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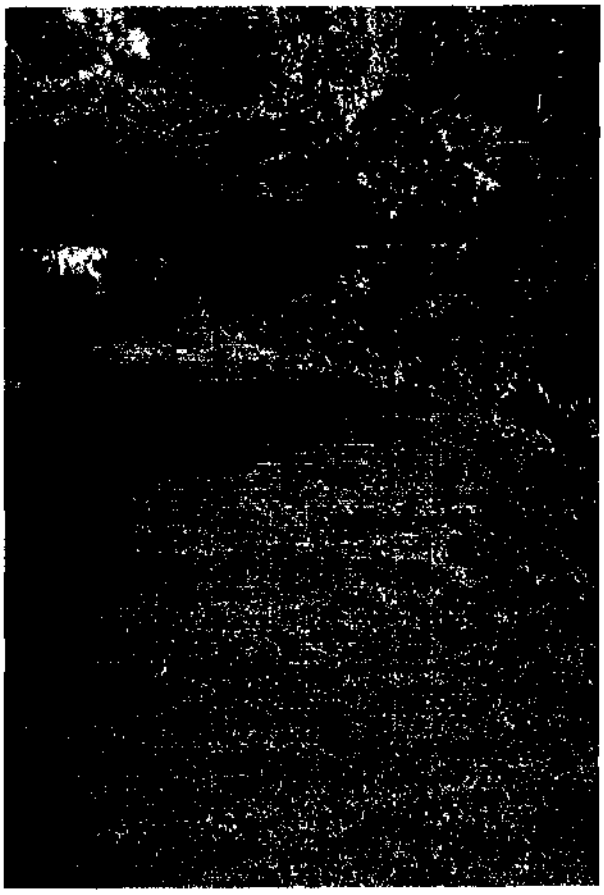

COMMENTS from CAST
1987-3
December 1987

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PERSPECTIVES ON THE SAFETY OF 2,4-D

COMMENTS from CAST
1987-3
December 1987

Council for Agricultural Science and Technology

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Foreword

The public faces what it may think are insurmountable obstacles in dealing with the relationship between human health and chemicals in the environment. Wide-ranging opinions exist on the benefits and risks associated with chemicals used in production agriculture, food processing, home lawn care, and other areas of daily life. Plenty of evidence exists that chemical use has benefited agriculture and the food supply through the control of pests and diseases of animals and plants. Yet consumers and producers alike are asking necessary and critical questions about the impact of these chemicals on human health.

One chemical used widely to control weeds on farms, forests, lawns, and golf courses for four decades is 2,4 dichlorophenoxyacetic acid or 2,4-D. It is suspected by some to cause cancer in humans.

The release of a paper by Hoar et al (1986) implicating 2,4-D in the increased incidence of non-Hodgkin's lymphoma in a group of Kansas wheat farmers led the CAST board to initiate a task force review of the 2,4-D literature. The task force, under the leadership of Dr. Lawrence J. Fischer and consisting mainly of epidemiologists, toxicologists, and weed scientists, met to review the situation, agree upon an outline for the report, and establish a writing protocol. The task force agreed to focus on epidemiology, exposure to 2,4-D by various segments of the population, and animal toxicology in the report. The resulting report, "Perspectives on the Safety of 2,4-D," addresses public concerns regarding health risks and use of the herbicide, and explains how animal toxicity studies are conducted, with specific reference to 2,4-D.

On behalf of CAST, we thank the task force participants, who gave of their time and expertise to prepare this report as a contribution from the scientific community to greater public understanding of chemical issues. We thank also the employers of the participants, who made the time of their staff members available at no cost to CAST. The members of CAST deserve special recognition. Their unrestricted contributions in support of the work of CAST have financed the preparation and publication of this report.

William W. Marion
Executive Vice President
CAST

Billy E. Caldwell
President
CAST

Contents

Summary

All available information gained from epidemiologic studies, and from controlled experiments in laboratory animals should be used in making a judgment regarding the safety of 2,4-D. Using such an approach, this task force concludes that 2,4-D, as it is generally used, does not represent a significant human health threat. However, users should apply it with the care and respect required of every chemical that can cause harmful effects in high doses. Many chemicals enjoying wide use, such as detergents, gasoline, and certain insecticides fall into this category.

A recent epidemiologic study concluded that human exposure to 2,4-D related to its use in Kansas agriculture was associated with an increased incidence of cancer. This finding should not be dismissed as wrong, nor should it be accepted as a correct reflection of the safety of 2,4-D. This study, in light of its strengths and weaknesses, must be evaluated with results from other studies, which indicate that 2,4-D use does not represent a significant cancer risk.

A cautious approach dictates that reports of possible carcinogenic effects of 2,4-D in humans serve to increase our scientific vigilance and investigation into the issue. Results from several ongoing epidemiologic studies of cancer and herbicide use will be available in the near future. If those results support the findings of the study conducted in Kansas, then the government should give serious consideration to restricting the use of 2,4-D. Should the forthcoming data not indicate a link between 2,4-D exposure and human cancer, then our present conclusion will stand.

Introduction

Use of the herbicide 2,4-D started about 40 years ago. It revolutionized weed control practices on farms, forests, waterways, and lawns. Users continue to apply 2,4-D to millions of acres because they find it effective. In general, they perceive it as fairly safe for themselves and the environment. Periodically, however, questions have been raised regarding the safety of 2,4-D for humans. Most recently the "Kansas Farm Worker" study indicated that high exposure to 2,4-D was associated with one particular type of cancer (Hoar et al., 1986). The results of this study, conducted by scientists at the National Cancer Institute (NCI), prompted renewed concern for the safe use of 2,4-D.

An excellent, recent review of the scientific literature does exist concerning the safety of 2,4-D (Canadian Centre for Toxicology, 1987). This report will not duplicate that effort. A CAST Task Force met in June of 1987 to discuss the safety of 2,4-D and to develop a report that would benefit the informed public. The goal of this document is to place in perspective both the current and older information relevant to the safety of 2,4-D to humans. Task force members hope that unwarranted fears will be laid to rest. At the same time health risks that may be present, or that have not yet been studied adequately, will be brought to the public's attention.

Safety evaluations made from partial or narrow segments of information should be avoided when a large amount of toxicity data are available. Instead, conclusions should be drawn from all available data. Readers should understand strengths and weaknesses of the procedures for producing information used in safety assessment. Consistent with these views, this report will discuss and integrate a variety of toxicologic information. It addresses the usefulness and conduct of epidemiologic studies in humans and discusses the question of whether or not 2,4-D exposure is associated with a higher risk of cancer. The report gives particular attention to the Kansas Farm Worker study. Next, it considers some important issues surrounding the extent of human exposure to 2,4-D. Finally, a discussion is presented concerning the relevance of laboratory animal studies in evaluating the safety of humans exposed to chemicals in general and to 2,4-D in particular. Throughout the report, an attempt has been made to engender an understanding of the methods by which information regarding chemical safety is generated and applied to assess human risk. This report should help readers draw conclusions about the question of 2,4-D safety. It should also provide the public a better appreciation for the difficulties involved in arriving at final conclusions regarding the safety of chemicals introduced into the environment.

