily exposures would be only 0.035 mg/kg. This bioaccumulation factor is less than might be expected (as calculated based on 1 dose per day) because the absorption rate constant in the pharmacokinetic model is less than the elimination rate constant (i.e., a flip-flop model).

Although the primary emphasis of this monograph is devoted to human exposure to phenoxy herbicides an additional point of concern when 2,4,5-T, is discussed, is that of the trace contaminant 2,3,7,8-tetrachloro-p-dibenzo-dioxin (TCDD).

Relative toxicities of the phenoxy herbicides and TCDD

Considerable confusion exists in the minds of most people with respect to the relative dangers of 2,4,5-T and the 2,3,7,8 isomer of TCDD. In a 2,4,5-T formulation it is not possible for a person, animal, or plant to receive a lethal dose of TCDD before receiving a much much larger and correspondingly lethal dose of 2,4,5-T. The following discussion provides an explanation why people who come into contact with 2,4,5-T are not harmed by the more toxic TCDD.

Fisher (1977) reported that the average amount of TCDD in 2,4,5-T is about 0.01 ppm. To compare the toxicities of the two compounds, assume that the NOEL of 2,4,5-T for humans is 20 mg/kg and for TCDD is 0.001 mg/kg (Tschirley, 1979). Dividing the 2,4,5-T NOEL by 0.001 (the TCDD NOEL) gives a value of 20,000. The toxicity of TCDD is thus 20,000 times greater than that of 2,4,5-T. Since 2,4,5-T is more concentrated than TCDD by a factor of 100 million, however, the effective

toxicity can be calculated by dividing 100 million by 20,000, which shows that in a 2,4,5-T mixture containing 0.01 ppm of TCDD the 2,4,5-T toxicity is potentially 5,000 times greater than that of TCDD.

This same sequence of calculations will be used for evaluating the effective toxicity of 2,4,5-T and TCDD in Agent Orange assuming that Agent Orange contained an average of 2 ppm (Young et al., 1978). For Agent Orange containing 2 ppm TCDD the calculations would be as follows: the composition of Agent Orange is essentially a 50-50 mixture of 2,4-D and 2,4,5-T (Young et al., 1978); the no-effect-level for 2,4-D is 24 mg/kg (Hall, 1980) and the no-effect level for 2,4,5-T is 20 mg/kg (EPA, 1978); since Agent Orange is a 50-50 mixture of these compounds an average no-effect-level of 22 mg/kg will be used. The herbicide: TCDD ratio would be 1,000,000: or 500,000:1; calculating a new toxicity relationship based on the 22 mg/kg no-effect-level for the herbicide and the 0.001 mg/kg level for TCDD reveals that pure TCDD is 22,000 times as toxic as the herbicides in Agent Orange. Since, there is 500,000 times more herbicide present in Agent Orange the relative toxicity of the mixture was:

$$\text{Relative toxicity} = \frac{\frac{1{,}000{,}000}{2}\ \frac{\text{concentration of herbicide in Agent Orange}}{\text{concentration of TCDD in Agent Orange}}}{\frac{22\ \text{mg/kg}\ \text{Herbicide NOEL}}{0.001\ \text{mg/kg}\ \text{TCDD NOEL}}} = 22.7$$

Thus, because of the large preponderance of the herbicides in the mixture (99.9998% Herbicide and 0.0002% TCDD) the relative toxicity from the herbicides would be 22.7 times greater than the effects from the TCDD.

Values for NOEL's are based on chronic (long-term) feeding trials;

some personnel in Vietnam may have had only occasional exposure to low levels of Agent Orange while others may have been exposed for longer periods to higher concentrations. Regardless of the source or duration of exposure, pharmacokinetic studies have shown that the phenoxy compounds are rapidly excreted from the body, and do not build-up to harmful levels. In rat studies TCDD has been shown to be primarily excreted in the feces with 50% eliminated the first day (Piper et al., 1973; Allen et al., 1976).

The following studies present information of vital importance to our evaluation of two groups of people who have had some phenoxy exposure.

If the assumptions used in the above calculations are valid and if Vietnam veterans have experienced health effects that can be attributed to their exposure to Agent Orange these data indicate that the defoliants themselves were more to blame than TCDD.

Ranch Hand personnel

The group of U.S. military personnel directly involved with transporting, mixing, and applying the herbicides used as defoliants in South Vietnam was referred to as "Ranch Hands." This group of Vietnam veterans probably received more exposure to Agent Orange than any other group since they handled the concentrated materials. Mechanics and pilots associated with spray missions may also have received an absorbed dose of the herbicides. By studying the health and mortality records of the Ranch Hands and workers in the U.S. who have been involved in the commercial application of the phenoxy herbicides for 10 years or more we have a large data base from which to

draw valid comparisons.

A follow-up study on the death rate of ranch hands has been conducted by the Air Force. Of the 1170 individuals who participated in the study (this represents 97% of the total number involved in the spray operation in South Vietnam) no statistically significant difference in the peacetime death rate have found between this group and the comparison group, which was made up of similarly aged American men who served in the armed forces but not in South Vietnam. Both groups appear to have experienced significantly less mortality than a similarly aged U.S. white male population (Air Force, 1982).

Domestic aerial applicators. In 1979 the National Agricultural Aviation Association conducted a study to evaluate the effects of exposure on aerial pesticide applicators. It was designed to determine if continuous or long-term exposure to pesticides had resulted in increased incidences of miscarriage and stillbirth in the applicators' families. The study was based on the assumptions that absolute safety exists, i.e., lack of hazard cannot be determined with regard to any chemical in its interactions with Homo sapiens or lower species; there is a dose/response relationship with regard to any chemical and its adverse or beneficial effects since individuals or populations receiving higher doses (exposures) will show more effect than comparable individuals or populations with lower doses or exposures; and individuals or populations who apply pesticides are more exposed as a result of their occupation than the general population.

Families of National Agricultural Aviation Association members and a similar population of siblings who had had no occupational exposure

to pesticides were compared. Questionnaires were developed and distributed to members all across the nation.

The results listed in Table 4-4 show that no significant differences in live births and miscarriages were found among the "exposed families" and the unexposed families.

Table 4-4. Comparisons among live births, miscarriages and stillbirths between the two basic populations. (Modified from WAA, 1980.)

	Agricultural Aviation Families		Non-Agricultural Aviation Families	
	(no.)	(%)	(no.)	(%)
Live Births	373	(92)	360	(88)
Miscarriages & Stillbirths	29	(8)	47	(12)

> Information on birth defects as related to parents occupation is quite rare. The occurrence of birth defects has neither substantially decreased or increased since pesticides were introduced suggesting that few if any widespread and powerful new teratogens were introduced (WAA, 1980).

In studies where hundreds of pesticide applicators have been compound to non-pesticide users no evidence has been found which would indicate that the use of phenoxy herbicides has harmed man. Using present day methods of statistical evaluation there is no evidence of

CHAPTER 4
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CHAPTER 5

Assessment of Harm Due To Phenoxy Herbicide Exposure

What research information is needed?

The complex nature of the issues surrounding phenoxy herbicides and the TCDD contaminants in 2,4,5-T requires that the concerned interested citizen use common sense as he tries to sort out the facts and keep an open mind to new ideas and new research information.

Seemingly, a countless number of studies and volumes of writings have already been devoted to learning about the phenoxy herbicides and their effects on man. Should more be done? As long as pertinent questions remain, scientists have an obligation to attempt to answer them. However, it is prudent to conduct only the studies for which there has been no clear cut answer and those that would appear to have attainable answers. Some areas where additional research would be beneficial include:

a) Determination of the bioavailability of TCDD from soil. Use of different solvent systems and other factors which could potentially enhance bioavailability or degradation of TCDD should be fully investigated. Work conducted to date indicates that the low water solubility of the compound makes it nearly inert in a soil environment. The Center for Disease Control (CDC) has indicated that 1 ppb TCDD in soil represents a threshold value for man's safety. Definitive new studies should be conducted which clearly demonstrate this threshold value. These new data could strengthen the CDC position.

The TCDD bioavailability issue is important due to the toxicity of the compound, the widespread dispersal of TCDD tainted oil in

Missouri, and the fact that several sources of TCDD in the environment have been documented. These sources include: fly ash from municipal incinerators (Olie, 1977); home fireplace soot, commercial sludge fertilizer and diesel truck mufflers (Bumb et al., 1980).

b) Origin and fate of dioxins in the environment. It has been shown that production of herbicides and other commercial chlorinated phenoxy compounds is not the only source of TCDD. If major sources of these toxic compounds exist in our environment we need to become more aware of them and take the proper precautions.

c) Assessing the bioaccumulation of TCDD in animals living in the areas of known TCDD contamination. Experiments could be patterned after those of Newton and Snyder (1978) who sacrificed a few test animals which have had most opportunity for TCDD exposure. By analyzing livers of animals living in the Times Beach area it should be possible to determine if a TCDD build-up is occurring. Animals living in or near this TCDD contaminated area should accumulate higher levels than humans.

d) A systematic collection and analytical scheme should be initiated which would allow the procurring of fat samples from human cadavors, some known to have had high exposure to phenoxy herbicides and others with no known exposure. Comparison of the extent of build-up of TCDD in human adipose tissue, if any, could then be made. These studies would be similar to, but much more extensive than those reported by Kutz (1981).

e) Improved methods for accurately determining rates of degradation of toxic compounds in our environment. Errors in evaluating

or calculating disappearance rates of chemicals highly toxic to man could result in decisions harmful to his health.

f) Determining source of the toxic components of a pesticide.

In the case of mammalian toxicity to pesticides, the effects of the active ingredient should be separated from those of the carrier or other additives. Some organic solvents may possess more toxic qualities than the "active" compound. It is important to be able to identify the source of any toxic effect observed.

g) Soft tissue sarcoma. Reports by Hardell (1981), but unsupported by several researchers, attempt to link phenoxy exposure and soft tissue sarcomas in humans. This possibility should be fully evaluated before the issue is put to rest. If a valid correlation exists this issue should be widely publicized and steps taken to remedy the situation.

h) Continuing in-depth assessment of the health characteristics of personnel in the Ranch Hand operation and commercial pesticide applicators. Evaluation of health records of these exposed groups offer valuable opportunities to assemble meaningful health hazard information due to the large numbers of personnel involved and the fact that this was the most highly exposed group in Vietnam.

i) Adequate testing of compounds being developed to replace the herbicide 2,4,5-T. An extensive amount of time and effort had been devoted to researching nearly all aspects of 2,4,5-T; it is possible that more environmentally troublesome compounds which have been studied far less extensively may be being used as a substitute for the readily decomposable, much-studied 2,4,5-T molecule.

What does the majority of scientific information tell us about man's potential for harm from being exposed to phenoxy herbicides?

A large preponderance of the scientific publications concerning the possible effects of the phenoxy herbicides and the low levels of TCDD present show that these compounds do not pose a threat to man's health. Following are a few examples of research, in addition to the author's studies on human exposure to phenoxy herbicides in the field which supports the safety of the phenoxy compounds.

USDA R.C. Nash Study

In a study by R.C. Nash of the United States Department of Agriculture, it was calculated that if a 175 lb farmer applied 2,4-D 30 days a year for 30 years he would receive and excrete less than one gram (about the weight of one-half of a dime). To put this into perspective this is several hundred times less than the acceptable daily intake (ADI) for a person over that time period (Nash, 1983). (The ADI is the amount of a chemical, based on all the known facts, which can be consumed every day for an individual's entire lifetime with no harm occurring. These values are expressed on a mg chemical per kilogram body weight basis. The ADI is based on the no effect level in the most sensitive animal species or, if the data are available, in man.)

