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AN SAB REPORT: ASSESSMENT OF POTENTIAL 2,4-D CARCINOGENICITY

REVIEW OF THE EPIDEMIOLOGICAL AND OTHER DATA ON POTENTIAL CARCINOGENICITY OF 2,4-D BY THE SAB/SAP JOINT COMMITTEE

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ABSTRACT

In August 1980, the EPA required oncogenicity testing of 2,4-D (2,4-dichlorophenoxyacetic acid. EPA reviewed the results of those studies completed to date (some of which reported an association of phenoxy herbicides, including 2,4-D, and non-Hodgkin's lymphoma (NHL)) and requested that a joint Committee of the Science Advisory Board and the Scientific Advisory Panel review the epidemiologic studies and other available relevant data. A joint Committee was formed, and met in Arlington, Virginia on April 1-2, 1993 to review human/canine epidemiological studies and animal toxicology studies *re* possible human carcinogenicity and mutagenicity.

Epidemiologic cohort studies have generally shown no increased risk of cancer, albeit that all of the populations for which specific exposure to 2,4-D have been identified were small, and the follow-up period usually short. Some case-control studies have shown a risk of Non-Hodgkin's Lymphoma (NHL) in association with farming but many of these studies did not control for exposure to other agents in addition to 2,4,D. The Committee concluded that current studies cannot distinguish whether observed risks reported are due to the use of 2,4,D. The single canine epidemiologic study suggested that pet dogs may be at risk from exposure to 2,4,D or to areas treated by a lawn care service. Although this study is supportive of a finding of carcinogenicity, there are questions about its applicability to human carcinogenicity because of poor information on exposure and possible non-comparability between canine and human lymphomas. Toxicology studies show that rats (but not other animal species tested) may develop astrocytomas from exposure to 2,4,D, but this outcome has not been reported in the human studies. An ongoing rat study at higher doses will clarify whether this finding is treatment-related or not. Tests of 2,4-D have not shown any mutagenic changes under experimental situations.

The Committee concludes that the data are not sufficient to find that there is a cause and effect relationship between the exposure to 2,4,D and NHL. Because there is some evidence that NHL occurs in excess in populations that are likely to have been exposed to 2,4,D, there should be continued examination of the issue through further studies. Other data gaps exist, and decision-making on 2,4-D would benefit from completion of rodent studies previously requested by EPA, particularly further animal carcinogenicity studies that test 2,4-D jointly with other substances that might reflect the human exposure situation; a replication of the dog epidemiology study; additional case/control studies, with careful attention to exposures; additional human cohort studies designed to assess both relative risk of NHL and the comparative risk of all mortality; and additional follow up and analysis of worker cohorts involved in the production of 2,4-D.

KEYWORDS: 2,4,D; 2,4-dichlorophenoxyacetic acid; carcinogenicity; astrocytoma; Non-Hodgkin's Lymphoma (NHL); farming; canine epidemiology

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1 EXECUTIVE SUMMARY

In August 1980, the EPA required oncogenicity testing in rats and mice of 2,4-D (2,4-dichlorophenoxyacetic acid -- one of the first herbicides to be registered in the United States. To date, the registrant has not completed all of the required studies). The EPA reviewed the results of those laboratory studies that were completed, and extant epidemiologic studies reporting an association of phenoxy herbicides, including 2,4-D, and non-Hodgkin's lymphoma (NHL). Continuing reviews of the data prompted the EPA to issue notice that the Agency had deferred decision on the final determination of the Special Review to obtain additional information. Subsequently, the Agency requested that a joint Committee of the Science Advisory Board and the Scientific Advisory Panel review the epidemiologic studies and other available relevant data. Such a joint Committee was formed, and met in Arlington, Virginia on April 1-2, 1993. The meeting was structured around the Charge summarized below:

a. (1) Do the human epidemiologic studies provide evidence that 2,4-D is a human carcinogen?

(2) Does the canine malignant lymphoma epidemiologic study demonstrate a relationship between exposure to 2,4-D and cancer in dogs? Is this study supportive or non-supportive of a finding of human carcinogenicity for 2,4-D?

b. Do data from laboratory animal testing of 2,4-D provide evidence of carcinogenicity in animals? Do these studies provide evidence of human carcinogenicity for 2,4-D?

c. What are the endpoints of concern, if any, from the mutagenicity database for 2,4-D? Do any of these data elicit concern as to the carcinogenicity of 2,4-D in animals or humans?

d. (1) What other existing data or information should be considered in the weight-of-evidence evaluation of the carcinogenicity of 2,4-D and how should they be incorporated?

(2) Are there informational gaps in the existing carcinogenicity database?

e. Considering all of the above items, what is the overall perception of the panel as to the weight of evidence that 2,4-D is a human carcinogen?

f. If it is concluded that there is some evidence of carcinogenicity, what methods might be used to evaluate the dose-response (potency) relationships either qualitatively or quantitatively?

The extant epidemiological cohort studies on persons involved with the manufacture or use of 2,4-D generally do not have sufficient power (because of short follow-up time and small study populations) to determine if there is any association between modest excess risk of STS or NHL and exposure to 2,4-D. Case-control studies have shown an excess risk of NHL in association with the occupation of farming, but, because of likely exposure to multiple chemical agents, it is not clear if this risk is indeed associated with exposure to 2,4-D itself.

The single epidemiologic study of pet dogs suggested that these animals may be at risk from exposure to 2,4,D or use of a lawn care service. This study has the same constraints of selection bias of cases and controls and recall and misclassification biases that could occur in human case-control studies. The applicability of the canine epidemiology data to lymphoma in humans is questionable since the cancers may not be similar in dogs and humans, and exposures to 2,4-D are not clearly established. To substantiate these results, the study should be replicated with improvement in the exposure measures and verification of the comparability of the cancers in dogs and humans.