Epidemiologic Studies

The Nature of Epidemiology

Epidemiology is the science that examines the distribution and causes of disease in populations. When exposure of humans to certain chemicals is suspected of causing disease, epidemiologists gather information on the extent of human exposure to the chemical. They use statistical methods to link exposure to an increased incidence of the disease. The goal of an epidemiologic study is to provide an accurate estimate of disease risk associated with an exposure situation.

Readers should understand that no substitute exists for human epidemiologic studies. However, they are expensive to conduct, difficult to design, and the results are rarely as clear as everyone would wish. Nevertheless, epidemiologic studies can provide information on adverse health effects caused by human exposure to physical, chemical, or infectious agents. Some epidemiologic studies of health effects provide clear and straightforward answers. One example is the association between cigarette smoking and lung cancer. Another is the clear-cut association between alcohol drinking and automobile-related fatalities. A third example is the harmful effects of radiation such as those produced by the atomic bombs on the exposed human populations of Nagasaki and Hiroshima. Little doubt exists about the cause of disease or death in these studies because of the severe impact on health caused by smoking, by alcohol-related impaired driving performance and by high radiation levels.

On the other hand, when we consider whether or not exposure to a particular pesticide such as 2,4-D causes adverse health effects, the reader will notice that a clear-cut answer is difficult to obtain. Several factors may contribute to this difficulty. First, the chemical in question may not provide severe enough biological damage to be easily detected as a causative agent by epidemiologic methods. In addition, the disease under scrutiny may have multiple causes that confound the identification of the pesticide as a contributing factor. Whether or not low intermittent exposure to a particular pesticide or chemical over a period of 20 to 30 years, for example, can contribute to the cause of cancer does not represent a simple scientific query. Note that cancer has an incubation period of 10 to 20 years in humans. Any other event or exposure, in addition to the pesticide, occurring during the preceding years must also be considered as a possible cause of the cancer. Exposure to radiation for treatment of a tumor, occupational exposure to asbestos, tobacco smoking, and heavy alcohol use, or any combination of such factors, would make it difficult to assign the cause of cancer to pesticide exposure alone.

Studying the causes of major long-term illnesses, scientists in this field usually use two primary methods. The first is the *cohort study* in which the emphasis is on locating and studying an indisputably exposed group of individuals. The term "cohort" indicates a group of individuals who share a similar degree of exposure to a chemical. Factory workers exposed repeatedly to a suspected cancer-causing agent would represent a typical cohort. A "control cohort" means a group of relatively nonexposed persons. Researchers compare the incidence of disease (e.g., cancer) in the exposed cohort to the incidence of disease in a nonexposed control cohort. Individuals in the control group are often matched as closely as possible in age, sex, and lifestyle to the persons in the exposed group. Time between initiation of exposure and the measurement of the disease's appearance must be considered. Cancer, as noted above, may not appear for 10 to 20 years after sufficient exposure has occurred. Cohort studies tend to be small in terms of total number of persons involved. Large numbers of exposed persons often are not available, and the number of exposed persons having a particular disease (e.g., cancer) may be small indeed.

Another type of study is the *case-control study.* It is superior to the cohort study in its ability to detect differences among groups in the total population, in part because the case-control study can use all cases of a disease from a large population. The larger the number of cases, the more accurately scientists can detect causes of disease. Disease-free persons selected for a control group are matched by age, sex, race, or other relevant variables with persons in case groups. Researchers interview individuals in case (disease) groups and control groups to learn of possible exposures to the suspected agent (e.g., 2,4-D) in the preceding 10 to 20 (or more) years. Difficulties do exist in asking questions about exposures which may have occurred repeatedly over the preceding 20 or more years. Unless exposures were dramatic, persons in case groups and control groups may lack accurate recall of events surrounding possible exposure. Accuracy of recall represents an inherent problem in most case-control epidemiologic studies. Some persons may forget exposure (under-reporting), while others may think they were exposed when they were not (over-reporting). A link between exposure and the disease is detected when there is a higher than normal incidence of the disease in groups of individuals exposed to the chemical. Finally, the epidemiologist must

determine that no significant difference other than that of chemical exposure exists between cases and controls to explain the increased occurrence of the disease.

Studies of 2,4-D As A Possible Cause of Human Cancer

Swedish epidemiologists reported results from a case-control study in the late 1970's indicating that Hodgkin's disease, non-Hodgkin's lymphoma, and soft tissue sarcoma occurred more frequently in forestry workers and farmers who were regularly exposed to phenoxy herbicides, including 2,4-D (Hardell and Sandstrom, 1979; Eriksson et al., 1981). It must be said that these three forms of cancer are not as easy for pathologists to identify and classify as are some other forms of cancer. Of the three, Hodgkin's disease (HD) is the most concisely described and defined. Pathologists have more often disagreed over the identification and classification of soft tissue sarcoma (STS) and non-Hodgkin's lymphoma (NHL). Disease classification difficulties can lead to problems with interpretation of the results obtained in epidemiologic studies.

The results from Sweden associating phenoxy herbicide exposure in forestry and agricultural workers to an increased risk for HD, STS, and NHL were severely criticized in scientific debate. In addition to possible disease classification problems, criticism focused on a lack of scientific rigor in the design of the studies. Forestry workers were exposed at that time to multiple pesticides, including 2,4,5-T, which is known to contain a dioxin contaminant that causes cancer in animals. Other criticisms included lack of adequate exposure information, bias in the recall of exposure, and lack of a clear dose response relationship. Despite their deficiencies, however, the Swedish studies pointed out the need for further investigations.

After the Swedish reports, case-control studies were made of New Zealand agricultural workers exposed to phenoxy herbicides (Smith et al., 1984; Pierce et al., 1986) and Vietnam veterans possibly exposed to Agent Orange, a 1:1 mixture of 2,4-D and 2,4,5-T (Greenwald et al., 1984). The results showed no increased risk of cancer due to exposure. These studies also have been criticized for some of the same reasons as were the Swedish studies. A more recent report presents results of a case-control study in Washington state (Woods et al., 1987). It shows a small increased risk of NHL in forestry workers and farmers who may have had prolonged exposure to herbicides and other types of occupational chemicals, but the results also show that increased risk could not be associated with any specific phenoxy herbicide product, including 2,4-D.