Oregon researchers (Newton et al., 1975)

The registered uses of 2,4,5-T in the forest were effective and did not present a significant threat to the quality of the environment. Data from experimental animals indicate that immediately after spraying 2,4,5-T at an accepted treatment rate, a 100 lb human could absorb all the TCDD on 1 acre of forest and suffer no toxic effect.

TCDD is so tightly bound by vegetation and soil that the probability of significant intake by humans is remote. It is calculated that a 1 lb/acre application of 2,4,5-T containing 0.1 ppm TCDD applied directly to the soil could result in a maximum of 0.1 parts per trillion TCDD in soil. TCDD does not appear in the seeds of plants grown in soil containing even large amounts of TCDD. Isensee et al. (1971), after applying TCDD to a Lakeland sandy loam and growing oats (Avena sativa) and soybeans (Glycine max), concluded that soil uptake of TCDD by plants is highly unlikely.

J.M. Witt American Chemical Society Symposium, Seattle 1983

To evaluate man's risks from another approach, a comparison of the health effects of 2,4-D has been made with aspirin.

A man swallowing 2 tablets of aspirin every 4 hours has a safety factor of 25; i.e. if he consumed 50 tablets in that time period, death is expected. By comparison, Witt indicates an individual who was directly under a spray boom applying 2 lb of 2,4-D per acre has a safety factor of 625. He would need to be sprayed 625 times on the same day before he could receive sufficient 2,4-D to cause death. Data on birth defects for these compounds show a similar pattern.

Following is a calculation for the risk of birth defects to the offspring of pregnant female sprayed with 2,4-D as prepared by Witt (1984).

1) A female standing directly under a spray plane applying 2 lb 2,4-D per acre would receive an exposure level of 20 mg 2,4-D per square foot of body area.
2) .5% of the exposure would be absorbed through her skin.
3) the half-life of 2,4-D: on plants, litter or soil 2 weeks to 2

months; in water - 1 week; in mammals 1 day.

4) pregnant females have approximately a 20 sq ft. skin surface.

The 2,4-D risk of birth defects for a pregnant female who was sprayed with a spray-mix of 2 lb/acre (=20 mg/ft^2); 50% of her skin would be exposed (10 ft^2); weight 110 lbs (=50 kg).

Calculations:

$$\frac{20 \text{ mg/ft}^2 \times 10 \text{ ft}^2}{\text{(exposure level) (50\% of skin area exposed)}} \quad \text{50 kg (body weight)}$$

$\frac{200 \text{ mg}}{50 \text{ kg}}$ = 4 mg/kg on bare skin areas x 0.05 percent absorbed

= 0.2 mg/kg absorbed dose

$\frac{20 \text{ mg/kg/day}^1}{0.2 \text{ mg/kg}}$ = $\frac{\text{No effect level}}{\text{absorbed dose}}$ = 100 = margin of safety

These data indicate the pregnant female could be sprayed 100 times daily before she would receive an absorbed dose of 2,4-D which is equivalent to the amount of the "no effect level" for birth defects. It is highly unlikely that anyone would be sprayed 100 times in one day.

United Kingdoms: Review of the safety of the herbicide 2,4,5-T

Following are conclusions from a comprehensive evaluation of the phenoxy-TCDD question by a major research team in the United Kingdom: (Kilpatrick et al., 1980)

> Given the acute toxic effects of TCDD any significant exposure to this chemical would have been reflected in the health of operators. Against this background of data on exposure to 2,4,5-T and bearing in mind the low levels of TCDD present in

[1]Since Witt (personal communication) believes the no effect level for 2,4-D is between 20 and 25 mg/kg/day he has chosen to use the more conservative value for these calculations.

ulations currently available in the UK there is no
to indicate that operators have been exposed to
gically significant amounts of this chemical.

ling information was based on three surveys which were
in 1970, 1975 and 1976, involved 1100, 21, and approxima-
erators, respectively. None of these surveys revealed any
f chloracne or any other disorders. 2,4,5-T has been used
ted Kingdom for nearly 30 years during which time some
ve repeatedly been exposed to the chemical and any TCDD con-
Thus, they have concluded that the general public is not at
the use of 2,4,5-T. A 1983 court decision in Nova Scotia on
tensive debates occurred evaluating the effects of 2,4,5-T
on man was in agreement with the United Kingdoms report
, 1983).

tion in medical literature

iewing the medical literature on TCDD (Holmstedt, 1980; and
, 1975), it seems fairly clear that chloracne is the most common
observed following exposure and is a sensitive indicator of
re. The medical reports on human reactions to TCDD indicate
systemic reactions are rare, if they ever occur, in the absence
loracne. In the industrial accidents where heavy exposure has
red, both the chloracne and systemic effects observed have
aled no significant changes in morbidity or mortality in the
cted workers. Holmstedt (1980) concluded that 'TCDD is of low
te toxicity to man compared to animal species, e.g. the guinea
'.

Relative risks of spraying 2,4,5-T

An oncogenicity (tumor causing) study reported by Kociba in 1978 showed that TCDD caused cancer in rats. Assuming the effective rate of 0.1 ug/kg body weight per day is comparable to that of humans, it is possible to calculate a risk factor for workers applying 2,4,5-T containing (assuming worst case) 0.1 ppm TCDD.

Leng (1978) discussed the "one hit" model which assumes that probability of tumor production is random and proportional to the total chemical contact.

> Under worst-case conditions for a female applicator weighing 60 kg applying 2,4,5-T containing 0.1 ppm TCDD, 5 days per week, 4 months per year, for 30 years, the average lifetime dose of TCDD would be one millionth of a microgram per kilogram of body weight per day (1×10^{-6} ug/kg/day). Based on a 99% upper confidence limit for the incidence of tumors in female rats given 0.1 ug/kg/day for 2 years in the Kociba study, and adjustment for differences in body surface area (more conservative than relative body weights), and in lifespan (70 vs 2 years) for humans compared to rats, she would have a calculated potential risk of 3.05×10^{-5}.

Male applicators exposed in the same way would have a risk only half as large since male rats in Kociba's study had a lower incidence of tumors. Table 5-1 indicates that cancer risk to a male smoker is 6000 times greater than to a backpack sprayer applying 2,4,5-T. The relative risk of a worker developing tumors from exposure to the TCDD in 2,4,5-T is far less than for people who drink water in Miami or New Orleans, or even fly cross-country once a year.

Table 5-1. Relative Annual Risk of Cancer Per Million People from Exposure to Various Causative Agents (Adapted from Wilson, 1980 and Leng, 1978).

	Risk x 10^6 per year
TCDD from Application of 2,4,5-T	
Female backpack sprayer	0.4
Male backpack sprayer	0.2
Eating and Drinking	
One diet soda per day (saccharin)	10
Average U.S. consumption of saccharin	2
Peanut butter, 4 tablespoons per day (aflatoxin)	40
Milk, 1 pint per day or cheese equiv. (aflatoxin)	10
Drinking water in Miami or New Orleans	1.2
Steak, 1/2 lb charcoal-broiled, 1 per week	0.4
Alcohol, light drinker (1 beer per day)	20
Alcohol in smokers vs. non-smoker	50
Tobacco	
Smoker	1200
Being in room with a smoker	10

Concluding remarks

The two largest data bases available for evaluating man's exposure to the phenoxy compounds are 1) the health records of hundreds of pesticide applicators, and 2) the health records of the Ranch Hand

personnel who were active in the transport, mixing and application of Agent Orange in Vietnam. By continuing to monitor the health of these groups we are studying those individuals who have received the highest dose of phenoxy herbicides. If adverse health effects are caused by exposure to these chemicals the evidence should become apparent when the health records of these groups are compared to those of a non-exposed population.

The amount of phenoxy herbicide present in man's air, food and water has been shown to be very low. Field workers who mix and apply these compounds receive a higher absorbed dose than others in our society with the possible exception of workers in phenoxy manufacturing plants. Some workers at these plants using chlorinated phenoxy compounds where explosions have occurred have received higher doses. Although the dose of herbicides received by those transporting, mixing, or applying these chemicals have not appeared to reach health threatening levels, those interested in reducing their exposure levels may easily do so by following simple suggestions listed in Chapter 3. It is recognized that some who have served in Vietnam have later suffered health problems. While probing literature in preparation for this monograph no scientific evidence has been found which would link those health problems to phenoxy or TCDD exposure. To answer questions on health related problems other avenues should be pursued. The ultimate answers to these problems are probably more complex than attributing them to phenoxy herbicide exposure.

After reviewing hundreds of research articles on the pros and cons of 2,4,5-T, scientific evidence strongly supports the safety of this

compound to man and the environment. Findings from agriculture show that in over 30 years of use no known health problems have been found when this herbicide is used according to label instructions.

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APPENDIX

Significance of TCDD in Man's Exposure to Phenoxy Herbicides

Due to the interest in this subject area and widespread national attention focused on it, many questions arise. Although some items may be somewhat redundant with earlier discussions, they are presented here for convenience.

Following is an index of questions addressed in this appendix:

Page A-55 Why do the Veteran's Administration and other government agencies continue to study Vietnam veteran health problems if the government is not admitting that Agent Orange exposure has caused the problems?

What is dioxin? Dioxin is a general term which describes an organic molecule essentially composed of two benzene rings joined by a double oxygen bond. When a chlorine atom is attached to any or all numbered positions of it, the molecule is referred to as a chlorinated dibenzo -p-dioxin. Chlorine atoms may be attached in the 2, 3, 7, and 8 positions. The molecule shown in Figure 1.1 is commonly referred to as dioxin or TCDD.

Is there more than one dioxin? As many as 75 different dioxin molecules can be formed by substituting different chloride atoms at the numbered positions given (Kociba et al., 1982). Types of chlorinated dibenzo-p-dioxins that can be found in the environment include: tetra, hexa, hepta, and octa. Several of these chlorinated dibenzo-p-dioxins are biologically active. The most active one known is the 2,3,7,8 tetra chloro dibenzo-p-dioxin. It is the most toxic of the 22 tetrachlorinated dioxins; this toxic molecule will be referred to herein as TCDD. Table A-1 lists some of the properties of TCDD.

Table A-1. Some TCDD Physical Properties (Bovey and Young, 1980).

Molecular weight	322
Melting point, °C	303-305
Decomposition point, °C	980-1000
Solubility in	ppm
Orange herbicide	580
benzene	570
chloroform	370
acetone	110
methanol	10
water	0.0002

TCDD is quite soluble in fats and very insoluble in water. In the direct presence of sunlight and a hydrogen donor it is degraded readily on leaves, water or soil surfaces. It has a low vapor pressure (1×10^{-7} Ton) and tends not to vaporize in the atmosphere thus its vapors can not be carried away by the wind. It is strongly bound to soil, consequently is very resistant to leaching and to entering the groundwater (Reggiani, 1981).

Why does TCDD exist? TCDD is formed as a low-level unwanted by-product during the manufacture of trichlorophenol from 1,2,4,5-tetrachloro-benzene (Sparschu et al., 1971). The production of trichlorophenol is the initial step in producing hexachlorophene and trichlorophenol, common antibacterial agents that have been incor-

porated into a number of soaps and cosmetics (Rawls et al., 1976). Trichlorophenol is also used in the production of 2,4,5-T.

How do we learn about TCDD? Information on the effects of TCDD exposure comes from at least three different sources. Industrial accidents have resulted in severe human exposure. Use of synthetic compounds containing TCDD, particularly the herbicide 2,4,5-T has initiated studies on humans and animals exposure exposed to the compound (Rose et al., 1972). Furthermore, several laboratory investigations have been completed during the past 10 years in an attempt to determine the toxic effects of TCDD (Zabik and Zabik, 1980).

