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Review of 2,4-Dichlorophenoxyacetic Acid (2,4-D) Epidemiology and Toxicology

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ABSTRACT: The scientific evidence in humans and animals relevant to cancer risks, neurologic disease, reproductive risks, and immunotoxicity of 2,4-D was reviewed. Despite several thorough *in vitro* and *in vivo* animal studies, no experimental evidence exists supporting the theory that 2,4-D or any of its salts and esters damages DNA under physiologic conditions. Studies in rodents demonstrate a lack of oncogenic or carcinogenic effects following a lifetime dietary administration of 2,4-D. Epidemiologic studies provide scant evidence that exposure to 2,4-D is associated with soft tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, or any other cancer. Overall, the available evidence from epidemiologic studies is not adequate to conclude that any form of cancer is causally associated with 2,4-D exposure. There is no human evidence of adverse reproductive outcomes related to 2,4-D. The available data from animal studies of acute, subchronic, and chronic exposure to 2,4-D, its salts, and esters show an unequivocal lack of systemic toxicity at doses that do not exceed renal clearance mechanisms. There is no evidence that 2,4-D in any of its forms activates or transforms the immune system in animals at any dose. At high doses, 2,4-D damages the liver and kidney and irritates mucous membranes. Although myotonia and alterations in gait and behavioral indices are observed after overwhelming doses of 2,4-D, alterations in the neurologic system of experimental animals are not observed with the administration of doses in the microgram/kg/day range. It is unlikely that 2,4-D has any neurotoxic potential at doses below those required to induce systemic toxicity.

KEY WORDS: 2,4-dichlorophenoxyacetic acid, herbicides, carcinogens, neurotoxins;, immunotoxins, neoplasms.

ABBREVIATIONS:

Abbreviation	Definition [brand name or common name]
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
2,4,5-TP	2,4,5-trichlorophenoxypropionic acid, [Silvex]
2,4-D	2,4-dichlorophenoxyacetic acid
2,4-DB	2,4-dichlorophenoxybutyric acid
2,4-DP	2,4-dichlorophenoxypropionic acid [dichlorprop]
DCPA	Dimethyl-1-tetrachloroterephthalate
Dicamba	2-methoxy-3,6-dichlorobenzoic acid
GLP	Good Laboratory Practice
HD	Hodgkin's disease (ICD9 code 201)
IARC	International Agency for Research on Cancer
ICD9	International Classification of Diseases, 9th revision

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MCPA	4-chloro-2-methylphenoxyacetic acid
MCPP	4-chloro-2-methylphenoxypropionic acid [mecoprop]
Mecoprop	4-chloro-2-methylphenoxypropionic acid [MCPP]
NHL	Non-Hodgkin's lymphoma (ICD9 code 200, 202)
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio
STS	Soft tissue sarcoma (ICD9 code 171)
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin

I. INTRODUCTION

This review was conducted at the request of the Industry Task Force II on 2,4-D Research Data to provide a comprehensive update of the evidence on human toxicity and cancer risks related to exposure to 2,4-D. It focuses heavily on the evidence accumulated between 1995 to 2001, because a number of authoritative, published peer-reviewed journal articles and reviews have added to, and confirmed, our understanding of the toxicological outcome from environmental exposure to 2,4-D.

The widely used herbicide 2,4-D was first synthesized in 1941, commercially marketed in the U.S. in 1944,[1] and has been produced throughout the world since the 1950s.[2] In the late 1970s and early 1980s, Hardell and colleagues suggested that 2,4-D was associated with Hodgkin's disease (HD), non-Hodgkin's lymphoma (NHL), and soft tissue sarcoma (STS) [3-6]. These reports were followed by studies of the risks of lymphomas and sarcomas in other groups of agricultural workers and in Vietnam veterans who had been exposed to herbicides.[7-11] An additional study by scientists at the U.S. National Cancer Institute in 1986 pointed toward an association between NHL and 2,4-D use.[12] Prompted by these reports, additional original research in animal models was performed to clearly define the potential cancer risks related to 2,4-D exposure. The toxicity of 2,4-D relating to non-cancer outcomes has also been studied extensively in animals, and these results confirm the lack of adverse observations made in humans. Numerous scientific papers and reviews have been written by research scientists and governmental regulatory bodies summarizing this vast database.

II. METABOLISM AND TOXICOLOGY

The carcinogenicity, chronic toxicity, genetic toxicity, and developmental and reproductive toxicity of 2,4-D have been the recent foci of an extensive series of multiple-species animal toxicology studies conducted according to Good Laboratory Practice (GLP) requirements. These studies provide important new information addressing these critical toxicological endpoints. Together with the chronic bioassay and toxicity studies reviewed by Munro et al. (in 1992) there is a considerable database that assesses the toxic potential of 2,4-D in test animals. In general, the dose levels used in these studies were on the order of 5000 times greater than the maximal documented exposure to humans under circumstances of high exposure, such as forestry workers.[13-15]

1. Major Factors Affecting Toxicity of 2,4-D

2,4-D is soluble in water and distributes widely throughout the body without preferential accumulation in any specific organ. The parent compound exists predominantly in the ionized form at physiologic pH (pKa=3.0) and does not readily diffuse across the lipid bilayer of cellular membranes. Active transport of the parent ion is required for entry into cells.[16-18] 2,4-D does not display any chemical propensity for accumulation in tissues and does not cross the intact blood-brain barrier.[19,20]

The major toxic effects of 2,4-D in rodents and rabbits are exhibited at levels that exceed the anion transport capacity of the kidney. In those species, renal transport mechanisms are rapidly saturated at doses in excess of 50 mg/kg body weight. Clear-

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ance of [^{14}C]-2,4-D from the plasma of treated male B6C3F1 mice after a single oral dose or a single intravenous dose of up to 90 mg/kg body weight depends on the magnitude of the dose administered. The lag in disappearance of radiolabel from the plasma at higher doses suggests a two-compartment clearance model with terminal $t_{1/2}$ of 28 to 45 h. At least half of the administered dose is cleared within 12 h. The apparent volumes of distribution also increase with dose, ranging from 143 to 300 ml/kg. Renal excretion and elimination in the urine is the major route of excretion, with an increasing proportion of the dose and its metabolites appearing in the feces at higher doses. Seven days after a single dose less than 1% of the administered dose can be found in the carcasses of exposed mice.[21] However, canines appear to be more sensitive to 2,4-D as indicated by NOEL values of 1 mg/kg/d for 13 weeks compared with values of 15 mg/kg/d in rats,[2] suggesting that renal clearance mechanisms are more readily saturated in the dog.