A number of cohort studies have been conducted using individuals known to have experienced exposure to

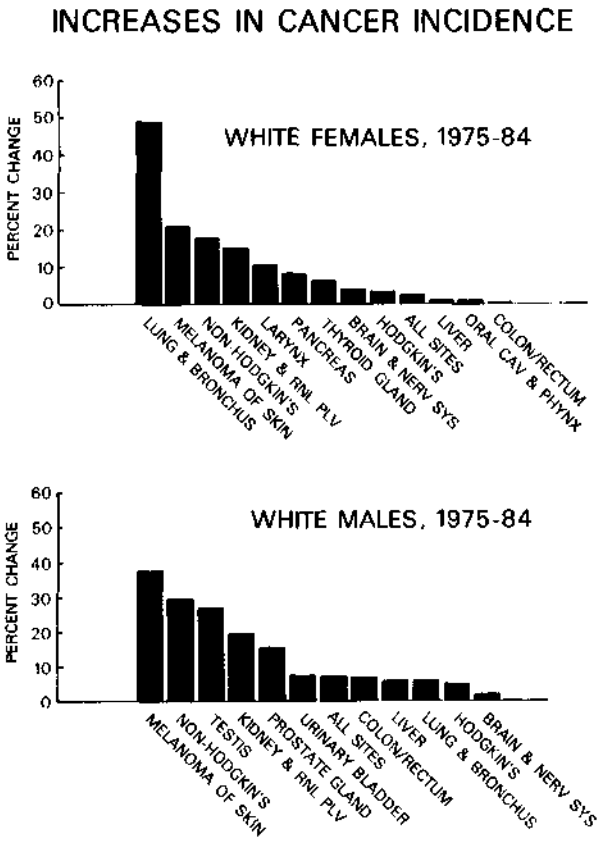

Figure 1. Increases in cancer incidence over a ten-year period in the United States. (From: 1986 Annual Cancer Statistics Review, December 1986, National Cancer Institute). The large increase in lung cancer in females is believed to result from a change in smoking habits many years ago. The cause is unknown for the increase in Non-Hodgkin's Lymphoma (NHL) in both sexes. Decreases in some forms of cancer have occurred over this period and are not shown here.

2,4-D. The Ranch Hand report on Air Force Personnel (Wolfe et al., 1985), the Ontario Hydro Study on Forestry Workers (Green, 1986) and a report on manufacturing personnel (Bond et al., in press) all indicate no link between 2,4-D exposure and cancer of any type. Although each of these studies contains relatively few exposed individuals, thus limiting their ability to detect an association between 2,4-D and the disease, it is persuasive that all three have obtained the same result.

The Kansas Study

For unknown reasons, deaths from NHL have increased 20 to 30% since 1975 across the United States (Figure 1; National Cancer Institute, 1986). Investigators assume causes for such an increase may have occurred 10 to 20 years ago. What factors could have contributed to this steady, gradual rise? National Cancer Institute

(NCI) epidemiologists questioned whether the introduction of herbicides into general agricultural use after 1946 could be a contributing factor. Geographic frequency maps of these lymphomas suggested possible higher incidence in agricultural areas in Iowa, Nebraska, Minnesota, and Kansas (Pickle et al., 1987; Cantor, 1982). These are areas where herbicide use has been quite intensive.

Realizing that multiple causes of cancers such as HD, STS, and NHL may exist, NCI investigators launched a well-designed case-control study in Kansas attempting to find an association between these cancers and exposure of farmers to herbicides, including 2,4-D. Scientists used a statewide cancer registry in which all cases of the three cancers detected within six years had been recorded. There were about 200 cases of each of the three types of cancer. People having these tumors were matched with control persons who did not have cancer. Researchers matched control (noncancer) persons using age, sex, race, and vital status (living or dead), since the study included both living and deceased cases.

Results of the Kansas study were widely publicized in the mass media, with news reports leaving the impression that exposure to 2,4-D produced an increased risk of cancer. The study did conclude that herbicide exposure to farmers under certain circumstances produced a higher incidence of NHL, but unlike the earlier Swedish studies, researchers found *no* association between herbicide exposure and STS and HD. Thus, the Kansas study only partially supported the Swedish results. This lack of complete agreement between different epidemiologic studies is not unexpected. A general lack of agreement among epidemiologic studies attempting to link 2,4-D and cancer has existed.

The Kansas study results indicate that farmers exposed to herbicides more than 20 days per year show a six-fold increased risk of NHL relative to nonfarmers. Farmers who didn't take protective measures when using herbicides showed the highest risk. Farmers who used protective measures or who did not directly apply the herbicide themselves experienced no increased risk of NHL. Should other studies confirm these results, it would indicate that *if* a true risk of cancer from phenoxy herbicide exposure exists, users can reduce it to very low or undetectable levels when they take appropriate care applying the chemicals.

The Kansas and Swedish studies do agree that there is a link between herbicide exposure and NHL. Scientists have argued, however, that the Kansas study contains several weaknesses which would tend to invalidate its conclusion that 2,4-D exposure results in an increased risk of developing NHL. (MacMahon, 1986; Morgan, 1986).

A fundamental problem with a case-control study is lack of accurate recall in an interview (Bradburn et al., 1987). Farmers in the Kansas study were asked to remember details of herbicide application that occurred over 20 years ago. If a farmer had died of cancer, his widow or children were asked to recall details such as the type of herbicide, the number of years of use and the days used each year. It is unlikely that an accurate picture of exposure can be gained this way. Certain results of the Kansas study show these inaccuracies. For example, 75% of farmers or their relatives said they used *no* herbicides on their farms. This result cannot be correct given Kansas agricultural practices. This then is an example of large scale under-reporting of herbicide use.

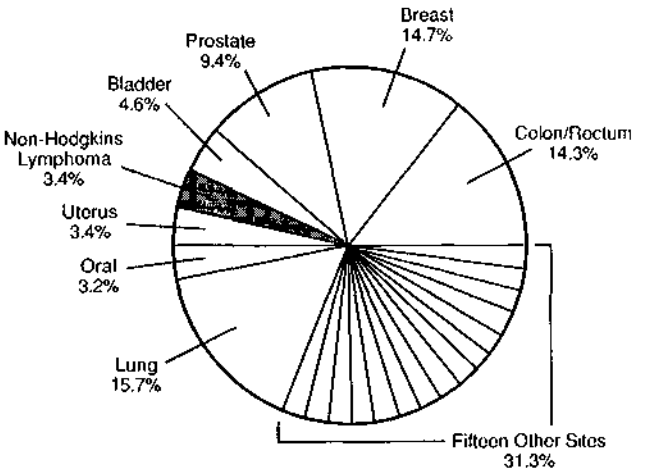

Figure 2. Incidence in 1984 (age-adjusted) of various sites of cancer in men and women of all races. (Data taken from 1986 Annual Cancer Statistics Review, National Cancer Institute, U.S. Public Health Service, page III-B-19)

A consistent dose-response relationship does not exist in the data obtained from Kansas farmers. Comparing cancer patients who had used herbicides for more than 26 years with those using them for six years did not show that longer use caused a higher risk of NHL. Another criticism is that the number of cancer cases in each exposure group was small. Often researchers calculated an increased risk based on the assignment of two to five cancer cases to a particular exposure group. Because the degree of exposure was based on memory or recall during an interview, which is recognized to be a relatively inaccurate process, errors in the assignment of cancer cases to a particular exposure group are expected. With so few cases in each exposure group, a small number of inaccurate exposure assignments can invalidate the conclusion that a particular exposure group exhibits a higher cancer risk.

