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REPORT ON 2,4,5-T

A Report of the Panel on Herbicides of the President's Science Advisory Committee

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EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY

MARCH 1971

REPORT ON 2,4,5-T

A Report of the
Panel on Herbicides
of the
President's Science Advisory Committee

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OFFICE OF SCIENCE AND TECHNOLOGY

MARCH 1971

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THE PRESIDENT'S SCIENCE ADVISORY COMMITTEE
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WASHINGTON, D.C. 20506

March 2, 1971

The publication of this report on the herbicide, 2, 4, 5-T, symbolizes an area of public policy decision-making in which science and, hence, scientists have a large responsibility. The report itself is a landmark. It examines in detail the scientific considerations leading to policy judgments about a pesticidal chemical.

The foresight of Dr. Lee DuBridge, Science Adviser to the President at the time this review was initiated in October 1969, is commendable. The Government agencies charged with responsibilities for regulating pesticides and for overseeing the integrity of the public's health, chose a course of regulatory action in October 1969 which restricted some uses of 2, 4, 5-T. This action was taken as a result of a new and unexpected research finding which emerged from experiments sponsored by the Government. At that time, Dr. DuBridge perceived the need for a thorough and critical review of all of the scientific information available on the herbicide -- including that dealing with biological properties and human health.

Importantly, the report's major recommendations already have been adopted by the appropriate Government agencies and specific actions have resulted. The original experiments were confirmed and extended by later research. A potent impurity, a family of dioxins, has been the subject of several research projects. These have taught us more about the herbicide's physical stability, environmental persistence and biological properties. A recommendation for a legislative mechanism to restrict temporarily the use of a pesticide on the occasion of an unexpected research finding implicating it as a health hazard (while further confirmatory research is performed) is reflected in the Administration's proposed legislation on pesticide regulation.

Although the report is concerned with highly technical matters, it does allude to some policy issues. It compares the scientific evidence available, and considered adequate, at the time of first registration of

2, 4, 5-T with the much greater level of scientific understanding demanded today. The Panel found evidence of measurable benefits from the use of 2, 4, 5-T but there was simply very little information that could be used to assess risk. Based on its experience in evaluating risks and benefits on the basis of incomplete information, the Panel cautions that judgments on benefits and risks associated with pesticidal chemicals require an unusual measure of prudence to assure that the public is neither subjected to undue risk nor unnecessarily denied the benefits of valuable chemicals.

The report does not speak in particular to the regulatory actions taken by the Government on 2, 4, 5-T (although I am satisfied that the review complements them in every respect). If any of the Government actions appear divergent from these recommendations, the divergence is consistently on the side of prudence and avoidance of the possibility of hazard to human health, and this is as it should be, for Government must act on the side of prudence. It provides those of us concerned with pesticides, their economic value and utility, their negative effects on the environment, and their other biological effects, with an excellent case study. The principles brought out in this study will be useful in dealing with other pesticides, and indeed with chemicals of other kinds.

Edward E. David Jr.

Edward E. David, Jr.
Chairman

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SUMMARY AND RECOMMENDATIONS

Summary

This review of the herbicide, 2,4,5-T, began with an examination of the results from an experimental screening study which implicated it as a potential teratogen. It quickly became evident that examination from such a restricted basis was inadequate. Therefore, the Panel decided to study more broadly important aspects of 2,4,5-T, including details of its chemistry and purity, its domestic uses and their relative importance, the military significance attached to 2,4,5-T as a defoliant, residue levels (in order to estimate probabilities of human exposure), general effects on the environment, as well as its toxicity. In examining the toxicity of 2,4,5-T, the Panel reviewed the information available from the literature (as well as some unpublished documents) which had been considered in the past in establishing policy decisions for the various uses to which this pesticide had been put.

Selection of 2,4,5-T as an example for detailed examination has had a number of advantages. There has been an extensive history of use and experience. 2,4,5-T was first registered on March 2, 1948, by the Amchem Products Company, Ambler, Pennsylvania. Since that time considerable information on its properties and uses has accumulated. Furthermore, it has been the subject of reviews by others in the past. Finally, the problem which brought it to the Panel's attention, suspicion of teratogenicity, appears to be a relatively manageable problem in contrast to many other biological effects, notably tumor production and genetic alterations. This is important since the recommendations which follow can be made with a degree of confidence that cannot be applied to carcinogenic or mutagenic effects. For example, the dose-response characteristic of teratogens is generally restricted to a relatively small range of dosage. Accordingly, a threshold below which no effect would be expected can be assigned with more certainty. Experiments to determine this range of values can be performed in a relatively short time and do not require very large numbers of animals.

The Panel is gratified that some of its recommendations are already being carried out, especially further experiments to confirm and ex-

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tend the results of the original screening that indicated 2,4,5-T to be teratogenic.

In considering the chemistry of 2,4,5-T, our attention was drawn to impurities which can result from the manufacturing process. Particular attention was focused on a single impurity, 2,3,7,8-tetrachlorodibenzo-p-dioxin, which occurs in commercial preparations of the herbicide in highly variable amounts unless particular care is taken to exclude it. This impurity is extremely toxic. Its amount depends upon variations in the reaction conditions. Other dioxins can be formed from various impurities in the starting materials. The dioxin impurity came to particular attention when the U.S. herbicide industry was asked to produce larger quantities of 2,4,5-T during the middle 1960's. However, its presence as an impurity and certain of its acute toxic effects had been known since 1957. Its concentration in commercial 2,4,5-T has been greatly reduced in the past year or so.

Analytic methods available for 2,4,5-T are accurate and reliable. With the possible exception of citrus fruits, determination of residues in food has not presented a serious analytic problem.

2,4,5-T is relatively labile in nature. Residues in soils and water are not persistent except under unusual conditions. The herbicide is not stored in plants or animals to a significant extent.

Production of 2,4,5-T in the United States rose rapidly between 1960 and 1968. Civilian use, most of which is for clearing of range land and rights-of-way and for treatment of pastures, declined about 50% between 1964 and 1966. Military use of 2,4,5-T as a defoliant, expressed as number of acres sprayed, rose sharply between 1964 and 1967 but has declined since then. Although accounting for only a small amount of the total usage of 2,4,5-T, its place in control of aquatic weeds is significant. There is a small but important list of agricultural uses where 2,4,5-T is applied to food crops. Potential human exposure is recognized in this direct application to food crops, in range and pasture lands grazed by domestic meat and dairy animals, and possibly, in water supplies derived from treated waterways and streams. The economic importance of the various uses is considerable, but is very much less than that of 2,4-D. Substitution of 2,4-D for 2,4,5-T can be made for certain uses.

Defoliation, using mixtures of 2,4-D and 2,4,5-T, has been employed in Vietnam since 1962, more intensively since 1967.

Although not rigorously demonstrated, its military usefulness has been considered to be very high.

The background of toxicological information on 2,4,5-T is thin. Most of the animal studies have been concerned with acute toxicity (single doses or repeated doses for short periods of time). Based on these experiments, the acute toxicity of 2,4,5-T was found to be low. Little is known of the details of the metabolic handling of the material although rapid excretion in the urine seems to be the rule.

The screening study supported by the National Cancer Institute on the toxicity of certain pesticides and other important industrial chemicals marks an important advance in toxicological testing in that the tests were designed to detect carcinogenic, teratogenic and mutagenic potential. The preparation of 2,4,5-T used in those tests was shown to be teratogenic in both rats and mice. There was no evidence that it was carcinogenic. While this study had a number of limitations which qualified its usefulness, the teratogenic results were sufficiently convincing so that the Panel urged, early in its discussions, that they be repeated and extended using better characterized preparations of 2,4,5-T. Analysis of a sample of the 2,4,5-T preparation used in the original teratogenesis study revealed a dioxin level of about 27 ppm. Such a considerable contamination by this highly toxic material raised the question as to whether the teratogenic effects observed were caused by 2,4,5-T itself, by the dioxin impurity or by other impurities in the commercial preparation tested.

The Panel was aware of press reports of increased birth defects in Vietnam attributed to the use of defoliants. The lack of accurate epidemiological data on the incidence and kinds of birth defects in the Vietnamese population before or since the military use of defoliants precludes any estimate as to whether an increase in birth defects has occurred. Calculations of potential human exposures from sources such as drinking water or direct fallout make this appear unlikely (though theoretically possible).

A review of the environmental effects of 2,4,5-T on nontarget organisms reveals few harmful consequences of its recommended uses. Induced changes in vegetation are followed by alteration in numbers of wild animals. Accelerated erosion of soil may follow the killing of brush with herbicides but mechanical removal causes greater erosion.

Recommendations

1. *Further studies.*

a. *The animal experiments which raised the question of the teratogenic potential of 2,4,5-T should be extended to include a wider range of doses administered to non-inbred strains of animals and to larger numbers of animals.*

b. *The importance of the impurities in 2,4,5-T as potential health hazards should be ascertained.* Recent experiments designed to distinguish between 2,4,5-T and the dioxin impurity have suggested that both the herbicide and the dioxin are potential teratogens in some experimental animals. However, experiments necessary to establish this answer have not been performed. In addition, there may be additional impurities in commercially prepared phenoxy herbicides which may be biologically active.

c. *The metabolism of 2,4,5-T in humans should be determined and compared to that in experimental animals.*

2. *The level of dioxin, a recognized impurity in 2,4,5-T should be rigorously controlled and limited to not more than 0.5 ppm.* A reduction to not more than 0.1 ppm should be urged. Several polychlorinated dioxins have been found to be highly toxic and capable of eliciting teratogenic effects, though they vary widely in toxicity. Since they may reach the environment from multiple sources. control over known sources should be exercised to the extent possible.

3. *A decision to restrict the use of 2,4,5-T should not be based on the isolated finding of toxicity but on the expected exposure following recommended use in relation to dose response effects.*

In general, the imposition of restrictions on the use of a pesticide would appear to be a function of two factors, the potential for human exposure and the nature of the toxic effects. For example, if carefully documented residue information points to little likelihood of exposure, the risk of adverse effects would be less significant than if exposure were widespread.

The Panel found no evidence to suggest that significant residues would result from recommended uses of 2, 4, 5-T on food crops. It is possible for residues to occur in tissues of animals grazing on recently treated pastures and range land. In fact, the only residues which have been identified in the total diet studies have occurred in meat and dairy products. However, the few cases in which residues have been discovered have all been at levels well below those which would be expected to result in significant toxicity for man.

The experimental finding of teratogenesis requires further elaboration before it can be interpreted as a human health hazard.

The risk of teratogenic effects should be placed in perspective. Teratogenesis induced by chemicals is a fetal response at a particularly sensitive period in embryonic development to lower doses of the chemical than are acutely toxic to the mother. Birth defects can be produced in the embryo through many mechanisms of injury when the agents are administered during critical periods of organogenesis. It is generally held that by careful choice of dosage, which may be close to the acutely toxic dose for the mother, most chemicals might be shown to be teratogenic in animals. For a variety of reasons, it is not possible to translate directly the results of experiments in animals to man. There are differences in sensitivity which arise from differences in metabolism. Comparative metabolic studies in man and animals, therefore, are important in interpreting toxicity for man.

The important consideration is not only the demonstation of teratogenicity, which may occur with many chemicals at seclected dosages, but the estimation of the likelihood of teratogenic effects with the amounts likely to be ingested incident to recommended use. To restrict or ban usage of chemicals on the basis of demonstration of teratogenicity at dose levels which far exceed actual or expected exposures is unreasonable and could well deny usage of chemicals whose benefits far outweigh risks.

4. Registrations of 2,4,5-T for uses on pastures and range lands should be treated as registrations for food crop uses.

It is possible for residues of 2,4,5-T to occur in milk and tissues of animals grazing on land recently treated with 2,4,5-T. To date, meat and dairy products have been the only food products in the total diet studies that contained measurable amounts of 2,4,5-T. Use on range and pasture land should be included in registration for use on food crops.

5. Monitoring of 2,4,5-T residues should be significantly expanded, especially for meat and milk. In sampling meat and milk, special attention should be given to geographic areas where treatment of pastures and range lands with 2,4,5-T is most common. The 2,4,5-T residues that may occur in meat and milk of animals allowed to graze on pastures and range lands treated according to current recommendations should also be restudied.

6. As new information is developed on pesticides, it should be disseminated promptly to individuals and organizations that are legitimately concerned as manufacturers, formulators, users and scientific investigators.

The case of 2,4,5-T is illustrative of inordinate delay in making available new research information as it became known. The screening study of pesticides which was carried out by Bionetics Corporation under contract with the National Cancer Institute was completed about August 1968. It was 14 months later when the Government announced its coordinated actions on restricting the use of 2,4,5-T It was only after an additional several months that the detailed data of the screening study were made publicly available. A centralized mechanism for handling and disseminating new information about pesticides could help alleviate this problem.

7. A mechanism should be established for restricting the use of a registered pesticide temporarily on the basis of information which implicates the chemical as a possible health hazard pending the collection of more definitive information.

If a pesticide is already in established use, the decision is particularly difficult. Long established use inevitably implies a dependence upon it by the consumer and a corresponding reluctance by the manufacturer to withdraw it from the market.

At the present time, a registration may be held in abeyance only by cancellation or suspension. Because of the serious import of these actions they are put into effect with considerable reluctance. They were not designed for situations such as the present with respect to 2,4,5-T where temporary withdrawal from use, without cancellation or suspension of registration, might have been a more appropriate action. Such an alternative course of action is not possible under present regulations.

There is need for a mechanism whereby the use of a pesticide or other chemical that may affect human health can be temporarily restricted or held in abeyance. Such action would permit the gathering of more definitive information in time for sufficient consultation to permit a decision that would protect the public health and not impose an undue economic burden on the producers, marketers, and users of a product. Coincident with the imposition of restrictions on a pesticide, a mechanism should be available for informing and educating pesticide users and applicators so as to make them more responsible agents. It is recognized that a change in the law governing pesticides would be necessary to accommodate this mechanism of a temporary restriction.

8. *There is an urgent need for a focus of responsibility in D/HEW to coordinate and monitor the toxicity and health activities related to effects of pesticides.*

Information about the health effects of a pesticide derives from a variety of sources including occupational exposures, residue monitoring, toxicological investigations, clinical experience and epidemiological studies. In the past, there has been no single focus within D/HEW which has been concerned with all of these sources of data and, more important, which has had the authority and responsibility to coordinate new investigative initiatives. The new Advisory Committee on Pesticides to the Secretary of D/HEW can be expected to serve as a source of expert advice but cannot fill the essential need for a focus of responsibility and authority at the level of the Office of the Secretary. Consideration of the functions to be fulfilled and the resources available suggests that this responsibility should be assigned to the Assistant Secretary for Health and Scientific Affairs because the various components of D/HEW concerned most with aspects of the health effects of pesticides report directly to him (National Institutes of Health, Food and Drug Administration, National Communicable Disease Center, Environmental Health Service).*

9. *Information provided in applications for registrations of pesticides should take into account not only the pesticide for which registration is sought but should identify other substances including vehicles used in formulations, "inert" ingredients, and impurities.*

Investigation of the synthesis of 2,4,5-T and examination of the manufacturing process revealed that an extremely toxic impurity, 2,3,7,8-tetrachlorodibenzo-p-dioxin, present in variable amounts in

*Since this report was written, the President established, through Reorganization Plan, the Environmental Protection Agency which is to be responsible for broad areas of regulation covering environmental matters. The Environmental Protection Agency will also have the capacity to carry out some research under its name. Hence, we recognize that some of the elements of coordination recommended in this section will be accommodated by this new agency.

commercial preparations of 2,4,5-T, may account for some of the toxicological characteristics assigned to 2,4,5-T itself. The presence of this impurity was recognized as early as 1957. However, the importance of this impurity was not generally recognized in the United States until after 1964. It appears logical that greater specificity in identifying the components and properties of the mixture of materials which are registered under a single name would increase the probability of identification of potentially toxic substances.

10. *Registration procedures should be based on toxicological studies of the particular compounds to be registered rather than extrapolations from studies on related compounds.*

Toxicological studies provided as information in behalf of 2,4,5-T registration were performed on a variety of related compounds (the free acid, several types of esters and a variety of salts). Results of these tests were regarded as being interchangeable and applicable to the related compounds. There is evidence to caution against this concept. The thorough testing of isomers, esters, salts, and related compounds is a very large and expensive task. Nevertheless, information about a potential health hazard may be incomplete unless all of the compounds to be used are tested.

INTRODUCTION

In 1964, The National Cancer Institute undertook through a contract a screening study of a number of pesticidal chemicals. Among the results of this screening study was the finding that birth defects could be provoked experimentally in rats and mice by the administration of relatively large doses of the herbicide, 2,4,5-T. By the time these results were reported, 2,4,5-T had been in common use as an herbicide for more than 20 years. Further, it had been employed along with 2,4-D as a defoliant in Vietnam since 1962, although in sizeable quantities only since 1967.

In October 1969 several agencies of Government moved in a coordinated manner to bring about restriction of the use of 2,4,5-T both within the United States and abroad (*1*). In terms of domestic agricultural use, restriction was placed on the use of 2,4,5-T on food crops pending the acquisition of further information that might permit the Food and Drug Administration to grant a tolerance. Use as a defoliant in Vietnam was restricted to non-populated areas.

For a number of reasons, it seemed wise to explore this issue in some detail. The most important of these reasons, perhaps, was the desire to examine the scientific evidence available to stand behind future policies governing the use of 2,4,5-T and to suggest directions for futher experimental research. Accordingly, a panel of experts was assembled by the President's Science Adviser to consider a number of aspects of a variety of herbicides some of which were used as defoliants in Vietnam. The present report represents their review of 2,4,5-T.

This review considers topics which are of concern to those who are faced with policy decisions for 2,4,5-T. We hope that it can serve as an example for the consideration of the health effects and safety of pesticides and other chemicals purposefully placed in the environment.

A number of issues are raised when the utility and safety of an already existing material is questioned. It is elementary but nevertheless true to say that the issues are complex. In a way, their examination can be compared to following a seemingly endless and continuously branching program. The subject of how much assurance of safety should be afforded is important.

Teratogenesis appears to be a more manageable problem than some other health effects (such as tumor production). Prediction of safety can probably be made with reasonable assurance. In addition, experiments to test a suspected substance are reasonably straightforward to conduct.