After an oral dose, plasma clearance in rats follows a multicompartment model with $t_{1/2}$ values of 0.2 to 1.1, 1.3 to 7.1, and 15.5 to 101.5 h [22] (the reported $t_{1/2}$ values are biphasic within each compartment, with the two values representing the initial and terminal phases of elimination). Approximately 85% of a dose of 10 mg/kg 2,4-D and 97% of a bolus dose of 150 mg/kg is recovered in the urine within 12 h following oral administration. Similarly, greater than 95% of a single intravenous injection of either 5 or 90 mg/kg 2,4-D is eliminated in the urine of treated rats.[23] No matter the route or magnitude of the dose administered, less than 1% of the total dose remains in the body of treated rats after 48 h.[24] Generally, the metabolic fate and elimination of 2,4-D and its esters is independent of dose or sex.[25-27] Comparable rates of elimination are observed in New Zealand white rabbits and rhesus monkeys[28] and lactating goats.[29] In the latter experimental model, the highest residual traces of radiolabeled [^{14}C]-2,4-D are localized in the kidneys at the end of the study (1.4 ppm of a total dose of 483 ppm/day for 3 days).

The pharmacokinetic profile in rats following a dermal dose of 2,4-D is markedly different from that observed following oral administration. Blood concentrations plateau between 2 and 8 h after dermal exposure, after which they decline rapidly.[22] In general, plasma clearance of dermal doses follow biphasic kinetics 8 h after the dose with tissue $t_{1/2}$ values of 0.6 to 2.3 h (first phase) and 25 to 29 h (second phase). The kinetics of the second phase have been attributed to the dermal reservoir of 2,4-D contributing to a slowed increase in plasma clearance during later phases of elimination.

The anionic transporter required for transport of 2,4-D out of the brain is markedly inhibited by doses of 100 to 200 mg/kg allowing for moderate accumulation in the parenchyma of the brain and cerebrospinal fluid.[20,30,31] High doses of 2,4-D compromise the blood-brain barrier as indicated by focal vascular damage, characterized by extravasation of albumin in the medulla oblongata and cortex, induced by 300 to 600 mg/kg.[32]

In humans, excretion of 2,4-D and its metabolites is almost exclusively urinary.[33] The mean $t_{1/2}$ of absorption of 2,4-D in healthy male humans is 3.8 h after ingestion of 5 mg/kg 2,4-D as a slurry in milk or as a powder chased with water. Clearance from the plasma followed first-order kinetics in two of three volunteers ($t_{1/2}$ = 7.3 and 11 h) and biphasic kinetics in the third ($t_{1/2}$ = 4.3 and 16 h). However, despite these minor differences in plasma clearance, urinary excretion followed first-order kinetics in all three subjects.

The salts and esters of 2,4-D uniformly undergo acid or enzymatic hydrolysis *in vivo* to yield 2,4-D acid. Taurine and glycine conjugates of 2,4-D are frequently found in the urine of rats given subcutaneous injections of the butyl ester.[34] Acid-hydrolyzable conjugates are variably found in the urine of workers exposed to 2,4-D esters.[33] In other human subjects no conjugates were identified using the sensitive analytical method of gas chromatography.[35] To date, no reactive intermediates of 2,4-D metabolism have been identified in any species. Metabolic transformation of 2,4-D is a minor factor in the metabolism and disposition of 2,4-D. Only 0.5 to 3.2% of the dose in rats;[24] a trace in goats;[29] and 4.8 to 27% in humans appears as polar, acid-hydrolyzable metabolites.

2. Developmental Toxicity and Reproductive Effects of 2,4-D

Studies to investigate the potential for 2,4-D and its salts and esters to induce developmental

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toxicity in rats and rabbits have been published recently.[36] Maternal toxicity associated with exposure was dependent on the dose level expressed as 2,4-D acid equivalents (a measure of the 2,4-D dose administered regardless of the formulation, such as salts of 2,4-D). The severity of the maternal effects was correlated to the 2,4-D acid equivalent dose, with increasing dose levels that exceeded renal clearance causing increasingly more severe maternal effects. In both species, maternal body weight effects began to be manifested at dose levels of 30 mg 2,4-D acid equivalent/kg/day. At higher dose levels (50 to 75 mg/kg/d in rats and 75 to 90 mg/kg/d in rabbits), body weights and feed consumption were more severely affected. At dose levels of ≥90 mg/kg/d in rats, clinical signs of toxicity (ataxia, muscular stiffness, and decreased motor activity) and mortality were noted. The no-observed effect level (NOEL) for maternal toxicity in both species across the family of 2,4-D salts and esters was approximately 10 mg/kg/d. Significantly decreased fetal body weights and increased fetal variations were seen in rats only at maternally toxic dose levels in excess of 90 mg/kg/d acid equivalent. At maternally toxic doses in rabbits, embryonal and fetal development were essentially unaffected. There were no effects on maternal reproductive measures, such as litter size, resorption rates, or fetal body weights, and there was no evidence of teratogenic activity. In summary, equivalent toxicity of the salts and esters is consistent with rapid and complete metabolic conversion to 2,4-D acid. No adverse fetal effects were noted at dose levels that did not also produce evidence of maternal toxicity or exceed renal clearance of 2,4-D, indicating that the developing rat and rabbit fetus were not uniquely sensitive to 2,4-D and its forms.