NHL is a relatively rare form of cancer, representing 3.4% of all cancer cases nationally (Figure 2; National

Cancer Institute, 1986). The small number of cases in a farming state such as Kansas makes detection of a cancer-causing effect of herbicides extremely difficult. If herbicide exposure in connection with farming causes a slight increase in NHL, relatively few cases can be expected to occur from this type of exposure. If a cancer with a higher incidence in the population (e.g., lung or colon/rectum) were being studied in connection with 2,4-D use, a larger number of cases would be involved and the likelihood of obtaining a statistically valid conclusion would be increased.

In spite of criticisms, the Kansas study is believed to represent a useful epidemiologic study. Such studies are recognized to have inherent problems and limitations (Colton, 1986), but most experts reviewing the Kansas study acknowledge the skill, size, scope, and quality of the investigation. They do not agree with the authors, however, that it is a strong or specific finding. Where does this leave the reader and the public? In general, knowledgeable scientists do not feel confident in connecting NHL and unprotected, prolonged use of 2,4-D. Nonetheless, it can be acknowledged that a statistical association has been revealed among a very small subgroup of Kansas farmers who applied herbicides without protection for an extended period of time. Researchers did not investigate whether viral infection, family history of cancer and radiation exposure—all suspected causes of NHL—could have occurred more frequently in the herbicide-exposed farmers. Nevertheless, readers must accept results from the Kansas study as a single piece of evidence in the solution of a puzzle demanding many pieces of evidence. It does not represent sufficient proof that exposure of the public to 2,4-D under its normal use constitutes a cancer risk. Other evidence is necessary, and this should become apparent upon reading subsequent sections of this report.

Ongoing Studies

At the present time, two other large case-control studies are in progress that will yield additional information on phenoxy herbicide exposure as a possible cause of cancer in humans. These studies are similar to the Kansas study and are being conducted in Iowa, Minnesota, and Nebraska by investigators from the National Cancer Institute. Those studies may or may not eventually confirm results found in Kansas. A preliminary report of results obtained in Iowa and Minnesota presented at a Soil Science Society of America meeting, indicates that no increased risk of NHL in farmers exposed to 2,4-D occurred (Cantor and Blair, 1986). Regardless of the final outcome of these studies, more definitive information will be available after their completion in 1988.

Human Exposure to 2,4-D

Consideration of possible adverse human health effects caused by 2,4-D requires knowledge of the extent of human exposure to the chemical. Assessing human exposure is one of the most difficult steps in calculating human health risks ascribed to chemicals. This section of the report will consider human exposure to the herbicide 2,4-D as it may occur in factory workers, chemical applicators, and in the general public.

Manufacturing Personnel

Epidemiologists have conducted studies on the health of factory workers manufacturing 2,4-D. Most published cohort epidemiological studies on the health of workers engaged producing 2,4-D do not include information on the amounts of 2,4-D to which they were exposed. One noteworthy exception is the mortality study by Bond et al. (1987). That report gives results of industrial hygiene measurements in 2,4-D-exposed workers performing different types of manufacturing operations from 1949 to 1983. Researchers measured concentrations of 2,4-D in the air surrounding workers. The highest amount of the herbicide found in the air was 4 milligrams per cubic meter (mg/m^3). This occurred in 1949 and involved operation of a drier. The next highest level recorded that year was 0.4 mg/m^3. These amounts were reduced over the years in that operation. By 1983 values ranged from none detected to 0.01 mg/m^3.

In these workers, no excessive deaths occurred from cancer or any other disease that scientists could attribute to 2,4-D exposure. Particular attention was given to studying the possibility of increased brain tumors, soft tissue sarcomas and lymphatic cancers in the workers. Like many cohort epidemiological studies, this one had relatively small numbers of subjects available for study. However, the results showing a lack of association between 2,4-D exposure and cancer conform to those from other studies of workers engaged in manufacturing 2,4-D (Axelson et al., 1980; Riihimaki et al., 1982; Wiklund and Halm, 1986). These studies, each containing small numbers of exposed individuals, combine to give substantial evidence that a cause and effect relationship between 2,4-D exposure and mortality from any cause does not exist.

Applicator Exposure

Applicator exposure to phenoxy herbicides, especially 2,4-D, has been carefully studied in Canada, Europe, Turkey, Scandinavia, and the United States. Research results vary considerably as to the actual amounts of 2,4-D or other herbicides that enter the bodies of applicators. Much of this variation is due to decided differences in applicators' work habits and hygienic practices. Some did not wash their hands, wore the same clothes all week long, and cleaned out plugged sprayer nozzles by blowing through them with their mouths. Others wore rubber gloves and supervisors made sure they avoided excessive contact with the herbicide. These workers washed their hands after contact with herbicides and changed clothes and showered daily. However, these reports all agree on the following: (1) inhalation of 2,4-D from the atmosphere due to spraying operations is minimal and need not be considered when determining worker exposure; (2) the major route of exposure is dermal, especially from hand contamination; (3) only about 6% of 2,4-D deposited on the skin is absorbed and the absorption rate is slow; (4) absorbed 2,4-D is excreted rapidly in the urine; and (5) the total amount of 2,4-D excreted in urine is approximately the same as that absorbed into the body after herbicide exposure.

Forestry Applicators

An excellent study by Frank et al. (1985) concerned the exposure of forestry workers engaged in applying 2,4-D from helicopters at the rate of 1.4 pounds per acre. This study is of particular interest because herbicide application in forests has been a major concern to some people, and has generated great attention from the media. The report includes two noteworthy points. First, from estimates of 2,4-D in urine, the highest dose to any worker was 0.022 milligrams per kilogram (mg/kg) of body weight per day. One method of judging the risk of 2,4-D exposure to humans is to compare this dosage with an acceptable daily intake (ADI)[a] of the herbicide in our diet. In 1971 the United Nations World Health Organization (WHO) and the Food and Agricultural Organization (FAO) appointed scientific panels which established an acceptable daily dietary intake of 2,4-D of 0.3 mg/kg of body weight per day. Comparing a 0.022 mg/kg/day dose in the highest exposed forestry worker to the ADI value of 0.3 mg/kg/day, workers could absorb approximately 15 times more 2,4-D before reaching the level scientists have deemed an unacceptable daily intake.