What is being done to learn the significance of man's exposure to TCDD? Dr. Frederick Kutz from the Field Studies Branch of the Exposure Evaluation Division of the Office of Toxic Substances in the U.S. Environmental Protection Agency offers some information on the philosophy and scope of their programs:

> The major orientation of the monitoring programs in the Office of Pesticides and Toxic Substances is toward the assessment of human exposure. Therefore, biological monitoring of human tissues and fluids assumes primary importance. Environmental components, such as air, drinking water, food, etc., which are intimately associated with human life, are considered secondarily. This prioritization scheme focuses monitoring programs on the protection of public health. Current ambient chemical monitoring responsibilities within OPTS include monitoring soils, raw agricultural crops, estuarine and marine organisms, water, human tissue, and air. Many of the programs have operated in cooperation with other Federal agencies, i.e., the National Center for Health Statistics, the U.S. Geological Survey, and the National Oceanic and Atmospheric Administration. These agencies collect selected specimens for chemical residue analysis by EPA-directed laboratories. Samples of the above human and environmental media are collected on a periodic basis from locations defined by statistically representative designs (Kutz, 1981).

In addition to the EPA, scientists in several other governmental agencies including FDA, USDA, and CDC and others are studying TCDD.

Related research is also being conducted by universities and chemical companies. An in-depth discussion of an applicator exposure study to 2,4,5-T containing trace levels of TCDD was presented in Chapter 3.

Is TCDD harmful to humans? It is a widely accepted fact that TCDD is one of the most toxic low molecular weight synthetic molecules known to man. As a result of its toxicity and occassional presence in the environment TCDD has emerged as a compound for which there is great public concern.

Since humans and test animals do not always have the same tolerance or sensitivity to a chemical it is difficult to establish a sound basis for exact comparisons. The question is: What is the relative toxicity of TCDD to humans and other mammals? In view of the extreme toxicity of TCDD this question becomes quite alarming when one reviews the facts on thalidomide. The lowest dose of thalidomide to produce teratogenic effects in mammals are: 30, 50, 100, and 350 mg/kg/day for mouse, rat, dog and hamster respectively. For humans this value is 0.5 mg/kg/day. Thus, humans are 60 to 700 times more sensitive to thalidomide than were the animals used to test it. This relationship is not necessarily true of all compounds, however. In fact, it appears that humans are less sensitive to TCDD than several other animal species. For TCDD a wide range in mammal toxicity exists as expressed as an acute and LD_{50} (Table A-2).

Table A-2. Acute oral LD_{50} of TCDD.

	Single-dose LD_{50}	Literature citation
	(Micrograms per kilogram body weight)	
Guinea pig	0.6-2.0	Schwetz et al., 1973
Rabbit	115	Schwetz et al., 1973
Rat	22-45	Greig et al., 1973
Dog	100-200	Greig et al., 1973
Chicken	25-50	Greig et al., 1973
Bullfrog	over 1000	Beatty et al., 1976
Hamster	1157-5051	Olson et al., 1980; Henck et al., 1981

Since humans are not routinely used to test compounds as toxic as TCDD there is little information available other than information which arises after an accident or some other "happening." Literature describes in the early 1970's a "happening" known as the Missouri Horse Arena Incident; today it has been extended and now includes Times Beach, Missouri. Following the spraying in 1971 of three horse arenas in Lincoln County, Missouri, with salvage oil contaminated with TCDD, a by-product of hexachlorophene production, a number of people who worked or played in the arenas developed medical disorders (Beale et al., 1977; Kimbrough et al., 1977; Lobes et al., 1972; Young et al., 1978). For a more detailed accounting of this "happening" see

Chapter 1. The most serious health effects were shown by a six-year-old girl who developed hemorrhagic cystitis and focal pyelonephritis. The urinary tract symptoms were preceded by headache, epistaxis, diarrhea and a general malaise. Her urinary tract symptoms cleared after a few days. An examination three months later revealed she was normal except for punctate hemorrhages of the bladder seen on cystoscopy. The father of the child had developed headaches and nausea while working in the arena. Her mother reported severe headache, nausea, diarrhea and abdominal pains, and arthralgia. A ten-year-old sister developed easy fatigability, epistaxis, headaches, abdominal pain, and diarrhea. All developed at least mild acne lesions (Reggiani, 1978). Follow-up studies on the mother and two children performed five years later were normal (Beale et al., 1977). The symptoms for all of the humans were relatively mild with the most severe being the hemorrhagic cystitis and focal pyelonephritis seen in the six-year-old girl. The symptoms had cleared on re-examination several years later. Exposure, at least to the children must have been significant in that they regularly played in the soil of the arenas. These symptoms can be contrasted with fatalities observed for horses and other animals. In total 62 horses, hundreds of birds, many cats, and a few dogs died (Carter et al., 1975).

Thus, the answer to our original question "Are dioxins toxic to humans?" is yes; but in contrast to thalidomide, humans appear to be much less sensitive to TCDD than are many test animals. This fact does not detract from the extreme toxicity of the TCDD molecule but does suggest that well designed experiments using sensitive test ani-

mals can perhaps provide meaningful information for humans.

Center for Disease Control (CDC) has indicated that soils containing 1 ppb could theoretically cause health problems. Since the Center for Disease Control was forced to make a quick decision before all of the scientific data could be thoroughly evaluated it is possible that they have set limits on TCDD concentrations that are too conservative. Soil particles strongly bind TCDD. This reduces the uptake of this compound by the body of test animals according to experiments conducted by Poiger and Schlatter (1980). They also showed that the longer TCDD remains in contact with soil the less available it becomes for uptake. Since humans ingest little TCDD, they have little direct external body exposure to it. Cast (1983) states that implications by Burke (1983) that "dioxin, described by a respected health research as a "doomsday chemical" that can be harmful to humans in microscopic amounts as low as one part per billion" can be equated to the effect of one part of dioxin per billion of soil is without substance.

As mentioned several times earlier, it is easy to confuse "exposure" and "absorbed dose." Chemical tests for amounts of TCDD in soil provides a measure of potential exposure but does little to provide a meaningful answer to how much does man absorb. As suggested by CAST, 1983 examination of the liver of wild animals inhabiting the high exposure areas can provide much information from which man can better evaluate the level of risk present.

Agencies faced with many human health decisions have difficult decisions to make. If they are to error, they should error on the

side of safety. As responsible servants they are also expected to make decisions based on all of the best scientific information available. Due to the worldwide impact these decisions may have these agencies should be permitted the luxury of continually reweighing the facts and the opportunity to alter their recommendations - be they for more stringency or less stringency.

Were phenoxy herbicides involved at Times Beach? No, the TCDD by-product occurred during the synthesis of hexachlorophene a bactericidal agent.

Are people being harmed by the TCDD present at Times Beach? The TCDD being found at Times Beach is present in soil which was contaminated with oil containing TCDD more than 10 years ago. The low water solubility (0.2 ppb) and adsorbing properties of TCDD prevents detectable levels from moving into man's food supply via growing plants. Without a grease or oil solubilizer the TCDD present today has little opportunity to move through the skin of man or other animals. Bovey and Young (1980) have discussed that in highly TCDD contaminated soils the burrowing animals, beach mice and hispid cotton rat, had the highest TCDD level in their liver. Liver from healthy animals contained from 10 to 1500 ppt TCDD. No current health problems attributable to TCDD in the Times Beach area have been reported. Only by carefully extracting the TCDD with special organic solvents and then using the best analytical gas chromatograph-mass spectrometry instrumentation is it possible to identify TCDD.

The normal health patterns of humans who have lived in these contaminated areas for the past 12 years in conjunction with the low

bioavailability of TCDD strongly suggests that TCDD is not available in the environment at levels harmful to plants, humans or other animals.

Since the discovery that soils removed from the horse arena and deposited in other Missouri communities still contain detectable TCDD levels, what is being done? Following the Center for Disease Control's announcement that TCDD of 1 ppb and above constitutes a danger to man, EPA has indicated that dollars in its "Superfund" will be used to purchase the areas and relocate the people involved. As of May, 1983 residents of two areas of Times Beach and Imperial, MO had been cited by EPA as communities qualifying for use of the Superfund for relocation purposes.

What can be done to clean-up or remedy the current TCDD containing areas? Five possible options are available as listed in Table A-3.

Table A-3. Possible waste stabilizing and permanent clean-up possibilities for Imperial, Missouri (Garmon, 1983).

Option	Years (est.)	Millions (est.)
Construction of a grout curtain (This involves digging a ditch around the contaminated area and filling it with a clay-like substance in order to prevent migration of the toxic material.)	3-4	$29
Removal of dirt and placement in an on-site vault	3-4	$9-11
Removal of dirt and placement in an off-site landfill or storage facility	4	$5-8
Incineration of dirt	8	$29+
Detoxification of dirt via application of chemicals (Use of a sodium hydroxide and polyethylene glycol mixture to dechlorinate - remove the chlorine atoms from - the dioxin now is being tested. Estimates of time and cost include that needed for further development of this technique.)	11	$58-77

How do humans come into contact with TCDD and other dioxins? In addition to trace levels in the phenoxy herbicide 2,4,5-T, Agent Orange and by-products of trichlorophenol production other sources are present.

Dr. Kutz of the EPA reports some of their investigations:

Because of the growing concern for the possibility of human exposure to toxic substances as a result of combustion, a study to provide statistically valid estimates of the level of organic emissions from combustion sources was begun. Among the main categories of concern are coal/refuse-derived fuel combustion, refuse combustion, and residential wood combustion. The compounds of interest are included in a broad category of substances termed "Polycyclic Organic Matter" (POM). These include polychlorinated biphenyls (PCBs), polychlorodibenzo dioxins (PCDDs), polychlorodibenzo furans (PCDFs), phenols, pyrenes, other polynuclear aromatic hydrocarbons (PAHs), and other organic compounds. In order to make a statistically valid estimate of national emissions, it is important to have information on emissions variabil-ity within any one facility. Therefore, a pilot study at two facili-ties was conducted in order to describe emissions variability. This variability was used to design the national study. One of the facilities sampled in the pilot burned 85% coal and 15% refuse-derived fuel (RDF), whereas the other burned raw municipal refuse. These facilities were sampled for 9 and 10 days, respectively, and samples of fuel, ambient air; water, bottom ash, fly ash, and flue gas were taken (Kutz, 1981).

Results of these gas chromatography-high resolution mass spectrometry analyses are presented in Table A-4. Research by Reggiani

Table A-4. Residues of dioxins and furans observed in flue gas of a municipal waste combustion facility.[1] (Kutz, 1981).

Isomer groups	Mean[2] concentrations (ng/cubic m)	Mean[2] quantities emitted (ug/hr)
Tri-CDD[3]	13	1,100
CDF[4]	300	26,000
Tetra-CDD	6.3	540
2,3,7,8-TCDD	0.4	34
-CDF	90	7,600
Hexa-CDD	16	1,400
-CDF	62	5,200
Hepta-CDD	7.6	640
-CDF	7.5	640
Octa-CDD	2.5	220
-CDF	0.6	52

[1]Not corrected for recoveries.

[2]Mean of 3 data points.

[3]CDD refers to chlorodibenzo dioxins.

[4]CDF refers to chlorodibenzo furans.

(1981) indicates that various polychlorinated dioxins, sometimes including TCDD, may be formed during various combustion processes,

such as municipal incinerators, fossil-fueled power plants, internal combustion engines, home fireplaces and cigarette smoke.

Knowledge that the toxic TCDD is introduced into man's environment through several sources does not necessarily make this a safer world in which to live but it does allow us to redirect the thinking of some of our environmental concerns. Since the presence and significance of TCDD as a contaminant in herbicides at levels from 1 to 70 ppm was found by Higginbotham (1968) the concentrations have been markedly reduced. Today's production methods routinely produce 2,4,5-T containing less than 0.1 ppm which is the legal level.