Requested animal test data at appropriate dose levels have not yet been completed. Nonetheless, the studies completed so far show that rats (but not other animal species tested) may develop astrocytomas from exposure to 2,4,D, an outcome which has not been reported in the human studies. An ongoing rat study at higher doses will clarify whether this finding is treatment-related or not. The chemical has not shown mutagenic changes under experimental situations -- it would have strengthened the observations in humans if there were laboratory data, especially in toxicologic studies of animals, to support any observations in humans.

The Committee concludes that, at this time, the data are not sufficient to conclude that there is a cause and effect relationship between the exposure to 2,4,D and NHL.

Because there is some evidence that NHL occurs in excess in populations that are likely to have been exposed to 2,4,D, there should be continued examination of the issue through further studies. The following research and data would be of most value:

a) completion of EPA requested rodent carcinogenicity studies and dog toxicology studies

b) animal carcinogenicity studies that test 2,4-D with other substances that might reflect the human exposure situation

c) a replication of the dog epidemiology study

d) additional case/control studies, with careful attention to exposures, particularly multiple exposures

e) human studies, particularly cohort studies designed to assess both relative risk of NHL and the comparative risk of all mortality (or all disease incidence, if possible)

f) additional follow up and analysis of worker cohorts involved in the production of 2,4-D

2 INTRODUCTION

2.1 Background

2,4-D (2,4-dichlorophenoxyacetic acid) was one of the first herbicides to be registered in the United States. This herbicide and its derivatives are commonly used on crops such as corn, wheat, sugar cane, rice, and on pasture land, to control broadleaf weeds. It is also used for weed control in residential settings, in forest management, and for growth control on certain crops.

In August 1980, EPA required oncogenicity testing in rats and mice of 2,4-D. The EPA reviewed the results of these laboratory studies and requested additional rat and mouse carcinogenicity studies which have not yet been completed. At that time, extant epidemiologic studies reported an association of phenoxy herbicides, including 2,4-D, and non-Hodgkin's lymphoma (NHL). This evidence prompted EPA to issue a preliminary notification on September 22,1986 announcing that there would be a Special Review. Continuing reviews of the data in the subsequent time periods have prompted the EPA to issue notice that the Agency had deferred the decision on the final determination of the Special Review for the purpose of obtaining additional information. Subsequently, to evaluate the additional information it had gathered, the Agency requested that a joint Committee of the Science Advisory Board and the Scientific Advisory Panel review the epidemiologic studies and other available relevant data. Such a joint Committee was formed, and met in Arlington, Virginia on April 1-2, 1993. The meeting was structured around the Charge described below.

2.2 Charge

The Agency asked the Special Joint Committee of the Science Advisory Board and the Scientific Advisory Panel to evaluate the weight of evidence of carcinogenicity of 2,4-D. Such an evaluation requires consideration of all evidence that supports and does not support a conclusion of carcinogenicity, along with the strengths, weaknesses, and uncertainties of the database. Although the Agency was interested in any insights the Committee may wish to share related to the carcinogenicity of 2,4-D, there was particular interest in the Committee's response to the following specific questions:

a. (1) Do the human epidemiologic studies provide evidence that 2,4-D is a

human carcinogen? What types of human cancer, if any, are associated with exposure to 2,4-D? How specific is the information to 2,4-D versus other pesticidal and non-pesticidal sources? What are the strengths and limitations of the human epidemiology database?

(2) Does the canine malignant lymphoma epidemiologic study demonstrate a relationship between exposure to 2,4-D and cancer in dogs? Is this study supportive or non-supportive of a finding of human carcinogenicity for 2,4-D? What are the strengths and limitations of the canine lymphoma study?

b. Do data from laboratory animal testing of 2,4-D provide evidence of carcinogenicity in animals? Do these studies provide evidence of human carcinogenicity for 2,4-D?

c. What are the endpoints of concern, if any, from the mutagenicity database for 2,4-D? Do any of these data elicit concern as to the carcinogenicity of 2,4-D in animals or humans?

d. (1) What other existing data or information should be considered in the weight-of-evidence evaluation of the carcinogenicity of 2,4-D and how should they be incorporated? Examples might include information on: exposure, absorption, metabolism in humans and animals, contaminants and inert materials in 2,4-D products.

(2) Are there informational gaps in the existing carcinogenicity database, and if so, can the committee suggest specific studies or other data which should be developed and/or submitted to the Agency?

e. Considering all of the above items, what is the overall perception of the panel as to the weight of evidence that 2,4-D is a human carcinogen?

f. If it is concluded that there is some evidence of carcinogenicity, what methods might be used to evaluate the dose-response (potency) relationships either qualitatively or quantitatively? What data might be needed to enhance this capability?

For the purposes of this review, the Committee was asked to consider the use of the following descriptive terms to express its conclusions about the weight-of-evidence of carcinogenicity of 2,4-D as requested in Question (5) above:

proven human carcinogen
highly probable that 2,4-D is a human carcinogen
probable that 2,4-D is a human carcinogen
somewhat probable that 2,4-D is a human carcinogen
improbable that 2,4-D is a human carcinogen
highly improbable that 2,4-D is a human carcinogen
inadequate data for conclusions about human carcinogenicity

These terms do not refer to any existing classification system for carcinogenicity used by governmental or international organizations. The precise way in which the Committee will consider the evidence for and against the human carcinogenicity of 2,4-D and the relative weights given individual elements is left to the committee. We do request that the committee develop a rationale for their conclusions that will accompany the descriptive term it applies to the weight of evidence of carcinogenicity.