The second major point of Frank et al. (1985) arose

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[a] An ADI is the estimated maximum amount of a material that people could eat every day of their lives without harmful effects and is based on knowledge gained from laboratory animal studies. An ADI value is calculated using a safety factor to account for sensitivity differences among humans and between humans and laboratory animals.

from results obtained from a human volunteer who stood directly under the spray swath for a single exposure. The chemical was applied at a rate of 1.4 lb of 2,4-D per acre and from a height of 36.6 feet. This is approximately twice the rate that workers would apply to a lawn. To create a "worst case" situation, spray was allowed to dry and the volunteer did not shower or change clothing. The amount absorbed was 0.44% of the total amount of 2,4-D deposited on the skin and clothing (shorts, T-shirt and sneakers). It totaled 0.0045 mg/kg of body weight. In this exaggerated exposure case, the dose of 2,4-D was only 1.5% of the ADI value for 2,4-D. Using the latest no-observed-effect-level (NOEL)[b] of 1 mg/kg for 2,4-D in laboratory animals (Mullison et al., 1986), this exaggerated human exposure resulted in a dose more than 200 times below that dose to which rats have been exposed for a lifetime without showing any adverse health effects. Since this result was from an exaggerated exposure situation created around one person, other researchers may or may not be able to reproduce its results. Nevertheless, the result agrees with other results indicating that exposure of 2,4-D to applicators or bystanders is not likely to produce overt toxicity.

Kohli et al. (1974) and Sauerhoff et al. (1976) conducted experiments to study the metabolism and excretion of 2,4-D. Human volunteers ingested single doses of 5 mg/kg of 2,4-D without observed ill effects. The rapid excretion of 2,4-D in the urine found in this study indicates that the chemical will not accumulate in the body upon repeated exposure. Nash et al. (1982) state that a 50- or 60-year-old, 80 kg (175 lbs.) farm or forestry worker with 30 years' exposure to 2,4-D for 30 days each year, may absorb and excrete 900 mg of 2,4-D in a lifetime. A lifetime intake in applicators ranging from 36 mg to 2900 mg has been calculated from urinary excretion data as reported by the Canadian Centre for Toxicology (1987). The range of exposures is large because the extent of lifetime exposure depends upon the total number of days during which an applicator applies 2,4-D.

General Public

A common use for 2,4-D is to control weeds in turf, particularly home lawns. What are the health risks when home "do-it-yourself" applicators treat their lawns? The answer to this question can be formulated using two primary factors: First, an estimate of the toxicity of 2,4-D to humans and second, an estimate of the human exposure resulting from an application to a lawn.

Spraying 2,4-D as a liquid or applying it in a granular fertilizer are the two usual methods by which 2,4-D is applied to lawns. The chances of human exposure are greater with spraying than with the use of the granular form because 2,4-D liquid concentrate normally is used to prepare the actual spray solution that is applied. Splashes and spills can occur when handling the concentrate, resulting in possible exposure to any part of the body that is not protected. Applicators may also have contact with the spray itself unless they wear protective clothing. By contrast, when the herbicide is applied with a granular fertilizer, the applicator does not handle a 2,4-D concentrate. Most fertilization is done using small gravity-fed mechanical devices an applicator pulls or pushes across the lawn. Since fertilizer particles are larger and more dense than spray droplets, they are less likely to be blown by the wind. Furthermore, applicators stand little chance of absorbing 2,4-D from the dry particles when they walk in shoes on treated grass.

Two other aspects of exposure to 2,4-D when it is used for weed control in lawns are the length of time required to treat a lawn and the number of treatments per season. Estimates show a lawn of moderate size, perhaps 50 feet x 100 feet, would require a maximum of one hour to treat whether sprayed or fertilized. Lawns measuring ½ to ¾ of an acre probably would not require more than three hours. For large areas the applicator probably would use larger and more efficient equipment. Typically, 2,4-D is applied once or twice during the season, often with ten or more weeks between applications. A home owner spraying a large lawn twice a season could have skin exposure for a maximum of six hours. When compared to exposure commercial applicators and certain agricultural workers experience, this represents a much lower health risk situation. If homeowners wear protective clothing—always a prudent precaution when spraying any pesticide—they increase their margin of safety.

Scientists have collected some data from experiments measuring the actual human exposure to 2,4-D from a lawn application. A commercial lawn care company studied 45 of its employees over a period of three work weeks to determine the amount of 2,4-D they absorbed when applying the herbicide (Yeary, 1986). The 45 workers were stationed at five different locations. The daily amount of 2,4-D that entered their bodies as estimated from urinary excretion measurements varied from 0.0025 mg/kg to 0.0035 mg/kg of body weight. Since the ADI value is 0.3 mg/kg, it was concluded that an adequate safety margin existed for the lawn care applicators. Approximately 100 times more 2,4-D would have to enter a worker's body each day before reaching the ADI value.

A frequent question people ask concerning 2,4-D is the extent of exposure that occurs from walking or sitting on newly sprayed lawns. Data measuring this type of

[b] NOEL is the daily dose that causes no adverse effects when fed to laboratory animals for extended periods (up to a lifetime).

exposure are not abundant, but some information is available from which estimations using an exaggerated "worst case" situation can be made. Thompson et al. (1986) provided information indicating the amount of 2,4-D that can be dislodged from a dry, newly sprayed lawn. Based on their results, a commonly used application rate of 0.75 lb/acre would give a dislodgeable residue of 0.35 mg of 2,4-D per square foot of lawn on the day of application. The imagined situation is one in which a child plays on a lawn that, unknown to the parents, has been sprayed with 2,4-D. Assuming that a 22 lb (10 kg) unclothed baby rolled on 10 square feet of this lawn, absorbing 6% of the dislodged 2,4-D through the skin, that child would receive a dose of 0.02 mg/kg of 2,4-D. How does this dose compare to a dose that has produced no harmful effects (including cancer) in laboratory animals given 2,4-D in the diet for a lifetime? Rats and mice have received 1 mg/kg per day in the diet for a lifetime without measurable changes occurring in any organs or tissues (Mullison, 1986). Assuming a similar sensitivity to that of test animals, the baby could receive a 50-fold higher dose and still not be above a dose that can be given to animals for a lifetime without causing adverse effects. For another comparison, the baby would receive a dose totaling 7% of the ADI, taking that value as a safe standard. These types of calculations provide some assurance that exposures during or after lawn treatment with 2,4-D are low. Comparison with results from animal studies show they represent no real health concern. However, it would be reassuring to have substantiating information on exposure derived from actual measurements of 2,4-D excretion in the urine of persons who had been in contact with sprayed lawns. Researchers could construct more accurate estimates if they possessed better information on exposure resulting from 2,4-D treated lawns.

Environmental Sources of Exposure

It is worthwhile to briefly consider the general public's exposure to 2,4-D in air, soil, food, and water (Mullison, 1987). The concentration of 2,4-D in the air during spray application was 2.1 micrograms per cubic meter (ug/m^3). Subsequent dilution in the general air mass reduces the general public's exposure away from the spraying area to extremely low amounts.

For many years Food and Drug Administration officials have conducted market basket surveys to determine pesticide levels in food. From 1965 to 1970, they found negligible traces of 2,4-D (15,000 times less than the ADI of 0.3 mg/kg) in the food (Mullison, 1981). From 1971 to 1973, they found an even smaller amount. From 1974 to 1985 they found no trace of 2,4-D. Soil surveys in agricultural use areas have shown little or no 2,4-D, which is not surprising since 2,4-D undergoes rapid degradation in soil under good plant growth conditions. Broadleaf plants are very sensitive to 2,4-D and can show the chemical's presence in soil. Over the 40 years that 2,4-D has been applied, under normal use conditions, no reports of its accumulation or persistence in soil at concentrations harmful to plant life have been reported in the scientific literature.