Another source of exposure could be through the use of cosmetics that have as one of their ingredients compounds derived from trichlorophenol (Rawls et al., 1976). Although no research has been reported on the absorbed dose of TCDD arising from these uses one can infer that due to the lipophyllic nature of TCDD its percutaneous absorption would be expected when present in creams applied to the skin.

A report by Schmittle et al., 1958 indicates that human and animal exposure to TCDD has also occurred from the improper disposal of distillate residues of chlorinated benzenes which are used as a starting material in the production of a variety of chemical products. They indicate that perhaps the most extensive occurrence of animal exposure to the dioxins (including dichloro-, trichloro-, tetrachloro-, pentachloro-, hexachloro-, heptachloro-, and octachlorodibenzodioxin) occurred in the United States in 1957. At that time, in order to increase the caloric content of poultry rations, feed manufacturers were using a wide variety of low cost fats. These fats were

collected from various sources and pooled. Some of the fats were contaminated with oily residues containing dioxins. These mixtures were sold to the feed manufacturers and incorporated in poultry feeds. As a result of the ingestion of these contaminated fats, millions of chickens died. Hundreds of thousands of the surviving contaminated chickens were processed for human consumption before the origin of the problem was discovered and steps initiated to prevent the use of this food. There are no data which suggests that humans were affected by consuming adulterded poultry products (Allen et al., 1978).

It is not surprising that there are no accounts of humans becoming ill from eating TCDD contaminated chicken because the high toxicity of the compound would probably kill the chicken. Thus, there is a built in safety factor since humans seldom eat meat from animals that they or the slaughter house has not killed.

Do phenoxy herbicides contain TCDD? 2,4,5-T and silvex contain trace levels of the contaminant TCDD. Although it has not been feasible to eliminate this contaminant entirely, present production methods are able to reduce the dioxin level routinely to less than 0.01 ppm in commercial 2,4,5-T with occasional batch containing as much as 0.05 ppm (McQueen, 1977). The legal limit for TCDD in 2,4,5-T is 0.1 ppm.

Is the TCDD present in 2,4,5-T harmful to animals which eat vegetation sprayed with the herbicide? As previously stated, TCDD is present in 2,4,5-T in only trace amounts but the extremely toxicity of even small amounts of TCDD has also been stated. The quotation from CAST (1978) will be used to answer the question:

> The amount of TCDD distributed in the United States in 2,4,5-T and silvex is probably no more than 1 ounce (28 g) annually. This material is distributed over approximately 5

million acres at the rate of 5 micrograms per acre. The most sensitive species known is the guinea pig, which has an LD_{50} of 0.6 microgram per kilogram (Johnson, 1971). If we assume that we have a grazing animal about the size of a sheep or deer (175 lb or 80 kg) and the sensitivity of a guinea pig, this animal would have to consume, without excretion, all of the treated vegetation on more than 9 acres of land to get a lethal dose. If the animal had the sensitivity of a rat, it would have to consume, without excretion, all of the treated vegetation on more than 400 acres.

There are no cases where livestock has been injured due to ingesting forage treated with 2,,4,5-T containing trace levels of TCDD. Perhaps the fact that phenoxy compounds (Lavy, 1980a) and TCDD (Jensen et al., 1981) are rapidly excreted from animals allow these chemicals to be absorbed without apparent harmful effects.

What is Agent Orange? Herbicide Orange, later Agent Orange, was a label given by the U.S. military forces to a 50:50 mixture of the n-butyl esters of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxy-acetic acid (2,4,5-T). One gallon of Herbicide Orange theoretically contained 4.21 lb of the active ingredient of 2,4-D and 4.41 lb of the active ingredient of 2,4,5-T. Orange was formulated to contain a 50:50 mixture of the n-butyl esters of 2,4-D and 2,4,5-T. The percentages of the formulation typically are shown in Table A-5.

Table A-5. Chemical composition of Agent Orange (Shepard, 1980).

Material	%
n-butyl ester of 2,4-D	49.49
free acid of 2,4-D	0.13
n-butyl ester of 2,4,5-T	48.75
Free acid of 2,4,5-T	1.00
inert ingredients (e.g., butyl alcohol and ester moieties)	0.62

Agent Orange also included amounts (from 0.02 to 15 ppm, or a weighted mean of 1.98 ppm) of the contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). According to Young et al. (1978), about 25 million kilograms (55,940,150 lb) of 2,4-D and 20 million kilograms (44,232,600 lb) of 2,4,5-T - for a total of 166 kg (368 lb) of TCDD - were distributed over approximately 1.4 million hectares (3.5 million acres) of South Vietnam from January 1962 to February 1971. It is significant to note that almost 40% of the entire amount of TCDD that was released in South Vietnam - or 64 kg (143 lb) was contained in Agents Green, Pink, and Purple, which materials were used on about 36.4 thousand hectares (90 thousand acres) from 1962 thru 1964. During this time few American troops were assigned to South Vietnam.

The name Herbicide Orange was a code name by the military for the herbicide combination given. Later the phrase "Agent Orange" was

coined. Barrels containing this plant defoliant were painted with an orange stripe to differentiate it from other compounds being used in Vietnam.

Why were defoliants used in Vietnam?

> The use of chemicals (herbicides) to control vegetation has been one of the most controversial subjects arising from the Vietnam conflict. The U.S. Air Force applied most of these herbicides in jungle areas to clear vegetation from the perimeters of military bases and camps, along lines of communication, and in enemy staging areas. The objective was to provide defoliated zones that would reduce ambushes and disrupt enemy tactics (Young, 1981).

Ninety percent of all Herbicide Orange was used to defoliate forests; it was especially effective in defoliating mangrove forests. Eight percent of Herbicide Orange was used in the destruction of broadleaf crops (beans, peanuts, ramie, and root or tuber crops). The remaining 2 percent was used around base perimeters, cache sites, waterways, and comunication lines (Shepard, 1980). The use of defoliants in Vietnam saved hundreds of U.S. military lives.

Were defoliants other than Agent Orange used in Vietnam?

Several others were employed; their code names are White, Blue, Purple, Pink and Green. The latter three which all contained 2,4,5-T were used in (Table A-6).

Table A-6. Number of gallons of military herbicide procured by the U.S. Department of Defense and disseminated in South Vietnam during January, 1962 - October, 1971 (Young et al., 1978).

Code name	Herbicide	Quantity	Period of use
Orange	2,4-D; 2,4,5-T	10,646,000	1965-1970*
White	2,4-D; Picloram	5,633,000	1965-1971**
Blue	Cacodylic Acid	1,150,000	1962-1971**
Purple	2,4-D; 2,4,5-T	145,000	1962-1965
Pink	2,4,5-T	123,000	1962-1965
Green	2,4,5-T	8,200	1962-1965
	Total	17,705,200	

*Last fixed-wing mission of Orange 16 April 1970; last helicopter mission of Orange 6 June 1970.

**Last fixed-wing mission 9 January 1971; all herbicides under U.S. control stopped 31 October 1971.

Were other pesticides used in Vietnam?

> The control of malaria and other mosquito-borne diseases in South Vietnam necessitated an extensive aerial insecticide application program in order to control these vector insects. From 1966 through 1972, three C-123 aircraft were used to spray Malathion, an organo-phosphate insecticide. These aircraft could be distinguished from the herbicide-spraying aircraft because they were not camouflaged. These aircraft routinely sprayed insecticide adjacent to military operations were in progress, or installations, as well as in areas where military operations were in progress, or about to commence." (Shepard, 1980).

Is Agent Orange as toxic as TCDD? As indicated above, TCDD was present in Agent Orange at an average concentration of nearly 2 ppm. This translates to a 50:50 mixture of 2,4-D and 2,4,5-T; the final mixture contained 99.9998% phenoxy herbicide and 0.0002% TCDD. Information taken from Cast (1978) states

> The evidence shows that TCDD is from 5,000 to 500,000 times more toxic to mammals than 2,4,5-T, depending on species. Under current standards set by the Environmental Protection Agency, the content of TCDD in commercial 2,4,5-T must be less than 1 part in 10 million parts of 2,4,5-T. In practice the content is about 1 part in 100 million (Fisher, 1977). On this basis, a single toxic dose of TCDD would be contained in from 200 to 20,000 toxic doses of 2,4,5-T, depending upon the test species. Thus, the current level of TCDD in 2,4,5-T does not contribute significantly to the toxicity of herbicidal preparations of 2,4,5-T.

A more detailed calculation of the relative toxicity of TCDD and the phenoxy herbicides in the mixture is presented in Chapter 4.

How long does TCDD persist in the environment? Crosby and Wong (1977) analyzed the persistence of TCDD in actual herbicide formulations on leaves, soil, or glass plates. When leaves were exposed to natural sunlight, most of the TCDD was lost from the leaves in less than 6 hours. This loss was due principally to "photochemical dechlorination." The herbicide formulation provides a hydrogen donor, which allows rapid photolysis to occur. Since Agent Orange has an excellent source of hydrogen donors. TCDD persistence should be markedly decreased. Thus, despite the known persistence of pure TCDD, it is not stable in thin films of formulated herbicide when exposed to outdoor light.

Plant uptake of TCDD from soils does not appear to be significant. Soybean and oat plants took up only trace amounts of TCDD in the first

10 to 14 days after exposure to sandy soil containing 200,000 times the amount of TCDD contained in an application rate of 2 pounds per acre 2,4,5-T (with 0.1 ppm TCDD). There was no detectable TCDD in the grain or beans at maturity, probably because of normal dilution by plant growth, volatilization, or photodecomposition on the leaf surface, or as a result of metabolism. TCDD is not translocated from the point of application on the leaf surface (Isensee, 1971). In five soils with widely varying properties, TCDD was found to be immobile even when subjected to leaching (Helling et al., 1973). The possibility of TCDD entering ground water is remote (Tschirley, 1971). If TCDD is incorporated into soil, it disappears slowly. It seems unlikely, however, that TCDD would be incorporated in soils under most conditions of use since it does not leach into the soil. TCDD is not produced from breakdown products of 2,4,5-T in soils or in sunlight (Kearney et al., 1972).

TCDD is nearly insoluble in water - 0.2 ppb. For this reason, it would be expected to remain on the surface of plants and soil at the application site. Because it is immobile in soils, Kearney et al. (1973) also concluded that there would be "no ground water contamination problems."

Recent studies on half life determinations of TCDD in soils indicate that 10-12 years are required for 50% of this compound to degrade. This very persistent molecule has earlier been shown to be quite toxic. Other factors of importance in assessing its hazard to humans is how much is present? how bioavailable is it? and ultimately how much is absorbed by humans?

Do green plants take up TCDD from the soil? Isensee et al. (1971) determined the uptake of TCDD from a Lakeland sandy loam soil using two crop species. Oats (Avena sativa) and soybeans (Glycine max) accumulated less than 0.15% of the TCDD applied to the soil. In a similar study Cuppelo et al. (1976) using sorghum (Sorghum bicolor) found that the amount of TCDD taken up from a Ulysses sandy loam soil was approximately one millionth of one percent of the amount of TCDD in the soil. One of the major contributing factors for the low % uptake is the low 0.2 ppb water solubility of TCDD. As a general rule, in the case of herbicides, those with low water solubilities tend also to be more tightly adsorbed to soil colloids thus further decreasing their potential for plant uptake.