3. DETAILED FINDINGS

3.1 Epidemiologic Studies and Human Carcinogenicity

3.1.1 Epidemiologic Evidence

The epidemiologic data reviewed by the Committee included case-control studies (primarily non-Hodgkin lymphoma cases), cohort studies of manufacturers of, and industrial users, of pesticides, and several reviews of the information available from epidemiologic studies. Recent studies received a more thorough review than those in the past. Following the discussion of the studies and the reviews, the Committee deliberated on all of the information to reach its conclusions.

The available epidemiologic studies have different characteristics. Some include occupational groups which might have had exposure to phenoxyherbicides in applications as farmers, lawn specialists and forest workers. Other studies include workers who have been involved in production of the chemicals in the workplace. Many of these occupational studies have attempted to identify the specific chemical exposures of the workers. In addition, studies have included case-control studies of NHL (non-Hodgkin's lymphoma) to try to identify the specific risk factors for cases with this condition. One problem which all studies have faced is the need to reconstruct exposures in the distant past. In addition, most of the populations under study have had exposures to many chemicals and contaminants in addition to the 2,4-D.

Numerous studies over the past several years have examined the association between farming, agricultural work or exposures to pesticides and the risk of NHL (Johnson, 1990). Most of the studies were non-specific in regard to the exact exposure that might have occurred in the population. However, in general, almost all of these studies have shown a positive association between this general occupational grouping and NHL. One particular problem underlies all of these studies, however: farming is associated with many exposures that depend on activities common to all farming, as well as those exposures which may depend on the specific type of farm (e.g., livestock versus agriculture), and on the type of crop and the geographic area in which that crop is raised. Farmers commonly are one of the large groups of heavy users of herbicides identified in case-control studies. If a study wishes to attribute a risk of NHL to herbicides, then it must prove that the risk is not due to farming in general but to the

specific chemical of interest. Most studies have not done this and we are to must resolve whether any elevated risk is due to 2,4-D, to farming, or to other exposures.

Several case-control studies have examined specific histories of exposures to pesticides and herbicides in the study subjects. Hardell *et al.* (1981) in Sweden found significant associations between soft tissue sarcomas (STS), Hodgkin's disease (HD) and NHL and phenoxyherbicide use. Vineis *et al. (*1986) suggested that STS was associated with exposure to phenoxyherbicides in women in a rice-growing region of Northern Italy. In a recent update of that study which compared the rates of STS, HD and NHL in regions with high and low soil levels for 2,4-D and 2,4,5-TP, the incidence of NHL (but not of STS) was significantly higher in the regions with the high levels. Other studies from New Zealand and the U.S. found no excesses of STS. Therefore the review has focused primarily on NHL.

The Hoar *et al*. (1986) study of 170 Kansas males with NHL reported that farming (OR 1.4; 95 % CI 0.9, 2. 1) and phenoxyherbicide use (OR 2.2; 95 % Cl 1.2, 4.1) were associated with a risk of NHL when non-farmers were used as a comparison. This observation, in part, prompted the 1986 announcement of a Special Review. The odds ratios for phenoxyherbicide use in general, and 2,4-D use in particular, increased with increasing duration of use and frequency of use per year. Almost all subjects reporting phenoxyherbicide use had used 2,4-D. Most subjects had exposure to other chemicals in addition to 2,4-D. A population-based study in Washington state (Woods *et al.,*1987) reported that among 576 male NHL cases and 694 male controls, there was an association between the disease and farming (OR 1.33, 95% Cl 1.03, 1.7). No statistically significant association was seen between NHL and phenoxyherbicides even at "high" exposure levels (OR 1.24; 95% Cl 0.8, 1.9). Forest sprayers had a high odds ratio (OR 4.80; 95% Cl 1.2, 19.4) but there were only 7 cases in this subgroup and all of them were exposed to a combination of 2,4-D and 2,4,5-T. One hundred-eighty- three male NHL cases in New Zealand (Pearce *et al*., 1987) showed no association between the disease and exposure to phenoxyherbicides (OR 1.0; 90% Cl 0.7,1.5). However, reportedly 2,4,5-T is usually used as a herbicide in New Zealand rather than 2,4-D (Zahm and Blair,1992). Another group in Sweden (Persson *et al*., 1989) has investigated exposures of 106 NHL cases identified from a local oncology registry and found a strong negative association with farming (OR 0.3; 90% CI 0.1, 0.7) but an odds ratio of 4.9 (90% CI 1.3, 18) with exposure to phenoxyherbicides. The Committee notes that this study included a different mix of cases in the category of NHL since the group includes

multiple myeloma and chronic lymphocytic leukemia but excludes the usual NHL classification (ICD category 202). This study does not provide complete information for evaluation. Since the number of exposed cases is small, these data have been considered separately from the other studies.