Among other problems, the purity of the chemical became an issue. In the case of 2,4,5-T separation of biological effects of the principal material from those of the impurities turned out to have unusual importance. For this reason, the resolution and accuracy of analytic methods available and used to detect 2,4,5-T and its impurities had to be evaluated. In ascertaining the probable hazard to man of an agricultural chemical, its toxicity in absolute terms must be related to the probabilities of human exposure. Residue information on 2,4,5-T therefore was explored.

Finally, there remains a series of policy questions which are at least as philosophical as they are technical, the most crucial one being how wide a margin of safety should a society adopt for itself.

The panel also touched on a narrower aspect of this question by posing an additional one. This is the practical problem, in the case of a material already in use, of how the Government should act in the interim between the time of acquisition of preliminary experimental data which reveal a chemical suspect and the performance of more definitive experiments which establish the risk.

REFERENCES

(1) Press Release on 2,4,5-T. Office of Science and Technology, October 29, 1969.

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CHEMISTRY

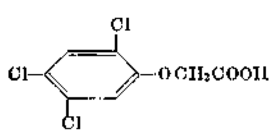
Summary

2,4,5-trichlorophenoxyacetic acid is produced commercially by a process which begins with tetrachlorobenzene as starting material. Technical grade 2,4,5-T is 90–92% pure acid. One of the important impurities, a polychlorinated dioxin, results both from impurities in the starting material and as side products of the desired reaction. A large number of esters and amine salts of 2,4,5-T have been developed as well as a variety of formulations in order to derive specific properties of volatility and solubility. About one-half of this total production can be accounted for by the 2,4,5-T acid and its n-butyl ester. The free acid is practically insoluble in water and, generally, the esters are slightly soluble. The amine salts tend to be more soluble. Among other things, penetration into the soil or leaching is a function of water solubility

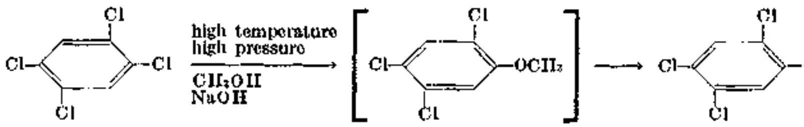
In general, 2,4,5-T residues can be expected to be relatively unstable materials in the environment. They are broken down by microbial action and by sunlight and esters are readily hydrolyzed to the free acid. Available analytic methods for detecting residues are quite sensitive. The sensitivity of gas chromatography with microcoulometric detection is about 0.01 ppm (10 ppb). Detection of residues in plant material appears to be uncomplicated by bound or complexed residues with the possible exception of residues in the peels of citrus fruits.

Chemical Synthesis of 2,4,5-T

The herbicide commonly known as 2,4,5-T or 2,4,5-trichlorophenoxyacetic acid has the chemical formula:



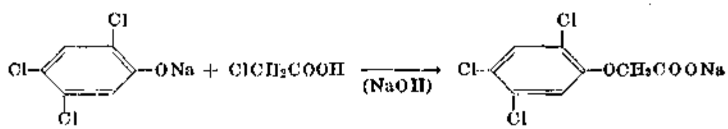
The usual starting material in the chemical synthesis of 2,4,5-T is 1,2,4,5-tetrachlorobenzene which can be reacted with methanol and sodium hydroxide in an autoclave under high temperature and pressure conditions to give the sodium salt of 2,4,5-trichlorophenol:


(2,4,5-trichloroanisole)

[1]

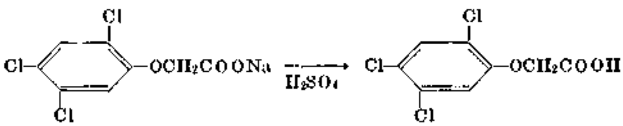
2,4,5-trichloroanisole is presumed to be an intermediate in this reaction. The high temperature and high pressure conditions of this step are also favorable for the production of a variety of other compounds from these starting materials. The choice of the proper temperature and pressure, and the control of these conditions throughout the reaction are critical for minimizing side reactions and hence impurities in the final product.

The aqueous trichlorosodium phenoxide is next reacted with chloroacetic acid under mildly alkaline conditions.



[2]

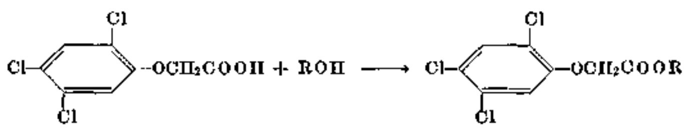
This product is then acidified with H_2SO_4 to produce 2,4,5-T.



[3]

The conditions for reactions [2] and [3] are mild compared with those required for the hydrolysis in step [1].

The acid reacts readily with a variety of alcohols to produce a large selection of esters, and with amines to produce amine salts.



Commercial Formulations of 2,4,5-T

The 2,4,5-T compounds used in commercial spray formulations include the acid, salts, and a wide variety of esters and mixtures of esters. These active components are then formulated with solvents and other ingredients to produce a bewildering array of commercial final products marketed under cryptic trade names.

2,4,5-T formulations are applied as solids or liquids. The solids usually involve 2,4,5-T esters incorporated with clays, talcs, Fullers earth, mineral silicates, or fertilizers. One of the major hazards in the use of 2,4,5-T is drift of the herbicide into areas where it is not desired due to volatility of the formulation or drift of fine particles in the wind. This hazard is reduced in one solid formulation for which the active material is deposited on polystyrene spheres with a very narrow and carefully controlled particle size distribution.

The liquid formulations require a solvent. Typical organic solvents are kerosene or diesel oil. In formulations that are mixed with water for spraying, emulsifiers and surfactants are necessary ingredients. A truly thorough attempt at estimation of the toxicity of the several commercial preparations of 2,4,5-T should take into account all of the added material, "inert" ingredients, vehicles and impurities.

2,4,5-T is most commonly employed as an ester or amine salt. (Table 1). The n-butyl ester is used as a defoliant in Vietnam in a 1:1 mixture with 2,4-D, known as Orange.

TABLE 1—*Production and value per pound of Major 2, 4, 5-T formulations—1967*

[Drawn from U.S. Tariff Commission, 24]

	Production (1000 lbs.)	Unit value per pound ($)
2,4,5-Trichlorphenoxy-acetic acid (2,4,5-T)	14,552	1.25
2,4,5-Trichlorphenoxy-acetic acid esters and salts, total	27,189	0.80
2,4,5-Trichlorphenoxy-acetic acid, n-butyl ester	19,422	0.68
2,4,5-Trichlorophenoxy-acetic acid, iso-octyl ester	4,653	1.16
All other (2,4,5-T esters and salts)	8,114	1.09

Solubilities

The solubility of the herbicide compound used may be important in determining the mechanism by which the toxic material enters the plant. It also determines the nature of the vehicle to be used in its dispersion.

The free acid form of 2,4,5-T is practically insoluble in water (*8*). The sodium salt is only soluble to a limited extent (less than 3%), a fact which precludes its use in the low volume application technique which has become more and more widely used in recent years.

The amine salts are considerably more soluble in water; however, they are somewhat difficult to prepare. Only the triethyl and trimethylamine salts can be obtained in a concentrate of 4 lbs. acid equivalent/gal. with satisfactory storage qualities. Furthermore, the marked insolubility of the calcium and magnesium salts of 2,4,5-T which are formed upon dilution with water causes nozzle clogging during application. Therefore, these formulations are not widely used. Ester formulations are most commonly used as oil-water emulsions.

The extent of leaching of various herbicide formulations was tested by applying these in solution to the tops of soil containing tubes. The depth of leaching could in general be compared with solubility. For example, the amine salt of 2,4,5-T was taken to a depth of nine inches whereas 2,4,5-T itself remains at three inches.

Aside from the herbicide itself, leaching of diesel oil, a vehicle commonly used in herbicide application, might present a threat to ground water quality. However, Lindin and Muller (cited in *13*) sprayed diesel oil at rates of 50, 250, and 500 gal./acre, and after sampling with a tube and leaching with rain water, they found only 1.5–2 ppm of diesel oil in sandy loam above 2.5 inches.

Purity of Technical Grade Material

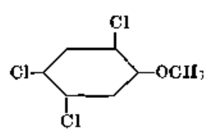
Technical grade 2,4,5-T manufactured for agricultural applications typically contains 90 to 92% 2,4,5-trichlorophenoxyacetic acid, and 8 to 10% impurities. The detailed composition of the technical material given by one producer is shown in Table 3.

TABLE 2.—*2,4,5-T product composition*

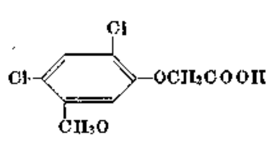
Percent by weight:	
91.0±1.0	2,4,5-trichlorophenoxyacetic acid
0.5±0.1	2,4,5-trichloroanisole
2.0±0.5	5-methoxy 2,4-dichlorophenoxyacetic acid
2.0±0.5	2-methoxy 4,5-dichlorophenoxyacetic acid
0.3±0.1	2, 4, 5-trichlorophenol
3.0±0.5	bis-2,4,5-trichlorophenoxyacetic acid
0.3±0.1	2,5-dichlorophenoxyacetic acid
0.2±0.1	SO_4
0.2±0.1	Sodium salt of 2,4,5-T
0.5±0.2	H_2O
less than 1 ppm tetrachlorodibenz-p-dioxin (TDD).	

The 1,2,4,5-tetrachlorobenzene starting material for the 2,4,5-T synthesis contains typically 3% other tetrachlorobenzene isomers and other chlorinated benzenes. These impurities can contribute to small amounts of a variety of other chlorinated products including dichlorophenoxyacetic acids and other isomers of the trichlorophenoxyacetic acid, although these products were not listed by the manufacturer as impurities (Table 3).

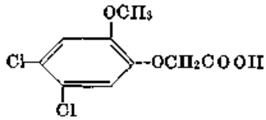
2,4,5-trichloroanisole,



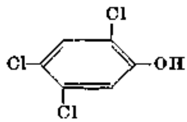
is proposed as an intermediate in step (1) of the manufacturing process. Incomplete reaction of this intermediate accounts for its presence in the final product. There is also a possibility that the 2,4,5-trichloroanisole intermediate can be hydrolyzed under the conditions of step (1) to give methoxydichlorophenoxyacetic acid as side products:



and

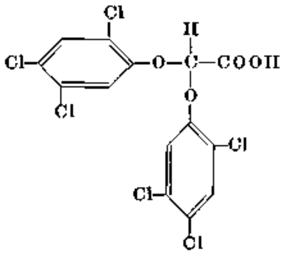


2,4,5-trichlorophenol,



results from the incomplete condensation of the sodium phenoxide with chloroacetic acid in step (2).

Bis-2,4,5-trichlorophenoxyacetic acid,



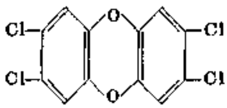
is an important impurity because the chloroacetic acid used in step (2) commonly contains some dichloroacetic acid. The 2,5-dichlorophenoxyacetic acid arises from small amounts of 1,2,5-trichlorobenzene in the tetrachlorobenzene raw material. Some sodium 2,4,5-T and sulfate ions are commonly carried into the product from the acidification (step [3]).

The standard assay for technical grade 2,4,5-T is a simple titration to give the acid equivalent of the product. On this basis most manufacturers market a product that has 97 to 98% acid equivalent. Analysis for actual 2,4,5-trichlorophenoxyacetic acid content by gas chromatography is less commonly given, although a standard method exists. The Department of Agriculture reported that the content of 2,4,5-T was often as low as 85% in commercial materials that meet the 97% acid equivalent specification. (*22*) Gas chromatography is used to monitor trace impurities in process control for step (1).

The impurities present in any commercial preparation of 2,4,5-T depend strongly on the purity of the starting materials and the reaction conditions. These can vary among various producers and among batches for a given producer.

The detailed processing methods and purification procedures also vary widely among the various producers. The variation in product analysis has not been carefully documented, and the toxicities of most of the impurities have not been tested. It is not prudent to assume that the combined toxicity of the mixture of materials in one preparation is representative of all of the preparations that are widely used.

One trace impurity produced in the manufacture of 2,4,5-T has received considerable attention. Tetrachlorodibenz-p-dioxin, commonly known at TDD,

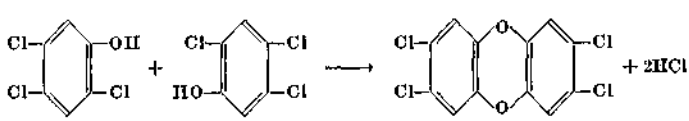


is produced as a side product under the conditions of step (1). Since this compound is known to be extraordinarily toxic, the history of the recognition and identification of this impurity is particularly interesting. Elucidation seems to have come from two principal independent sources.

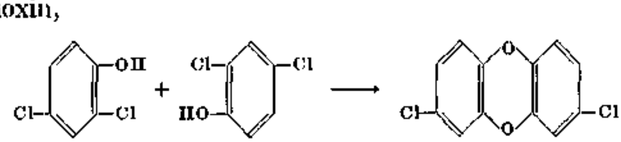
The sporadic occurrence of an impurity in specific lots of animal feed in 1957 brought significant losses to poultry farmers in southeastern and central U.S. Chicks were afflicted with hydropericardium, and suffered gross kidney and liver damage. Empirical tests for the presence of the "chick edema factor" were announced by the the FDA in 1966 (*11*). The test used electron capture gas chromatography to examine a fraction of a sample isolated from the fat. The presence of a specific set of peaks with given retention times indicated the presence of the factor. The empirical test is used as a screening procedure. When the presence of the factor is indicated by gas chromatography, a chick bioassay test is required for confirmation. The absence of the factor is a requirement of the edible tallow used for making fatty acids that go into food emulsifiers.

The chick edema factor was identified by X-ray crystallography as 1, 2, 3, 7, 8, 9-hexachlorodibenz-p-dioxin in 1967 by Wootton of Proctor and Gamble (*25*) from 4 mg of toxic material extracted from 100 lbs. of contaminated fat obtained from trade sources. The toxicity of this compound and related compounds was reported by representatives of the Food and Drug Administration in 1968 (*11*).

A clue to the possible origin of the dioxins was suggested in their synthesis by condensation (*21*). Two molecules of 2, 4, 5-trichlorophenol condense directly to give TDD:



Two molecules of 2, 4-dichlorophenol condense to give the dichlorodibenz-p-dioxin,



and mixtures of various isomeric chlorinated phenols give mixed chlorinated dioxins.

The FDA group reported the following toxicities:

TABLE 3.—*After Higginbothan, et al, (12).*

Reactants	No. of Cl atoms in dioxin	Chicken embryo bioassay	
		μg/egg	percent mortality
2,4-dichlorophenol	2	500	70
Chlorinated dibenz-p-dioxin [1]		0.05	100
2,4,5-trichlorophenol	4	0.25	100
2,4,6-trichlorophenol	4	5.0	50
2,3,4,6-tetrachlorophenol	6	1.0	100
Pentachlorophenol	8	5.0	27
Reference toxic fat components	Mixture	3.0	100

[1] Mixed 3 & 4 chloro species.

The tetrachloro species, which will be the important product from the condensation of 2,4,5-trichlorophenol, requires only 0.25 μg for 100% mortality in the chick embryo bioassay. A mixture of the tri- and tetrachloro species was reported in one study to be more toxic than the tetrachloro species alone (*12*). However, more recent unpublished observations by the same authors have pointed toward a singularly high degree of toxicity of the four chlorine members of the family. The conditions required for the production of the tetrachlorodibenz-p-dioxin, TDD, are present in step (1) of the commerical 2,4,5-T synthesis, so this material can be present in the original herbicide. Members of the family of dioxins have been recognized in a variety of environmental situations. The origins of these are not clear in every case (*23*).

The second source of information about the toxicity of dioxin compounds came from observations of occupational exposures in plants manufacturing 2,4,5-T. These are reviewed in another section of this report. One of the diseases reported was a particularly refractory form of skin rash known as chloracne. This was also seen in workers involved in the production of other compounds, The first report of chloracne in 2,4,5-T plant workers was in 1957 (*14*). The authors in this case suggested that the dioxin impurity may have been the factor which caused the chloracne.

In 1964, the Dow Chemical Company (*6*) attempted to increase the production of 2,4,5-T by changing the reaction conditions. Plant operators became affected with chloracne. The Dow Chemical Company closed their facility and, early in 1965, alerted other manufacturers of their problem. The active agent was identified as 2,3,7,8-tetrachlorodibenz-p-dioxin. In addition, an analytical method for its detection was standardized and various methods for removing the impurity were devised. By 1965, sufficient technology was available to allow the manufacture of 2,4,5-T and 2,4,5-trichlorophenol containing no more than 1 ppm of 2,3,7,8-tetrachlorodibenz-p-dioxin. By 1966, a new Dow plant, conforming to those specifications, was put into operation. TDD levels in technical grade 2,4,5-T from another manufacturer are listed year by year in Table 4. Dioxin levels in 2,4,5-T currently manufactured are reported not to exceed 1 ppm.

TABLE 4.—*History of TDD concentration in technical 2,4,5-T*

[Analysis of material from one manufacturer]

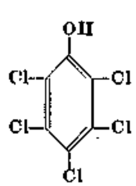
Date	ppm, TDD
1958	11
1959	11
1960	8
1961	5
1962	10
1963	11
1964	12
1965	5–32
1966	3–18
1967	1–25
1968	1–25
1969	<1

Analytical Methods

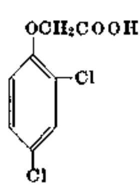
1. *Standard Procedures.*

A typical method for the analysis of herbicide residues in oil seed crops has been described by G. Yip of the FDA (*27*). The method involves extraction of 50 grams of oil with sodium bicarbonate solution, acidification, and extraction of the herbicides with chloroform. The herbicide residues in the acid form are then esterified with diazomethane to produce the methyl esters which are finally analyzed by programmed temperature gas chromatography. Both electron capture and microcoulometric detection schemes are used. The microcoulometric detector consists of a quartz tube condensation chamber where the herbicide is pyrolyzed at 800° C in the presence of oxygen. The HCl formed is carried into a microcoulometric titration cell where the chloride is titrated with silver ion. The sensitivity of this analytical scheme is about 0.01 ppm.