Water is a natural resource that is receiving a great deal of research attention. Several general surveys have shown 2,4-D does not accumulate in rivers, lakes, or groundwater. Traces occasionally have been found (usually less than 1 part per billion parts of water (ppb) or 0.001 mg/liter). In light of the large amount of laboratory data on levels of 2,4-D harmful to animals, this low amount cannot be considered a problem. Federal regulations published in 1975 allow 100 ppb of 2,4-D in drinking water and a March 31, 1987 EPA health advisory indicates that lifetime exposure should not involve drinking water containing more than 70 ppb.

Conclusions Regarding Exposure

Information is available on the exposure of farmers, foresters, pesticide applicators, and the general public to 2,4-D. It shows that persons are not exposed to hazardous amounts of 2,4-D when label recommendations and prescribed methods of application are used. This statement can be made in view of the short life of 2,4-D in the environment; its rapid excretion in mammals, including humans; its moderate acute toxicity; and except for occasional traces, its virtual absence from the food we eat, the water we drink, and the air we breathe.

Toxicity Studies in Laboratory Animals

The potential for 2,4-D to produce harmful effects in man can be estimated using knowledge gained from studies of its toxic effects in laboratory animals. Researchers have conducted and reported on animal toxicity tests throughout the more than 40 years that 2,4-D has been used as a herbicide. Hundreds of relevant scientific reports have been published. This report makes no attempt to review them. Rather, we will provide a discussion of the importance and limitation of animal studies and summarize the conclusions that can be drawn regarding the potential toxicity of 2,4-D in humans.

Advantages and Limitations of Animal Studies

Animal toxicity studies continue to be an integral and essential part of evaluating human risks. While a variety of microbial, cellular and tissue systems are available for screening selected potential effects, a thorough evaluation of the response of a complex mammalian animal system remains the most comprehensive way to test the toxicity of a chemical. Part of the science of toxicology is extrapolating from experimental effects in animals to human risk. Animal testing presents some unique advantages and some distinct limitations in the risk evaluation process.

An advantage of animal testing is that researchers can deliver measured dosages of chemicals in a controlled manner by several exposure routes. They can use appropriate controls at each important phase of research. Because certain laboratory animals can ingest, absorb, metabolize, and excrete chemicals similarly to man, attempts are made to select test animals that handle each specific tested chemical in a manner most similar to humans. Thus, the species of test animal is important. For one chemical mice may make better predictors for humans, while for a different chemical, rats may be more predictive.

Increasing response to increasing dosage is another basic principle of toxicology. Animal dosing studies are valuable, because controlled chemical administration can be used to elicit the dose-response relationship in a predictable manner. The more predictable and controlled a test animal's response, the more reliably researchers can make comparisons to human beings.

Another advantage in using test animals is that researchers can select age, sex, state of health, nutritional factors and reproductive status, which may facilitate prediction for specific human populations such as the developing fetus or a malnourished individual. Thus, prediction is enhanced by being able to target specific risk factors. In addition, chemical administration can be selected for short- or long-term evaluation. This can be done over an animal's entire life, as in cancer studies.

Animals may be given dosages of chemicals substantially beyond the expected human exposure. This fact allows the fullest expression of adverse response and increases assurance that the possibility of a toxic response in humans will not be missed. Commonly, the lowest dosage in animals causing no observed effect, NOEL, is used to calculate an ADI for man. Usually, the NOEL determined in animals is divided by a factor of 100 to 2,000 to calculate an ADI for humans. In this way a safety factor is introduced to insure that humans are protected should they be more sensitive to a particular chemical than are laboratory animals.

Some inherent limitations of animal studies must be considered: (1) The genetic makeup of all animals is unique, and one can never find an animal model that is exactly the same as the human. (2) Spontaneous disease in animals may alter the response to chemicals in a way not duplicated by human disease. (3) Animals usually do not live as long as humans. (4) Animals possess different metabolic rates than humans. (5) Anatomical differences from humans such as placental type may not allow precise prediction of placental response or fetal susceptibility to chemicals. (6) For cancer studies, spontaneous tumors in an animal population may be quite different than in humans. (7) Homogeneity of responses in animals may not adequately reflect heterogeneity in the human population. (8) Seasonal and diurnal variables may be important in animal studies but not applicable to a human population. (9) Finally, it should be noted that animal studies use relatively small numbers of subjects due to logistical and cost factors. Such studies must depend on tightly controlled experimental conditions and statistical evaluation of the results.

Toxicity of 2,4-D from Single and Repeated Doses

Laboratory animal studies evaluating the ability of 2,4-D to cause death after a single high dose have indicated that the chemical shows moderate acute toxicity (World Health Organization, 1984). The LD_{50} (lethal dose in 50% of the animals tested) ranges between 300 mg/kg and 1000 mg/kg, depending on the animal species and the type of 2,4-D formulation tested (World Health Organization, 1984). Dogs are slightly more sensitive than most species to 2,4-D's lethal effect. In that species the LD_{50} is approximately 100 mg/kg. Humans have ingested large amounts of 2,4-D in suicide attempts and have survived single doses on the order of 100 mg/kg (Berwick, 1970). It is not unreasonable to

speculate that the LD_{50} in humans is in the same range as that for the majority of animal species tested.

Lethality studies also have been conducted by administering smaller doses of 2,4-D each day over a 3- to 16- week period. Researchers have tested many species and compiled the results for review (World Health Organization, 1984). These studies indicate that scientists have observed no adverse effects at doses of 30 mg/kg/day in rats or 10 mg/kg/day in dogs. Other toxicity studies indicate that 2,4-D is not extremely more toxic when given over a long period of time because the chemical does not accumulate in the body after prolonged exposure.

Researchers do not know the precise cause of death after ingestion of large doses of 2,4-D. Damage to muscles and nerves controlling muscular movement has been suggested in the acute (single, high dose) toxicity of the chemical (Singer et al., 1982; World Health Organization, 1984; Wagner, 1983). Recent neurological studies in laboratory animals, however, do not indicate an effect of 2,4-D on the nervous system (Toyoshima et al., 1985; Mattsson, Albee et al., 1986, Mattsson, Johnson et al., 1986). The occurrence of 2,4-D toxicity after a massive dose in humans represents a rare situation and detailed information from this type of medical emergency is not readily available.

Studies of the toxicity of 2,4-D given in single, high doses may not help to predict human effects from 2,4-D that might occur when applicators use the chemical as a herbicide. More relevant are studies in which animals are exposed to much lower doses of 2,4-D for nearly a lifetime. Recent results from lifetime feeding tests show no adverse effects in rats and mice fed 1 mg/kg/day (Mullison, 1986). Somewhat higher daily doses than these (e.g., 45 mg/kg) produce a loss of body weight and slight changes in the kidneys of the animals, while still higher doses will shorten their lifespan.