Hoar-Zahm *et al*., (1990) conducted a population based, case-control study of NHL in Eastern Nebraska. Among 201 white male cases and 725 white male controls, they found no increase in NHL in subjects with a history of ever having worked or lived on a farm (OR 0.9; 95% Cl 0.6, 1.4). However, when cases who had exposure to mixing or applying 2,4-D were compared to non-farm workers (who, in this case, never worked or lived on a farm), the odds ratio increased to 1.5 (95% CI 0.9,2.5) and there was an increase in the odds ratio associated with the number of days per year of application. However, in this study, only three cases were in the subset of those cases with 21 days or more of exposure. In addition, the authors report that organophosphate exposures demonstrate similar increases in odds ratios with increasing days of annual exposure. When the data are corrected for exposure to this other chemical, the odds ratio for ever handling 2,4-D drops to 1.1. As the authors themselves point out, "Because of the small numbers of subjects and the high proportion of subjects with multiple exposures, it Is not possible in this study to entirely disentangle these relationships. There may be some residual confounding." The recent population-based case-control study in Iowa and Minnesota of 622 white men with NHL and 1245 white controls (Cantor *et al*., 1992) reported an odds ratio associated with the history of being a farmer of 1.2 (95% Cl 1.0, 1.5), with adjustment for other variables such as age, state, vital status, smoking, etc. The odds ratio for use of phenoxyacetic acids compared to non-farmers was 1.2 (95% Cl 0.9, 1.6). The specific use of 2,4-D showed similar odds ratios in various analyses. These investigators provided additional information from a subset of re-interviews of subjects with a history of use of pesticides with exposure days per year evaluated. These data indicated odds ratios of 0.6 and 0.4 for exposure periods under 10 days of use and an odds ratio of 1.1 (95% Cl 0.5, 2.4) for those exposed 10+ days per year. Another recent study from Australia included 52 men in a combined group of HD and NHL who were compared to cancer and population controls (Smith *et al.,* 1992). There were no significantly elevated odds ratios but, for the subset who had used phenoxyherbicides or chlorophenols for more than 30 days total exposure, the odds ratio was 2.7 (95% Cl 0.7, 9.6). This study did not separate 2,4-D exposure from other exposures, nor HD from NHL .

Johnson (1990) has reviewed the findings from cohort studies of manufacturing facilities and suggested that few cohorts had sufficient numbers of deaths to enable the observation of the risk of STS, HD or NHL Thus, all cohorts needed additional follow-up. Bond's early study (Bond *et al.,* 1988) did show a significant excess of all lymphopoietic cancers in workers involved in 2,4-D production (O/E, 5/1.6, SMR=312) but there were only 68 total deaths in the cohort. The subsequent update did not analyze the data separately for this work area. A study of 4,459 Danish workers (Lynge,1985) employed in herbicide manufacture identifies 940 workers who produced the herbicide but showed no risk of NHL. Wiklund *et al.* (1986) reported no risk of NHL in Swedish agriculture and forestry workers but did identify an excess of HD in silviculture and non-traditional agricultural occupations. In a second study (Wiklund *et al.,*1989), the incidence rates of cancers in Swedish pesticide applicators were examined. No significant excess risks were identified although the authors noted excesses of testicular cancer (SIR = 1.55), other endocrine cancers (SIR = 1.33) and nervous system cancers (SIR = 1.27). A Canadian study of 70,000 farmers identified from various farm registries (Wigle, 1990) reported no overall excess of NHL, However, there was an excess of NHL mortality in the subgroups which reported $900 or more in fuel costs annually and, for smaller farms under 1000 acres, the risk of NHL increased with the number of acres sprayed. The authors report that the chlorophenoxy compound in general use in the area was 2,4-D but the exposure was not tied directly to cases of the disease. In the large International Agency for Research on Cancer (IARC, 1990) international study of 18,910 production workers or sprayers, no excess of NHL was observed but the authors noted non-significant excesses of STS, cancers of the testicles, thyroid, other endocrine glands and nose and nasal cavity based on small numbers of deaths.

3.1.2 Types of Human Cancer Associated with 2,4-D Exposure

In the early 1980s, several case-control studies from Sweden suggested a positive association between exposure to chlorophenoxy herbicides, including 2,4-D, and cancer in humans. Specifically, associations were suggested with STS and with NHL. In the late 1980s, two case-control studies in Kansas and Nebraska suggested an association between exposure to 2,4-D and NHL. No positive association was seen with STS. These two forms of cancer in humans are the only ones for which a positive association with 2,4-D has been suggested in any study. There are other case-control studies of NHL which have failed to reveal an association. Most studies have only demonstrated an association in subgroups in the populations.

In general, follow-up studies of persons engaged in the manufacture and application of 2,4-D have two limitations. Study populations are small or follow-up time is (on average) relatively short. As such, these studies generally have insufficient power at this time to determine if exposure to 2,4-D is associated with a modest excess risk of STS or NHL.

3.1.3 Specificity of Information Relating to 2,4-D

The epidemiologic studies often do not provide information on exposures specific to the chemical 2,4-D. Most of the studies relate the risk to the general category of phenoxyherbicides--a group which might include 2,4,5-T and substances contaminated with TCDD. If no association is shown and 2,4-D use was limited in either amount or time, these studies might have missed an association. If there is an apparent risk and the information on specific exposures is missing, then chemicals other than 2,4-D may account for the apparent risk.

Several case-control studies and cohort studies are specific with respect to exposure to 2,4-D only. In the case-control studies in Nebraska and Iowa/Minnesota, questions were asked specifically about exposure to 2,4-D. However, because the information on exposure was obtained only by questionnaire, some degree of uncertainty is attached to the exposure assessment. In addition, the persons have identified several exposures to chemicals which are often correlated with exposure to 2,4-D. In these situations it is often impossible to be sure that confounding is removed. Few studies have examined the risk by duration of exposure in order to establish a cumulated dose response. In the recent studies the investigators have identified a dose response relationship, using the number of days per year the subject was exposed as a variable. However, the measure does not take into account the number of years in which the subject was exposed at that dose. This measure does appear to have an exposure response relationship but, when years of exposure are considered there is no response. This "dose response" is not similar to that usually seen in epidemiology. The exposure in one year, regardless of when it occurred during a lifetime, creates a higher risk of disease than multiple exposures over many years. This finding would require further biologic explanation if it is real. The finding may occur because of the individuals who fell in the "high" category of yearly use. Selective analysis of small sub-groups in a large study may lead to erroneous results because the investigators are simply describing the characteristics of the outliers in the data set

3.1.4 Strengths and Limitations of the Human Epidemiology Database

The strength of human epidemiology is that the data relate directly to humans. No extrapolation from non-human species is needed.