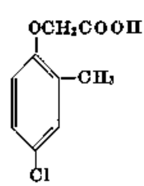
A gas chromatogram obtained from cottonseed oil treated with a mixture of seven herbicides each at 0.02 ppm is shown in Fig. 1. The seven herbicides used in this test of the method included:



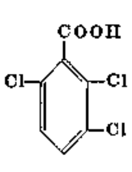
PCP



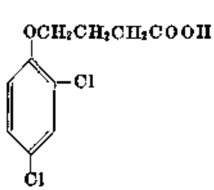
2,4-D



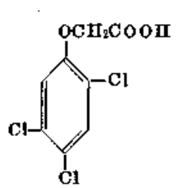
MCPA



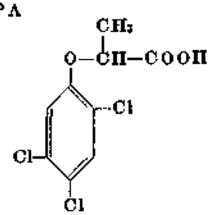
2,3,6-TBA



2,4-DB



2,4,5-T



2,4,5-TP

420-165 O - 71 - 4

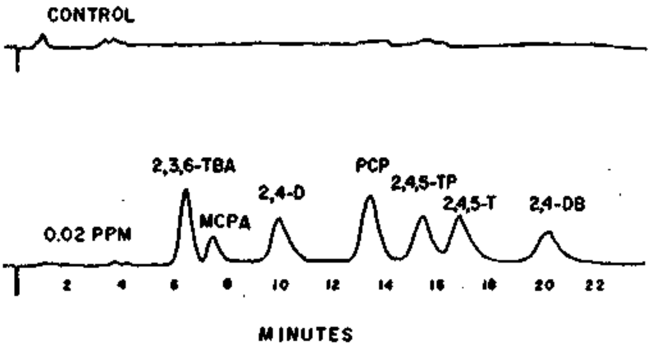


FIG. 1—Gas chromatogram of the 0.02 ppm sample of herbicide mixture and a control. Both curves represent 35 g of cottonseed oil.—After Yip (*27*).

All of these residues are well separated and readily detected after 22 minutes. Recoveries of these residues from the vegetable oil samples were better than 90% in the 0.02 to 0.08 ppm range. At the time this method was developed, samples of commercial oils including cottonseed, corn, safflower, soybean, peanut, and olive oils were analyzed for residues of these herbicides. No peaks were discerned in the chromatogram of any sample.

Although the relative retention time of 2,4,5-trichlorophenol, a common formulation impurity and one of the metabolic decomposition products of 2,4,5-T was not reported, it should be less than that of pentachlorophenol, and thus amenable to detection by this scheme. (*9*)

Yip has also developed a paper chromatographic method which allows qualitative determination of the same esters (*28*). A workable separation of the methylated acids was obtained using 35% dimethyl formamide in ether as the immobile phase and 2.2,4-trimethyl pentane as the mobile phase. The sensitivity of the paper chromatographic technique is 0.1 ppm.

The procedure recommended by Yip (*26*) for analysis of residues on green crops involves high speed of blending finely chopped greens with a mixture of H_2SO_4, ethanol, petroleum ether and ethyl ether. The solids are removed by centrifugation and the liquid extracted with sodium bicarbonate and chloroform, as for samples of vegetable oils. The procedure for wheat involves first grinding the wheat kernels in a mill to pass a 30-mesh screen. The ground wheat is then blended with 95% ethanol at high speed. The solids are separated by centrifugation and the residues extracted from the supernatant liquid as above.

2. *Bound Residue*. The above methods are adequate for the analysis of 2,4,5-T residues that are in the form of the free acid or various esters. The detailed analytical method provides steps for the separate examination of the residues present in free acid and ester forms although the esters are rarely found as residues in crops.

An issue of primary concern, however, is whether there can exist in crops residues of 2,4,5-T chemically bound such that they are not extracted and detected by the standard analytical method. Crosby (*4*) showed that a water soluble, ether insoluble hydrolyzable form of 2,4-D is present in bean plants treated with 2,4-D. It has been reported that 2,4-D as well as other herbicides can be converted to coenyzme-A thioesters (*3*); this is a possible form for the "bound" material. It has also been suggested that 2,4-D may be bound as 2,4-dichlorophenoxy acetylglucoside (*15*). 2,4,5-T could presumably undergo analogous reactions to give the corresponding bound forms.

The analytical method that has been used in most plant residue studies provides no information on the fraction that may be present in bound form. In a study of 2,4-D residues in forage and milk, the residue levels shown in Tables 5 and 6 were found by the standard analytical method (*16*) (*29*).

TABLE 5.—*Residue of 2,4-D in forage samples from pastures sprayed with butyl ester or 2-ethylhexyl ester of 2,4-D at a rate of 2 lbs/acre. Average of 1 to 5 determinations.* —*After Klingman et al*, (*16*)

Date, May	2,4-D residues, ppm, from				
	Butyl ester			2-ethylhexyl ester	
	Acid	Butyl ester	Ethyl ester	Acid	Ethylhexyl ester
6[a]	0	0	0	trace	0
6[b]	58.3	0.10	0.04	36.6	11.8
8	19.2	0.18	0.02	38.6	6.7
10	9.0	0.03	0.03	23.8	2.0
13	5.0	0	0	13.7	1.4

[a] Sampled just before spraying.
[b] Sampled within ½ hr after spraying.

Residues detected by the standard method were largely in the form of the acid rather than the original esters. Some degradation of the butylester to the ethyl ester apparently occurred. Essentially no trace of residue was found in milk from dairy cows grazing in pastures sprayed with 2,4-D (Table 6).

TABLE 6.—*Residue of 2,4-D in milk, as determined by two methods of analysis, from dairy cows grazing in pastures sprayed with esters of 2,4-D at 2 lb/A on morning of May 6, 1963. Samples taken from morning milkings only.*[a]—*After Klingman, et al* (*16*).

Date, May	Days after spraying	2,4-D residues in milk, ppm from			
		butyl ester		2-ethylhexyl ester	
		FDA	SWRI	FDA	SWRI
6	[b]0	0	0	0	0
7	1	0.01	0.01	0.01	0.03
8	2	.01	.01	.01	.02
9	3	.01	.01	.01	<.01
10	4	.01	.01	<.01	.01
11	5	.01	.01	<.01	.01
13	7	.01	.01	.01	.01

[a] Cows were kept in pastures continuously, except during milking. All data were rounded to nearest 0.01 because this is about the practical limit of precision of the methods used. FDA=Food and Drug Administration and SWRI=Southwest Research Institute.
[b] Milk was sampled in the morning before pastures were sprayed.

The presence of bound 2,4-D in the grass samples from the pasture sprayed with the ethylhexyl ester of 2,4-D was also checked. To demonstrate the presence of bound 2,4-D, the acid and ester were extracted from the forage samples as usual. The filtrates were then extracted three times with ethyl ether to remove any residual 2,4-D acid and finally heated on a steam bath for 16 hours under highly acidic conditions. Presence of bound 2,4-D would be indicated if amounts of 2,4-D found in the hydrolyzates were significantly higher than those found in the filtrates before hydrolysis. Results are shown in Table 7.

TABLE 7.—*Ppm of 2,4-D in grass of ethylhexyl ester-sprayed pasture, free and bound. (29)*

Days after spraying	Initial extraction	Filtrates before hydrolysis	Hydrolyzate
Control	40	0.063	(1)
2	50	0.430	(1)
4	20	0.246	0.64
7	19	0.230	1.31

[1] Trace.

The presence of small amounts of bound 2,4-D is shown by the value obtained from the hydrolyzates. There is a trend toward increasing formation of bound 2,4-D with time. No bound residues could be detected in milk in these experiments. The results from these experiments suggest that although bound residues were detected, most of the residues were present as acid or ester and there would not have been a major discrepancy between the results of the standard method and the actual total residue concentration.

There is evidence for the binding of residues of 2,4,5-TP (Silvex), the phenoxy propionic acid analog of 2,4,5-T. A careful study of 2,4,5-TP residues in orange peel, however, suggests that a rather high percentage of the growth regulator residues can be present as insoluble "bound" materials *(10)*. 2,4,5-TP fractions could be separated on the basis of solubility into four types: free acid, ester (hexane soluble), complexed acid (water soluble, hexane insoluble), and heat-labile complexed acid (heat-released). It was possible to detect the water soluble complexed acid as the methyl ester after basic hydrolysis and identification. The labile form was released after heating for 24 hours at 104–105° C. The concentrations of these various forms during a 13-week period are shown in Fig. 2.

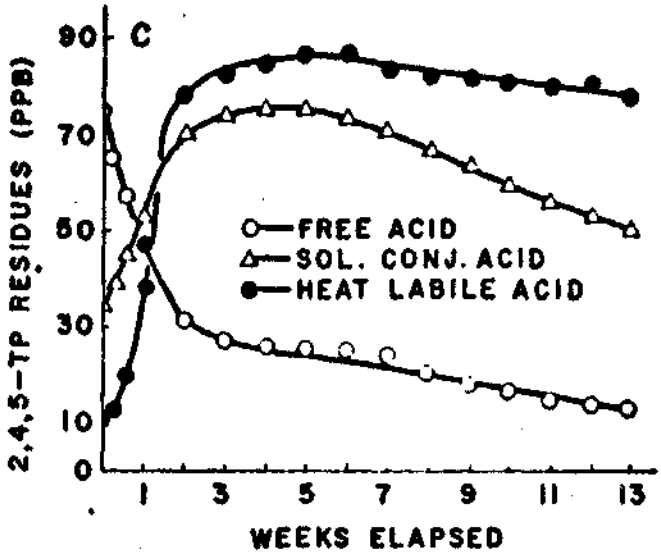


FIGURE 2.—After Hendrickson and Meagher (*10*).

These results suggest that the original 2,4,5-TP amine salt is first converted to the free acid. This acid then is converted to a soluble conjugated form. However, it appears that the insoluble complexed form ultimately becomes a major fraction of the total residue. The results of this and other studies of herbicide residue in citrus (*7*), (*18*) emphasize that the residues of halogenated phenoxyacetic acids may take several forms in plant tissues. Unless an effort is made to release the bound residues, the standard analytical scheme does not provide a suitable basis for estimating the total residue concentration.*

CHEMICAL STABILITY OF 2,4,5-T

1. *Photochemical Degradation.*

Ultraviolet light has been shown to alter drastically the structure of many pesticides under laboratory conditions. Knowledge of whether sunlight under "field conditions" can also affect these transformations is critical. The detailed chemistry and toxicology of the resulting decomposition products could be significant to agriculture and the public health.

Although the photochemistry of 2,4,5-T has not been investigated, considerable effort has been expended to elucidate the pathway for photochemical decomposition of 2,4-D. It might be expected that these compounds react in a similar way. Several studies indicate that

*It is possible that only the pure acid and ester residues produce physiological effects on man and animals, while the bound forms are inert and non-toxic. The standard analytical scheme would then provide a useful measure of the effective concentration of residue in toxic form. The relative physiological effects of bound and unbound residues are unknown.

2,4-D is, in fact, degraded in the presence of ultraviolet light to phenolic products (*19*), (*1*), (*2*). Some evidence is available which indicates that sunlight also detoxifies 2,4-D as Penfound and Minyard (*20*) showed that malformations of water hyacinth and kidney bean plants were more severe in shaded plants than in those receiving full sun. The most recent photochemical study (*5*) is the first to compare the transformations induced by sunlight and ultraviolet light.

Photolysis in the presence of sodium bicarbonate (2×10^{-3} *M*) and water leads to several isolable products: 2,4-dichlorophenol, 4-chlorocatechol, 2-hydroxy-4-chlorophenoxy-acetic acid, and the major product, polymeric humic acids.** Although the transient 1,2,4-benzenetriol could not initially be isolated, it could be trapped if oxidation of this intermediate was inhibited by carrying out the photolysis in the presence of excess sodium bisulfite.

These results suggest the following sequence:

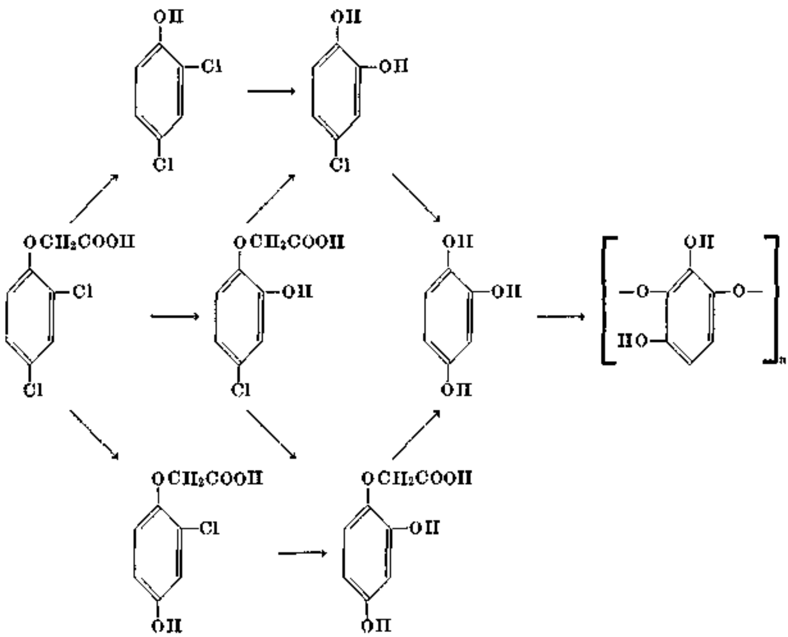


FIGURE 3 Proposed mechanism of 2,4-D photodecomposition After Crosby (*4*)

Analogous results were obtained from irradiation in sunlight.

2. Hydrolysis.

The esters of 2,4,5-T are readily hydrolyzed to the free acid under acidic or basic conditions. The esters are rarely found in residues in crops. The rates of hydrolysis of course depend on the detailed stereochemistry of the ester substituent. The rate of hydrolysis is reduced as the bulk of the ester group is increased close to the oxygen linkage.

**No attempt was made to determine the fate of the two carbon fragment.

3. Thermal Stability.

2,4,5-T is stable with respect to thermal degradation to at least its melting point of 153° C.

4. Biochemical Degradation.

2,4,5-T is slowly degraded in soil which contains organic matter under warm, moist conditions. The generally accepted half-life for this process is several weeks. However, the decay in 2,4,5-T concentration is usually not a simple first order process since the population of organisms that metabolize 2,4,5-T increases in the presence of 2,4,5-T. In areas pre-treated with 2,4,5-T, the lifetime for degradation is significantly reduced. Three months appears to be the accepted length of time for 2,4,5-T residues in soils to disappear completely. The rate of disappearance appears to be independent of the quantity of application. Some of the organisms responsible for 2,4,5-T biodegradation have been isolated and identified. (*17*) The subject of residues is more fully examined in Section VI.

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USES AND SIGNIFICANCE

Summary

2,4,5-T has become important in land and waterway management. It has been very useful for brush and weed control. A result has been a growing dependence upon it. The Government itself has encouraged the use of 2,4,5-T through an agricultural cost sharing program.

Nearly 8 million acres were treated with 2,4,5-T in the United States in 1964. The major use was brush control on rangelands, pastures, and rights-of-way. Other uses were on certain food and non-food crops, in aquatic weed control and in forestry.

In 1964 and 1966 almost half of the 2,4,5-T was used on rights-of-way. Over two million acres of rights-of-way were treated in 1964 which is one quarter of the total area treated with this herbicide.

Civilian uses of 2,4,5-T dropped nearly 50% from 1964 to 1966. More recent, unpublished information from the Department of Agriculture suggests that this trend continued through 1968 but may have begun to reverse itself within the past year. This decrease accompanied price increases and shortages of supply associated with the demand for 2,4,5-T as a defoliant and tactical weapon in Vietnam. If acreage decreased proportionately, about four million acres would have been treated in 1966.

To some extent, other herbicides can be substituted for 2,4,5-T (notably 2,4-D). If all alternative herbicides were available the banning of 2,4,5-T would appear to lead to an additional cost of nearly $52 million in land and waterway management or nearly a 100% increase over the current expenditures. These figures assume practices designed to achieve the current level of management and agricultural production. If other phenoxy herbicides are also banned, the additional costs from elimination of 2,4,5-T alone would amount to $172 million or over three times the present investment. Agricultural costs are estimated to rise $32 million and $44 million, respectively, under the two assumptions, while costs of right-of-way management would rise $12 million and $75 million, respectively.

Agricultural production has become dependent upon the use of herbicides. Their use in the United States has increased rapidly during the past few years. They are employed as substitutes for the more costly practices of hoeing, cultivating, mowing, chopping, burning, and various other cultural practices for the control of weeds.

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One of the principal uses of the herbicide, 2,4,5-T, is for control of weeds and brush on pasture and rangeland. Large quantities are also used to control brush along roadways and under powerlines. The principal crop use of 2,4,5-T is on hay and pasture.

In forest production, 2,4,5-T has proved useful for selective weed control. 2,4,5-T acts upon deciduous hardwoods leaving the conifers with little injury. This treatment has been helpful in releasing conifers from deciduous hardwood competition in mixed stands.

Production

Total herbicide production in the United States has increased rapidly:

*1960	75,000,000 pounds (*3*)
1965	220,000,000 pounds (*8*)
1968	403,000,000 pounds (*12*)

For 2,4,5-T (acid, esters and salts), production has increased as follows:

1960	7,900,000 pounds (*7*)
1965	13,500,000 pounds (*10*)
1966	18,100,000 pounds (*10*)
1967	27,200,000 pounds (*10*)
1968	42,500,000 pounds (*12*)

A portion of this production is exported and a portion shipped abroad for military use.

Uses

1. *Domestic.*

a. *Farm use.*

In 1964, of the estimated 13,000,000 pounds of 2,4,5-T produced in the United States, only 13 percent or about 1,655,000 pounds were used in agriculture (Table 1). About 40 percent of the quantity employed in agriculture was used for weed control along fence rows, ditch banks, farm roadways, and other non-crop uses. The remaining 60 percent or 979,000 pounds was employed on crops (including hay, pasture and rangeland).

Since 1964, the use on farms has been decreasing. In 1966, 760,000 pounds were applied which is less than 50% of the 1964 amount (*13*). Use on hay, pasture, and rangeland declined 35 percent, and other crop use decreased by 31 percent, whereas non-crop use decreased about 84 percent.

b. *Forestry, Rights-of-way, Aquatic Weeds and Lawn and Turf.*

In 1964, about 888,000 pounds of 2,4,5-T were used in private nonfarm forest management for control of undesirable trees and brush (Table 1); in 1966, this declined to 408,000 pounds (Table 3).

An estimated 4,368,000 pounds were applied to rights-of-way, roadways, fire lanes, and similar areas for tree and brush control in

*Changes in the method of reporting after 1960 make this figure difficult to compare with later figures.