In U.S. Air Force Experimental plots at Eglin AFB, Florida where massive quantities of 2,4,5-T were applied to soil, TCDD concentrations were 150, 160, 700, and 44 ppt at soil depths of 0-2.5 cm, 2.5-5 cm, 5-10 cm and 10-15 cm, respectively. In an ecological survey conducted over a 5-year period in that area more than 123 different plant species were present. No TCDD was found in any of the plant species analyzed (Young et al., 1975). Due to the extremely low levels of TCDD present in most soil and its low water solubility, TCDD plant uptake from soil is virtually nil thus escaping detection sensitive gas chromatographic determinations with capabilities for detecting TCDD in the low ppt range.

Does TCDD magnify in the food chain? The term bioaccumulation means the uptake of a chemical and some storage of it by an organism. Since TCDD is present in such low levels in the environment ingestion, inha-

lation or dermal absorption is minimal (Norris et al., 1977). An EPA study monitoring fat from beef animals indicated that bioaccumulation of TCDD in grazing animals could occur, but levels were not high enough to be regularly detected by instruments with a 10 ppt sensitivity.

The results of these various tests indicate that, if TCDD is present in the environment in a form that is available to organisms, then bioaccumulation will occur if organisms are exposed. This concept is supported, both from an examination of the physical-chemical properties of TCDD, as well as by studies of its behavior in animals exposed through feeding studies or in laboratory model aquatic ecosystems. The degree to which bioaccumulation of TCDD occurs in the field depends not only on the physical-chemical properties of the compound, but also on the persistence and availability of TCDD in the environment. Mechanisms of degradation and dilution that operate in the natural environment reduce the opportunities for organisms to be exposed, and thereby reduce the degree to which bioaccumulation might occur.

A wide-scale monitoring of water, sediment, fish, beef, and human milk from areas in the Midwestern United STates where 2,4,5-T has been applied also showed no detectable TCDD residues at minimum detection levels that averaged 10 ppt. These monitoring efforts indicate that substantial bioaccumulation of TCDD (sufficient to produce residue levels in excess of 10 ppt TCDD in the majority of the population) is not occurring in animals in or near areas treated with 2,4,5-T in current operational programs (USDA, 1982).

Is TCDD in the environment harmful to animals? As shown in Table A-2 several animal studies have been completed to evaluate the toxicity of the TCDD molecule. Thus guinea pigs are quite sensitive to the molecule while hamsters may be as much as 8000 times less sensitive. The question to be answered is - is there enough TCDD in the environment to harm animals?

Several animal studies have completed but the only formal study designed to test the accumulation of TCDD in animals in the wild Newton et al. (1978), could detect no TCDD in tissues of mountain beaver at the end of 45 to 60 days of feeding on 2,4,5-T treated vegetation. The area had been sprayed with 2 lb 2,4,5-T per acre at the beginning of the feeding period.

Shadoff et al. (1971) analyzed animals for accumulation of TCDD from regions in Midwestern United States where 2,4,5-T is commonly used. They did not detect any TCDD in samples of fish, water, mud and human milk from Arkansas and Texas. Their detection limit was 10 ppt.

Jensen et al., 1981 fed artificially exaggerated levels of 24 ppt TCDD to seven beef cattle for 28 days. No adverse effects were observed in the animals during the 50 weeks of the feeding study. They consumed approximately 0.02 ug/kg in 4 weeks. Beef fat which contained the highest level of TCDD, contained 61 to 95 ppt. These levels dissipated when the cattle were put on non-treated feed.

These data represent residues obtained following an artificially exaggerated TCDD ingestion rate when compared to the intake that might be obtained grazing grass sprayed with 2,4,5-T. Typically, the ini-

tial deposit of 2,4,5-T on grass is 100 ppm for each pound of herbicide applied per acre (Morton et al., 1967). Since 2,4,5-T presently contains <0.05 ppm of TCDD, the treated grass could have a maximum initial TCDD level of 5 ppt. This residue decreases with time, having a half life on grass somewhere between the 4-h value found on excised leaf surfaces (Crosby and Wong, 1977) and a value of 1 week in a field experiment where grass was sprayed with a 2,4,5-T formulation (Getzendaner and Hummel, 1975). Assuming these half-lives, the TCDD level would decline to between <0.001 and 0.3 ppt in 1 month. TCDD residue levels obtained in the Jensen study in which a continuous 24-ppt diet level was fed should not be confused with the greatly reduced potential for TCDD residues in normal herbicide use.

The results of the Jensen feeding study provide a foundation of ruminant animal data supporting the conclusion that residues of TCDD would be detected in beef fat if range animals had been exposed to measurable levels of TCDD. However, no TCDD has been found at levels above the detection limit in beef samples taken from areas which would maximize exposure to TCDD through treatment with 2,4,5-T, except for 3 samples out of 89 from treatment areas (Shadoff et al., 1977) which came from an area in Missouri where highly TCDD contaminated soil from Missouri Horse Arena incident had been deposited (Pesticide Chemical News, 1976). Rabbits force fed with TCDD contained in soil or organic solvents absorbed higher levels from the organic solvents than from the soil which tightly binds TCDD (Bonaccorsi et al., 1983).

What are the short- and long-term effects of TCDD? We could answer this question quite simply and correctly by indicating we do not yet

have all of the answers. However, this same answer could be given for most all compounds that have biological activity. Since some information is available, portions of this will be discussed. Much of this information is based on animal feeding studies. These effects could be more severe or less severe in man since TCDD has been shown to be to some extent species-specific, however indications are that man is less sensitive to TCDD than are several other animal species (Stevens, 1981).

TCDD appears to be excreted primarily in the feces of the rat (Piper et al., 1973) and is assumed to be associated with unabsorbed compound. Calculated half-lives of 10-30 days were markedly longer than those from the phenoxy herbicides. The extreme toxicity as exhibited by the very low LD_{50}'s (Table 5-2) for TCDD in combination with a relatively long residence time in animals provide this compound with an enhanced potential for causing harmful effects in animals.

Due to the extreme toxicity of this compound man should take precautions to insure that he is not being exposing himself to dangerous levels. Whether it is possible for him to expose himself to health threatening levels in the environment is debateable. Nevertheless, he also owes it to himself to make a rational attempt to become as well informed as possible to the actual levels of exposure he can conceivably be expected to receive.

Workers involved in accidental exposure to TCDD as a contaminant of trichlorophenol or in factories synthesizing the compound have reported a number of adverse health reactions (May, 1973; Poland et al., 1971). Besides chloracne, which is the best known and most sen-

sitive sign of exposure to TCDD, other reported toxic manifestations include conjunctivitis or blepharoconjuctivitis, hepatotoxicity, gastrointestinal and kidney disturbances, anorexia, weight loss, fatigue, hyperpigmentation, hirsutism, porphyria cutanea tardia, neuromuscular problems, and psychological changes. However, it has not been established with certainty that all these clinical symptoms were related to TCDD exposure.

In their section on "Public Health Hazards" the National Research Council of Canada (NRCC, 1978) indicates that exposure to high concentrations of phenoxy herbicides as residues in food or water is relatively unlikely, the primary risk to human health may be expected to be from occupational exposure during manufacture and application. Bleiberg et al. (1964) and Poland et al. (1971) reported surveys of workers in a plant producing 2,4-D, 2,4,5-T, and the di- and trichlorophenols. Chloracne was found in 13 of 73 employees examined and, in the earlier survey, several cases of porphyria and uroporphyrinuria were described.. These effects were observed before and just after major steps were taken to decrease the TCDD content of the products produced in this plant. These are signs of TCDD poisoning although the exact nature of the chemicals to which the workers were exposed is unknown. In another study no differences were observed in 220 men exposed to 2-8 mg 2,4,5-T/day for 1 to 960+ days (Johnson, 1971). The control group contained 4600 men. "The workmen were given extensive physical examinations including a battery of at least 20 laboratory tests." No chromosomal effects were reported. Their level of exposures were not specified.

Based on dose response studies in animals and limited epidemiologic data at this time there is no conclusive evidence that TCDD is mutangenic, teratogenic, or carcinogenic to man (Bovey and Young, 1980).

If TCDD enters a human would it accumulate? In animal studies in which ^{14}C-labeled TCDD was given orally to rats the largest accumulation occurred in liver and fat. These tissues contained 10 to 50 times as much as other body tissues. This fact does not answer the question of accumulation. TCDD is eliminated primarily through the feces for guinea pigs, rats, and mice. The total excreted through this route was 94, 99, and 74%, respectively for the above animals. Urinary excretion accounted for the difference. The half life for elimination was 30, 31, and 17 days respectively for guinea pigs, rats, and mice (Neal et al., 1982).

Dr. Frederick Kutz (1981) of the EPA has analyzed human adipose tissue for TCDD content. His statements follow.

> Several investigators have indicated that minute quantities of 2,3,7,8-TCDD are present (in the low parts per trillion range) in specimens of adipose tissue collected from members of the general population. We also have conducted a very limited number of analyses of this type. As control specimens for some analytical studies done by the EPA Dioxin Monitoring Program in early 1980, six specimens of human adipose tissue were collected from residents of an urban Ohio county. These specimens were exised during post-mortem examinations from individuals with no recorded or known exposure to 2,4,5-T or silvex. The source of TCDD in these specimens was not phenoxy herbicides. Subsequently, the samples were analyzed in duplicate following the EPA Dioxin Monitoring Program protocol. Instrumental determinations were conducted at two independent laboratories.
>
> The results demonstrated that all specimens contained residues of 2,3,7,8-TCDD. Levels ranged between 5 and 12 parts per trillion, with a detection limit below 5 ppt. It should be emphasized that all studies conducted to date, including this one, have been accomplished utilizing small

sample sizes and deliberate specimen selection criteria. Consequently, these data cannot be construed as being representative of the general population.

Why is the Seveso, Italy accident important to the TCDD exposure questions? By evaluating health problems suffered by humans which have been exposed to high levels of TCDD, we will be in a better position to attempt to quantify exposure to the Vietnam veteran and Vietnamese living in the defoliated areas.

Stevens (1981) provides a quantitative approach to the animal deaths and human health factors.

> About noon on July 10, 1976, a factory north of Milan which produced trichlorophenol had an explosion which released boiling reagents into the atmosphere. Most of the cloud settled on a 110 hectare (1 ha = 2.47 acres) area in the town of Seveso where it deposited about 2 kg of TCDD. This area was designated Zone A and a larger, more distant area of 269 ha which received only 20 g of TCDD was designated Zone B. The 733 residents of Zone A were evacuated 2 weeks after the explosion. The 4800 residents of Zone B were not evacuated but were prohibited from raising or using produce from either Zone B or the surrounding 1430 ha Zone R. These amounts of TCDD would produce average concentrations of 1800 and 7 ug of TCDD per square metre in Zones A and B respectively. Analyses carried out days to weeks after the explosion showed a very spotty distribution with a range in Zone A from 5447 ug per square meter to not detectable (Pocchiari, Silano & Zampieri, 1979). Actual concentrations on vegetation and soil shortly after the explosion were undoubtedly higher than these recorded values. Birds began dying in Zone A a few days after the explosion. Birds preen their feathers regularly. The surface area of the feathers is many times that of the skin surface so even a small bird must have at least 0.1 m^2 of feather surface. If the feathers held the average concentration of 1800 ugm^{-2}, then 180 ug would be present on a bird weighing only 30 to 100 g. Thus the bird could ingest 1000 $ugkg^{-1}$, about ten times the acute LD_{50} for birds (Young et al., 1978). Rabbits which ate fresh vegetation from local fields died next. A 1 kg rabbit consuming vegetation from an area of one square meter would take in at least 1800 ug, over ten times the LD_{50} for rabbits. More cats than dogs died since cats both groom frequently and eat birds. Later a number of sheep and cattle died; most livestock in Zone A was destroyed. In Zone B, however, birds and rabbits would consume TCDD in the order of 7 $ugkg^{-1}$ (below the actue toxic dose) and here few of these animals were found dead.