Evaluation of epidemiologic data is difficult because the information is obtained from non-experimental, observational studies. Biases may arise in the collection of the data. The possible effect of confounding factors which are related to both the exposure of interest and the risk of disease may make it difficult to interpret the results. The ability of epidemiologic studies to provide convincing evidence of causation under such circumstances is limited. Causation is suspected if several studies are consistent in their findings; if the association between the agent and the risk of disease is strong (the odds ratio is high); and if the association adheres to biologic theory. Support from animal data will help to make the case for causation, particularly by establishing biologic plausibility and the existence of potential mechanisms. However, failure to detect an association, particularly if studies have limited statistical power due to small sample size or short follow up time, are not sufficient to disprove an association. In the case of 2,4-D, the studies are not consistent and the associations found are weak. The data can not determine whether the weak association is due to the agent being a weak carcinogen,to an exposure level which may be low, to uncorrected sources of confounding or bias, or to random variation in response from study to study which might be experienced if the relative risk was unity. In general, unless they are extremely large, epidemiologic studies are not able to provide convincing evidence of health effects for a weak causal association.

Thus, in assessing the weight-of-the-evidence of the epidemiologic studies which relate to 2,4-D exposure, one has to make a subjective judgment as to the weights given to the various studies and their conflicting conclusions. There are different results from many of the studies; some have indeed shown a relationship between 2,4-D and NHL. However, there are inconsistencies in the results (even of the positive studies) which raise doubts as to whether the relationship is causal.

However, most epidemiologists acknowledge that epidemiologic studies are insensitive and therefore unable to provide unambiguous evidence when exposure to

some agent is a weak cause of cancer. Thus, if a toxicant increases the risk among exposed persons by some small percentage, say ten percent, epidemiologic studies are unlikely to provide a clear demonstration of that excess risk. This is because of the non-experimental nature of data arising from epidemiologic studies and the small size of the effect. Misclassification of exposure levels and/or of the presence of disease may distort epidemiologic associations. Other unmeasured factors, including sampling variability, may cause apparent associations in epidemiologic data. On the other hand, lack of an observed association may be due to small study populations, insufficient follow up time, or a low exposure to a carcinogenic agent. Ultimately any decision as to the meaning of a body of epidemiologic data, or indeed any scientific data, is a matter of qualitative judgment rather than of quantitative inference.

Over the past six years, a number of scientific panels, convened under the auspices of various groups, have evaluated the human carcinogenicity of chlorophenoxy herbicides in general and of 2,4-D in particular. Their findings are summarized below:

a) *1987 - International Agency for Research on Cancer (IARC)*: In Supplement 7 of the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, the IARC Working Group judged that there was limited evidence that chlorophenoxy herbicides were carcinogenic to humans. There was no clear delineation of data related to 2,4-D as opposed to other chlorophenoxy herbicides, some of which contain dioxin (TCDD).

b) *1988 - Council on Scientific Affairs, American Medical Association:* As a general statement relating to all pesticides, the Council concludes: "At this time, the results of these and other studies of agricultural workers (as well as of Vietnam veterans who were allegedly exposed during military service and pesticide production workers) offer only conjectural evidence at best that pesticides may be carcinogenic." In a table, 2,4-D is listed as having inadequate evidence relating to human carcinogenicity.

c) *1991 - Harvard School of Public Health Panel*, Michel A. Ibrahim, Chair: (A panel convened by the Center for Risk Analysis at the Harvard School of Public Health under sponsorship of the National Association of Wheat Growers Foundation. The panel concluded: "Although a cause-effect relationship is far from being established, the epidemiological evidence for

an association between exposure to 2,4-D and non-Hodgkin's lymphoma is suggestive and requires further investigation. There is little evidence of an association between use of 2,4-D and soft-tissue sarcoma or Hodgkin's

disease, and no evidence of an association between 2,4-D use and any other form of cancer."

d) *1992 - I. C. Munro et al.:* (A review relating to the safety of 2,4-D by a panel of toxicologists and epidemiologists, supported by the Industry Task Force II on 2,4-D Research Data. The authors conclude: "The case-control epidemiological studies that have been the source of the cancer risk hypothesis are inconclusive. Problems in assessing exposure based on patient's memories make these studies difficult to interpret. Cohort studies of exposed workers do not generally support the specific hypothesis that 2,4-D causes cancer. Taken together, the epidemiological studies provide, at best, only weak evidence of an association between 2,4-D and the risk of cancer."

Thus, the general conclusion reached by others as well as by the members of this Panel is that there is, at most, weak evidence for an association between exposure to 2,4-D and cancer in humans.

3.2 Canine Epidemiologic Study

3.2.1 Exposure to 2,4-D and Cancer in Dogs

To summarize the results of the Hayes *et al.*, (1991) canine lymphoma epidemiologic study and its relevance to the evaluation of carcinogenicity of 2,4-D, it is useful first to discuss the design of the study in generic terms and then to look at the specific details of the Hayes et al. (1991) study.

The Hayes *et al.* (1991) study is one of a limited number of case-control studies utilizing animal pathology records to identify subjects for investigation of environmental risks (e.g. Glickman and Domanski 1986; Glickman *et al.*, 1989; and Reif *et al.*, 1992).