1964 (Table 1); in 1966, this had decreased to 2,315,000 pounds (Table 3).

About 162,000 pounds were applied to aquatic habitats in 1964 for weed control on about 81,000 acres (Table 1); in 1966, this had dropped to 75,000 pounds (Table 3).

TABLE 1—*Estimated use of 2,4,5-T in the United States, 1964 (13)*

Use category	Land treated per 1,000 acres	Quantities of active 2,4,5-T applied per 1,000 pounds	Proportion of total quantity applied (Percent)
Farm use:[1]			
Hay, pasture, and rangeland	2,441	581	7
Other farm use	[2] 1,010	1,074	12
Total farm use	3,451	1,655	19
Non-farm use:			
Federal Government agencies [3]	296	656	7
Lawn and turf treatment [4]	1,200	600	7
Rights-of-ways [5]	2,175	4,368	49
Private non-farm forests [6]	430	888	10
Aquatic treatment [7]	81	162	2
Other uses [8]	306	583	6
Total non-farm use	4,488	7,257	81
All uses	7,939	[9] 8,912	100

[1] Based on "Quantities of Pesticides Used by Farmers in 1964," AER 131. Farm data excludes Alaska and Hawaii. In some farm uses, all acres in a field were reported treated while only spots actually received 2,4,5-T, thus making the rate per acre seem low.
[2] Sum of the acres of all crops, except hay, pasture, and rangeland treated, plus an acreage estimate for noncropland receiving treatment. The acreage of noncropland was estimated by allocating the quantity of 2,4,5-T used for such purposes at the rate of 2 pounds per acre.
[3] Based on 1969 usage of the Departments of Agriculture, Interior, and Defense; and 1951–69 average usage by the Tennessee Valley Authority.
[4] Based on estimated 500,000 acres of turf and 700,000 acres of lawns treated. Estimates based on "Extent and Cost of Weed Control with Herbicides and an Evaluation of Important Weeds," ARS 34-102; and unpublished data.
[5] Based on sources cited in footnote 4 with rate of application same as for federally treated rights-of-way. Does not include rights-of-way treated by Federal agencies.
[6] Estimated at 4 times the acreage treated and quantities of pesticides applied to public forests.
[7] Based on sources cited in footnote 4 and rates used on federally treated waterways.
[8] Includes governments other than federal and any other usage.
[9] Based on table 28 of the Pesticide Review 1969, Ag. Cons. Stab. Service.

TABLE 2.—*Farm use of 2,4,5-T on crops, by category of use, United States, 1964 and 1966 (13)* [1]

Use category	Active ingredients per 1,000 pounds		Acres treated per 1,000 acres		Percentage of planted acres treated with 2,4,5-T (percent)	
	1964 [2]	1966 [3]	1964 [2]	1966 [3]	1964 [4]	1966 [5]
Hay, pasture, and rangeland	581	379	2,441	861	0.4	0.1
Corn	72	58	255	337	0.4	0.5
Wheat	16	26	55	59	([6])	0.1
Sorghum	5	6	48	18	0.3	0.1
Rice	([7])	23	([7])	16	([7])	0.8
Other grains	264	34	196	99	0.4	0.2
Other crops	41	127	117	175	0.1	0.2
All crop usage	979	653	3,112	1,565	0.3	0.2

[1] Does not include Alaska and Hawaii. Use in 1964 generally reflects current practices. Use in 1966 was unusually small and not representative of current practices because of domestic shortages due to increased military purchases.
[2] Revised estimates based on Quantities of Pesticides Used by Farmers in 1964. U.S. Dept. Agr., Agr. Econ. Rpt. No. 131, Jan. 1968.
[3] Data from the ERS Pesticide and General Farm Survey, 1966.
[4] Acres treated as a percent of acres grown as reported in Stat. Bul. 384 and *Agricultural Statistics* 1968.
[5] Acres treated as a percent of acres grown as reported in Crop Production, 1967. U.S. Dept. Agr., Cr. Pr. 2-2(7-67).
[6] Less than one-tenth percent.
[7] Included in other grains in 1964 only.

TABLE 3.—*Quantities of 2,4,5-T used and percentage change in use, United States, 1964 and 1966 (13)*

Use category	Quantities of active 2,4,5-T applied per 1,000 pounds		Reduction from 1964 usage in percent
	1964 [1]	1966 [2]	
Farm use: [1]			
Hay, pasture, and rangeland	581	[2] 379	35
Other farm use	1,074	[2] 381	65
Total farm use	1,655	[2] 760	54
Nonfarm use:			
Federal Government agencies	656	[3] 450	31
Lawn and turf treatment	600	[4] 300	50
Rights-of-way	4,368	[5] 2,315	47
Private nonfarm forests	888	[6] 408	54
Aquatic treatment	162	[7] 75	46
Other uses	583	[8] 292	50
Total nonfarm uses	7,257	3,840	48
All uses [9]	8,912	[9] 4,600	48

[1] See table 1.
[2] Data from 1966 ERS Pesticide and General Farm Survey, U.S. Dept. of Agric.
[3] Based on decreases in Forest Service spending on timber improvement, and cooperative programs with states.
[4] Assuming 50 percent shift to dicamba.
[5] Residual after providing for other requirements.
[6] Based on same rate of reduction as total farm use.
[7] Based on same rate of reduction in 2,4,5-T use on hay, pasture, and rangeland.
[8] Assuming 50 percent of the 1964 use of 2,4,5-T was retained.
[9] Based on tables 2 and 3.

About 600,000 pounds of 2,4,5-T were applied to lawns and turf in 1964 (Table 1); in 1966 this had fallen to 300,000 pounds (Table 3).

c. *Fruit.*

Small quantities (less than 10,000 pounds) of 2,4,5-T were used as a growth regulator to thin fruit in the spring and hold it on the tree until harvest in the fall (*9*).

d. *Federal Agencies.*

The DOD, USDI, and USDA are the chief Federal agencies that use 2,4,5-T on the lands they manage. During 1964 in continental United States the Federal agencies used a total 656,000 pounds (Table 1).

In 1969 the DOD treated 162,000 acres with 221,000 pounds of 2,4,5-T in continental United States (*16*). The majority of that used by the Department of Defense was by the U.S. Army Corps of Engineers Civil Works Program for the control of aquatic weeds in navigable waters, in and around reservoirs, on stream banks and rights-of-way. The use of heribcides on DOD installations is generally restricted to small areas such as training sites, lawns, fringes of air fields, fence rows and ammunition storage areas.

During 1969, the USDI treated 52,900 acres of rangeland with 38,200 pounds of 2,4,5-T; in addition 2,200 acres of aquatic habitats were treated with 5,600 pounds (*17*).

In 1969, the USDA treated 107,000 acres of timberland with 221,000 pounds of 2,4,5-T. In addition, 34,000 acres of rangeland and

2,000 acres of rights-of-way were treated with 94,000 pounds (unpublished figures).

e. *Economic Importance.*

It is estimated that herbicides contribute significantly to the profits of agriculture. For example, if phenoxy herbicides (including 2,4,5-T) were not available, the net loss to rice producers in the United States has been estimated at $7.6 million per year. This represents some 2% of the farm value of all of the rice produced in the United States per year or about 25% of the value of production from acres treated with phenoxy herbicides (*13*).

2,4,5-T has a major use for control of brush under transmission lines. It is estimated (*13*) that the control of brush with 2,4,5-T on rights-of-way costs about $6.50/acre. Other chemicals which could be substituted for 2,4,5-T on most of this acreage would cost $42/acre. Manual control costs about $44/acre.

The loss to agriculture if 2,4,5-T were no longer available would be about $32 million (based on normal use in 1964 (see Table 4)). Because of military demands for 2,4,5-T in Vietnam, the quantity used in agriculture has declined by about one-half (Table 3).

It has been estimated that the increased costs of alternatives for 2,4,5-T for nonfarm use were about $20 million for 1964 (Table 4). Between 1964 and 1966 these uses were also cut in half (Table 3).

If 2,4,5-T were not available and other phenoxy herbicides could not be used as alternatives, it is estimated that the domestic cost would be approximately $172 million (about $44 million for farm use and $128 million for nonfarm use (Table 5).

f. *Registered Uses.*

The registered uses of 2,4,5-T are shown in Table 6 for food-crop use and in Table 7 for non-food crop use (*14*).

TABLE 4.—*Economic effects of banning 2,4,5-T, if other phenoxy herbicides and all other registered herbicides could have been used, United States, 1970 (13)*

Use category	Estimated acres treated with 2,4,5-T[1]	Acres that could be treated with alternative	Acres requiring additional cultural practices	Cost of 2,4,5-T and application	Cost of alternative herbicides and application	Cost of additional cultural practices	Net increased cost of using alternative[2]
	1,000 acres	*1,000 acres*	*1,000 acres*	*1,000 dollars*	*1,000 dollars*	*1,000 dollars*	*1,000 dollars*
Farm use:							
Hay, pasture, rangeland[3]	2,441	488	1,953	4,052	1,781	32,443	30,172
Other farm use[4]	1,010	879	774	3,968	3,245	2,486	1,763
Total farm use	3,451	1,367	2,727	8,020	5,026	34,929	31,935
Nonfarm use:							
Federal Government[5]	296	281	15	3,287	3,765	735	1,213
Lawn and turf[6]	1,200	1,200	60	2,850	3,720	240	1,110
Rights-of-way[7,8]	2,175	1,958	217	33,772	36,028	9,548	11,804
Private nonfarm forests[7,9]	430	387	43	3,738	4,411	3,363	4,036
Aquatic areas[7,10]	81	72	8	608	760	240	392
Other[11]	306	291	15	2,219	3,026	375	1,182
Total nonfarm use	4,488	4,190	358	46,474	51,710	14,501	19,737
Total all uses	7,939	5,557	3,085	54,494	56,736	49,430	51,672

[1] From Table 1.
[2] Cost of alternative herbicides and application plus cost of additional cultural practices less cost of 2,4,5-T and application.
[3] The alternative herbicide was 0.5 lbs. silvex and 1 lb. 2,4-D on 20% of the acres treated. Cultural treatments on the other 1,953,000 acres include renovating a third of the acres at $15.66 an acre; then bulldozing 72% of the remaining two-thirds at $23.16 an acre, and mowing the other 28% at $1.50 an acre.
[4] Most acres of individual crops treated with 2,4,5-T in 1964 could have been treated with 2,4-D. Silvex was applied with 2,4-D on the noncropland. Rates of 2,4-D use on crops were assumed to be the 1966 average rate of all phenoxy usage for that crop except for other grains where 2,4-D was used at the same rate as 2,4,5-T. Supplemental hand or mechanical control was used on some of the corn, sorghum, and noncropland. Additional acres of wheat, other small grains, and other crops were grown to maintain production in spite of yield losses. In rice production, additional fertilizer and a change in the crop rotation were required to maintain production and offset loss in quality.
[5] Based on 1969 use by the Departments of Agriculture, Interior, and Defense; and TVA. Two lbs. each of 2,4-D and silvex were substituted for 2,4,5-T on 95% of all acres treated in 1964. Remaining acres required additional cultural, mechanical, and manual controls averaging $40.00 per treated acre.
[6] All acres could have been treated with 0.5 lbs. each of 2,4-D and silvex, but $4.00 of manual work was also required on 5% of all acres.
[7] Two lbs. each of 2,4-D and silvex were used as substitutes for 2,4,5-T on 90% of all acres.
[8] Ten percent of the acres required hand cutting at $44.00 per acre.
[9] Ten percent of the acres were mowed, hand cut, or undesirable species girdled at a cost of $78.21 per acre.
[10] The remainder required cleaning with a drag line at $30.00 per acre for treated acres.
[11] Two pounds each of 2,4-D and silvex were used to replace 2,4,5-T on 95% of these acres. The remaining acres required mechanical control by hand or with machines at $25.00 per acre on which used.

TABLE 5.—*Economic effects of banning 2,4,5-T if no other phenoxy herbicides could have been used but all other registered herbicides could have been used, United States, 1970 (13)*

Use category	Estimated acres treated with 2,4,5-T [1]	Acres that could be treated with alternative	Acres requiring additional cultural practices	Cost of 2,4,5-T and application	Cost of alternative herbicides and application	Cost of additional cultural practices	Net increased cost of using alternative [2]
	1,000 acres	*1,000 acres*	*1,000 acres*	*1,000 dollars*	*1,000 dollars*	*1,000 dollars*	*1,000 dollars*
Farm use:							
Hay, pasture, and rangeland [3]	2,441	----------	2,441	4,052	----------	40,551	36,499
Other farm use [4]	1,010	628	618	3,968	6,386	5,167	7,585
Total farm use	3,451	628	3,059	8,020	6,386	45,718	44,084
Nonfarm use:							
Federal Government [5]	296	83	213	3,287	3,901	10,863	11,477
Lawn and turf [6]	1,200	1,200	1,200	2,850	2,310	4,800	4,260
Rights-of-way [7]	2,175	1,631	544	33,772	84,812	23,936	74,976
Private nonfarm forests [8]	430	----------	430	3,738	----------	33,630	29,892
Aquatic areas [9]	81	----------	81	608	----------	2,430	1,822
Other [10]	306	----------	306	2,219	----------	7,650	5,431
Total nonfarm use	4,488	2,914	2,774	46,474	91,023	83,309	127,858
Total all uses	7,939	3,542	5,833	54,494	97,409	129,027	171,942

[1] From Table 1.

[2] Cost of alternative herbicides and application plus cost of other treatments less cost of 2,4,5-T and application.

[3] Cultural treatments include renovating a third of the acres at \$15.66 an acre; then bulldozing 72% of the remaining two-thirds at \$23.16 an acre, and mowing the other 28% at \$1.50 an acre.

[4] Weeds on some acres of most crops treated with 2,4,5-T in 1964 could have been controlled with nonphenoxy herbicides. Important chemical substitutes used include dicamba, atrazine and oil on crops and picloram on noncropland. Supplemental hand or mechanical control was also required on some corn, sorghum, small grains, and noncropland. Additional acres of wheat, other small grains, and other crops were grown to maintain production in spite of yield losses. In rice production additional fertilizer and a change in the crop rotation were required to maintain production and offset loss in quality.

[5] Based on 1969 used by the Departments of Agriculture, Interior, and Defense; and TVA. Two pounds of picloram with a drift reducing adjuvant were substituted for 2,4,5-T on 75 percent of federally maintained rights-of-way. All other acres required cultural, mechanical, and manual control averaging \$51.00 per acre.

[6] All acres can be treated with 0.5 pound dicamba but supplemental manual work costing \$4.00 per acre was required on all acres.

[7] Two pounds of picloram with a drift reducing adjuvant were substituted for 2,4,5-T on 75 percent of all acres. The remainder required hand cutting at \$44.00 an acre.

[8] All acres had to be mowed, hand cut, or undesirable species hand girdled at a cost of \$78.21 per treated acre.

[9] All acres needed to be mechanically cleaned with a drag line at \$30.00 per acre treated.

[10] All acres required mechanical control by hand or with machines at \$25.00 per acre.

USDA Summary of Registered Agricultural Pesticide Chemical Uses
2,4,5-Trichlorophenoxyacetic Acid

(Principal formulations: EC esters; amine salts; Type pesticide: Herbicide and plant regulator)

Use	Tolerance (ppm)	Dosage	Limitations
		lb. actual/A.	
Pastures: Grasses	Extended	3	Heavy brush. Apply when in full leaf and after grass is well established.
		1	Light brush. Apply when leaves are fully expanded.
Rangeland clearance	Extended	4	Apply in spring by airplane when brush is in heavy foliage stage (40-90 days after leaves unfold).
Apples (McIntosh)	Extended	20 ppm spray (acid equivalent).	Preharvest drop control. Apply a single application 4-5 days before drop normally begins.
Blueberries (low bush)	Extended	1.0 (acid equivalent).	Spray on revolving cloth-covered drum held above blueberry foliage. Apply during June and July of season preceding a burn. Do not apply within 2 years of harvesting berries.
Grains, cereal (undesignated).	Extended	0.5	Apply when grain is in tiller to boot stage and weeds are in actively growing condition. Do not apply from boot to milk stage or in seedling stage.
Pastures: Grasses	Extended	3	Heavy brush. Apply when in full leaf and after grass is well established.
		1	Light brush. Apply when leaves are fully expanded.
Rangeland clearance	Extended	4	Apply in spring by airplane when brush is in heavy foliage stage (40-90 days after leaves unfold).
Rice	Extended	1.25	Apply tiller to boot and before flooding (4-8 weeks after rice emerges).
		1.5	Apply after flooding (2-3 weeks) or 7-10 weeks after planting.
Sugarcane	Extended	1	Preemergence use only. (Louisiana). If cane is shaved and off-barred, treat immediately following this operation.
		4.5	Preemergence use only. (Hawaii). Apply just before cane emerges.
		1	Postemergence (weeds in established cane). Apply over row when weeds are growing vigorously. Do not apply after cane is 2 feet tall.
Lakes; Ponds	Extended	4 (with 20 lbs./A. 2,4-D as ester).	Broadcast application in early spring to summer. Do not use treated water for crop irrigation or livestock drinking water.

TABLE 7.—*The nonfood crop uses of 2,4,5-T. The doses listed below are given in pounds of 2,4,5-T and equivalent in 100 gallons of spray using water or oil as the vehicle. (USDA, Pesticide Regulation Division, as amended by Pesticide Regulation Division Notices 70-11 (4/20/70) and 70-13 (5/1/70).*

Non-food crop uses	Pounds 2,4,5-T acid	Comment
Around farm buildings and yards	2	
Farm fence rows, lanes and roads	2-6	
Pine release in hardwood forest	2-6	
Industrial buildings including: Around factories, elevators loading platforms, oil refineries, etc.	12-16	
Industrial sites: Airline beacon stations, airport runways, coalyards, electric transformer stations, lumberyards, parking areas, radio towers, railroad sidings, sawmills.	3-12	
Recreational areas including: Race tracks, wildlife management	5, 6-10	
Rights-of-way: Fire lanes, highways, pipelines, powerlines, railroads, telephone and telegraph.	4-20	
Vacant lots	2-4	

2. *Military Uses of 2,4,5-T.*

The phrase, military uses, refers to the employment of 2,4,5-T as a defoliant in operations. Basic research on herbicides proceeded through the period 1941–1947. The work was encouraged by efforts to develop defoliating agents for use in jungle areas of the South Pacific area during World War II (*2*). A major demonstration of the utility of the mixture now known as Orange (1:1 mixture of the butyl esters of 2,4-D and 2,4,5-T) as a defoliant for military purposes was conducted in 1959 (*1*).