Researchers have tested whether or not 2,4-D causes birth defects and altered reproduction in laboratory animals. Results from studies in several different species have been compiled (Wagner, 1983). Doses greater than 80 mg/kg to pregnant animals will cause some fetal death. Lower doses show lesser effects in offspring (e.g., lower birth weight). Doses below 10 mg/kg to pregnant rats produce no adverse effects on offspring.

Harmful effects of 2,4-D observed in testing laboratory animals occur at doses that are very high compared to those occurring in humans using 2,4-D. Human exposure to single or multiple life threatening doses of 2,4-D only occurs in an accidental or catastrophic situation, or due to intentional ingestion. On the other hand, we know that low doses of some chemicals can produce cancer. Safety testing of most chemicals includes animal tests to evaluate their potential for causing cancer.

Cancer Testing Using Laboratory Animals

Cancer represents a change in normal cells resulting in their uncontrolled growth and loss of normal function. Cells in the body that are transformed by cancer can exist in a particular organ, such as the lung. They may multiply to produce a tumor which eventually damages the organ. Cancer cells may spread to other organs, causing multiple sites of damage. This uncontrolled growth and spread may continue until death ensues.

The process by which normal cells change into cancer cells is called carcinogenesis. Both chemicals occurring in nature and synthetic chemicals may cause cancer. Viruses, bacteria, other life forms, and radiation may also contribute to the carcinogenic process.

Normal cells may transform into cancer cells, involving at least two distinct stages termed initiation and promotion. Initiation, the first and primary event, involves a change in DNA, the genetic material carried in all cells of the body. A chemical could cause change by attaching itself to DNA or by participating in biochemical processes ultimately resulting in abnormal DNA. Creation of abnormal DNA in a cell also can occur spontaneously, unrelated to the presence of a foreign chemical.

Cells can repair DNA damage, whether it is caused normally or due to attack from foreign chemicals. However, sometimes the repair system is overwhelmed by an excess of a DNA-damaging chemical. If a cell does not repair damaged DNA, it is initiated or primed to change into a cancer cell. Then the initiated cell undergoes a chemically-induced change called promotion. A chemical acting as a promoter changes an initiated cell into a cancer cell. Scientists do not understand the processes connected with promotion as well as those connected with initiation. A single chemical can act both as an initiator *and* a promoter, producing cancer by itself. In other cases, two chemicals are involved, one causing initiation and another causing promotion. Chemicals that act only as promoters will not damage DNA. They can only cause cancer if critical DNA damage already has occurred as the result of naturally-occurring events or due to the presence of a DNA-damaging foreign chemical.

Laboratory tests are available to determine whether chemicals can act as initiators or promoters. Several procedures are available to examine whether a particular chemical can damage DNA. These tests often use animal cells or bacteria and are usually carried out in a test tube. They require only 1 to 2 days and can detect initiators (also called genotoxic or mutagenic chemicals). A chemical causing unrepaired DNA damage will produce detectable mutations in cells growing in a test tube. This provides a signal that the chemical may cause cancer. Short-term tests for chemicals that act as pro-

moters are not yet available. Current methods to detect a promoter require its repeated administration to animals that have previously received a single dose of a DNA-damaging chemical. Detection of promoters requires waiting months for animals to develop tumors or lesions that will become tumors. Tests for initiators (mutagenic chemicals) are performed regularly, but tests for chemical promoters are carried out less frequently.

The ability of a chemical to produce cancer (i.e. tumors) in laboratory animals is usually assessed before the government approves that chemical for a use that may involve human exposure. Cancer tests are conducted by exposing rats and mice to the chemical for nearly a lifetime period (approximately two years). The chemical is usually placed in the animals' feed, but can be given by other means. Individual groups of animals are given different amounts of chemical in their feed. A control group receives no chemical treatment. Typically, three different amounts of chemical are given to three groups of animals for low-, medium-, and high-dose treated groups. Researchers choose a maximum tolerated dose (MTD) for the highest dose. This MTD produces some measurable effect on the animal, such as a small loss of body weight besides possibly causing cancer. Lower-dose animal groups may exhibit no obvious effects from the chemical and may or may not produce cancer as determined by microscopic analysis. Even the lowest dose administered usually will be much higher than that to which humans may be exposed each day. Scientists must use high doses in these animal tests because their goal is to detect a chemical's cancer-causing potential. It would be useless in animal cancer tests to attempt to mimic expected human exposure. Relative sensitivities of animals and humans to cancer induction are never known at the time researchers conduct the test.

After approximately two years of chemical exposure (about the lifetime of the test animal), the animals are sacrificed. Using microscopic techniques to visualize structural details of the tissue, pathologists examine all major organs for evidence of cancer. The number of cancer sites (tumors) in each animal is recorded. A certain number of animals in each study group may be sacrificed after one year of exposure to examine whether tumors are present at a younger age.

Tumors may be present in some control animals, i.e., animals that receive no chemical treatment. These animals exhibit the normal rate of cancer due to causes not related to chemical exposure. If significantly more animals in the treated groups exhibit tumors than in the control group, the inference is made that the chemical caused an increased incidence of cancer. More animals should exhibit cancer as test chemical doses increase. This dose-related increase in cancer incidence strengthens the conclusion that the chemical causes cancer. A small increase in cancer incidence observed *only* in the animals receiving the highest dose is somewhat less conclusive. Cancer testing also must determine a dose that does *not* produce an increase in tumor incidence. No increase in tumors related to chemical exposure should appear in animals receiving the lowest test dose of the chemical.

Attempts to detect cancer-causing properties of chemicals using relatively high doses in laboratory animals represent well-accepted procedures in toxicology. Researchers have found many cancer-causing chemicals this way. They have associated only a small fraction of these chemicals with cancer occurrence in humans. Two reasons suggest themselves for why humans exposed to chemicals that produce cancer in laboratory animals do not show increased cancer rates.

First, epidemiologic methods used to detect causes of cancer in humans are less sensitive than the animal testing procedures described above. Next, laboratory animals are not always identical to humans in their responses to chemicals. Nevertheless, scientists rarely find a human carcinogen that does not cause cancer in animals. This degree of predictability provides a basis for continued use of animal testing procedures to detect cancer-causing chemicals and to estimate the risk of chemical-induced cancer in humans.

Carcinogenicity of 2,4-D in Animal Studies

Early attempts to determine if certain phenoxy herbicides cause cancer may have been confounded by traces of dioxin impurities resulting from the chemical manufacturing process. The most notable example was the presence of a potent, cancer-causing dioxin (2,3,7,8-TCDD) in the herbicide 2,4,5-T. Dioxins occasionally found in 2,4-D are not among the most toxic types of these persistent chemicals (Environmental Protection Agency, 1980). This explains why toxic changes observed in laboratory animals treated with high doses of 2,4-D over an extended period of time are not the same as toxicity occurring from administering potent or nonpotent dioxins (EPA, 1980). Toxicity resulting from large amounts of 2,4-D exposure in animals can be attributed to the herbicide and not to dioxin contaminants. It follows that *if* 2,4-D exposure were to cause cancer in laboratory animals, this could be attributed to the herbicide and not to traces of nonpotent dioxins.