Generally, developmental effects in rats were confined to the highest dose levels tested for each analogue (2,4-D dimethylamine; 2-ethylhexyl 2,4-D ester; 2,4-D diethanolamine salt; 2,4-D isopropylamine; 2,4-D triisopropanolamine; and 2,4-D 2-butoxyethyl ester). Doses in excess of 90 mg/kg/d acid equivalents produced the most significant decreases in fetal body weight and a slight delay in ossification of the skull, sternebrae, metatarsals, and metacarpals. Occasionally, extra ribs (cervical or lumbar) were observed at these high doses, with the exception of 2-ethylhexyl 2,4-D ester. Alterations in fetal development in the rabbit were independent of maternal toxicity that occurred at renal saturation levels of 40 mg/kg.[37] By comparison, the alterations in rat fetal morphology are consistent with renal saturation levels in excess of 50 mg/kg.[36]

Recent studies on the subchronic and chronic effects of 2,4-D acid, dimethylamine salt, and 2-ethylhexyl ester in mice and rats did not show any histopathologic alterations in the testes at any dose.[38-40] It is clear from the large amount of data available that 2,4-D, its salts, and esters are not teratogenic in mice, rats, or rabbits unless the ability of the dam to excrete the chemical is exceeded. Although there are numerous investigations on reproductive outcomes in humans exposed to 2,4,5-T and to mixtures of 2,4-D and 2,4,5-T, which have been reviewed and summarized by IARC,[1,41] there are few studies of reproductive toxicity in humans that investigate 2,4-D by itself. No studies since 1991 were located in the scientific literature. Thus, there is no convincing evidence in the literature that 2,4-D is associated with human reproductive toxicity.

3. Subchronic and Chronic Effects of 2,4-D

Subchronic toxicity studies in dogs were conducted on three forms of 2,4-D: the parent form, 2,4-D acid; 2,4-D dimethylamine salt; and 2,4-D 2-ethylhexyl ester. The three studies were designed to allow for comparison of the toxicity of the three forms.[42] Doses in the subchronic studies (on an acid equivalent basis) ranged from 0.5 to 7.5 mg/kg/d. Treatment-related findings in the three studies included reductions in body weight gain, food consumption, and minor increases in blood urea nitrogen, creatinine, and alanine aminotransferase. The data from the three subchronic studies demonstrated the comparable toxicity of the three forms and support a subchronic NOEL of 1.0 mg/kg/d for all three forms. Due to the similarity in toxicity of the three forms of 2,4-D, a 1-year chronic toxicity study was performed on the parent acid to fully characterize the potential toxicity of 2,4-D in the dog.[42] 2,4-D acid was well tolerated at doses up to 7.5 mg/kg/d. The clinical pathology alterations were similar to those seen in the subchronic studies and were not progres-

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sive. The histopathology alterations observed were not severe in nature, and the NOEL in the chronic study was determined to be 1.0 mg/kg/d. Major histologic findings included perivascular, chronic active hepatic inflammation in both sexes at 5 and 7.5 mg/kg/d, and mildly elevated sinusoidal pigment in females. Increased pigmentation of the renal tubular epithelium was found in both sexes at these doses.

There was no evidence of activation of the immune system or any immunotoxic response in these dog studies.[42] Thus, immunotoxicity as a precursor to malignancy in dogs was not noted even after heavy and prolonged 2,4-D exposure. The chronic and subchronic studies in beagles support the conclusions of Munro et al.[2] that 2,4-D is unlikely to produce significant alterations in the lymphatic system of exposed organisms or induce lymphatic system tumors. These findings are in sharp contrast to the epidemiological study of Hayes et al., 1991[43] in which dogs with significantly lower exposures to 2,4-D were at an increased risk for malignant lymphoma (see discussion below). Moreover, subsequent studies of subchronic and chronic effects of 2,4-D in dogs[42] do not support this epidemiologic study, and its conclusions have been directly challenged following a reanalysis of the original data.[44] Nevertheless, definitive studies of the genotoxic potential of 2,4-D in dogs (e.g., micronuclei evaluation) remain to be conducted.

Subchronic toxicity studies were also conducted in rats on the same three forms of 2,4-D.[38] Doses in the subchronic studies (on an acid equivalent basis) ranged from 1 to 300 mg/kg/d. Major treatment-related findings in the three studies included decreases in red cell mass, decreases in T3 and T4 levels, decreases in ovary and testes weights, increases in liver, kidney, and thyroid weights, and cataracts and retinal degeneration (high-dose females). These data again demonstrated the comparable toxicity of the forms of 2,4-D and support a subchronic NOEL of 15 mg/kg/d for all three forms in the rat.

4. Genotoxicity and Mutagenicity of 2,4-D

A recent detailed review of the genotoxic effects of 2,4-D, its salts, and esters has been published.[25] In addition, investigations of 2,4-D and seven of its salt and ester forms in gene mutation in bacteria (Ames test), forward mutations at the HGPRT locus of Chinese hamster ovary cells, the induction of DNA damage and repair in rat hepatocytes, the induction of chromosomal aberrations in primary cultures of rat lymphocytes, and induction of cytogenetic abnormalities in mammalian cells *in vivo* in the mouse bone marrow micronucleus test have been published recently in the literature.[45-47] All of these studies were negative and add to the weight of evidence that 2,4-D does not have any genotoxic/mutagenic potential *in vitro* and *in vivo*.

5. Oncogenicity of 2,4-D

An early study showed an increase malignant astrocytoma in rats exposed at 45 mg/kg/d and not at lower doses.[48] However, recent GLP studies on the oncogenicity of 2,4-D in the rat and mouse have been published.[49] Doses ranged from 5 to 150 mg/kg/d in the 2-year rat study and 5 to 300 mg/kg/d in the 2-year mouse study. The rat study examined the carcinogenicity of 2,4-D acid in diet at doses of 0, 5, 75, and 150 mg/kg/d for 2 years in an attempt to ensure that the top two doses would likely attain a maximum tolerated dose. The low dose (5 mg/kg) was intended to establish a chronic rat NOEL. The parallel mouse study used doses of 0, 5, 62.5, and 125 mg/kg/d for 2 years to establish the maximum tolerated dose and NOEL. However, due to excessive toxicity in males at the high and middle doses, all male mice were terminated at 1 year. No oncogenic effect was noted in either species. It should be noted that 2,4-D does not form reactive electrophile metabolites that are more typically associated with carcinogenicity. Moreover, the GLP studies should be given greater inferential weight than older, smaller studies performed with less robust methods.