A preliminary series of defoliation trials was conducted in Vietnam between July 1961 and April 1962 (*3*). Operational spraying began in Vietnam in 1962 and increased sharply after 1967. Reviews on this subject are available (*3*, *5*, *6*).

Two herbicide formulations used in military operations in Southeast Asia include 2,4,5-T:

Agent	Composition	Lb./Gal. of active material
Purple	n-butyl ester 2,4-D 50% (wt.) n-butyl ester 2,4,5-T 30% (wt.). Isobutyl ester 2,4,5-T 20% (wt.).	8.0
Orange	n-butyl ester 2,4-D 50% (wt.) n-butyl ester 2,4,5-T 50% (wt.).	8.9

Purple mixture was discarded early because it was found to be no more effective than Orange. Orange is applied at a rate of 24 lb. per acre from both fixed wing aircraft and helicopters. C-123 aircraft fly at 150 feet altitude at 130 knots. A swath of 240 feet per pass is sprayed. Typically, a formation of 3–9 aircraft fly at the same time.

The following table shows the total areas sprayed each year between 1962 and 1968.

TABLE 8.—*Land area in Vietnam to which defoliants have been applied between 1962 and 1968 (15)*

Year	Number of acres sprayed
1962	4,940
1963	24,700
1964	83,486
1965	155,610
1966	741,247
1967	1,486,446
1968	1,267,110

It has been estimated that under usual operating conditions 90% of the released material is confined to a band about 2.0 km wide on either side of the 80 meter spray path (*15*). This figure is based on the spectrum of particle sizes, the direction and speed of the crosswind, and the altitude. Under realistic conditions but with a crosswind at right angles to the flight path, only 0.1% of the spray would be deposited between 1 and 2 km from the center line of the flight path.

As shown in Table 8, the total area sprayed for defoliation in 1968 was less than in 1967. Defoliation was discontinued in April 1970.

Defoliation operations have been carried out to some extent in virtually all sections of South Vietnam. The major use has been within War Zone C, War Zone D, and the Rung Sat Special Zone. These three areas comprise about one-fifth of the total area to which defoliants have been applied.

The Rung Sat Special Zone is an area which surrounds the shipping channel into Saigon. 113,600 acres had been sprayed by the end of January 1968 (*6*). War Zone C is northwest of Saigon between the Song Be River and the Cambodian border. 227,000 acres had been treated in War Zone C by January 1968. War Zone D, in which 405,000 acres were treated, is northeast of Saigon between the Song Be and Song Dong Hai Rivers (*6*). Repeated application was made in some areas.

The general purposes for which defoliation operations have been used include:

a. Defoliation of lines of communication. Sites of frequent ambush have been defoliated to afford better visibility along roads and trails.

b. Defoliation of areas where Vietcong tax collectors customarily exacted payments from the populace.

c. Defoliation of enemy infiltration routes.

d. Defoliation of enemy base camps. The rationale in this case was based on the observation that the enemy tended to move out of a base after the area had been sprayed.

e. Clearing of vegetation around American base camps and fire bases in order to clear fields of fire and improve observation.

Importance of 2,4,5-T as a military defoliating agent.

Systematic studies have not been carried out to quantify the value of defoliation in Vietnam. However, many of those concerned with the program believe that the military advantages are clearly evident (*4, 15*). The following evaluations are extracted from testimony offered by Rear Admiral W. E. Lemos before the Subcommittee on National Security Policy and Scientific Developments of the Committee on Foreign Affairs (*4*).

a. Major defoliation has been accomplished in War Zone C. Prior to defoliation, 7 brigades were necessary to maintain US/GVN presence. After defoliation, only 3 brigades were required.

b. The Commander of Naval Forces in Vietnam in a report to General Abrams stated: "As you know, a major concern is the vegetation along the main shipping channel. Your continuing efforts under difficult and hazardous flying condition, in keeping this area and the adjacent inland areas devoid of vegetation have contributed considerably in denying the protective cover from which to ambush the slow-moving merchant ships and U.S. Navy craft."

c. In 1968, the Commanding General of the First Field Force reported: "Defoliation has been effective in enhancing the success of allied combat operations. Herbicide operations using C–123 aircraft, helicopters, truck mounted and hand sprayers have become an integral part of the II CTZ operations against VC/NVA. The operations are normally limited to areas under VC/NVA control remote from population centers. The defoliation program has resulted in the reduction of enemy concealment and permitted increased use of supply routes by friendly units. Aerial surveillance of enemy areas has improved and less security forces are required to control areas of responsibility. An overall result of the herbicide program has been to increase friendly security and to assist in returning civilians to GVN control."

d. The U.S. Commander in the III CTZ related: "Herbicide operations have contributed significantly to allied combat operations in the III Corps. Defoliation is an important adjunct to target acquisition. Aerial photographs can often be taken from which interpreters can "see the ground" in areas that previously were obscured. Defoliation also aids visual reconnaissance. USAF FAC's (forward air controllers) and U.S. Army aerial observers have discovered entire VC base camps in defoliated areas that had previously been overlooked."

e. In the south in the IV CTZ, C–123 herbicide operations are limited. This is because of the vast areas of valuable crops which are not to be destroyed, even though they may be in enemy hands. Therefore, commander of the IV Corps area in presenting his evaluation cited the value of helicopter operations as follows: "A significant helicopter defoliation mission was conducted in the vicinity of SADEC in August 1968. The target area consisted of 3 main canals which converged and formed a strong VC base. The dense vegetation permitted visibility of only 10–15 meters horizontally and nil vertically. The area was sprayed with approximately 135 gallons of herbicide White and over 90 percent of the area was defoliated. As the result of the defoliation, an ARVIN battalion was able to remain overnight in the area for the first time in five years. Many enemy bunkers were open to observation. Since the defoliation, the VC presence has decreased to the point that only RF/PF forces are now necessary for local security."

f. As a part of the 1968 evaluation report of herbicide operations, the U.S. Senior Advisor in the IV Corps Tactical Zone area reported: "A section of National Highway 4 in Phong Dinh Province was the site for a defoliation operation on 24 June 1968. Since January 1968, a series of ambushes was conducted against SVN convoys and troop movements. Because of the total inability of ground troops to keep the area clear of VC, this area was sprayed using 685 gallons of herbicide White. The target area was primarily coconut palm and banana trees that had been abandoned by their owners for several years. During the period of abandonment the vegetation had become so dense that convoy security elements were not able to see more then five meters into the underbrush and had to rely on reconnaissance by fire to discover the hidden enemy. This method of protection had proven ineffective. Three RF/PF companies with U.S. advisors were used to secure the target for the helicopter operation in addition to an armored cavalry troop. Since the defoliation mission was completed, convoys have used the highway 2 or 3 times a week without attack or harassment. Only one RF platoon has remained in the area to provide local security to the hamlet and highway."

g. In certain instances, we know the VC have been forced to divert tactical units from combat missions to food-procurement operations and food transportation tasks, attesting to the effectiveness of the crop destruction program. In local areas where extensive crop destruction missions were conducted, VC/NVA defections to GVN increased as a result of low morale resulting principally from food shortages.

The most highly valued item of equipment to field commanders in Vietnam is the helicopter. There was some question when the helicopter spray equipment was first procured whether field commanders would divert the use of helicopters from combat operations for herbicide spray operations. The very fact that the commanders have used their helicopter spray equipment to the fullest and have asked for more is certainly proof that herbicide operations have been helpful in protecting the American Soldier and contributing to successful accomplishment of the ground combat mission." (*4*)

Cost Sharing Programs

The Agricultural Stabilization and Conservation Service of the U.S. Department of Agriculture has provided a cost sharing program for farmers in order to encourage desirable farm and conservation practices. Included in this Agricultural Conservation Program are two programs in which 2,4,5-T was used:

1. *Control of competitive shrubs on range and pastures.*

In 1968, $7 million were paid to farmers who treated 1.9 million acres. Approximately one-half of this land was treated with chemicals, a substantial part of which was 2,4,5-T. The remainder was treated by mechanical means.

2. *Control of specified noxious weeds on farmland or biennial weeds on pasture and range lands.*

In 1968, $1.75 million were paid to farmers to treat 700,000 acres. In some cases 2,4,5-T was used, although in most cases, 2,4-D and other chemicals were employed.

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TOXICOLOGY

Summary

Relatively little toxicological information has been available on 2,4,5-T. Most of the experiments prior to the National Cancer Institute screening study were of acute, single-dose or short-term toxicity. The longest period of observation was 90 days. It was assumed (not unreasonably) that the several phenoxy herbicides behaved in similar fashion toxicologically. Hence, an understanding of aspects of the toxicology of 2,4,5-T was inferred from experiments with 2,4-D. The sample sizes used in many of the early toxicity studies were so small that it is difficult to draw statistically valid inferences. The studies indicated that 2,4,5-T is only moderately toxic. Relatively little is known about the mechanisms of toxicity of 2,4,5-T or of its metabolism in man and animals.

The screening study of pesticides carried out under contract for the National Cancer Institute tested the teratogenicity of a number of compounds, including 2,4,5-T. 2,4,5-T appeared to be teratogenic in mice and rats. Subsequent studies have confirmed these observations and in addition indicated that purified 2,4,5-T containing less than 1 ppm of the toxic contaminant tetrachlorodibenz-p-dioxin as well as 2,4,5-T contaminated with 27 ppm dioxin are teratogenic. It has also been reported that dioxin by itself is teratogenic. Tumor production by 2,4,5-T was not found.

Accounts of birth defects in defoliated areas of Vietnam have been reported. The information available does not permit the conclusion that 2,4,5-T used in Vietnam has been the cause of human birth defects.

2,4,5-T is classed as a plant hormone since, in appropriate amounts, it accelerates plant growth. The mechanism of the herbicidal effect is not fully understood. However, it is generally believed that excess growth stimulation and herbicidal properties are related. Herbicidal effects occur when these materials are used in large doses.

A. Acute Toxicological Investigations

Toxicological studies on 2,4-D were first reported in 1944 (*8*). However, there were no published reports of toxicological investigations of 2,4,5-T until 1953. In that year, Drill and Hiratzka (*5*) reported a series of studies of acute and subacute toxicity of 2,4,5-T on dogs. The material used was commercially available 2,4,5-T (presumably the acid) and was administered in capsules mixed in dog food. The single acute dose ranged from 50–400 mg/kg/. Chronic toxicity was studied in this case by oral administration in doses of 2-20 mg/kg/day, 5 days per week over a period of 13 weeks. Observations and measurements made included determination of the number of days until death ensued, changes in body weight, general observations of abnormal physical signs, gross pathology of organs, and selected histology. The number of animals used was small (as few as one per dose and as many as four per dose). In brief, the findings of this study suggested that a single fatal dose for dogs lay somewhere between 100 and 400 mg/kg. It was inferred by the author that the acute LD_{50}* was around 100 mg/kg for dogs. Repeated daily doses of 20 mg/kg led to the death of all four animals tested within 11–75 days. Repeated daily doses of 10 mg/kg did not prove fatal over a 90-day period. There were some overt signs of toxicity including weight loss, stiffness of hind legs, muscular weakness and, occasionally, bleeding from gums.

The Dow Chemical Company, a manufacturer of 2,4,5-T, undertook a series of studies of acute toxicity of this material beginning around 1950. This series included a variety of species of animals and a number of the various salts and esters of 2,4,5-T and several of the various formulations. The details of these studies have never been published in the open literature. A number of them have been submitted as background material for a petition for the granting of a tolerance for the herbicide for uses of food crops. In 1954, a summary of some of this work was published by Rowe and Hymas (*17*). Table 1 lists the various herbicidal agents tested.

*LD_{50} median lethal dose=the amount of a toxic agent which will be lethal to 50% of the test animals to which it is administered under the conditions of the experiment.

Table 1. Herbicidal formulations.

TABLE 1.—Herbicidal formulations studied by Rowe and Hymas (*17*)

Trade name	Active ingredients (percent)
2,4-Dow weed killer (formula 40)	65.0 Alkanolamine salts of 2,4-D
Esteron 44	44.0 Isopropyl ester of 2,4-D
Esteron 245 (old formulation)	33.3 Isopropyl ester of 2,4,5-T: 12.1 Mixed amyl esters of 2,4,5-T
Esteron 245 (present formulation)	65.3 Mono-, di-, tripropylene glycol butyl ether esters of 2,4,5-T
Esteron ten-ten	70.5 Mono-, di-, tripropylene glycol butyl ether esters of 2,4-D
Brush killer 50-50	27.2 Butyl esters of 2,4-D; 26.5 Butyl esters of 2,4,5-T
Brush killer T	52.2 Butyl esters of 2,4,5-T
Esteron 76 (used in oil solution only)	37.1 Isopropyl esters of 2,4-D; 39.0 n-Butyl ester of 2,4-D
Esteron 76E (used in either oil solution or water emulsion)	36.8 Isopropyl esters of 2,4-D; 38.8 Butyl esters of 2,4-D
Esteron brush killer (old formulaton)	25.6 Isopropyl esters of 2,4-D; 24.4 Isopropyl esters of 2,4,5-T
Esteron brush killer (present formulation	34.8 Mono-, di-, tripropylene glycol butyl ether esters of 2,4-D 33.0 Mono-, di-, tripropylene glycol butyl ether esters of 2,4,5-T
Kuron (was called II-1078)	64.5 Mono-, di-, tripropylene glycol butyl ether esters of silvex
Dow MCP amine weed killer*	69.1 Alkanolamine salts of MCP

*2-methyl-4-chlorophenoxyacetic acid.

Table 2 presents a summary of the acute oral toxicities of the various herbicide components.

TABLE 2.—Acute oral toxicities of various phenoxy acetate herbicidal chemicals. Rowe and Hymas (*17*)

Material	Species	Sex	Vehicle	l.d.50 (19/20 confidence limits) (mg./kg.)
2,4,5-T (2,4,5-Trichlorophenoxyacetic acid)	Rats	M	Olive oil	500 (391–640)
	Mice	M	Olive oil	389 (246–610)
	Guinea pigs	M and F	Olive oil	381 (307–472)
	Chicks	M and F	Olive oil	310 (211–456)
	Dogs (4)		Capsule	100 Range (50–250)
2,4,5-T, isopropyl ester	Rats	M and F	Olive oil	495 (420–584)
	Guinea pigs	F	Olive oil	449 (362–557)
	Mice	F	Olive oil	551 (380–799)
2,4,5-T, mixed butyl esters	Rat	F	Corn oil	481 (313–739)
	Rabbit	M	Corn oil	712 Range (500–1,000)
	Mice	F	Corn oil	940 (674–1,312)
	Guinea pigs	F	Corn oil	750 Range (500–1,000)
2,4,5-T, mixed amyl esters	Rats	F	Olive oil	750 Range (500–1,000)
MCP (4-chloro-o-toloxyacetic acid or 2-Methyl-4-chlorophenoxyacetic acid).	Rat	M	Corn oil	700 Range (500–1,000)
MCP, amine salt	Rat	M	Water	1,200 Range (1,000–2,000)
	Guinea pigs	M	Water	1,200 Range (630–2,000)
silvex, (2[2,4,5-trichlorophenoxy] propionic acid).	Rat	M and F	Corn oil	650 (560–760)
silvex, mixed butyl esters	Rat	F	Corn oil	600 Range (250–1,000)
	Rabbits	F	Undiluted	750 Range (500–1,000)
	Chicks	M and F	Corn oil	1,190 (707–2,000)
silvex, mono-, di-, tripropylene glycol butyl ether esters.	Rat	F	Corn oil	621 (473–814)
	Guinea pigs	M	Corn oil	1,250 Range (500–2,000)
	Mice	F	Corn oil	1,410 Range (1,000–2,000)
	Chicks	M and F	Corn oil	1,190 (847–1,670)
	Rabbits	F	Undiluted	819 (610–1,070)

Similarly, Rowe and Hymas reported the results of oral feeding of several commercial formulations of 2,4,5-T and related compounds (Table 3).

Table 3.—*Summary of oral toxicities of a variety of phenoxy acetate herbicidal formulations. Rowe and Hymas (17)*

Material	Species	Sex	Vehicle	l.d.$_{50}$ (10/20 confidence limits) (mg./kg.)
2,4-Dow weed killer	Guinea pigs	F	Water	Range 2,000 (1,000-3,000)
2,4-Dow weed killer (formula 40)	Rats	F	Water	Range 850 (700-1,000)
Esteron 44	Rats	M	Olive oil	Range 650 (300-1,000)
Esteron 245 (old)	Rats	F	Emulsion in water	Range 1,000 (300-2,000)
Esteron 245 (new)	Rats	M	Olive oil	Range 800 (600-1,000)
Esteron ten-ten	Rats	F	Olive oil	760 (660-860)
Brush killer 50-50	Rats	F	Emulsion in water	1,070 (700-1,650)
	Guinea pigs	F	Emulsion in water	1,160 (820-1,630)
	Mice	F	Corn oil	800 (624-1,070)
	Rabbits	F	Undiluted	Range 1,420 (500-2,000)
	Chicks	M and F	Undiluted	4,000 (2,700-5,900)
Brush killer T	Rat	F	Emulsion in water	1,200 (783-1,850)
	Guinea pigs	F	Emulsion in water	1,410 (875-2,200)
	Mice	F	Olive oil	1,230 (938-1,620)
	Rabbits	M	Undiluted	849 (604-1,190)
	Chicks	M and F	Undiluted	2,000 (1,350-2,960)
Brush killer 76	Rats	F	Corn oil	Range 750 (500-1,000)
Brush killer 76E	Rats	F	Corn oil	Range 300 (250-1,000)
Esteron brush killer (old)	Rats	M	Emulsion in water	Range 1,000 (300-3,000)
Esteron brush killer (new)	Rats	M and F	Corn oil	860 (800-930)
	Guinea pigs	M	Corn oil	1,220 (1,040-1,430)
	Guinea pigs	F	Corn oil	1,000 (1,390-1,840)
	Rabbits	M and F	Corn oil	900 (790-1,160)
	Chicks	M and F	Corn oil	Range 2,000 (1,000-3,000)
	Steers		Undiluted	Greater than 1,000

Rowe and Hymas concluded that the acute LD_{50} for 2,4-D, 2,4,5-T, and their various formulations and combinations fell in the range of 300–1000 mg/kg. There was some variation among species with dogs appearing relatively more sensitive than other species of animals.