The study investigated the association between exposure to lawn chemicals and

the incidence of lymphoma (as a model for human non-Hodgkin's lymphoma) in dogs hospitalized at three veterinary hospitals. Two types of controls were selected from the registry: dogs diagnosed with other malignancies and dogs in the veterinary hospital for other reasons. Subjects were matched on age, year of hospital visit and hospital. Exposure and confounder data were solicited by mail questionnaire. If no response was received after a second mailing, a telephone interview was attempted. Nearly 20% of the owners of the study subjects could not be located. Of the 1,436 owners who were located, all but four completed either the questionnaire or interview. Information was collected about the breed of dog, age of dog, lawn care practices and pesticide use of the owner, and the dog's access to the pesticide treated yards. A statistically significant association was found between case-control status and owner's use of 2,4-D and/or use of a commercial lawn care service. When exposures were separated, the individual odds ratios were similarly elevated although not statistically significant (an issue of inadequate statistical power). The excess risk for both owner use of 2,4-D and use of a commercial lawn care service was three times higher than either use alone. Significant trends were found for the frequency of owner use (number of applications per year) although not for the duration of owner use (number of years of application). No significant trends were found for use of commercial lawn care service.

The investigators considered both confounding and bias as alternative explanations for their findings. Adjustment for confounders did not affect the results. The investigators were concerned that the pet owners' knowledge of their dogs disease status might be associated with reported use of 2,4-D. The proportion of case owners who reported no exposure to 2,4-D or who did not allow the dog access to the yard did not differ by whether they know what disease the dog had. In addition, demographic and socio-economic comparisons of the case and control groups did not reveal any striking differences. Finally, because these dogs were seen in a veterinary hospital, upon death, many underwent autopsy, limiting the opportunity for outcome misclassification.

At the Committee's meeting, Dr. Hayes clarified a number of issues not discussed explicitly in the published study. Specific data (Hayes 1993) were presented to show that there were not substantial differences in study results between tumor and non-tumor controls, between telephone and mail respondents, and among the three participating veterinary hospitals. Further, risks for exposure to other pesticides (e.g., malathion and carbaryl) were not elevated. To evaluate the degree to which the reported exposure data were representative of "real-world" experience, they were compared to a similar

lawn care use survey conducted by EPA and found to be similar.

The strengths of the study are:

a) a very high response rate of those owners located;
b) no difference found between the responses of the two control groups;
c) no difference was found between the mode of response (phone or mail);
d) lawn care use data corresponded closely to a similar EPA survey;
e) a high rate of autopsy (diagnostic confirmation).

There are a number of limitations to the study relating to possible selection bias and exposure misclassification:

a) there was a locational bias in the study, with fewer cases residing in rural areas or within 2 miles of an industrial facility;
b) the questionnaire did not list specific pesticides but relied on owner recall to provide the name of the products used;
c) reported pesticides were reclassified by the investigators into those containing 2,4-D and those not containing 2,4-D;
d) questions regarding the frequency of use were about use of all lawn chemicals as a whole rather than specific to each chemical identified by the owner;
e) dogs roam and thus may experience exposures to 2,4-D not reported by their owners;
f) there was no evaluation of possible viral etiology.

Another issue raised addressed the propriety of using dogs as a good model for human carcinogenicity. It was pointed out that dogs are more acutely sensitive to 2,4-D, and this is attributed to a different clearance mechanism which saturates at concentrations 10-100 times lower than for humans. However, data reported regarding exposures likely experienced by these animals indicated that they were receiving exposures at least 10 times lower than this clearance saturation level. Additionally, it was noted the prevalence of malignant lymphoma was substantially higher in this data

set than in other registries. However, this is due in part to the type of registry (veterinary hospital , as opposed to population-based).

Overall, in spite of its limitations, this study was viewed by the Committee as supporting an association between 2,4-D use and professional lawn care, and malignant lymphoma in dogs. The study would be strengthened by providing more precise exposure data and by demonstrating that canine lymphoma is an appropriate model for human NHL.

A number of suggestions were made regarding improving the interpretability and validity of this study. It was recommended strongly that the study be replicated on an independent data set. When conducted, more attention should be placed on the details of the exposure assessment and on the referral pattern by which the dogs ended up in the registry.

Some additional suggestions were made for more detailed evaluation of data from the Hayes *et al*. (1991) study and any replications. To evaluate possible referral bias, the residence locations of cases and controls should be compared and evaluated with respect to human demographics, socio-economic status, and case-control status.

3.3 Animal Testing and Carcinogenicity

The documentation submitted by the EPA and several published studies were reviewed by the Committee. In 1987, the EPA Health Effects Division Carcinogenicity Peer Review Panel (HED PRC) found that data on 2,4-D provided limited evidence for carcinogenicity in male rats and classified the compound as a Group "C" or "Possible Human Carcinogen." The FIFRA Scientific Advisory Panel (SAP) concluded that this evidence was "equivocal" and that "... 2,4-D should be classified as a Group "D," or "Not Classifiable as to Human Carcinogenicity." The Agency agreed with the SAP that "...the evidence for carcinogenicity was not strong, and categorized 2,4-D as a Group D Carcinogen pending receipt of the repeat rodent carcinogenicity studies and additional forthcoming epidemiological data." However, the animal testing database is still incomplete six years later.

A subsequent review by a panel of 14 scientists was convened by the Harvard School of Public Health in 1989 (Ibrahim *et al.*, 1991). They essentially agreed with the

FIFRA SAP review of the animal data and stated "Considered together, these two animal studies do not provide impressive evidence that exposure to 2,4-D causes cancer in animals. Based on the results from the rat study, the workshop participants concluded that there was weak evidence supporting an excess of brain cancer occurrence in the male Fischer 344 rats receiving the highest dose."