6. Neurotoxicity of 2,4-D

There are several published reports linking 2,4-D exposure to myotonia in humans.[50-52] In dogs, myotonia frequently presents as a delayed effect in

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the absence of systemic toxicity or after the animal has recovered from the acute toxic syndrome.[52] In animal models, doses in excess of those required to saturate the anion efflux mechanisms in the blood-brain barrier (>100 mg/kg) are required to cause accumulation in the central nervous system (CNS). Such excessively high doses induce concomitant signs of systemic toxicity, which is expected because they also saturated the renal clearance mechanism. Specifically, high oral or transdermal doses of 2,4-D (50 to 500 mg/kg) produce myotonia in skeletal muscle.[50-54] The additional effects of exposure to high doses of 2,4-D include alterations in CNS neurotransmitter content and behavioral changes[54-59] and alterations in blood-brain barrier transport mechanisms.[18,20,32,60,61] Recently, single-dose acute (up to 150 mg/kg) and 1-year chronic neurotoxicity screening (up to 150 mg/kg/d) studies in male and female Fischer 344 rats (10/sex/dose) were conducted on 2,4-D.[62] The findings of these studies indicated a mild, transient locomotor effect from high-level acute exposure, and retinal degeneration in female rats from high-level chronic exposure. The no-observed-effect level for acute neurotoxicity was 15 mg/kg/d and chronic neurotoxicity was 75 mg/kg/d.[62]

Human observations suggest an association between exposure to 2,4-D and neurologic effects ranging from persistent peripheral polyneuropathy,[63,64] demyelination and ganglion degeneration in the CNS,[63-65] reduced nerve conduction velocities,[66] and myotonia[67] to suicide, depression, anxiety, aggression, and posttraumatic stress syndrome.[68-71] None of these studies controls for the effects of age, exposure to TCDD, or other confounding factors. Furthermore, the degree of exposure to 2,4-D in these studies was poorly documented, and the doses associated with these effects are unknown. Therefore, it is unlikely that 2,4-D has any neurotoxic potential at doses below those required to induce significant systemic toxicity.

III. CANCER RISKS IN HUMANS

A. Previous Reviews of the Carcinogenicity of 2,4-D

Between 1986 and 1997 there were numerous reviews of the carcinogenicity of 2,4-D. IARC in 1986 concluded that there was limited evidence that occupational exposures to chlorophenoxy herbicides are carcinogenic to humans.[72] However, this review did not identify the risks specific to 2,4-D insofar as it did not differentiate among the many herbicides in this class of materials. The report highlighted the absence of replication of site-specific cancer risks and the lack of a consistent exposure-response relationships across studies in its decision.

In 1987, the Ontario Pesticide Advisory Committee of the Ontario Ministry of the environment concluded the evidence was inadequate to classify 2,4-D as a carcinogen.[73] In 1991, an expert panel, convened at the Harvard School of Public Health, concluded that a link between 2,4-D and cancer was far from established. The majority of the panelists felt it was possible to unlikely that 2,4-D could cause cancer, with a minority holding the opinion that the evidence was barely adequate to support any conclusion.[74] The panel noted the need for more reliable and precise estimates of exposure and the need to distinguish more clearly between 2,4-D and other agents in future epidemiologic studies in order to resolve these uncertainties.

In 1992, an expert group commissioned by the manufacturers of 2,4-D conducted a comprehensive review of the human and animal evidence of toxicity and carcinogenicity of 2,4-D.[2] That review noted that the cancer hypothesis was derived from case-control studies in which exposure assessments (derived from subjects' memories) were problematic and, in contrast, cohort studies of exposed workers did not support the findings of increased cancer risk. Furthermore, animal studies clearly indicated that 2,4-D was unlikely to be a genotoxic agent and that it was not associated with cancer induction after long-term exposures.

Between 1987 and 1996, the U.S. Environmental Protection Agency reviewed 2,4-D four times under its Health Effects Division Carcinogenicity Peer Review Committee (CPRC), once by its Science Advisory Panel (SAP), and once by a Science Advisory Board (SAB)/SAP Joint Committee.[73] At its first meeting, in 1987, the CPRC classified 2,4-D as a possible human carcinogen (interim Group C), based on evidence of brain tumors in male F344 rats, which were not confirmed in females or in either sex of B6C3F1

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mice. The epidemiology evidence was not viewed as providing a definitive link between 2,4-D and NHL in humans. The SAP disagreed with this classification, placing 2,4-D in Group D (not classifiable as to human carcinogenicity). At its second meeting, the CPRC disagreed with the SAP and maintained its Group C decision, but in its third meeting changed its classification to Group D, now in concurrence with the SAP. In 1993, the joint panel of the SAB/SAP determined that the evidence in animals was equivocal, and the evidence in humans was not sufficient to conclude a causal relationship existed between 2,4-D and NHL, again placing 2,4-D in Group D.[73] In 1996, the CPRC reviewed the updated animal and human evidence and again concluded that 2,4-D should remain classified as a Group D agent (not classifiable as to human carcinogenicity). This decision was based on 1995 carcinogenicity studies in both rats and mice that did not show compound-related statistically significant increases in tumors and epidemiologic evidence that was inadequate to conclude that a causal relationship existed between 2,4-D and cancer.

In 1996, the joint meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the World Health Organization Core Assessment Group prepared a toxicological monograph on 2,4-D for the purpose of estimating the acceptable daily intake for humans.[25] That group concluded that the epidemiologic studies do not provide consistent evidence of cancer risk related to 2,4-D. The suggestions of an association with both soft tissue sarcoma and lymphomas came from case-control studies in which risk was related to the general category of phenoxyacetic acid herbicides, within which the risks related to 2,4-D could not be specified. It was also noted that cohort studies did not confirm that 2,4-D was associated with any category of lymphomas or soft tissue sarcomas.