Military applications of 2,4,5-T as a defoliant have utilized combinations of 2,4-D and 2,4,5-T in formulations known as Orange and Purple. There has been some acute toxicological testing of the mixture, Purple, on small animals. Purple contains 50 per cent butyl ester of 2,4-D, 20 per cent isobutyl ester of 2,4,5-T and 30 per cent n-butyl ester of 2,4,5-T. The details of this work have not been published but have appeared in summary form in a review. (*8*) (Table 4)

TABLE 4.—*Acute animal toxicity of Purple* (*8*)

Route	Toxicity	Dosages (mg/kg)		
		Rat	Rabbit	Dog
Oral	LD_{50}	566		
	LD_1	213		
Intraperitoneal	LD_{50}	586	1,994	a 500
	LD_1	121	363	>250
Intratracheal	LD_{50}	500		a 500
	LD_1	244		>250
Percutaneous	LD_{50}	5,562	12,034	
	LD_1	3,178	493	>1,250

a=approximation

There have been a few accounts of testing for acute toxicity of 2,4,5-T on domestic animals (*14*, *17*). These indicated that repeated doses of 100 mg/kg of 2,4,5-T were tolerated without overt signs of illness in sheep and steers. In one instance 1000 mg/kg/day proved fatal to a steer after the third day. 500 mg/kg/day provoked signs of acute toxicity in steers after the third day (*17*). The numbers of animals used in these studies were very small (single animals in some cases).

It has been assumed by some that the metabolism (and, hence, toxicity) of 2,4,5-T would resemble that of the other phenoxy acid herbicides. This is probably a reasonable assumption although it has not been systematically examined. There have been two recent reviews of the toxicity of phenoxy acid herbicides (*3*), (*19*). Included in these reviews are accounts of acute human toxicity of 2,4-D. The accounts include incidents of excessive occupational exposure, suicidal efforts, intended oral feeding and parenteral administration as a form of treatment for coccidioidomycosis From descriptions such as these, it has been inferred that around 50 to 100 mg/kg of 2,4-D is acutely toxic to humans. However, there are inconsistencies in this scanty information.

Occupational Experience

Occupational exposures (in the 2,4,5-T manufacturing process) have provoked illness in workers. However these effects have been attributed to the dioxin impurity (tetrachlorodibenz-p-dioxin). (See Section III, Chemistry). The toxicity of this impurity is considered later in this section.

National Cancer Institute Screening Study for Carcinogenesis and Teratogenesis

In 1964, the National Cancer Institute contracted for a screening study of a number of pesticides. Among the purposes of this large scale examination was to determine whether compounds in common use might be tumorigenic, or teratogenic or mutagenic (*12*). The results of testing for carcinogenesis have been summarized by Innes et al (*9*). The results of testing for teratogenesis with 2,4,5-T have been analyzed and summarized by Courtney et al (*2*).

Screening for tumorigenicity was performed on two hybrid strains of mice. The materials, which were from commercial lots, were given by single subcutaneous injection or by continuous oral feeding. For each dose and each strain, 18 animals of each sex were used. Oral feeding was started when the animals were seven days old and was continued for 18 months. The dose chosen corresponded to a maximal tolerated dose. This was the experimentally determined maximum level resulting in zero mortality for 19 daily doses. The dose of 2,4,5-T used in the oral feeding studies was 21.5 mg/kg. Of the 72 mice which started the study, 12 died or were cannibalized before the end of the 18 months. Of those surviving, nine animals exhibited tumors. Of the total number necropsied (survivors plus premature deaths), 12 animals exhibited tumors. These included 4 reticulum cell sarcomas, 2 pulmonary adenomas, 5 heptomas, and 1 benign calcifying epithelioma.

These results were compared with the tumor incidence in a group of untreated control animals and in a group of animals treated with known tumorigens. 2,4,5-T was not found to provoke a significant increase in tumors after chronic administration.

In addition to 2,4,5-T, several related phenoxy compounds were also screened for tumor production. These compounds included:

2,4-D
2,4-D isopropyl ester
2,4-D butyl ester
2,4-D isooctyl ester
α-(2, 4-dichlorophenoxy) propionic acid
α-(2, 5-dichlorophenoxy) propionic acid
α-(2, 4, 5-trichlorophenoxy) propionic acid

Three of these compounds administered by the subcutaneous route [α-(2,4-dichlorophenoxy) propionic acid; α-(2,4,5-trichlorophenoxy) propionic acid; and 2,4-D isopropyl ester] elicited an increase in tumor incidence in comparison with negative controls but the statistical significance was less than 0.02.

Screening for teratogenic effects was performed on four strains of mice and, in the case of 2,4,5-T, on one strain of rats. 2,4,5-T was one of 53 compounds examined in this study. Other related agents included were:

2,4-D
2,4-D isopropyl ester
2,4-D butyl ester
2,4-D isooctyl ester
2,4-D methyl ester
2,4-D ethyl ester

α-(2,5-dichlorophenoxy) propionic acid
2,4-dichlorophenol
2,4,5-trichlorophenol
2,4,6-trichorophenol

Compounds were administered subcutaneously in solution of dimethyl sulfoxide in maximally tolerated doses to pregnant female animals. Administration occurred between the 6th and the 14th days of gestation in mice. The animals were sacrificed on the 18th day and the fetuses were examined for abnormalities. With the finding of apparent increase in birth defects, the experiments were repeated with oral administration of the agents. Because of the finding of an increase in birth defects in the case of 2,4,5-T, this compound was studied more intensively (wider range of doses and two species of animals).

Evaluation compared the influence of these chemicals on the total incidence of birth defect. In addition, a further analysis attempted to reduce the interlitter statistical influences by calculating the incidence of birth defects on a litter-by-litter basis (2)

2,4,5-T was tested in the C57BL/6 and AKR strains of mice, and in a hybrid strain produced by mating C57BL/6 females with AKR males. Three dosage levels (21.5, 46.4, and 113.0 mg/kg) were used orally and by injection. Numbers of litters varied from 6 to 18 in the experimental animals (6 to 12 in the orally fed animals). Three different patterns of dosage and sacrifice were used (dosage during days 6–14, 6–15, and 9–17). The findings from this set of experiments were increases in incidence of fetuses with cleft palate and fetuses with cystic kidney when compared to controls. There was also an indication of a dose-response relationship. Table 5, reproduced from Courtney, *et al.* (*2*) summarizes the findings. The numbers in the columns representing the percentages of abnormal fetuses per litter were derived by averaging the percentages of abnormalities per litter for each dosage.

Because of these results, an additional series of experiments was conducted in Sprague-Dawley rats. Four dosage levels were used (4.6, 10.0, and 21.5 and 46.4 mg/kg). Two types of fetal abnormalities were recognized, cystic kidney and enlarged renal pelvis. Courtney et al., (*2*) in reviewing these experiments, analyzed the results on the basis of abnormalities per litter. In reducing the sample size from the total number of fetuses to the total number of litters, these authors felt that the resulting sample size for the 21.5 mg/kg dosage was too small and, hence, deleted the data for this dose. Table 6 is a summary of these data.

The inferences which have been drawn from these experiments are that 2,4,5-T appears to provoke a higher than expected level of fetal death and fetal abnormality in rats and mice in the dosages used. Further, there appeared to be a suggestion of a dose-response relationship over the range of doses used.

Comments of the screening study contracted for by the National Cancer Institute have already been published (*18*). The following observations by the Panel are concerned with the portion of this study in which the teratogenic potential of 2,4,5-T was tested.

1. The study involved a great number of variations in procedure (strain of mice used, dates when tests were performed, and routes of administration). These variations make the task of evaluation difficult.

2. Too few animals and litters of animals were used. Since biological variability is considerable, the sample size must be adequately large to demonstrate specific effects of the chemical agents in question. At least 10 pregnant females to assure at least 100 conceptions is suggested. The Food and Drug Administation suggests 20 females per test group.

3. There appears to be an unusually high level of embryo lethality and teratogenicity among untreated and vehicle-treated groups. Either the experimental conditions were less than optimal or the strain of animals was developmentally unstable.

4. The strain of mouse most often used (C57BL/6) appeared to have had undesirable traits as a test animal, being variably and uncertainly responsive to the substance being tested. A reasonably homogeneous, colony-bred stock which has been maintained in the laboratory long enough for the investigator to have accumulated substantial background data on fecundity, spontaneous malformation and intrauterine death rates is generally regarded as preferable to inbred stocks for teratological testing.

TABLE 5.—*Teratogenic evaluation of 2,4,5-T in mice (2)*

Compound	Vehicle	Dose (mg/kg)	Litters (No.)	Live fetuses per litter (av. No.)	Fetal mortality per litter (percent)	Abnormal litters (percent)	Abnormal fetuses per litter (percent)	Percentage of fetuses per litter with:	
								Cleft palate	Cystic kidney
C57BL/6 strain treated days 6 to 14									
Nontreated	None	None	72	5.8	26	38	11	<1	1
Control	DMSO	(*)	106	5.5	29	42	12	<1	2
Control	Honey	(*)	32	7.1	16	41	14	0	1
2,4,5-T	DMSO	21.5	6	7.7	3	50	12	0	0
2,4,5-T	DMSO	113.0	18	4.4	42	†86	†57	†22	†41
2,4,5-T	Honey	46.4	6	8.5	8	‡100	‡37	2	†33
2,4,5-T	Honey	113.0	12	4.8	†47	†100	†70	†23	†48
C57BL/6 strain treated days 9 to 17									
Nontreated	None	None	8	5.1	36	71	31	0	7
Control	DMSO	(*)	10	6.1	23	30	8	0	0
2,4,5-T	DMSO	113.0	10	7.7	11	†100	†77	†29	†60
AKR strain treated days 6 to 15									
Nontreated	None	None	58	7.1	16	10	5	<1	<1
Control	DMSO	(*)	72	6.9	15	24	4	<1	<1
Control	Honey	(*)	12	8.8	9	0	0	0	0
2,4,5-T	DMSO	113.0	14	6.9	23	†71	†29	†28	1
2,4,5-T	Honey	113.0	7	5.3	‡42	†100	†55	†55	0

*Dose, 100 µl per mouse.
†P=.01.
‡P=.05.

TABLE 6.—*Teratogenic evaluation of 2,4,5-T in rats*

Compound	Vehicle	Dose (mg/kg)	No. of litters	Average No. live fetuses/litter	Percent fetal mortality/litter	Percent abnormal litters	Percent abnormal fetuses/litter	Percent of fetuses per litter with:	
								Enlarged renal pelvis	Cystic kidney
Nontreated	None		7	9.9	11	43	9	9	0
Control	Honey	(†)	14	8.7	1	57	12	12	<1
2,4,5-T	Honey	4.6	8	8.2	12	88	**36	11	21
2,4,5-T	Honey	10.0	7	7.1	***28	86	**46	17	**30
2,4,5-T	Honey	46.4	6	2.7	***50	67	§60	27	§33

†200 µl/rat (2).
**Statistical Significance Level=0.05.
***Statistical Significance Level=0.01.
§The sample size was possibly too small to show a significant difference.

5. It is puzzling that virtually no skeletal malformations were encountered in either controls or test group. Skeletal defects usually account for a substantial part of the easily detectable malformations that occur spontaneously or after treatment in rodent species. Hardly a strain that has been carefully studied in properly cleared and stained specimens has failed to show vertebral and rib variations.

6. There were some known teratogens used in these experiments (trypan blue, 6-aminonicotinamide). It is puzzling to find that these agents failed to produce significant teratogenic and embryo-lethal effects consistantly. This raises questions about the precision with which these teratogenicity tests were performed.

7. 2,4,5-T appeared to be clearly teratogenic in two strains of mice treated with 2,4,5-T at 113 mg/kg via either of the two routes of administration. In rats, 2,4,5-T appeared only equivocally teratogenic at any dosage but clearly embryo-lethal from 10.0–46.4 mg/kg.

8. The lack of an unequivocally defined dose-response relationship renders these results less than completely satisfying.

Reports of Birth Defects Among Humans Following Exposure to 2,4,5-T

Shortly after the report of the teratogenesis screening in experimental animals of pesticides, there appeared a series of articles in the lay press which described the occurrence of birth defects in parts of Vietnam where defoliants had been used. These articles appeared in at least six different newspapers in South Vietnam between June 26 and July 5, 1969. Both congenital abnormalities and hydatid moles* were described. Translations of the articles have alluded to the possibility that defoliants might be responsible for these defects. The implication was offered that these abnormalities had increased in frequency in the recent past. No documentation has been available.

Toxicity of Dioxin

It was pointed out in an earlier section of this report that one of the impurities which arises in the manufacturing process of 2,4,5-T is 2,3,7,8-tetrachlorodibenzo-p-dioxin. This substance has considerable interest because it is highly toxic, because a close relative was a toxic constitutent in chicken feed and because it has caused chloracne, a severe skin disease, among workers engaged in the manufacture of 2,4,5-T.

The dioxin impurity has assumed a further importance as an impurity in commercially available 2,4,5-T. With the observation that production lots of 2,4,5-T containing approximately 27 ppm dioxin could be teratogenic, it became important to ascertain whether it was 2,4,5-T itself or some impurity which was the teratogen. Recent experiments at the National Institute of Environmental Health Services indicate that partially purified 2,4,5-T ($<$0.1 ppm tetrachlorodibenzo-p-dioxin) shows teratogenic activity in the mouse. Pure tetrachlorodibenzo-p-dioxin shows teratogenic activity also, but not at low enough doses to account for the activity of the partially purified 2,4,5-T. We cannot exclude the possibility that other impurities may contribute significantly to the observed teratogenic activity of 2,4,5-T.

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*(An abnormality of pregnancy which involves the placenta and the membranes surrounding the fetus.)

In the following paragraphs, the history of the discovery of dioxin is examined in relation to the experimental observation of the teratogenic properties of 2,4,5-T. Secondly, data on the toxicity of this material are presented.

In March 1949, an accident occurred at a 2,4,5-T plant owned by the Monsanto Chemical Company which led to the release of some of the intermediate chemicals into the plant. As a result, 117 cases of a severe skin disease known as chloracne were found among the exposed workers. Chloracne is characterized by comedones, blackheads, inclusion cysts, and pustules with eventual scarring over the neck, back, and chest. In addition to the cases which were traced to the accident, a number of other clinical cases of chloracne were recognized among workers in the 2,4,5-T plant who were not in the vicinity of the accident. (*10*) Kimmig and Schulz (*11*) reported in 1957 that chloracne occurred among workers engaged in the manufacture of 2,4,5-T in Germany. These authors demonstrated that the agent responsible for chloracne was tetrachlorodioxin. In 1964, the demand for 2,4,5-T in the United States began to rise mainly due to its increasing use as a defoliant in Vietnam. A greater demand was placed on each of the domestic manufacturers to produce more herbicide. Coincident with the increased production was the discovery of chloracne among some 60 2,4,5-T workers. (*7*) The Dow Chemical Company reduced its operations substantially for a period of several months in order to investigate the origin of the toxic hazard. It was found that the amount of dioxin formed varied with the temperature and pressure of the early reaction steps. The Dow Chemical Company made its findings known to the other domestic manufacturers. Looking back it is evident that dioxin levels varied widely among commercial 2,4,5-T samples, as seen in Table 4 of Section III. Rigorous control is now exercised to reduce dioxin levels in the final product to less than 1 ppm.

A recent review of occupational disease attributed to dioxin has been prepared by Poland *et al* (*15*). These authors studied 73 male employees in a 2,4,5-T factory, some of whom had been observed six years previously by Bleiberg (*1*) who then noted the prevalence of chloracne. Poland et al (*15*) also found chloracne among the same population although estimates of exposures were not made. Poland attributed the chloracne to the dioxin impurity. They also examined the prevalence of a type of porphyria, thought to be toxic in origin, known as porphyria cutanea tarda (elevated urinary porphyrin excretion, skin fragility and vesicular eruptions). Uroporphyrinuria had been noted during the early visit to the plant by Bleiberg (*1*) but it was not found during the later study. Elevated urinary copro-porphyrin levels were noted, however, but there appeared to be no correlation with the severity or presence of chloracne (*1*, *15*). The later series of observations found much of the chloracne still remaining but the porphyria had disappeared. Chloracne was attributed to the dioxin impurity but the origin of the porphyria was less certain.

In order to measure the toxicity of the dioxin impurity, the Dow Chemical Company undertook a series of acute toxicity studies on small animals in 1967 (*16*). Single doses of 2,3,7,8-tetrachlorodibenzo-p-dioxin were administered orally to lots of five animals for each of several doses. The number surviving and the time of death were noted. The animals used were male rats, female rats and female guinea pigs. Table 7 gives the results of these experiments:

TABLE 7.—*Single-dose oral toxicity of dioxin* (*18*)

Species	LD_{50} mg/kg
Male rat	0.022
Female rat	0.045
Female guinea pig	0.0006

With this background in mind, the purity of the 2,4,5-T material used in the National Cancer Institute screening study assumed a new importance. A sample of this material was submitted to chemical analysis by gas chromatography. The result was the finding of 27 ± 8 ppm of dioxin.

Testing for Teratogenicity

The study of teratogenic effects in experimental animals is characterized by a great deal of empiricism. However, in general testing for teratogenic potential is a more manageable problem than are a number of other types of biologic testing. There are large numbers of agents known to be teratogenic to animals. In fact, it has been held that virtually any material is potentially teratogenic if administered in an appropriate dose at the critical time in gestation. Interestingly, however, only a few chemicals have been recognized as human teratogens.

In general, an embryo-toxic dose of a material is separated from a maternal toxic dose by a small margin (perhaps no more than a factor of 10). Only slightly below the embryo-lethal or toxic dose is a no-effect dose (separated, perhaps, by a factor of 2). Between the highest level which has no effect on the developing fetus and the embryo toxic level is a steep dose-response relationship. In testing for teratogenicity, the lowest dose on the dose-response curve (threshold for any embryo toxicity) is identified. All doses below this level are, by definition, no effect doses. By accepting an extra margin of safety below this dose (a factor of 1/10–1/100), reasonable freedom from teratogenic effects can be predicted.