The early toxic effects in man were not due to TCDD but to other chemicals, for example sodium hydroxide. Chloracne has been the only prominent effect found to be caused by TCDD; 193 cases have been diagnosed with 50 cases in residents of Zone A. The diagnosis in the 143 cases outsize Zone A is confused because these were found by screening 49,000 people for an incidence of 0.3% and this percentage is reported to be the incidence of chloracne in more northern industrial Italian cities not involved in the accident. However, in Zone A the incidence of chloracne was 7%: 23 times this base rate. In addition, about 10% of the Zone A population showed either minor clinical signs of polyneuropathy or laboratory evidence of slowed nerve conduction times. Transient changes in liver enzymes were noted in a few cases. There have been no deaths, no serious disease, no immunological changes, no birth defects, no increase in spontaneous abortions; and no chromosomal changes attributable to TCDD (Pocchiari et al., 1979). Cases of chloracne outside Zone A were probably due to external contact with transported TCDD. The overall pattern indicates that the mean concentration of TCDD in Zone A was below the minimum toxic dose but the spotty distribution produced minimal signs and symptoms in about 10%. Since most clinical findings were in children under age 12, 30 kg will approximate the average weight. To reach the MTD of TCDD of 0.1 $ugkg^{-1}$ would require an intake of 3 ug. The mean concentration of TCDD was 1800 ugm^{-2} which must have been considerably lower than the level needed to provide the MTD. It will therefore be assumed that the 10% affected were exposed to about three times this mean value or 5400 ugm^{-2}. The intake transfer factor for Seveso would then be 5400/3 or 1:1800.

TCDD is most toxic for guinea pigs and least for dogs. The acute toxicity for chickens, mice, rats, cats and monkeys are all within a proportional order of magnitude, and chronic toxicity in man, monkeys and rats is not very different (Young et al., 1978). Hence the reason that human toxicity was low in Missouri and Seveso while animal toxicity was high, related not to innate differences in sensitivity but to a very much lower intake of the environmental TCDD. Humans wear shoes and clothing, they do not groom with their mouths, they wash themselves and their food and they do not eat vegetation in bulk. These features account for the intake transfer factors of 1:2300 calculated from a single individual for whom accurate measurements of environmental TCDD and of the duration and type of exposure were known, and of 1:1800 calculated from the signs and symptoms of about 75 individuals with less accurate TCDD measurements and of their exposure. The agreement is good and the average value of 1:2050 will be used for the intake transfer factor.

In the Seveso accident TCDD was released in a village at rates per acre that were millions of times greater than those that occur from

2,4,5-T treatments (Reggiani, 1978). Beljan et al. (1981) discussing the Seveso accident states

> Thus far, one of the most extensive "human experiments" is being conducted on the residents of Seveso, Italy. The whole story may not be known for another five years; but preliminarily, it appears that the dermatological effects were reversible; there has been no progression of neurological damage; differences in immune response between exposed and nonexposed persons have not been significant; and there has been no notable increase in infectious diseases. There may never be an entirely clear picture from Seveso of the effect of TCDD on reproduction or the fetus, because it is suspected that a number of women elected to have therapeutic abortions. No major pathology, however, was reported by the area physicians.

May (1982) reported an accident involving TCDD which occurred in the United Kingdom in 1968. During the manufacture of 2,4,5 trichlorophenol (TCP) an accident led to the release of crude TCP containing a higher than normal concentration of 2,3,7,8-TCDD. A total of 79 cases of chloracne was reported, but there was no clinical evidence of other dioxin-related diseases. The majority of the cases responded favorably to simple treatments. Ten years later, symptoms had disappeared completely from half the cases under observation while in the remainder symptoms were insignificant.

Since it has been shown that TCDD is widely distributed in the environment, does that mean that it is present in the food we eat? If normally present it is below our level of detection as shown by several food surveys. In a study designed to favor the conditions for a positive identification of TCDD the following action was taken. Beef fat containing residues of ronnel and its metabolite 2,4,5-trichlorophenol at 46.0 and 2.8 ppm, respectively, was examined before and after cooking for presence of 2,3,7,8-tetrachlorodibenzo-

p-dioxin. Fat samples fortified at 2000 ppm with 2,4,5-trichlorophenol or its sodium salt were cooked at 500°F for periods of 6 to 22 hr. No tetra-dioxin was found in any of the samples, using a method with a sensitivity limit of 0.05 ppm (Watts et al., 1973).

Can man be harmed from absorbing or ingesting 2,4-D or 2,4,5-T?

Berwick (1970) reports an incident where a man accidentally ingested a 110 mg/kg dose of 2,4-D (isooctyl ester). Besides depression and irritation of the central nervous system, the victim suffered from myopathy, GI irrigation, nephroprethy and toxicity to the liver. This individual recovered fully. Several other cases give us additional information on man's susceptibility to phenoxy herbicides. Symptoms of poisoning occur at an oral dose of around 3 to 4 grams (Hayes, 1963). In an experiment conducted on himself, a man consumed 500 mg of purified 2,4-D each day for 21 days without ill effects (Assouly, 1951). In another case, 18 intravenous doses - the last 12 of which were 800 milligrams or more - were delivered to a patient over the course of 33 days for the treatment of coccidioidomycosis; there were no side effects even after the 18th dose of 2,000 mg. The last injection of 3,600 mg produced illness - but, by the end of 48 hours, the subject had completely recovered (Beljan et al., 1981).

Some information on phenoxy toxicity to man has been gained by evaluating data gathered from suicide victims. The lethal oral dose for 2,4-D as based on findings from a 23-yr-old male is slightly over 80 mg/kg; a man weighing 80 kg would thus require at least 6.4 grams of the material to kill him. Nielsen et al. (1965) reports this

suicide with an estimated 6.5 g of 2,4-D. The time from ingestion to death was 18 hours. This 80 mg/kg dose was received all at one time. If low doses are received over a long time period man's body effectively rids itself of phenoxy compounds.

Rats, when fed levels of 2,4-D at or above the NOEL for teratogenicity, developed peripheral neuropathy (impaired functioning of outermost joints of forearms and hindlimbs (Squibb et al., 1983). In all cases grip strength of the rats returned to normal 6 weeks after daily dosing ended.

Peripheral neuropathy was reported for two individuals who had significant dermal contact with 2,4-D (Berkley et al., 1963; Todd, 1962). No evidence has been shown that indicates that chronic exposure to 2,4-D in man will cause peripheral neuropathy.

How toxic is 2,4-D to workers applying this herbicide in the forest? Using the above information on acute poisoning in the suicide case let us now make a calculation from data on applicator exposure to 2,4-D provided in Chapter 3 (Lavy et al., 1982). The group of workers receiving the highest dose were the pilots and the batchmen, both of whom received 0.0198 mg/kg. If we assume similar toxicity between the dose received orally by the suicide victim and that received as a consequence of dermal absorption by the field workers the following calculation can be made. The 80 kg suicide victim's level of ingestion was 80 mg/kg; the group with the highest absorbed dose in the 2,4-D applicator exposure study (Lavy et al., 1982) was 0.0198 mg/kg. The calculation:

$$\frac{\text{Lethal acute dose}}{\text{One time applicator exposure dose}} \quad \frac{80 \text{ mg/kg}}{0.0198 \text{ mg/kg}} = 4040$$

reveals that the workers could have absorbed 4040 times more 2,4-D than they did before they would have received a lethal dose. Thus, a 4040 fold margin of safety was involved for the most highly exposed workers in the study. In reality the margin of safety would be much higher since the approximately 0.0198 mg/kg was the total absorbed dose of 2,4-D occurring over the 5-day observation period. As discussed previously, absorption through the skin in a relatively slow process, thus the body has the ability to excrete it at a faster rate than it can enter through the skin. This rapid elimination of the phenoxy compounds does not allow them to build-up in the body. The fact that over 95% of the absorbed phenoxy dose is excreted from the worker's bodies within 6 days probably accounts for the fact that many aerial applicators have made a career of applying phenoxy herbicides with no apparent detrimental health effects. Recent applicator exposure studies from New Zealand indicate that calculated results when compared to epidemological data show that chemical applicators are at no greater risk from teratogenic or carcinogenic hazard that the general population (Ferry et al., 1982).

Should a concerned pesticide applicator quit worrying about exposure to pesticides since the scientific facts indicate no imminent danger is present? All pesticides have biological activity; as such they should be handled with due caution as prescribed on the label. Non-applicators receive much, much less exposure than others in our society. Education, protective clothing, and a desire to work in a

safe manner are prerequisites for concerned pesticide applicators who wish to limit their absorbed dose of the pesticide.

To put into perspective the potential dermal exposure received by workers applying 2,4,5-T by backpack sprayers at a 2 lb/acre rate compared to the TCDD levels discussed in other examples in this monograph (see Table A-7).

Table A-7. Comparisons of TCDD levels as reported in different studies.

Commodity	Concentration reported (ppb)
Soil from Missouri horse arenas	33,000
Soil from near Seveso explosion site	5,500
Soil from Times Beach, Missouri	300
CDC expressed concern level	1
Soil concentration present when top 3 inches is treated with 2#/acre 2,4,5-T (containing 0.04 ppm TCDD)	0.00008
Present on humans applying 2,4,5-T (containing 0.04 ppm TCDD) at a rate of 1.6 lbs/acre in the forest	0.00005

If one's chances of being harmed by phenoxy herbicides and TCDD are so low, why do we keep hearing about the danger on TV and reading about it in the newspapers? Several different answers are possible:

1) The issues being discussed are complex; assuming the news story writer heeds all of the facts available to him, it would not be a simple task to convey the message to a broad audience.

Results of an extensive literature search and discussions with scores of concerned laymen reveals that the U.S. public has heard little factual information pertaining to the man's exposure to phenoxy herbicides and TCDD. The objectives of the news media and of reporters of scientific data are often at opposite poles. The journalist does not provide details on the millions of cars traveling the highways each day. But a car which crashes, bursts into flame, and kills three people makes front page news. Likewise, the public is seldom told of the major role that pesticides play in allowing the U.S. farmer to achieve production levels which provide us an opportunity to ship our abundant food supplies to millions of starving people around the world. But if a child inadvertently drinks concentrated gasoline or insecticide and dies this story makes news. The scientist on the other hand collects data to determine how safe cars are, or how to make them safer; he seeks to find new means to feed people; he tests to determine the danger levels of cars or pesticides; realistically, these facts do not make good front page stories.

Evidence overwhelmingly supports the concept that phenoxys and TCDD when in a <u>concentrated</u> form, can harm man and animals. The news media responds to this side of a complex story. The evidence also convincingly shows that man can <u>not</u>, through his occupational use of the herbicides or through his food supply, attain a dose of the phenoxy herbicides or TCDD approaching a health threatening level. The

scientist bases his endorsement on the current use of these materials after assessing the issues and interpreting them to the best of his ability.

2) The public hears news stories; most do not pursue scientific literature. The audience is more accustomed and perhaps more receptive to listening to catastrophic happenings than to statements such as "these pesticide levels do not constitute a threat to man's health."

3) It is much easier to speculate that something bad may happen in the future than it is to prove unequivocally that 20, 40, or 80 years from now a compound will not present a danger to man or his grandchildren.

4) Politically, it is more efficacious to vote on the side of safety than it is to invest the time and determination to search out the facts. The masses informed by the media represent more votes than those reading the scientific journals.

5) Some Vietnam veterans have health related problems; for many individuals it will not be possible to arrive at the exact source of the problem due to complex world in which we live. In fairness to this group of individuals only factual scientifically validated information should be offered as the cause.