The Committee agrees that the above conclusions were warranted at the time they were made, and since there is no additional animal data, we find no reason to change the Harvard Panel's conclusions at this time. The Committee noted that additional rodent bioassays are underway (approximately 12 months into a 2-year study) in response to the criticism that the studies were not conducted at the Maximum Tolerated Dose (MTD). The results of these studies should resolve the question as to whether the finding of a marginal increase in brain neoplasms (astrocytomas) in male rats in the original study was related to 2,4-D or not. If the neoplasms are truly treatment related they should be reproduced in the ongoing study, particularly since it includes higher doses than the original study. The Committee also noted that preliminary data on the current rat subject studies suggest that the original studies may have been closer to the MTD than originally thought, as evidenced by the **17** percent decrease in body weight gain for male rats, and the 25 percent decrease for females observed at 45 Mg/Kg dosage; this level is near the maximum dose of 75 Mg/Kg used in the original study. This gives added weight to the original findings.

In summary the Committee felt that, at most, there was only equivocal evidence of carcinogenic activity in animals and more studies are needed to determine the compound's potential carcinogenicity.

3.4 Mutagenicity of 2,4-D

The industry supplied mutagenicity data (as summarized by EPA) demonstrating that 2,4-D in various forms was uniformly negative in the Ames assay, mouse micronucleus assay, and unscheduled DNA synthesis assays. The published data supplied by the EPA for review did not provide any information to contradict the industry results.

A number of cytogenetic studies have been published with several reporting negative results while others reported positive cytogenetic endpoints. Due to the

variation in results, this data base deserves special evaluation. In 2 publications (Linnainmaa, 1983; Mustonen *et al*. (1986), studies evaluating sister chromatid exchange or chromosome aberration were negative when blood samples were evaluated from forest workers involved in 2,4-D spraying where exposure occurred under field conditions. In each case either air concentrations and/or urine measurements were made to determine exposure. Several studies evaluated cytogenetic effects in cultured human lymphocytes with both negative (Mustonen *et al*., 1989) and positive results (Mustonen *et al*., 1986; El Zoka and McKenzie; Turkula and Jalal, 1985; Korte and Jalal,1982). The lack of a dose response decreases the confidence in the reported positive results.

The form and purity of the 2,4-D is frequently not reported in the publications that describe positive results in human peripheral lymphocytes exposed in culture. Evaluation of rat peripheral lymphocytes exposed to 2,4-D in culture have produced negative results for cytogenetic changes (Linnainmaa reference identified as chapter 23, source unknown; Linnainmaa, 1984; Moustonen, 1989). Evaluation of cytogenetic effects in CHO cells have been negative (Linnainmaa reference identified as chapter 23, source unknown, Linnainmaa, 1984). Cytogenetic studies in bone marrow have been positive in rats (Adhikari and Grover, 1988) and negative in mice (Schop *et al*., 1990). However, the source and the purity of the test material is not identified in the positive study in rats (Adihikari and Grover, 1988). Bone marrow cytogenetic studies in the Chinese hamster have yielded negative results (Linnainmaa, Carcinogenesis , 1984). A recent study described a positive result in the mouse hair follicle aberration assay (Schop *et al.*, 1990). Since this assay has not been widely utilized, the predictive value of a positive result is uncertain.

The conflicting cytogenetic results do not provide evidence for genotoxicity of 2,4-D. Studies with positive results have significant experimental deficiencies as noted above, thus limiting the value of these studies for assessing genotoxicity. Therefore, although there are serious data deficiencies, the currently available evidence suggests that 2,4-D is non-genotoxic. The lack of genotoxicity may reduce the concern for potential carcinogenicity of 2,4-D, but it is recognized that not all carcinogens are necessarily genotoxic.

3.5 Other Data and Data Gaps

Human case control studies provide conflicting information. The findings of the extant cohort studies may be interpreted as either positive or negative. The one epidemiologic animal study (dogs) is consistent with some of the human studies, but several reservations apply. Animal or *in vivo* mutagenesis and carcinogenesis studies do not support an interpretation of carcinogenicity for 2,4,-D, but data gaps exist. The chemical had apparent carcinogenicity only in rats, where the outcome was astrocytoma, a cancer not reported in the human data. In addition, there is no proposed, plausible biological mechanism that can explain the discrepant findings.

To provide an adequate evaluation of 2,4-D, we need the following research and data:

a) rat, mouse, and dog toxicology studies requested by EPA

b) animal carcinogenicity studies that test 2,4-D with other substances that might reflect the human exposure situation.

c) a replication of the dog epidemiology study, preferably done using newly diagnosed cases, and with careful attention to exposure of 2,4-D and other pesticides and solvents. We also need to have some additional analyses of the collected data to see if a referral bias exists for the cases (eg. referral from an area with a different exposure prevalence), as well as biological and toxicological data which will tie the animal data to the human situation.

d) additional case/control studies, with careful attention to exposures, particularly multiple exposures. The single largest drawback to the existing case/control studies is our equivocal and indirect measure of exposure. Incidence (morbidity) studies should take precedence over mortality studies and proxies should be avoided, if possible.

e) human studies, particularly cohort studies designed to assess both relative risk of NHL and the comparative risk of all mortality (or all disease incidence, if possible). This means that attention must be paid to attaining nearly 100% follow-up and a comparison group must be selected for the entire cohort, that is a realistic standard for the cohort. General population

mortality is not a suitable comparison standard . A comparison cohort must be found, or one constructed, that is a realistic predictor of the prevalence of disease in the exposed cohort.

f) additional follow up and analysis of the human cohort studies of workers involved in the production of 2,4-D. In addition, it would be useful to ask the manufacturer to provide data for workers involved in 2,4-D production from the update to Bond's (1988) study, to provide greater specificity for this agent than was reported.