A problem arises in extrapolating findings in experimental animals to man. The embryotoxicity of a chemical agent is, in theory, a function of the degree of exposure of the developing embryo to the agent. This appears to be a function, in turn, of the persistence of the material in the maternal circulation. Thus, in order to extrapolate animal findings to humans, the animal must be "calibrated" to humans for each chemical agent. That is, the rate of disappearance of the agent from the animal circulation must be compared quantitatively to that in humans. As a first approximation, corresponding doses in mg/kg would be taken as proportional to the blood clearance rates for the two species.

These principles make possible the design of testing procedures for reproductive defects caused by chemical substances. The scheme described is of a general nature but can be applied to 2,4,5-T. The first step involves determination of the chemical nature of the material in question. Secondly, animal studies should be done to establish embryotoxic levels. In the case of 2,4,5-T, some additional studies have been carried out to confirm the results of the National Cancer Institute screening study. In addition, studies should be undertaken on pure 2,4,5-T and on its various impurities to identify the teratogenic agent or agents. Hybrid strains of animals should be used rather than highly inbred strains. At least two animal species should be used. Preferably strains of colony or random bred rats and mice should be used which have been maintained in the laboratory long enough for the investigator to have accumulated substantial background data on fecundity, spontaneous malformations and intrauterine death rates.

By careful testing, using a small series of doses, a TD_{50} dose (that dose which will cause teratogenesis in 50 percent of fetuses) can be ascertained. At the low end of the dose-response curve is found, presumably, a threshold dose below which no detectable teratogenic effects would be expected. Actual experimentation locates TD_{small} at which teratogenicity occurs in only a few percent of all fetuses.

The next step is to compare the expected human exposure with the animal TD_{small}. If these differ by as much as a factor of 100, it would seem reasonable to consider the material safe with regard to teratogenesis. If the difference between the human exposure and the animal TD_{small} is as little as a factor of 10, the margin probably is insufficient. Between 100 and 10 lies a certain amount of flexibility for further action. Finally, in order to extrapolate the animal data to human experience, rates of excretion and detoxification in animals and humans should be compared.

Summary of Recent Experiments

Following analysis of the results of the screening study carried out for the National Cancer Institute, it was felt that confirmatory studies should be undertaken. Two sets of experiments were begun independently by the Dow Chemical Company and by the National

Institute of Environmental Health Sciences. At the time of this writing, some of these experiments have been completed and the results have been reported.

1. Dow experiments.

2,4,5-T (containing ⋜1.0 ppm dioxin) was administered orally to pregnant Sprague-Dawley rats on days 6–15 of gestation. (*6*) The doses used were 1, 3, 6, 12, and 24 mg/kg/day. The 2,4,5-T was administered in 0.25% Methocel®. The results were compared with those obtained from controls which received the vehicle only.

No clinical or gross pathologic signs of adverse effect were observed in treated females during the period of treatment. Litter size, number of fetal resorptions and birth weights appeared to be unaffected. Furthermore, there was no increase in the incidence of birth defects compared to control animals.

In a related study by the Dow Chemical Company on the teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (*4*), this material, in pure form, was administered to pregnant Sprague-Dawley rats. The doses used ranged from 0.03 to 8.0 mg/kg/day. Between 0.125 and 0.5 mg/kg, intestinal hemorrhages were seen in the fetuses. Dioxin was very embryolethal at the highest dosages (2.0 and 8.0 mg/kg).

2. NIEHS experiments.

The National Institute of Environmental Health Sciences undertook a series of experiments in which 2,4,5-T (containing various amounts of dioxin impurity) was administered to pregnant mice and rats (*13*). Three strains of mice were used (1 random bred and 2 inbred stains) and a random bred strain of rats. Four different lots of 2,4,5-T were employed:

a. "Eastman Organic"—contained ⋜ 1.0 ppm dioxin.

b. "Dow Technical"—contained ⋜ 0.5 ppm dioxin.

c. "Dow Pure"—contained ⋜ 0.1 ppm dioxin.

d. 2,4,5-T samples used in the original tests performed for the National Cancer Institute—containing about 27 ppm dioxin.

In addition, pure 2,3,7,8-tetrachlorodibenzo-p-dioxin was administered to a series of mice and rats.

These materials were tested in various dosages in mice by injection in dimethyl sulfoxide (DMSO). In the random bred (Charles River) mice, the dosage schedule for 2,4,5-T covered the range of 50–150 mg/kg/day. In the other strains of mice, a narrower range of doses was tested. In rats, the dosage range was 10.0–21.5 mg/kg/day and here the material was administered orally in sucrose. Pure dioxin was administered subcutaneously in DMSO in rats and mice (1 and 3 mg/kg/day in mice and 0.5 and 2 mg/kg in rats).

In mice, both 2,4,5-T (in the purest form available) and dioxin produced birth defects and increased fetal toxicity. The birth defects were qualitatively similar to those seen previously in the National Cancer Institute screening study and included cleft palates and renal defects. In rats renal defects and excess fetal mortality were seen but seemed to be related to dioxin content rather than 2,4,5-T.

3. FDA Experiments (unpublished data acquired in the spring of 1970).

Teratogenic studies were performed by giving the test compound by oral intubation to pregnant hamsters on day 6 through 10 of organogenesis. Embryos were removed by caesarian section on day 14 of pregnancy. Samples of 2,4,5-T tested were:

a. "Dow Technical"—contained ≦ 0.5 ppm dioxin.

b. "Dow Technical"—contained ≦ 0.1 ppm dioxin.

c. "Dow Pure"—contained ≦ 0.1 ppm dioxin.

d. Hercules X-17394—contained no detectable dioxin.

e. Monsanto NL-07-020—contained 2.9 ppm dioxin.

f. "K & K" sample—contained about 45 ppm dioxin.

g. Eastman Kodak (recrystallized in FDA)—contained no detectable dioxin.

In addition pure 2,3,7,8-tetracolorodibenzo-p-dioxin (Dow) was administered to hamsters.

These materials were tested in various doses from 40–100 mg/kg. All of the 2,4,5-T samples produced increased embryotoxicity and gastric and/or intestinal hemorrhages. Birth defects consisted chiefly of poor head fusion and absence of eyelids.

The pure tetradioxin produced increased fetal toxicity at 0.31 and 1.43 μg/kg and gastric and/or intestinal hemorrhages at the lowest dose, 0.02 μg/kg.

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RESIDUES OF 2,4,5-T IN THE ENVIRONMENT

Summary

2,4,5-T residues disappear from soil with moderate speed, probably through action of microorganisms, persisting as long as three months. During this period they are potentially available for transport to non-target areas.

It appears unlikely that residues from recommended applications of 2,4,5-T could appear in hazardous quantities in water. Typical applications are to forested areas or those infested by weeds where most of the herbicide appears to be intercepted by the plants. Residues do not seem to persist in water, however, they do remain longer in bottom sediments.

Residues from rangeland and pasture applications may find their way into cattle permitted to graze soon after spraying. Cattle excrete the intact herbicide rapidly but 2,4,5-T residues have occasionally been found in meat and dairy products. Although the residue levels are low, they dictate caution about pasturing soon after rangeland treatment.

The rate of application of 2,4,5-T in Vietnam is 13 lbs. of the butyl ester per acre (26 lbs. of Orange per acre). This rate is about 2–6 times as high as that used on rangelands domestically. Moreover, much larger areas are treated in Vietnam. Orange is not used on food crops but on forests. Hence, human exposure to contaminated food crops would be unlikely. If, during the vulnerable period of gestation, all a pregnant mother's food came from locations treated with Orange at 26 lbs/acre within the preceding week or so, the daily dose of 2,4,5-T might conceivably reach 15 mg/kg/day, which by comparison to some animal data might prove to be embryotoxic. Such estimates are based on a very extreme, worst-case calculation.

Residues of 2,4,5-T resulting from recommended uses in the United States

The herbicide 2,4,5-T is applied for weed control to a relatively few crops. However, it is used more extensively for control of weeds in rangelands and pastures, non-croplands and aquatic areas (Table 1).

It is not considered to be a persistent pesticide by comparison with many of the chlorinated hydrocarbon insecticides. Nevertheless, its use at rates of recommended application results in measurable levels of residue in soils, water, air, plants, and animals which persist for relatively short periods of time after application. The potential effects of such residues on the health of man and other animals have been little studied and are poorly understood. Data available suggest that residues resulting from recommended rates of application are not of sufficient magnitude to justify concern as potential health hazards. Unfortunately, most of the toxicity studies conducted thus far have been relatively short-termed and of value for determining acutely toxic doses only. Substantial amounts of data are available of the sort reported by Palmer and Radeleff (*14*). Data from such studies indicate that 2,4,5-T is not acutely hazardous for cattle, sheep, and chickens when applied at recommended rates. They considered rates of application above 30 pounds per acre to be hazardous.

Recent concern over the possible adverse effects of long-term exposure to relatively small amounts of 2,4,5-T as residues in food, feed, and water makes it desirable to review the information available on levels and persistence of such residues.

1. Soils—The possibility of residual toxicity to crops grown on soils treated with 2,4,5-T has emphasized the need for information on the levels of residues resulting from various rates of application and their persistence. Substantial amounts of data have been accumulated on these points and there is relatively good agreement in results of most studies. Taking into account differences in soil type, temperature, and moisture and the phenomenon of bacterial proliferation in response to a new substrate, it appears that 2,4,5-T residues in soils may persist for as long as three months. The persistency of residues seems to be independent of the rate of application.

TABLE 1.—*Some examples of domestic uses of 2,4,5-T for control of weeds. (Suggested guide for weed control, 1969). U.S.D.A. Agriculture Handbook No. 332*

Crop or area	Rate of application, pounds per A
Sugarcane	1.0
Grasses grown for seed	0.75
Rice	0.5–1.5
Permanent pastures and rangelands	0.5–8.0
Non-cropland, rights-of-way, floodways, ditchbanks, fence rows, and industrial sites	1.0–4.0
Aquatic weeds	1.0–4.0

Laboratory studies suggest that breakdown of 2,4,5-T residues in soils result from the action of microorganisms which are capable of using these chemicals as sources of energy and carbon. Two species have been reported to use 2,4,5-T as a source for energy and carbon. (*1*) The microbiological degradation of the phenoxyacetic acid herbicides in the forest floor material probably resembles that in soils. (*13*)

Under the conditions of this environment substantial amounts of 2,4,5-T remained after 4 months. The relatively rapid degradation of residues of phenoxyacetic acid herbicides in the soil makes it unlikely that there will be any accumulation of 2,4,5-T from one season to the next. Rates of removal from soils by plants and invertebrates are uncertain.

A major concern about residues of persistent pesticides is that they do not always stay in the target area. The fact that residues of 2,4,5-T may remain in the soil for periods of three months, or more, makes it subject to transport to non-target areas. Soil particles contaminated with 2,4,5-T may be transported by wind or water to areas far removed from the site of application. The extent to which this occurs seems to have received little or no attention.

The choice among esters is often influenced by such considerations as reduced volatility (which may reduce spreading to non-target plants), slowness of hydrolysis, and avoidance of crystallization after the vehicle has evaporated.

Experiments on leaching of 2,4,5-T products and vehicles suggest that amine salts are leached more rapidly than the free acid *(8)*.

2. Water—Residues of pesticides in water are of concern because of the possibility of their getting into drinking water for man and other animals, of their potential adverse effects on aquatic organisms, and of the potential adverse effect on sensitive crop plants of irrigation water contaminated with these chemicals. Contamination of surface waters with herbicide residues is a matter of special concern since surface water provides most municipal water supplies. Nearly all of the water for livestock and other animals is supplied from surface water.

Since nearly 100 million acres of land are treated with herbicides in the United States each year, about 3 million acres of which are forest or rangelands, it is inevitable that substantial contamination of surface waters occurs. However, most of the contamination is indirect as a result of drift from target areas.

The manner in which contamination occurs, whether from drift or from direct application, determines the level of residues deposited. In applications made to forested areas or to bodies of water heavily infested by weeds extending above the water, much of the toal amount of herbicide applied will not reach the water directly. As much as 88 percent of the total amount applied may be intercepted by such plant covers as liveoak which are much less dense than those of water hyacinth or alligator weed. *(16)* There appears to be little information available on the possibility of future release to water of residues in plants.

Streams in forests in Oregon sprayed with 2,4,5-T or mixtures of 2,4,5-T and 2,4-D in a 1:1 ratio at the rate of 2 pounds per acre showed maximum residues of 70 ppb which disappeared within 17 days. *(15)*

Even at the heaviest rate of application recommended for control of weeds in permanent pastures and rangelands and aquatic species, 2,4,5-T residues would not be substantial even at the maximum levels that could be expected. For example, 8 pounds of herbicide per acre applied to a body of water 3 inches deep would result in residues of only 12 ppm, Table 2. An animal drinking from even such an unusually shallow source could not get a dose that would be expected to cause chronic toxicity. For example, a cow weighing 500 kg may be expected to drink as much as 50 l. of water per day during the warm seasons of the year which would result in the ingestion of about 1.2 mg/kg/day. However, a more realistic example could be expected from applications of 2,4,5-T to rangelands at 4 pounds per acre. Treatment of a body of water one foot deep at this rate would result in residues of only 1.5 mg/l. A 500 kg cow drinking from such a source could get no more than 0.15 mg/kg/day.

Adverse effects of residues of 2,4,5-T on aquatic species such as fish and some of the bottom dwelling invertebrates might be expected from the heavier recommended uses of this herbicide to shallow bodies of water. For example, 24-hr. LC_{50}* for bluegill is 1.4 ppm for the butoxyethanol ester of 2,4,5-T (see table 1 on page 67). Concentrations higher than this would result from the direct application of 4 pounds per acre to bodies of water no more than 6 in. deep.

TABLE 2.—*Estimated maximum level (mg./l.) of residues of 2,4,5-T at various rates of application to bodies of water ranging from 3 inches to 10 feet in depth.*

Depth of Water	Rates of application, pounds per A							
	1	2	4	6	20	26	80	100
3 inches	1.5	3.0	6.0	9.0	30.0	39.0	120.0	150.0
6 inches	0.75	1.50	3.0	4.50	15.00	19.50	60.0	75.0
1 foot	0.38	0.75	1.50	2.25	7.50	9.75	30.0	37.50
2 feet	0.19	0.38	0.75	1.13	3.75	4.88	15.0	18.75
3 feet	0.13	0.25	0.50	0.75	2.50	3.25	10.0	12.50
4 feet	0.09	0.19	0.38	0.56	1.88	2.44	7.50	9.38
5 feet	0.08	0.15	0.30	0.45	1.50	1.95	6.00	7.50
6 feet	0.06	0.13	0.25	0.38	1.25	1.63	5.00	6.25
7 feet	0.05	0.11	0.21	0.32	1.07	1.39	4.29	5.36
8 feet	0.05	0.09	0.19	0.28	0.94	1.22	3.75	4.69
9 feet	0.04	0.08	0.17	0.25	0.83	1.08	3.33	4.17
10 feet	0.04	0.08	0.15	0.23	0.75	0.98	3.00	3.75

There appears to be little likelihood of 2,4,5-T appearing in hazardous quantities in ground water or drainage channels from local applications. Brown and Nishoka (*3*) reported that 2,4,5-T was not detectable in samples of water-suspended sediment mixtures from 11 streams in the western United States.

However, a subsequent study of the same streams (*11*) making use of improved techniques showed 28 of 235 samples taken from 17 rivers during 1966–68 to be positive for 2,4,5-T residues. Twenty-one of these

*LC_{50}, median lethal concentration of a toxicant, typically placed in the ambient environment of the organisms whose survival is measured. Usually, the environment in question is aquatic. The terms, LD_{50} and LC_{50}, may be used interchangeable for aquatic organisms.

were from three rivers, the Arkansas, Brazos, and Canadian. All of the seven samples taken from the latter were positive. The amount of residues found was extremely small, ranging from 0.01 to 0.07 ppb. Samples were taken uniformly throughout the year and there appeared to be little effect of season on incidence or levels of 2,4,5-T residues.

Samples were analyzed as received with no effort made to separate water and sediments. It is possible that a high percentage of the residues was contained in the sediment since there is evidence that phenoxyacetic acid herbicide residues persist longer in sediments than in water. In either case, these data provide strong evidence that residues of 2,4,5-T in water which result from use of the herbicide in this country are not hazardous.

3. Plants—The levels of residues of 2,4,5-T in plants have received much less attention than has been devoted to insecticide residues. The comparatively short residual life of this material together with the fact that it is usually applied several weeks, or even months, in advance of harvesting dates, has allowed it to be used in most cases without danger of significant residues in the harvested product. However, it is recommended for control of weeds in permanent pastures and rangelands at rates which result in significant levels of residues that have been reported to persist, under some conditions, for as long as 6 weeks, Table 3. However, there has been relatively good agreement in results obtained by various workers who have reported on persistence of residues of 2,4,5-T applied to forage grasses in rangelands and pastures. The data of Morton, *et al.* (*12*) indicate levels in pasture grasses ranging from 10 to 32 ppm after about one month which agrees reasonably well with the 7 ppm reported by Baur, *et al.* (*2*) in range forage grasses.

TABLE 3.—*Rate of disappearance of 2,4,5-T residues from various types of forage crops. Estimated from semi-logarithmic plots in Figures 1–4.* (*12*)

No. days from treatment	Concentration, ppm (2,4,5-T)		
	2 pounds per A butoxyethyl-ester	2 pounds per A acid	1 pound per A amine
0	300	100	100
2			
4			
7	130	70	70
14	70	35	45
21	55	20	30
28	45	15	15
35	32	12	10
42	20	11	8
49	12	11	6
56	7	11	5
63		8	4
70		7	3
77		6	3
84		5	2
91		4	2
98		3	2

Substantial levels of residues occur in forage plants treated with 2,4,5-T at 2 lbs/acre, and appreciable quantities sometimes persist for as long as 3 weeks. This suggests that beef cattle permitted to graze pastures or rangelands immediately after treatment, or that diary cattle permitted to graze such areas 7 days after application at maximum rates recommended, may be exposed to dosages that are too high for safety (Table 4). Estimates of the levels of residues that might occur in forage grasses treated at higher rates indicate a possibility of transfer of residues to milk and even chronic toxicity (Table 4). However, the fact that no evidence of toxic effects has been reported and that residues of 2,4,5-T have been rarely found, and even when found have been at very low levels in dairy products that have been analyzed by FDA in total diet studies, argues against the probability that residues of this herbicide in forage crops pose any significant hazard.

