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Item ID Number	05557 ☐ **Not Scanned**
Author	MacLeod, Colin M.
Corporate Author	Panel on Herbicides, President's Science Advisory Com
Report/Article Title	Report on 2,4,5-T
Journal/Book Title	
Year	1970
Month/Day	July
Color	☐
Number of Images	0
Description Notes	See item 882 for a later version.

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JUL 23 197

REPORT ON 2,4,5-T

PANEL ON HERBICIDES

PRESIDENT'S SCIENCE ADVISORY COMMITTEE

31 July 70
Received from
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REPORT ON 2,4,5-T

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SUMMARY AND RECOMMENDATIONS

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I. SUMMARY AND RECOMMENDATIONS

A. 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In examining the toxicity of 2,4,5-T, the Panel reviewed the information available from the literature (as well as some unpublished documents) which had been considered in the past in establishing policy decisions for the various uses to which this pesticide had been put.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 alteration. 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, expecially further experiments to confirm and extend 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 presence depends upon variations in the reaction conditions. Other dioxins (some more toxic than 2,3,7,8-tetrachlorodibenzo-p-dioxin) 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 it accounts 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 non-target 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.

B. 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, such as those on repeatedly recrystallized 2,4,5-T. 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.

d. 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. The family of compounds, known as polychlorinated dioxins, have been found to be highly toxic and capable of eliciting teratogenic effects. The several dioxins vary widely in toxicity. Further, it appears that they may arise in the environment from multiple sources. Therefore, control over known sources should be exercised to the extent possible.

2. Restriction on use of 2,4,5-T.

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 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 demonstration of teratogenicity, which may occur with many chemicals at selected 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.

3. 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.

4. 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.

5. Prompt and expeditious release of information.

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.

6. Interim imposition of restrictions on pesticide use while additional information is being collected.

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.

7. 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).

8. 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 amount in 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.

9. Registration procedures should include toxicological studies on related compounds where judgment indicates this to be desirable.

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. For example, the National Cancer Institute study indicated carcinogenic propensities of some but not all 2,4-D esters. 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.

II. 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 further 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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SUMMARY - Section III - Chemistry

2, 4, 5-trichlorophenoxy acetic 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.