B. Epidemiology Studies

Unless they contain specific reference to 2,4-D, this review does not include the numerous cohort and case-control studies of farmers, agricultural workers, and forestry workers[7,75-112] as such reports are largely uninformative regarding the risks of cancer related to 2,4-D. In addition, farming and agriculture involve exposures to numerous agents and activities other than herbicides (including animals, infectious agents, engine exhausts, machine maintenance, fertilizers, grain, plant, and wood dusts, molds and fungi, and unique lifestyle factors) for which cancer risks are undefined and which may be correlated with herbicide use. Moreover, herbicides are not used on a substantial proportion of farms.[92] Use typically occurs only a few days per year, and it occupies a small proportion of a farmer's time. Thus, in general, the average exposures in farming are less than among workers whose principal activities are the production, formulation, and application of pesticides, including herbicides, on which this review is focused.

The principal epidemiologic studies of 2,4-D have been either cohort or case-control studies. In cohort studies, subject groups are defined by exposure (e.g., 2,4-D exposure vs. not exposed), groups are followed over time to determine cancer incidence or mortality, and disease rates are compared among the groups. In case-control studies, subjects are chosen based on disease status (e.g., Hodgkin's disease vs. none), and the past exposures of the cases and controls are compared.

C. Cohort Studies (Summarized in Table 1)

Cohort studies of 2,4-D exposed populations often have a distinct advantage over case-control studies in the reliability of the exposure assessments. This review focuses on those cohorts in which herbicide use or exposure was believed to involve direct contact with chemicals in their concentrated form, as in herbicide manufacturing and application. Many of the cohort studies reported below are based on written job records from which the specific chemical exposures are derived, or on records of the specific herbicide products that were manufactured or applied. In many of the occupations and industries reported, a number of phenoxyacid herbicides were present, including materials contaminated with TCDD. Whenever possible, a distinction is made in this review between subjects who had potential exposure to TCDD and those who did not, inasmuch as the evidence of carcinogenicity of TCDD in both

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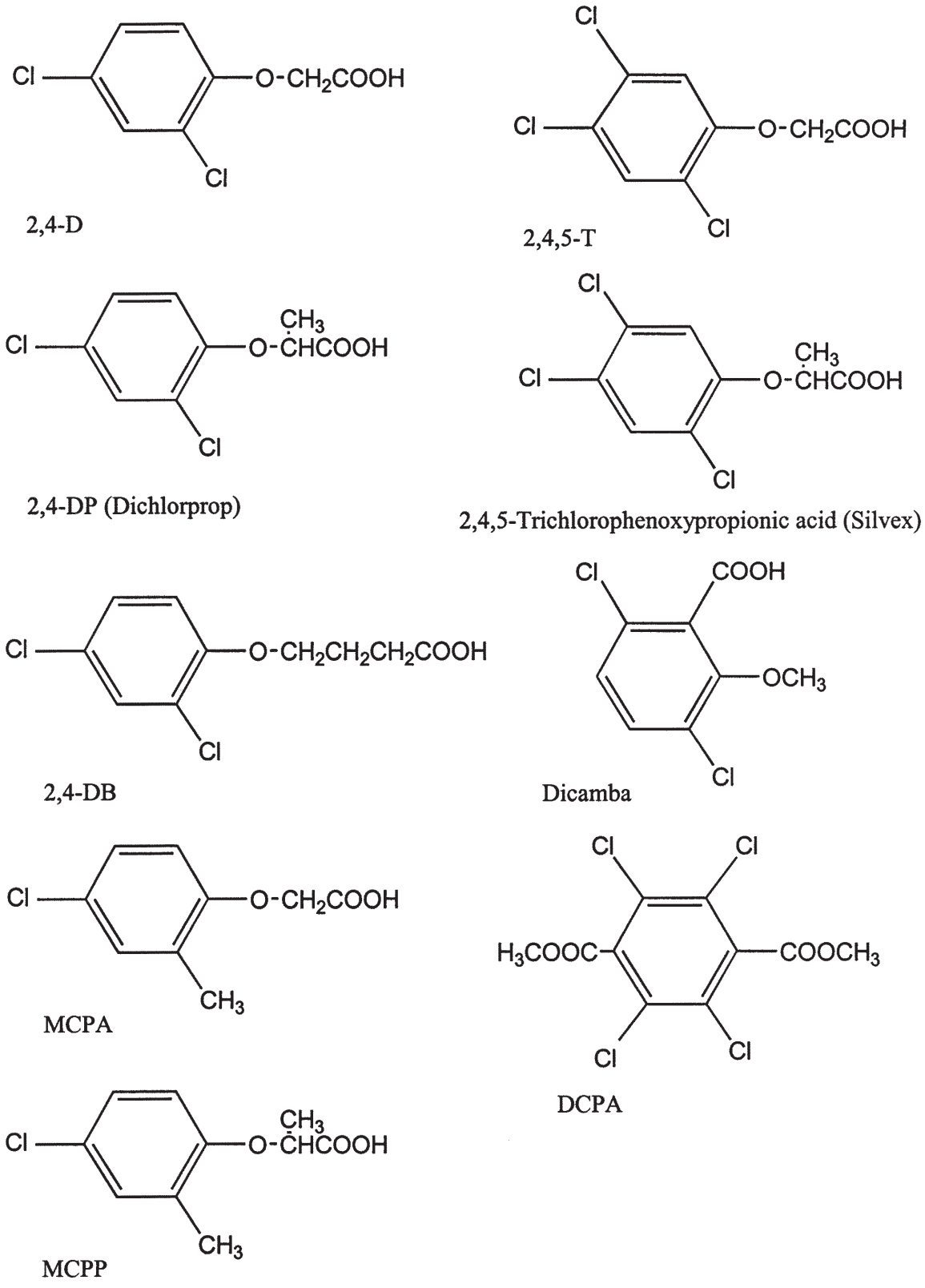


FIGURE 1. Structural diagrams of 2,4-D and other phenoxy herbicides.