TABLE 4.—*Estimated rates of disappearance of 2,4,5-T residues from forage treated at different rates with corresponding maximum amounts of herbicide that might be ingested by cattle pastured on forage treated at the rates indicated.*

No. weeks after treatment	2,4,5-T butoxyethylester			
	2 lbs/A [b]		4 lbs/A [c]	
	mg/kg in forage	mg/kg/day [d] ingested	mg/kg in forage	mg/kg/day [d] ingested
0 [a]	300	25	600	50
1	130	11	260	22
2	70	6	140	12
3	55	4	110	8
4	45	4	90	8
5	32	3	64	6
6	20	2	40	4
7	12	1	24	2
8	7	0.6	14	1.2

[a] Within 30 min. of treatment.
[b] Estimated from semilogarithmic plots of graph in Table 2. (*16*)
[c] Extrapolated from [b] using maximum rates of 2,4,5-T recommended for permanent pastures and rangelands in Agriculture Handbook No. 332, 1969.
[d] Assuming a 500 kg cow eating 45 kg forage per day.

4. Animals—Residues of 2,4,5-T in animals, as in plants, have received much less attention than some of the fat soluble, long-persisting organochlorine insecticides. The residues that occur from ingestion of the phenoxy herbicides are eliminated rapidly and there is evidence that accumulation occurs in only a few species. Erne (*6*) in one of the most thorough studies of the distribution and elimination of 2,4,5-T reported that it was readily absorbed and distributed completely in the body. He found that it was eliminated rapidly. Plasma half-life values from single oral doses of 100 mg/kg of the amine salt to male rats and pigs were 3 and 10 hours, respectively. Highest levels of residues were found in the kidney, liver, lungs, and spleen with levels sometimes exceeding plasma levels. There was little evidence of penetration into the brain or adipose tissues. The main excretory route was the kidney. His data (7) showing weak but "certain" protein binding of 2,4-D suggest that this may also occur with 2,4,5-T.

5. Food and feed—Results of studies of pesticide chemical residues in total diet samples by the Food and Drug Administration during the period 1964–68 provide convincing evidence that 2,4,5-T residues are not a significant health hazard in food in the United States. During this 5-year period 30 composite samples of about 82 food items each have been collected each year from retail markets in 25 or more cities. Each composite sample, representing a 2-week diet for a 16- to 19-year-old male, is analyzed by multiresidue methods for more than 60 chlorinated organic and organophosphorus insecticides and for herbicides, carbamates, and selected inorganic chemical residues. Examination of these samples is carried out at levels of sensitivity much lower than those normally used for products tested for compliance with tolerances.

Data reported for the period June 1967–April 1968 (*4*) show incidence and levels of 2,4,5-T residues that are typical. Only one sample of diary products was contaminated. About 2 percent of diary products and 1 percent of meat, fish, and poultry were reported to contain residues of 2,4,5-T. All of these residues were at trace levels, below 0.01 ppm. No residues of 2,4,5-T were found in any of the other 10 classes of foods.

It is significant that residues of 2,4,5-T were detected only in foods of animal origin. The most likely source is forage from pastures and rangelands treated with 2,4,5-T for weed or brush control.

Duggan and Lipscomb (*5*) summarized the results of sampling for herbicide residues in prepared food from the totat diel studies over a period of four years. From these studies, they estimated the likely dietary intake of all of the herbicides searched for to below:

Year	Estimated dietary intake (mg/kg/day)
1965	0.0012
1966	0.00022
1967	0.00005
1968	0.00006

Since 2,4,5-T residues are only a small percentage of these total herbicide residues found in foods it seems safe to conclude that there is little likelihood of exposure from this source.

Residues of 2,4-D and 2,4,5-T resulting from recommended uses by the military for defoliation.

All the available evidence indicates that 2,4-D and 2,4,5-T behave similarly in animals with respect to absorption, distribution, metabolism, and elimination. Since mixtures of these herbicides are used in the defoliation program in Vietnam, it does not appear reasonable to consider them separately.

The large-scale application of 2,4-D-2,4,5-T mixtures for defoliating military target areas in Vietnam poses some possibly unique hazards to humans. Application rates of about 26 lbs/acre of a 1:1 mixture of the n-butyl esters of the chemicals are generally heavier than those used for agriculture and brush clearing in the United States. (There have been a few, limited applications of 2,4-D reported to lakes, streams, and reservoirs in the United States at rates of 80–100 lbs/acre for aquatic weed control.) There are other differences. There are vastly greater areas involved in Vietnam. Because of the nature of the military targets—heavily wooded, jungle areas—it is not likely that many crops are grown in or near treated areas. Although defoliation procedures appear to be under rigid control with all reasonable precautions taken to prevent application to crops, the nature of military operations makes it likely that accidents may occur and that mistakes may be made which result in direct applications to non-target areas. In such cases it is possible that food crops and water supplies in restricted localities could receive heavy doses of the 2,4-D-2,4,5-T mixture. A much more likely possibility is drift of relatively small amounts of the herbicides to non-target areas. The n-butyl esters of both 2,4-D and 2,4,5-T are volatile and substantial amounts of both chemicals may vaporize at temperatures prevalent in Vietnam and escape from the target area.

If mixtures of 2,4-D and 2,4,5-T were applied directly to food crops at the rates being used in Vietnam for defoliation (about 26 lbs/acre), it is theoretically possible that amounts potentially hazardous to humans could be deposited on food. The butyl ester of 2,4,5-T applied to an improved pasture at the rate of 2 pounds per acre was found to result in an initial deposit of about 300 ppm on the forage (*12*). Direct application to food crops at 26 pounds per acre could not reasonably be expected to result in initial residues greater than 3900 ppm. Assuming initial residues on food crops as high as 3900 ppm from direct application at the rate of 26 pounds per acre is unrealistic. Such an assumption requires that: 1) surface/volume ratios of food items be similar to that of forage grasses; 2) all portions of food items, e.g., husks of corn, peels of banana, shells of coconut, be consumed; 3) there is no loss of herbicide during preparation and cooking; and 4) translocation of herbicide into portions of the plants used for food, e.g., root crops, banana pulp, and coconut flesh and milk, results in residues as high as if these portions had been treated directly. None of these is true. Some items of food could not be contaminated by direct contact with the spray formulation. Translocation from foliage to underground roots of sweet potato and fruits of peanut and into aboveground fruits such as coconut would be required for these foods to be contaminated.

Table 5 breaks down an estimated diet for a 60-kilogram Vietnamese into three parts according to the rapidity with which 2,4-D and 2,4,5-T might be translocated into the portions consumed for food.

Table 6 estimates the maximum believable concentrations of the herbicides in such a diet as being 3900 ppm initially, 1560 ppm after one week and 910 ppm after 2 weeks (See Table 2 for estimated rates of disappearance of 2,4,5-T residues from forage). The maximum dosage retained, substantially greater than any realistic figures, is about 30/mg/kg/day.

TABLE 5.—*Estimated for a 60-kilogram Vietnamese divided into three groups based on the rapidity with which 2,4-D and 2,4,5-T, might be translocated into portions consumed for food.*[1]

A. Foods into which very rapid movement is possible, not necessarily probable, and maximum concentration is attained immediately

	Dietary portions consumed g/person/day
Leafy green vegetable	52
Other vegetables	196
Condiment vegetable	40
Bananas	107
Other fruits	75
Total	470

B. Foods into which moderately rapid movement is possible, though not necessarily probable, and maximum concentration is attained within 1 week

Cereals	500
Fish and meat	311
Fish sauce	1
Spices	1
Coconut flesh	25
Coconut milk	12
Total	850

C. Foods into which movement is relatively slow and maximum concentration is attained within 2 weeks

Root vegetables	80
Beverage	5
Sugar and vegetable oils	95
Total	180

[1] Components of diet and amounts consumed adapted from "Federation of Malaya Nutrition Survey", Report Interdepartmental Committee for Nutrition for National Defense, 1964, 365 pp. (Modified in consultation with Vietnamese students at Louisiana State University.)

TABLE 6.—*Calculation of upper limits for daily dose of 2,4-D and 2,4,5-T combined when all food is fully exposed to one aerial application at 26 lbs/A.*[1]

[Maximum possible contamination, mg/kg/day]

Food Group	gm/person/day	Immediate	After 1 week	After 2 weeks
Group A	470	30	12	7
Group B	850		22	13
Group C	180			3
Total		30	34	23

[1] See Table 5.

The possibility that any of these assumptions might approach reality is probably nil. Many crops that are treated directly at such high rates show severe damage within a few days and would not be harvested. Translocation or penetration of residues into coconut meat and milk and banana pulp would take some time to occur, if at all, and would probably be at levels much lower than amounts deposited on foilage. The amount of residues of these chemicals that would penetrate into kernels of mature rice through palea and lemma is probably a very small percentage, if any, of the dose applied. There does not appear to be information on these points, however.

Probably the greatest potential hazard from contaminated food would be from ingesting leafy green vegetables, other vegetables, and fruits.

Much of the drinking water in the villages of Vietnam is from shallow, open wells and from rainwater collected from the roofs of thatched houses. Direct application of heavy rates of herbicide to these sources could result in the ingestion of substantial amounts of the chemicals in rainwater collected from roofs of houses. Assuming that about 270 mg of herbicide is applied per sq. ft. of surface, that water supplies are collected from rain falling on a roof having a total area of 200 sq. ft., and that all of the herbicide is washed off immediately after application and collected in containers holding 200 liters, a 60 kg person drinking 31. of water could get about 10 mg/kg/day. No information is available on the amounts of these chemicals that can be washed off a thatched roof by rainfall. However, data on rates of dissipation of 2,4-D and 2,4,5-T from dead litter material in pastures show rates of disappearance slower than for green tissues (*12*). Thus, it appears reasonable to expect considerably less than 100 percent of the amount applied to be washed off a thatch roof treated with 2,4-D and 2,4,5-T. Even if it were all washed off, it appears to be unreasonable to expect it all to be captured in vessels having a combined capacity of only 200 liters. Therefore, any reasonable assumption would be that a person getting drinking water from such a source contaminated at the maximum rate possible would get much less than 10 mg/kg/day.

Drinking water from a shallow well contaminated at the maximum rate expected from a 26 lb/acre application, assuming a depth of 4 feet for water in the well, would amount to less than 0.5 mg/kg/day, and thus would pose no hazard.

Other possible routes of entry into humans from accidental direct application to non-target areas would be by inhalation and penetration through the skin. There is inadequate information available on these points to form any concept of the potential hazard of residues from these sources. Way (*17*) has suggested that there is little hazard of transport across the skin barrier. However, these materials are fat soluble which might encourage their percutaneous absorption. At least one study of the acute toxicity of the defoliant, Purple, (esters of 2,4-D and 2,4,5-T) suggested that skin absorption of the animals tested occurred but was perhaps 10–20 times slower than absorption from the GI tract (*10*). In the extreme situation of a nude, pregnant female, prone beneath an area of spraying of the defoliant, Orange, the maximum impingement of 20.2 mg/kg of 2,4,5-T on her skin might be expected. This should probably be viewed as equivalent to 2.0 mg/kg of an oral dose.

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SOME ECOLOGICAL EFFECTS

Summary

Elimination of types of vegetation on which mammals, birds, fish, and insects and other species depend, can severely reduce or eliminate them from the treated habitat. However, altering the vegetation makeup may also benefit certain types of wildlife. The elimination of water hyacinth from some water bodies, for example, has proved a necessity for the survival of sport fishery programs.

2,4,5-T has been found to affect non-target organisms in a number of ways:

1. Although chickens, quail and mallard ducks appear to be relatively resistant to 2,4,5-T, the herbicide has been reported to reduce egg production in domestic chickens.

2. Some formulations of 2,4,5-T, such as certain esters, have been found to be quite toxic to fish and oysters.

3. The hydrocyanic acid content of sudan grass was found to increase 70 percent following treatment with 2,4,5-T. Nitrate levels in certain plants may increase up to 36 percent following treatment with 2,4,5-T, making them more toxic to mammals. Increasing the toxicity of plants to wildlife might have important effects in nature.

5. 2,4,5-T may cause some species of microorganisms to decrease in number while having no effect upon other species. In soil, 2,4,5-T has been found to largely disappear in about three months.

2,4,5-T has been found to influence non-target organisms both directly and indirectly through habitat changes. The impact of 2,4,5-T on the principal classes of non-target organisms is presented in the following sections.

Mammals

Roe and Hymas (*12*) presented data to indicate that the acute oral toxicity LD_{50} of 2,4,5-T to various species of mammals was about 500 mg/kg.

2,4,5-T has some repellent action. When cottontail rabbits (*Sylvilagus floridanus*) were given a choice of either 2,4,5-T treated vegetation or untreated, the rabbits consumed almost none of the treated vegetation. (*14*)

Applying 2,4,5-T or 2,4,5-T in combination with 2,4-D at recommended dosages for brush control in Michigan, resulted in killing the oak type vegetation and released the pine and encouraged a dense ground cover of grasses and other herbs, taller berry producing shurbs, and tree sprouts. (*7*) The low growing food and cover were ideal for deer, rabbits, grouse, and other forest animals.

Chemical brush control was carried out in power-line right-of-way with 2,4-D and 2,4,5-T applications. Woody brush was practically eliminated. White-tail deer (*Odocoileus virginianus*) have used both the treated and untreated areas and their use of both areas increased during the four years of investigation. (*2*) The deer made less use of the treated areas during the winter months because there was less food available. The deer fed most heavily in the treated areas in the spring and early summer on various grasses and herbs. Deer also bedded down in the treated areas in patches of sedge and grass. Numbers of cottontail rabbits were found to increase in the treated areas because of improved food and cover.

Birds

Fifty percent mortality in birds occurred for the following doses (2,4,5-T fed in the daily diet for less than 10 days): 5,000 ppm for young bobwhite quail (*Colinus virginianus*); 5,000 ppm for young mallard ducks (*Anas platyrhynchos*). (*4*) Approximate LD_{50}'s based on estimated food consumption, were: 9,000 mg/kg for the bobwhite; 21,000 mg/kg for the mallard.

The use of 2,4,5-T and 2,4-D for brush control under power lines improved the environment for ruffed grouse (*Bonasa umbellus*) (*2*). The grouse were found on the edges within 150-200 feet of the right-of-way rather than on the right-of-way itself. This emphasized the importance of the right-of-way as a creator of edge effects. Wild turkeys (*Meleagris gallopavo*) were also observed to make effective use of the rights-of-way treated areas. The young turkeys were attracted to the openings for feeding on various insects which were more abundant on the grassy right-of-way than within the wooded areas.

Chickens were exposed daily for 14 days to grass treated with 2,4,5-T (15 percent active agent) at ¼ oz/gal of water and 2-½ oz/gal. (*5*) The low 2,4,5-T treatment led to a 9 percent reduction in egg yield and the higher dosage to an 18 percent reduction but there was no change in the fertility or hatchability of the eggs. The exposed chickens also lost some weight.

Fish

The 24-hour LC_{50}* for rainbow trout (*Salmo gairdnerii*) exposed to 2,4,5-T was 12 ppm; however, Bohmont (*1*) reported a 48-hour LC_{50}

*LC_{50}, median lethal concentration of a toxicant which kills 50 percent of the test organisms.

for rainbow trout at 1.3 ppm. Bohmont also calculated the 48-hour LC_{50} for bluegills (*Lepomis macrochirus*) to be 0.50 ppm.

Young silver salmon (*Oncorhynchus kisutch*) exposed to a combination of 2,4,5-T and 2,4-D (about 10 percent of each chemical in the formulation) at concentrations of 50 ppm or more were observed to be "immediately distressed and would snap their jaws, dart about the aquarium, and leap out of the water before loss of equilibrium and death." (*8*)

Mullet (*Mugil cephalus*) exposed to 50 ppm of 2,4,5-T for 48 hours exhibited no noticeable effects. (*3*)

Table I gives 24- and 48-hour LC_{50}'s of bluegill sunfish to various 2,4,5-T formulation. (*9*) The esters appeared to be most toxic, probably due to better solubility. No attempt was made by Hughes and Davis to explain the wide variation in results obtained from different batches of the same formulation.

TABLE 1.—*The LC_{50} of bluegill sunfish to 2,4,5-T formulations.* (*9*)

	24-hour	48-hour
Dimethylamine	144	144
Isooctyl ester*	31	31
Isooctyl ester*	28	26
Isooctyl ester*	10.4	10.4
Propylene glycol butyl ethyl ester	17	17
Butoxyethanol ester	1.4	1.4

*Different batches of the same formulation.

Molluscs

The exposure of oysters (*Crassostrea virginica*) to 2.0 ppm of 2,4,5-T acid for 96 hours had no effect on shell growth. (*3*)

Invertebrates

The minimum lethal dosages (ppm) which produced a kill exceeding 25 percent with 2,4,5-T are listed for the following fish food organisms: *Daphnia* 1.5; *Eucypris* 0.5; *Hyallella* 0.7; *Palaemonetes* 1.2; *Amphiagrion* 7.5; *Pachydiplax* and *Tramea* 8.0; and *Chironomus* 6.0. (*16*)

The exposure of brown shrimp (*Penaeus aztecus*) to 1.0 ppm of 2,4,5-T for 48 hours had no noticeable effects. (*3*)

Plants

Swanson and Shaw (*15*) demonstrated that the hydrocyanic acid content of sudan grass was increased by 70 percent in pllts treated with 1 lb/acre of 2,4,5-T.

When 9 species of weeds were treated with sublethal dosages (0.25 lb/acre of 2,4,5-T, the nitrate content of the plants decreased from 5 to 32 percent in 4 species but increased from 3 to 36 percent in the other species. (*6*) The 36 percent increase occurred in *Impatiens biflora*.

The exposure of phytoplankton to 1.0 ppm of 2,4,5-T for 4 hours caused no decrease in growth. (*3*)

Microorganisms

Magee and Colmer (*11*) reported that 2,4,5-T at 1,500 to 2,000 ppm produced inhibition of respiration to *Azotobacter* however, 2,4,5-T was found not to affect *Streptomyces* at 2 and 50 lb/acre.

Persistence

2,4,5-T applied at a rate of ½ to 3 lb/acre was found to persist for 2 to 5 weeks with little or no leaching, under summertime conditions in a temperate climate and moist loam soil. (*10*) Sheets and Harris (*13*), however, reported that 2,4,5-T generally persisted for about 3 months under moist soil conditions.

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