6) As discussed previously, on a per gram basis, the toxicity of the phenoxy herbicides is much, much less than that of TCDD. This monograph has presented information which shows that phenoxy herbicides are not a major source of TCDD in our environment today. Dioxin (TCDD) will continue to be of keen interest to man due to its extreme toxicity and its persistence in the environment.

Other than in production plants what groups of humans are exposed to the highest amounts of pesticides? Commercial pesticide applicators and mixers receive doses that are hundreds to hundreds of thousands times greater than others in the vicinity.

Do phenoxy herbicides cause soft tissue sarcomas in man? Reports from Sweden (Hardell, 1981) suggest that man's exposure to phenoxy herbicides used in forestry and agriculture results in an increased rate of soft tissue sarcomas. Many researchers have been critical of the work charging that he failed to accurately separate other potential tumor causing factors.

> Workers are unlikely to recall with any accuracy the chemicals being used some years in the past and it seems somewhat simplistic to differentiate between workers exposed to phenoxy acetic acid herbicides and those not exposed to this group of herbicides (Kilpatrick, 1980).

Estimates of the level of exposure occuring or length of time involved are obscure. The fact that several different sarcoma types were found also make the findings suspect.

A study in the Netherlands was conducted by the State Occupational Health Service to evaluate claims by newspapers that personnel involved with 2,4,5-T work in a forested community were encountering a higher prevalance of tumors. A total of 54 of their most highly exposed personnel were selected from a group of 400 workers who had had some exposure. This 54 man group was matched with 54 non-exposed workers (matched by sex, age and residence). Acne and liver dysfunction data were used as the criteria for evaluating the workers. No differences in acne or urinary porphyrin patterns were shown for the forestry workers exposed to 2,4,5-T and the non-exposed group (Van

Houdt et al., 1983).

The question of soft-tissue sarcoma is important and must not be avoided. Current research has failed to show a cause and effect relationship between exposure to phenoxy herbicides and soft tissue sarcomas. This subject is receiving continuing attention by research being conducted by the National Institute for Occupational Safety and Health (NIOSH).

Were there dangerous components of Agent Orange besides TCDD? This herbicide was a 50-50 mixture of the n-butyl esters of 2,4-D and 2,4,5-T. The 2,4,5-T component contained a trace level of TCDD. In normal use patterns such as these employed in U.S. agriculture and in South Vietnam defoliation efforts levels harmful to man would not be encountered. As discussed earlier (see page) 2,4,5-T represents more of a health hazard to man than does TCDD which is present as a trace component.

What happens if 2,4,5-T, which contains a trace level of TCDD, comes into contact with a human? An in-depth discussion of an applicator exposure study where 2,4,5-T was applied by helicopter crews, mist blower crews and backpack spray crews was presented in Chapter 3. Nearly all crewmembers were exposed. None became ill. These results agree with findings discussed by Kilpatrick (1980). Dermal absorption was cited as the primary entry mechanism into the body. Excretion in urine over a 6-day period accounts for over 95% of the absorbed dose. Individuals who mixed the concentrate received the highest absorbed dose. The most highly exposed group, the mixers, could have received an absorbed dose 300 times greater than their actual dose before they

would have attained a no-adverse-effect dosage for teratogenicity. Another way of expressing this fact is that a safety factor or "A Margin of Safety" of 300 was present. The 20 mg/kg no-adverse-effect dosage for 2,4,5-T teratogenicity as established by the working group in EPA Position Document 1 is a conservative value when employed for other human health effects. Since the developing fetus is quite sensitive to toxins this value of 20 mg/kg represents a realistic level for evaluating exposure of females of childbearing age. Thus, the results from the monitored human applicator exposure studies to the phenoxy herbicides showed that the dose the workers received was well below any level which could harm their health.

Of the personnel exposed to Agent Orange in Vietnam, only members of Ranch Hand operations could have received exposure levels as high as the field crews discussed here. Ground troops walking through vegetation sprayed with Agent Orange probably received much lower exposure than the Ranch Hand personnel based on evaluation of the following limited study. A worker walking through a field, which 2 hours earlier had been treated with an ester formulation of 2 lb/acre 2,4,5-T was outfitted with 6 gauze patches attached to his clothing allow to measurement of the extent of dislodgeable 2,4,5-T residues occurring. Analysis of the patches revealed no detectable 2,4,5-T in spite of the fact that the worker walked through chest-high to 15-feet-tall sprayed vegetation. The gas chromatographic technique could have detected levels as low as 10 micrograms.

Calculations presented in Chapter 4 indicate that 2,4,5-T, a pesticide relatively non-toxic to man, represents a greater threat to

man's health than does the highly toxic TCDD - due to the trace amount of TCDD present in 2,4,5-T. As also shown in Chapter 4 some of our commonly used insecticides have toxicity properties that are 60 times greater than 2,4,5-T. Aerial application of some insecticides, classified as very toxic, can be accomplished in a manner that does not appear to pose a health threat to the crewmembers applying them. Were U.S. ground troops in Vietnam "at risk" from Agent Orange since they could not shower daily? Records of 2,4,5-T excretion in urine from commercial applicator exposure studies indicate that although the backpack crewmembers sprayed only 1 day per test some of them received an absorbed dose 1 or 2 additional days during the 6 days following the application day. Observations of the spray operation and crewmember habits suggest that not all of these people changed clothing and bathed daily. Contaminated boots, gloves, or other clothing probably contributed to additional exposure they received 3, 4, or 5 days after the application was completed. As presented in the Lavy (1978) National Forest Product Association report the mixers received the highest exposure, 0.069 mg/kg while the backpack sprayers received 0.048 mg/kg and the flagger received 0.003 mg/kg. An observer in the forest who was sprayed 2 or 3 times with 2,4-D received 0.00056 mg/kg. Following are the margins of safety* for each:

Mixers	299
Backpack sprayers	417
Flagmen	6,666
Observer (sprayed with helicopter 2 or 3 times)	5,333

NOTE: The actual margin of safety is probably much higher than these values since the NOEL values were obtained from sensitive test animals who daily consumed these compounds in their food; most crewmembers are not exposed daily.

These data indicate that workers in the Ranch Hand Operation would have been exposed much more heavily than ground troops; thus, if health problems were to arise due to Agent Orange exposure it should be expressed in health records from the Ranch Hand personnel.

If U.S. military ground troops who were exposed to Agent Orange did not take daily showers, they too had the potential for continuing exposure from exposed skin or clothing. Even though the exposure for ground troops may have been prolonged due to the clothes they were wearing these levels would not build up in their bodies since the phenoxy herbicides are readily excreted in urine.

The maximum exposure levels that the ground troops could have received were less than that received by crewmembers of backpack spray crews in the U.S. who did not receive health threatening exposure application levels. A survey of long-term health studies of aerial applicators of phenoxy compounds has not revealed any health associated problems (WAA, 1980).

Could Agent Orange harm soldiers exposed to it? Information obtained by calculating the trace levels of TCDD in 2,4,5-T and interpreting the human symptomology exhibited by the large TCDD exposed population in Seveso, Italy suggest that humans exposed to 2,4,5-T or Agent Orange have not encountered either serious acute or any chronic health threatening doses of TCDD. Stevens (1981) uses the TCDD exposure fin-

dings derived from the Missouri Horse Arena Incident and the Seveso, Italy accident to assess the hazards to humans in Vietnam:

> Agent Orange is an oily liquid composed of equal volumes of the n-butyl esters of 2,4-D and 2,4,5-T. TCDD, present in Agent Orange in an average concentration of 2 ppm, is extremely insol-uble in water but readily soluble in Agent Orange. The herbicide was delivered as a coarse spray with droplets of 320-350 um diameter (Young et al., 1978). While gases readily enter the lungs, only droplets which are less than 10 um can enter (Walton, 1971), thus Agent Orange could not be absorbed from the lungs. Each gallon of Agent Orange contained 10.7 lbs (4.9 kg) of total herbicide (Young et al., 1978). One acre is 3660 m^2 so the spraying rate of three gallons per acre converts to metric mass units of 4.1 gm^{-2}. Since the mean TCDD concentration in Agent Orange was 2 ppm, the delivered amount of TCDD would be 8 ugm^{-2}. The average concentration of TCDD in Zone B in Seveso, where the people were not evacuated, was 7 ugm^{-2} (Pocchiari et al., 1979).
>
> The conditions for destruction of TCDD in Vietnam were almost ideal. TCDD is very stable in the dark but is photodechlorinated in position eight. The resulting 2,3,7-TriCDD is 10,000 times less toxic (McConnell & Moore, 1979). Photodechlorination requires light, an organic hydrogen donor (Agent Orange works well) and the reaction proceeds three times faster at 30°C, the mean annual daytime temperature in Saigon, than at 23°C (Liberti et al., 1978). When Agent Orange is applied to leaves in full sunlight, the half-life of the contaminant TCDD is only 2 h (Crosby & Wong, 1977). Grass receives less light and some TCDD reaches the soil; the half-life of TCDD applied to turf is about 6 days (Young et al., 1978). Since spraying was done in early morning (Young et al., 1978), a single day of full sun would decrease the TCDD on the leaves from 8 to 0.3 ugm^{-2}. About 90% of Agent Orange was sprayed on forests and only 6% of that reached the forest floor (Young et al., 1978) to yield 0.5 ugm^{-2} of TCDD. Hence under forest cover, troops passing through, even under direct spraying, would receive less than 1 ugm^{-2} in their environment. For the 10% not sprayed on forests, the early morning concentration of 8 ugm^{-2} would be less than half of that by evening. For most soldiers who had any exposure to Agent Orange, that exposure would consist of walking through vegetation which contained no more than 1 ugm^{-2} of TCDD. Using the transfer factor of 1:2050, the soldier would take in 5×10^{-4} ug of TCDD. For a 70 kg soldier this represents 7×10^{-6} $ugkg^{-1}$ or 1/14,000 of the minimum toxic dose of 0.1 $ugkg^{-1}$. If soldiers were exposed to direct spraying from airplanes the intake would still be only 1/1750 of the MTD. Even if a soldier were exposed to 8 ugm^{-2} each day of his one year tour in Vietnam and each day was treated as a new exposure, his cumulative intake would be only 1.4 ug or 0.02 $ugkg^{-1}$ of TCDD.

> Since it would take about 5 years of daily close contact with Agent Orange to reach toxic levels of TCDD, claims that illnesses in Vietnamese (Tung et al., 1971, 1973) and Americans (Bogan, 1979) were due to Agent Orange are without merit" (Stevens, 1981).

Stevens' description above of the prospects for significant TCDD exposure of U.S. military personnel in Vietnam were made with no reference to the fact that a portion of the TCDD absorbed during the exposure period would also be excreted. Assuming the other considerations to be valid, then an even greater margin of safety could be projected. There is another important but difficult fact to evaluate regarding the U.S. spraying program in Vietnam. Many soldiers were accustomed to seeing U.S. planes routinely spray jungle and base perimeter areas; for many it would have been impossible to distinguish between the spraying of malthion, an insecticide, or one of the several defoliants.

How could one know if he had been exposed to significant levels of Agent Orange? From the studies on humans accidently exposed to large doses of TCDD in Seveso, Italy in 1976 the most common symptom was the development of chloracne. However, not all of the exposed population developed chloracne.

This particular skin disease is, in fact, regarded as the clinical marker for TCDD exposure. Systemic disorders in man from exposures to TCDD are not likely to occur if chloracne is not present. Such symptoms as impaired liver function, nephropathy, GI irritation, myopathy and neuropathy, including depression and irritation of the central nervous system, have been reported after exposure to large amounts of TCDD in industrial accidents; however, these symptoms have not been

progressive, and they have always cleared with time (Beljan, et al., 1981).