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TABLE 1
Cohort Studies of Phenoxy Herbicide Manufacturers and Applicators

Study/year	Cohort	Exposures	Relative risk (95% CI) [# cases] STS	NHL	HD
Cohorts in which TCDD exposure was unlikely					
Wiklund, 1988 [114]	Licensed pesticide applicators	MCPA, mecoprop (TCDD unlikely)	SIR=0.91 (0.37-1.88) [7]	SIR=1.07 (0.70-1.55) [27]	SIR=1.47 (0.82-2.42) [15]
IARC, 1997 [123]	Phenoxy herbicide manufacturers and applicators	Chlorophenoxy herbicides and chlorophenols (not exposed to TCDD)	SMR=1.35 (0.16-4.88) [2]	SMR=1.00 (0.46-1.90) [9]	SMR=0.27 (0.01-1.51) [1]
Zahm, 1997 [130]	Herbicide applicators in lawn care service	2,4-D, DCPA, MCPP, dicamba (very little TCDD)	[0 cases, expected not given]	SMR=1.63 (0.33-4.77) [3]	[0 cases, expected not given]
Lynge, 1998 [131]	Phenoxy herbicide manufacturers	MCPA, small amounts of 2,4-D and 2,4,5-T (negligible TCDD)	SIR=2.47 (0.4-4.1) [4]	SIR=1.10 (0.4-2.6) [6]	NR
Cohorts in which TCDD exposure was unknown					
Cantor, 1991 [119]	Licensed aerial pesticide applicators	Not specified (TCDD unknown)	NR	[1 case, 2.3 expected]	NR
Fleming, 1999 [133]	Licensed pesticide applicators: male private applicator subcohort (farmer applicators) (morbidity study)	Not specified, phenoxy herbicides very likely (TCDD unknown)	[0 cases, 1.0 expected]	SIR=0.91 (0.59-1.33) [26]	SIR=1.50 (0.65-2.96) [8]
Fleming, 1999 [134]	Licensed pesticide applicators: male private applicator subcohort (farmer applicators) (mortality study)	Not specified, phenoxy herbicides very likely (TCDD unknown)	[0 deaths, expected not given]	[1 death, 3.1 expected]	SMR=1.13 (0.13-4.09) [2]
Cohorts in which TCDD exposure was known to exist					
Burns, 2001 [115]	Herbicide manufacturers and formulators	2,4-D (and TCDD for subcohort exposed between 1945-83)	NR	SMR=1.0 (0.21-2.92) [3]	SMR=1.54 (0.04-8.56) [1]
Asp, 1994 [120]	Herbicide applicators (mortality)	2,4-D and 2,4,5-T (TCDD probable)	[0 deaths, expected not given]	[0 deaths, expected not given]	[0 deaths, expected not given]
Asp, 1994 [120]	Herbicide applicators (morbidity)	2,4-D and 2,4,5-T (TCDD probable)	[0 cases, 0.99 expected]	[1 case, 2.83 expected]	SIR=1.67 (0.2-6.02) [2]
IARC, 1997 [123]	Herbicide manufacturers, formulators, and applicators	Chlorophenoxy herbicides and chlorophenols (TCDD exposed)	SMR=2.03 (0.75-4.43) [6]	SMR=1.39 (0.89-2.06) [24]	SMR=1.29 (0.56-2.53) [8]

NR = not reported

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animals and humans is considered to be strong, and exposure to phenoxy herbicides contaminated with TCDD may be an important confounder of associations between 2,4-D and cancer.

Wiklund in 1987[113] and again in 1989[114] reported on a cohort of 20,245 Swedish licensed pesticide applicators who were exposed mainly to MCPA and, since the mid-1960s, to mecoprop, with substantially less exposure to 2,4,5-T and 2,4-D. The majority of subjects were from occupations in agriculture and forestry (70%) and from horticulture (10%). For STS, seven cases were reported (SIR = 0.91, 95% CI 0.37 to 1.88); for NHL, 27 cases were reported (SIR = 1.07, 95% CI 0.70 to 1.55); and for HD, 15 cases were reported (SIR = 1.47, 95% CI 0.82 to 2.42). Risk increased numerically for all three tumor types with increasing years since first licensure, but no significant trend was seen. This study shows no evidence of increased risk of STS or NHL and shows a weak association between HD and herbicide use. The results do not clearly relate to 2,4-D, and the role of TCDD as a contaminant in 2,4,5-T cannot be assessed.

Burns in 2001[115] updated earlier reports[116,117] from a cohort of 1517 chemical workers who manufactured or formulated 2,4-D between 1945 and 1994. There were three cases of NHL (SMR=1.00, 95% CI 0.21 to 2.92). Analyses by cumulative dose of 2,4-D and lagged by 20 years indicated that all three cases fell in the lowest exposure category. There was one case of Hodgkin's disease with 0.6 expected. Although STS was not reported separately, cancer mortality due to "other and unspecified sites", under which STS was subsumed, was increased, based on 10 cases (SMR=1.51, 95% CI 0.77 to 2.70). This study had excellent vital status follow-up (99.9%) and cause of death ascertainment (99.7%), as well as exposure estimates based on measured exposures to 2,4-D. These findings provide little, if any, support for an association between 2,4-D and either NHL or Hodgkin's disease. The weak association between 2,4-D and cancer of unspecified sites is uninterpretable with respect to STS, insofar as the opportunity for exposure to TCDD existed among the subcohort included in the earlier reports.[117,118]

In 1991 Cantor reported the results of a mortality study among 9677 licensed aerial pesticide applicators[119] who were exposed to pesticides while mixing, formulating, and loading chemicals and while cleaning the spray apparatus and tanks on their planes. No specific chemical exposures were reported, although it is likely that herbicide use was frequent. Results for STS and HD were not reported. For NHL, one case (2.63 expected) was reported. This study is uninformative with respect to STS and HD. It supports the conclusion that herbicides, including 2,4-D, are not associated with NHL.