3.6 Weight of Evidence for 2,4-D Carcinogenicity

Epidemiologic studies of 2,4-D have included both case-control studies of NHL in geographic areas where the numbers of farmers might be high and cohort studies of manufacturers of the chemical as well as applicators and farming populations. The case-control studies have focused on the association of the general class, phenoxyherbicides, with NHL. Many studies did not specify the specific chemical so the exposure to 2,4-D had to be inferred from the usual use in the area. In general the studies indicated an approximately 20% to 30% increased odds ratio associated with farming. If phenoxy acids were responsible for the observed excess of NHL in farmers, the odds ratio for the association between the chemicals and NHL should be much higher than the 1.2 to 1.3 seen for farmers because the etiologic exposure is now more specific. This is not the case. In the NCI studies of NHL in Kansas and Nebraska (but not in Iowa) the odds ratio increased with the number of days per year of exposure to suggest a dose-response relationship. However, in these studies as well as some others there was no sign of increasing risk with number of years of use. So, unlike many other carcinogens, there is no indication of a cumulative dose effect on risk -- only an increasing risk with heavy exposure at some time during the lifetime. Thus the lack of an increase in the risk ratio when we move from a non-specific exposure (as with farming to a more specific exposure (as with 2,4-D) and the absence of a positive dose response where cumulative exposure by years is used is not consistent a causal relationship between the chemical and NHL.

The cohort studies in general have not suggested an increased risk of NHL for individuals exposed to 2,4-D. However, many of these studies had a small exposed population and did not have sufficient follow-up to be expected to show a risk even if it

did exist. Therefore the negative results are relatively uninformative as to whether there is an effect from this chemical. As with most epidemiologic studies the retrospective assessment of exposure is suspect in all these studies. However, for most studies, the subjects may well have had many chemical exposures which were not taken into account in the analysis. Exposure to some of the chemicals are highly correlated, making individual assessment of the exposure to a single chemical difficult or impossible. Thus, while the epidemiologic studies suggest it is possible that 2,4-D may be carcinogenic in humans, the evidence is not strong enough to support a causal relationship to the specific phenoxyherbicide or any other farm exposure. However, there is suggestive evidence of an association between exposure to 2,4-D and NHL in some of the studies, and this observation requires further investigation. Future studies must try to establish the exposure to 2,4-D and distinguish its effects from those of farming in general and from other specific chemicals and pesticides used in the same environment.

When epidemiologic studies alone cannot establish a carcinogenic effect in humans, it is often possible to combine that data with animal studies to establish with high probability that the agent is carcinogenic. In the case of 2,4-D the chemical has possibly produced astrocytomas, but only in rats. Since this cancer site is different from that reported in man and, since the effect has not been seen in studies of 2,4-D in other laboratory animals, these findings do not lend further support to the evidence from the human studies . However, both rats and mice have shown changes in growth and thyroxine levels from 2,4-D. Two cohort studies have reported non-significant increases in thyroid, testicular and other endocrine cancers which deserves further study with an increase in the follow-up of these groups. At this time, with the exception of the suggestive association of lymphomas and exposure to 2,4-D in free-living dogs , the animal data offer no support for the (conflicting) observations in humans, since the carcinogenic effects are very weak, and are limited to a different cancer site and effects which are demonstrable in only one species.

4 CONCLUSIONS

The epidemiologic cohort studies which have tried to identify a hazard from exposure to 2,4,D have generally shown no increased risk of cancer. However, all of the populations which have identified specific exposure to the chemical have been small and the follow-up period usually short. Thus, the number of deaths in the groups have been too small to expect to demonstrate a risk of NHL. No other cancer site in humans has been related to the specific exposure to 2,4,D. Sprayers in the international study had an increase in STS, but the exposures were not specifically to 2,4,D.

Some case-control studies have shown a risk of NHL in association with the occupation of farming but many did not indicate whether this relationship was due to a specific exposure to 2,4,D. In the studies in which identification of specific exposures was attempted, the risk did appear to be due to self-reported phenoxyherbicide exposure in some studies but not in others. The risk did not seem to be much higher than the risk from farming as a general work exposure and the risk increased primarily due to number of days of use per year but not from duration of use. This is not what one would expect if 2,4,D were the agent causing the excess of NHL in farmers. Most of the association appeared to be due to exposure at the highest number of days of use but the number in this group was small. In the study where adjustment was made for other farm exposures, the elevated risk associated with exposure to 2,4,D decreased to a non-significant OR of 1.1 after control for use of organophosphates. Thus the studies cannot distinguish whether any observed risks reported in these studies are due to the use of 2,4,D or some other aspect of farming as an occupation.

The single epidemiologic study of pet dogs suggested that these animals have a risk from owner-reported exposure to 2,4,D or use of a lawn care service. This study has the same constraints of selection bias of cases and controls and recall and misclassification biases that could occur in human case-control studies. The applicability of the canine epidemiology data to lymphoma in humans is questionable since the cancers may not be similar in dogs and humans, and exposures to 2,4-D are not clearly established. To substantiate these results, the study should be replicated with improvement in the exposure measures and verification of the comparability of the cancers in dogs and humans.

The toxicologic data have shown that rats may develop astrocytomas from

exposure to 2,4,D but other animal species have not shown this cancer, nor has it been reported in the human studies. The animals clearly have changes in growth patterns from heavy exposure to the chemical. An on-going rat study at higher doses will clarify whether this finding is treatment-related or not.

The chemical has not shown mutagenic changes under experimental situations. Although the Committee recognizes that it is not necessary for a carcinogen to also be a mutagen, it would have strengthened the observations in humans if there were laboratory data, especially in toxicologic studies of animals, to support any observations in humans.

Therefore, our conclusion at this time is that while there is some evidence that NHL may occur in excess in populations which are likely to be exposed to 2,4,D, the data are not sufficient to conclude that there is a cause and effect relationship between the exposure to 2,4,D and NHL. The data are, however, sufficient to require continued examination of the issue through further studies.

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