Whether or not 2,4-D itself may cause cancer in laboratory animals is not a new question. Oncogenicity studies in both mice and rats were included in the initial data for 2,4-D that were required by EPA. While no carcinogenic effects were evident in rats, mice, or dogs, the studies were considered insufficient under newer Federal Insecticide, Fungicide, Rodenticide Act (FIFRA)

Pesticide Assessment Guidelines. In 1980 the Environmental Protection Agency (EPA) required that these studies, in addition to many routine acute and chronic toxicological studies be repeated for product registration (Office of Pesticide Programs, EPA, 1980).

One of the leading scientific groups charged with the safety evaluation of chemical substances, including food additives, pesticides, dyes, and others, is IARC, the International Agency for Research on Cancer. In both 1977 and 1982 IARC reviewed all available data on 2,4-D. It reported them inadequate for a definitive judgment on whether or not 2,4-D caused cancer in laboratory animals (IARC, 1977 and 1982). This was consistent with the EPA's decision to require additional data.

Following the EPA call for more data, major manufacturers of 2,4-D formed an industry task force to sponsor the very expensive studies required to re-register their products. Two chronic feeding studies were commissioned by that task force. They have recently been completed and submitted to the EPA. While their results are subject to differences in interpretation, as lifetime feeding studies often are, readers should consider results from these two most recent studies along with previous data to address the question of whether or not 2,4-D is carcinogenic in laboratory animals.

One of the recent lifetime feeding studies was conducted in Fischer 344 rats at dose levels that were clearly in compliance with the requirement for an MTD (Hazelton Laboratories, 1986). Changes were seen in the kidneys of rats given highest doses. This satisfied the MTD requirement. No abnormal changes were observed at the lowest dose of 1 mg/kg/day. This result provides a NOEL. Male rats, but not females, fed the highest dose (45 mg/kg/day) exhibited a statistically higher frequency than did concurrent study controls of a brain cell tumor known as an astrocytoma. No increased incidence of tumors occurred in rats given 1, 5, or 15 mg/kg of 2,4-D each day. Researchers have argued that the higher incidence of tumors in rats receiving the highest dose of 2,4-D is due to chance. Fischer 344 rats usually exhibit tumor development at highly variable rates. Also, an increased tumor incidence in only the highest dose group does not represent a clear dose-response phenomenon and is not strongly supportive of the hypothesis that 2,4-D causes cancers. A report from the laboratory conducting this study stated, "This finding is, nevertheless, suggestive of a possible carcinogenic effect at a dose of 45 mg/kg/day." Indeed, 2,4-D may be a weak neurocarcinogen in rats, but this effect has been questioned because it has not obeen observed previously in laboratory animals given 2,4-D. It also appears that animal response characteristics in this study are not the same as those previously observed in tests with other neurocarcinogens (Koestner, 1986).

The second recently completed chronic feeding study was conducted using mice from the cancer-sensitive B6C3F1 strain (Hazleton Laboratories, 1986). Test results exhibited no evidence of 2,4-D-related carcinogenicity in any tissue or organ system. Under current policy for chronic studies submitted to the EPA, this study did not achieve an MTD. That is, the highest dose did not produce a loss of body weight or cause other signs that the animals were not in good health. However, the highest dose used in this study (45 mg/kg/day) was 600 times the maximum reported human exposure. Even at this high dose no evidence appeared of increased incidence of cancers, including brain tumors.

Known neurocarcinogens in animals are generally found to be mutagens. Scientists have conducted numerous mutagenicity studies on 2,4-D, both *in vitro* and *in vivo*. They do not support the generalization that 2,4-D is genotoxic (mutagenic). Recently, the Canadian Centre for Toxicology (1987) assembled researchers to review in great detail all available data from studies on 2,4-D that pertain to its possible mutagenicity. This expert panel examined 29 *in vitro* mutagenicity studies. Nineteen were negative; of the remaining 10, nearly all resulted in equivocal data (e.g., effects that were not dose-related or from test material that was not adequately identified or defined). Negative results were reported in tests using both bacterial and mammalian cell lines. Some tests on both cell lines showed positive results, but in all cases the studies can be criticized because of the use of cytotoxic doses, or conditions that in some way compromised their validity.

In vivo studies on the genetic toxicity of 2,4-D also did not confirm any suggestion of mutagenicity. Canadian Expert Panel members reviewed twelve studies. Eight were negative, one yielded equivocal data and three were positive only at doses that otherwise are toxic to the organism. Research has established that 2,4-D is cytotoxic at very high doses. Mutagenicity studies are readily confounded by cytotoxicity or nonspecific cell damage.

This rather large battery of studies does not provide convincing evidence that 2,4-D is mutagenic. As mentioned above, neuropathologists agree that neurocarcinogens generally are mutagens. All data showing a lack of mutagenicity for 2,4-D add further doubt to an interpretation that it produces an increased incidence of astrocytomas in Fischer 344 rats.

Results from the most recent cancer studies in rats and mice do not present a clear answer regarding whether or not high doses of 2,4-D can cause an increase in tumors in laboratory animals. These results are not unexpected because if a chemical is not carcinogenic, or is an

extremely weak carcinogen in animals, tests often will show mixed results. Tumors in rats and mice do normally occur. A positive test requires a slight but statistically significant increase in the normal tumor rate as a result of 2,4-D administration. Repeated attempts to show a slight increase in tumor rates with a noncarcinogen may produce a small percentage of incorrect results, but the majority of such tests should yield correct results. In the case of 2,4-D, a number of cancer studies have been conducted in rats and mice, nearly all of which have yielded results indicating that the chemical does not cause an increase in the normal incidence of tumors.

In summary, evidence that feeding 2,4-D to laboratory animals causes cancer remains very weak. When assessed together with earlier animal studies, recent data do not provide sufficient evidence to warrant a serious concern that 2,4-D is an animal carcinogen. The results are consistent with those from epidemiologic studies which to date have not shown 2,4-D to increase the risk of human cancer. Other scientists who have recently reviewed available data from animal tests and epidemiologic studies in humans reached the same conclusion. In March 1987 the Expert Panel on Carcinogenicity of 2,4-D reported to the Ontario Ministry of the Environment that "the existing animal and human data are insufficient to support the finding that 2,4-D is a carcinogen" (Canadian Centre for Toxicology, 1987). A Scientific Advisory Panel of the U.S. EPA consisting of nationally recognized scientists from the academic community has recommended to the agency that 2,4-D be reclassified from a possible human carcinogen (Group C), to another chemical group (Group D). This reclassification recommendation shows the panel believes that inadequate human and animal evidence exists for classifying 2,4-D as a possible carcinogen for humans (Koestner, 1987; Federal Register, 1986).

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