In 1994 Asp reported the results of an 18-year prospective study of chlorophenoxy herbicide applicators in Finland,[120] which updated two earlier reports on the same cohort.[10,121] Workers sprayed a mixture of 2,4-D and 2,4,5-T between 1955 and 1971. There were no deaths due to STS, NHL, or HD. Cancer morbidity was also reported. There were no cases of STS (0.99 expected) and one case of NHL (2.83 expected). Two cases of HD were identified (SIR=1.67, 95% CI 0.2 to 6.02). These results do not support a conclusion that STS, NHL, or HD is associated with exposure to 2,4-D.

Investigators at IARC reported on cancer mortality in a multinational cohort of workers exposed to chlorophenoxy herbicides and chlorophenols in 1991[122] and again in 1997.[123] In the 1997 report, 21,863 male and female workers in 36 cohorts from 12 countries were included. Subcohorts included in the IARC study that have been reported separately[11,124-129] are not described separately herein unless additional findings were presented in these separate reports. The investigators identified subcohorts that were and were not exposed to TCDD or higher chlorinated dioxins. This division was based principally on employment during the period of production, formulation, or spraying of 2,4,5-T and chlorophenols (13,831 workers were exposed to TCDD and 7553 workers were not exposed to TCDD). It was noted that TCDD contamination does not occur in the production of 2,4-D and MCPA (4-chloro-2-methyl-phenoxyacetic acid). Among the TCDD exposed cohort, there were six soft tissue sarcomas (SMR=2.03, 95% CI 0.75 to 4.43) and among the cohort not exposed to TCDD there were two soft tissue sarcomas (SMR = 1.35, 95% CI 0.16 - 4.88). These results indicate there was a weak association between

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STS and exposure to 2,4-D among subjects who were not exposed to TCDD.

The IARC investigators[123] also reported results for non-Hodgkin's lymphoma and Hodgkin's disease. Among the TCDD exposed cohort, there were 24 NHL (SMR=1.39, 95% CI 0.89 to 2.06), whereas among the cohort not exposed to TCDD there were 9 NHL (SMR=1.00, 95% CI 0.46 to 1.90). These results support the conclusion that there was no increased risk of NHL among subjects exposed to 2,4-D and who were not exposed to TCDD. For Hodgkin's disease, among the TCDD exposed cohort there were 8 HD (SMR=1.29, 95% CI 0.56 to 2.53) whereas among the cohort not exposed to TCDD there was 1 HD (SMR=0.27, 95% CI 0.01 to 1.51). These results support the conclusion that there was no increased risk of either NHL or HD among subjects exposed to 2,4-D and who were not exposed to TCDD.

In 1997, Zahm reported the results of a mortality study of pesticide applicators employed by a lawn care service company.[130] This study was initiated in response to the 1986 case-control study by the same author that reported a twofold excess risk of NHL among farmers who used phenoxy herbicides.[12] The cohort of lawn applicators was potentially exposed to 2,4-D as many as 90 to 120 days per year. Among male lawn applicators there were no cases of STS or HD reported (expected numbers were not reported), and there were three cases of NHL (SMR=1.63, 95% CI 0.33 to 4.77). The three NHL cases all had potential exposure to 2,4-D, DCPA, MCPP, dicamba, and organophosphate insecticides. The authors also noted that DCPA was used extensively and contained very low levels of TCDD. There were no significantly increased cancer risks in this cohort. This study does not support the conclusion that either STS or HD is associated with exposure to 2,4-D. It provides weak evidence of an association between NHL and lawn chemical use, including 2,4-D. However, the risks related to 2,4-D alone cannot be specified.

Lynge reported in 1998 the results of a cancer incidence study among 2119 Danish phenoxy herbicide workers exposed between 1947 and 1993.[131] The main product to which they were exposed was MCPA. Limited amounts of 2,4-D and 2,4,5-T were also produced at one of the plants studied.[128] There were four cases of STS (SIR=2.47, 95% CI 0.4 to 4.1) and six cases of NHL (SIR=1.10, 95% CI 0.4 to 2.6). The authors interpreted this to suggest an association between STS and exposure to MCPA and related phenoxy herbicides, and no association between NHL and phenoxy herbicides. However, this report contains little information on risks related to 2,4-D. It appears that these cases of STS and NHL were also reported by Kogevinas[132] (see below) who drew a similar conclusion. There was no appreciably increased risk of any other type of cancer, including HD.

Fleming reported in 1999 the morbidity[133] and mortality[134] experience of 33,658 licensed pesticide applicators in Florida who were followed from 1975 through 1993. There was no information on the specific chemicals used by the applicators; however, all subjects were licensed to apply restricted use pesticides. Of greatest interest is the subcohort of private applicators who were licensed to use pesticides in agriculture or on property owned or rented by themselves or their employers. This group, which included farmers, ranchers, and horticulturists, comprised 68% of the cohort, including 20,505 males. It is likely that this group used phenoxy herbicides regularly in their work, as well as other, unspecified pesticides.

The morbidity study[133] reported among the male private applicators 26 cases of lymphosarcoma (NHL) (SIR=0.91, 95% CI 0.59 to 1.33), eight cases of HD (SIR=1.50, 95% CI 0.65 to 2.96), and 0 cases of STS (1.0 case expected). These results are consistent with the conclusion that agricultural pesticide applicators are not at increased risk of NHL or STS, and that the weakly increased risk of HD is not inconsistent with the role of chance. The mortality study[134] reported similar findings. Among male private applicators, there was one death due to lymphosarcoma (NHL) (3.1 expected), two deaths due to HD (SMR=1.13, 95% CI 0.13 to 4.09), and 0 deaths due to STS (3.2 expected). These results in the aggregate are consistent with the conclusion that pesticide applicators are not at increased risk of fatal or nonfatal NHL, HD, or STS.