In the Seveso exposed population evidence of chloracne was present 2 weeks after exposure,however some cases took as long as 7 weeks to develop. A total of 175 cases (Pocchiari, 1978) was reported; this accounted for 0.6 to 1.2% of the population exposed.

It is highly unlikely that U.S. military personnel in Vietnam were exposed to TCDD levels high enough to cause chloracne, however, if it did occur evidence of chloracne should have developed within 2 to 7 weeks of the time exposure occurred.

Chloracne has been described as the primary symptom for men exposed to chlorinated organic compounds, are there other symptoms that would accompany these symptoms? Chloracne development commonly follows industrial accidents involving man's exposure to TCDD. Evaluation of health records of 174 humans, who developed chloracne after the explosion or occupational exposure to some form of dioxin since 1960, revealed no obvious effects of other systemic disorders (Crow, 1981).

What has happened to the health of those in Vietnam who mixed and applied Agent Orange? These individuals are a part of the Ranch Hand group where ongoing tests are being conducted. To date this group has not reported health related problems due to their job assignment. If one could accurately extrapolate from exposure data on humans who mix and apply phenoxy herbicides as a vocation in the U.S., no deleterious health effects would be expected.

Could Agent Orange affect the fertility of males? Male mice were fed a replication of substances similar to Agent Orange (Lamb et al.,

1980). In previous studies some female mice when exposed to 2,4,5-T at high doses during pregnancy delivered offspring with cleft palate, cystic kidney or retarded growth; no other laboratory animals had shown this effect. Although the dose levels in this study of male mice were sufficient to affect the liver and the thymus, and to reduce growth rates, there was no alteration in the concentration or motility of sperm or in the proportion of abnormal sperm; no significant decrease in fertility was shown and the development of the offspring of treated males appeared to be normal.

Can birth defects be caused by pregnant women being exposed to the phenoxy herbicides and TCDD? The human event most sensitive to harm is that of possible birth defects in the developing fetus of pregnant women. The level of any compound required to cause this effect in test animals is much less than the levels required to show other health problems (Hunter et al., 1981). Much of this section has also been taken from Hunter et al., 1981.

Experiments with test animals can be used to determine a "no-effect" level (NEL), which describes a definite amount of applied chemical at which no risk exists and birth defects do not occur. The level for the most sensitive test species can then be extrapolated to human exposure. The likelihood of contacting this level of exposure during field use of the chemical will determine its hazard.

The NEL's[1] for 2,4-D, 2,4,5-T and TCDD are 24 mg/kg/day, 20

[1]Although the term NEL, "No effect level", is used here there remains a dose-response curve for teratogenicity at levels below the NEL's listed. For phenoxy compounds teratogenicity is not a problem because the chemical clears the body so rapidly.

mg/kg/day and 0.03 ug/kg/day respectively. (Figures for 2,4,5-T and TCDD are in accordance with the U.S. Environmental Protection Agency.)

To attain this much exposure a 60 kg pregnant woman would have to ingest 1.6 g/day of 2,4-D, 1.2 g/day of 2,4,5-T or 1.8 ug/day of TCDD (equivalent to 19 g/day of 2,4,5-T containing the maximum permissible level of TCDD) during the critical period of fetal development (Australian Consultative Council, 1978). To help evaluate the possibility of this much exposure occurring consider 1) pesticide applicators are among the most highly exposed group of humans, and 2) applicator exposure to 2,4,5-T as discussed in Chapter 3 revealed that the most exposed crewmembers received less than 0.1 mg/kg/d (Lavy, 1978).

Exposure could occur by either:

a. direct contact with the sprays; or

b. residues of chemical in food or water.

a. skin absorption and inhalation of sprays

Calculations of direct spraying onto 1 square metre of a woman's skin (approximately 2/3 of total area) and allowing for a 10% absorption rate (based on EPA data) would give safety factors of 40 for 2,4,5-T; 600 for TCDD and 60 for 2,4-D.

Thus the NEL will be reached for each of these three chemicals by a woman standing in an open paddock, with two-thirds of her skin exposed, while a low-flying aircraft spraying 2,4-D or 2,4,5-T at the normal rate makes between 40 and 600 passes directly over her each day for many consecutive days during the sensitive period of fetal development. Also the woman makes no attempt to wipe or wash the spray

off for many days.

It is highly unlikely that the above scenario could occur; however, it is desirable to err on the safe side, but there are limits beyond which it becomes unrealistic.

Assuming 100% of absorption of inhaled chemical, a 10 minute exposure would give safety factors of 15,000; 225,000; and 31,000 for 2,4,5-T, TCDD and 2,4-D respectively (Australian Consultative Council, 1978).

b. residues in food and water

Table A-8 shows the amounts of spray or foodstuffs which must be ingested by a 60 kg woman in order to obtain the "no-effect" level.

Table A-8. Amounts of food or spray mix to be ingested per day to reach the NEL of 2,4-D, 2,4,5-T, and TCDD with respect to a 60 kg pregnant woman, as determined from experiments with laboratory animals (Modified from Australian Consultative Council, 1978).

Source	2,4-D	2,4,5-T	TCDD
Spray mix[a]	.45 l	0.6 l	9.0 l
Water[b]	72,000	60,000 l	900,000 l
Milk[c]	14,500	12,000 l	180,000 l
Meat[d]	7,200	6,000 kg	90,000 kg

[a]2,4,5-T is diluted approximately 400-fold for conventional spraying.
[b]Assuming the 2,4,5-T concentration is at the maximum recommended residue level of 0.02 ppm.
[c]Assuming residue level of 0.1 ppm in milk.
[d]Assuming residue level of 0.2 ppm in meat.
NOTE: With respect to the residue levels assumed for water, milk, and meat, these levels are virtually never obtained with normal field use.

The calculations involved in determining the values in Table A-8 represent an exaggeration since:

1. The 0.02 ppm maximum recommended residue level for 2,4,5-T in water is based on potential run-off, or direct application to surface waters in catchment areas; not to the residue occurring in normal field use which, in the bulk of instances, is below the

level of detection; and

2. The residue levels chosen for milk and meat are taken from experimental work in which animals were deliberately fed 2,4,5-T at much higher levels than would be expected to occur through the ingestion of treated pasture. Under normal agricultural use residues of 2,4,5-T in meat and milk are extremely unlikely to occur.

In addition to the facts mentioned above, the use patterns of 2,4,5-T are such that potential accumulation of the herbicides would be unlikely. They are used only in areas where weed pressure is high and very few individual areas would be treated more often than once in any year.

As with 2,4,5-T general residue surveys have shown that 2,4-D is rarely found in food, and when found the levels are well below the maximum permissible residue levels. The latter values have been set to cover relatively unusual circumstances.

Domestic users of 2,4-D and 2,4,5-T can be assured that provided the label recommendations are followed, no harmful effects will be caused to any unborn child, unlike other well documented risks associated with cigarette smoking and alcohol (Chlorinated Dioxin Task Force, 1978; U.S. Dept. of Health Educ. and Wel., 1978).

Studies were designed to determine whether paternal exposure to TCDD or other dioxins might be associated with adverse pregnancy outcomes. Wives of husbands potentially exposed were compared to a group whose husbands had no known exposure to any dioxin. During the study in groups over 2700 conceptions and 2400 live birth resulted; overall no statistically significant associations were found between any expo-

sure and pregnancy outcomes (Townsend et al., 1982).

Does human mother's milk contain TCDD? This question is of interest since if mother's milk did contain TCDD, a large proportion of her infants nourishment could contain the toxin. If a nursing mother's body contained TCDD the fat content of the milk would most likely contain some TCDD. Before TCDD could be found in human mother's milk it must be present in her body at a concentration detectable by modern methodology. Techniques are now available which permit the scientist to be able to detect TCDD at, or below, the 1 ppt level. In studies reported by Shadoff (1980) of 4 correctly analyzed human milk samples none contained levels of TCDD above the 1 ppt detection limit. This finding is not surprising since man's food supply seldom contain detectable levels of TCDD.

Another report in 1980 states "All 103 mothers' milk samples from the 2,4,5-T spray area were negative for dioxin, EPA noted this week. The Agency said the samples were taken from 2,4,5-T spray areas in California, Oregon and Washington in 1977. Samples were also collected in control areas of California and Alaska not sprayed with dioxin-containing pesticides, the agency said. It noted that the samples were checked on equipment capable of measuring residues down to 1 to 4 parts per trillion" (Pesticide and Toxic Chemical News, 1980).

How do the teratogenic effects of TCDD and 2,4,5-T compare? TCDD is a much more toxic compound than 2,4,5-T. Cranmer (1978) has calculated that TCDD is 10,000 times more teratogenic than 2,4,5-T. However, since 2,4,5-T is present at levels which are 10,000,000 times greater

than TCDD, the TCDD would be required to bioaccumulate by at least 1000 times before it would equal the toxic effect that the larger amount of 2,4,5-T possesses. As discussed earlier the low application rates of 2,4,5-T (approximately 2 lb/acre) coupled with its short half-life (20-40 days) in the environment make it impossible for the agricultural use of 2,4,5-T to represent a threat to man's health. Were U.S. military personnel who used Agent Orange informed about its properties at the time of its use in Vietnam? Facts regarding how to handle these herbicides were printed in a Department of Army information manual in 1969 (Irish et al., 1969). The publication indicated that spillage onto skin or clothing should be removed promptly to avoid possible irritation through prolonged skin contact. This same report also stated "These chemicals present no hazard to man or animals in areas subjected to defoliation at the time of or following spray application."

Results from experiments conducted later, which were designed to measure the amount of 2,4,5-T and 2,4-D exposure received by field workers routinely mixing and applying these chemicals, appear to substantiate the statements presented by Irish et al. in 1969. Results from the most highly exposed 2,4-D and 2,4,5-T applicators revealed that the amount of exposure occurring did not result in absorbed doses approaching health threatening levels (Lavy et al., 1980; Lavy et al., 1982; Nash et al., 1982; Nigg, 1983).

What evidence do we have which indicates that use of defoliants in South Vietnam has not caused man health problems?

Ground troops would have been exposed to that material which penetrated the canopy. Using phenoxy herbicides similar to Agent Orange Tschirley (1969) found that about 6% of the material applied actually reached ground level. The percentage falling to the ground was lower in areas where forest canopy was the thickest. From studies on commercial applicator exposure studies we have learned that those standing under aircraft which was applying phenoxy herbicides do not receive nearly as much exposure as those who mix and prepare the concentrated materials (Lavy et al., 1980; Lavy et al., 1982).

Personnel in Vietnam who routinely mixed the concentrates and applied the defoliants to the jungle (the Ranch Hand personnel) would have received a much higher absorbed dose than ground troops. Ongoing monitoring of the health effects of this group has not indicated an increased incidence in death rate or in health problems. Possibly one of the reasons that a man is not injured when exposed to the phenoxy compounds is that his absorbed dose of phenoxy compounds is rapidly and nearly quantitatively excreted in his urine, thus, no build-up occurs in his body. Since these materials are not stored in fatty tissues of humans any health problems arising from their use should occur near the time of exposure.

Why do the Veteran's Administration and other government agencies continue to study Vietnam veteran health problems if the government is not admitting that Agent Orange exposure has caused the problems? As responsible interested agencies, the VA, CDC et al. are continuing to

search for possible scientific evidence which could link Agent Orange exposure to the health effects being reported. The search for new facts should not be interpreted to mean that these agencies believe there is a positive relation between exposure to Agent Orange and consequent health problems; it is their duty to explore all of the factors which could contribute to the health problems reported.

APPENDIX
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