The morbidity study[133] also reported increased risks of prostate and testicular cancer among all male applicators, and the mortality study reported increased risks of prostate cancer (but not testicular

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cancer). These findings, which have not previously been observed among pesticide applicators, require additional study before their relationship to phenoxy herbicide exposure can be specified. Prostate cancer has, however, been reported in excess among farmers.[84] No other cause of morbidity or mortality was appreciably increased among Florida pesticide applicators. An earlier study of Florida licensed structural pesticide applicators reported by Blair[135] provided no information on STS, NHL, or HD and included a high proportion of workers exposed to organochlorine insecticides. It is viewed as uninformative with respect to 2,4-D.

Overall, the cohort studies provide an important perspective on the risks of STS, NHL, and HD among phenoxy herbicide manufacturers and applicators. First, the morbidity studies provide estimates of risk for nonfatal cancers. Inasmuch as HD, NHL, and STS all may have appreciable long-term survival, incidence data provide reassurance that the lack of increased risk in the mortality studies is not due to the exclusion of nonfatal or less aggressive forms of HD, NHL, or STS. Second, the morbidity studies add substantial numbers of cases that were not identified in the mortality studies, thus increasing the power of these aggregated studies. It is important to differentiate the cohorts on the basis of exposure, particularly with respect to TCDD. In Table 1, the cohort studies are summarized after grouping them according to whether TCDD exposure was unlikely, unknown, or known to exist. There were four cohorts exposed to phenoxy herbicides in which TCDD exposure was unlikely. Two of these,[114,131] from Scandinavia, were predominantly exposed to MCPA and had little exposure to 2,4-D.

Two cohorts were believed to have appreciable exposure to 2,4-D.[123,130] These two cohorts reported a total of two cases of soft tissue sarcoma and no clear evidence of excess mortality. They also reported a total of 12 cases of non-Hodgkin's lymphoma, with the larger study showing no evidence of increased risk and the smaller study (three cases observed) showing evidence of a moderate association around which the confidence interval was quite broad. In summary, both of these studies are consistent with the conclusion that there is no association between 2,4-D exposure and non-Hodgkin's lymphoma. With respect to Hodgkin's disease, the two cohorts reported a total of one case with neither cohort showing evidence of a positive association with exposure. Overall, these cohorts do not support the conclusion that 2,4-D exposure is associated with soft tissue sarcoma, non-Hodgkin's lymphoma, or Hodgkin's disease.

The two cohorts that were predominantly exposed to MCPA[114,131] in the absence of TCDD showed weak associations between exposure and both NHL and HD and inconsistent results for STS. All of the confidence intervals included 1.0, indicating that a conclusion of no association is reasonably well supported by the data.

There were two cohorts of professional pesticide applicators in which TCDD exposure was unknown.[119,133,134] Both of these cohorts were agricultural applicators, among whom phenoxy herbicide use was very likely; however, the use of 2,4-D, specifically, was unknown. Neither cohort reported any cases of STS and both reported deficits of NHL, supporting an interpretation that agricultural pesticide applicators are not at increased risk of these cancers. Both cohorts reported weak associations with HD, suggesting that agricultural pesticide applicators may be at slightly increased risk of this disease. However, both confidence intervals included 1.0, indicating that a conclusion of no association is also reasonably well supported by the data.

The three cohorts exposed to 2,4-D in which TCDD exposure was known to exist gave inconsistent results.[115-117,120,121,123] The IARC study, which was larger than the other two studies combined, suggested a moderately increased risk of STS and weakly increased risks of NHL and HD. The other two studies reported deficits of NHL based on a total of four cases and slight excesses of HD based on a total of three cases. All of the confidence intervals included 1.0, indicating that a conclusion of no association is also reasonably well supported by the data.

In summary, the cohort studies do not provide adequate evidence to conclude that exposure to 2,4-D is associated with STS, NHL, or HD.

D. Case-Control Studies of Soft Tissue Sarcoma (Summarized in Table 2)

Hardell [3] in 1979 reported a study of 52 males with soft tissue sarcoma and 208 general popula-

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TABLE 2
Case-Control Studies of Soft Tissue Sarcoma.

Study/year	Cases/controls	Exposures	Odds Ratio (95% CI)
Hardell, 1979 [3,3]	52 male cases diagnosed between 1970-77 in Sweden. 208 population controls	Phenoxyacetic acids (2,4-D; 2,4,5-T; and TCDD).	5.3 (2.4-11.5)
Eriksson, 1981 [136]	110 cases diagnosed between 1974-78 in Sweden. 220 population controls	Phenoxyacids (2,4-D; MCPA, mecoprop, 2,4-DP, 2,4,5-T; and TCDD).	6.8 (1.3-17.3)
Smith, 1983 [137]. Smith, 1984 [138]	80 male cases diagnosed between 1976-80 in New Zealand. 92 other cancer controls	Phenoxyacetic acids (2,4,5-T predominantly and 2,4-D)	1.3 (0.6-2.5)
Vineis, 1986 [9]	31 female cases diagnosed between 1981-83 in Italy. 73 population controls.	Phenoxy herbicides (2,4-D; 2,4,5-T; MCPA).	2.7 (0.6-12.4)
Hoar, 1986 [12]	133 male cases and 948 general population controls in Kansas	Phenoxyacetic acids (2,4-D and 2,4,5-T)	0.9 (0.5-1.6)
Woods, 1987 [139]. Woods, 1989 [97]	128 cases diagnosed in 1981-84 and 694 population controls in Washington State	Phenoxy herbicides (2,4-D; 2,4,5-T)	0.8 (0.5-1.2)
Smith, 1992 [140]	30 cases diagnosed between 1976-87, 30 other cancer controls, and 30 population controls	Phenoxy herbicides or chlorophenols	1.0 (0.3-3.1)
Kogevinas, 1995 [132]	11 cases and 55 controls from cohort of workers exposed to phenoxy herbicides, chlorophenols, and dioxins	2,4-D (controlling for exposure to 2,4,5-T and MCPA in multivariable models)	1.4 (0.1-15.8)

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tion controls. Exposure to herbicides and chlorophenol was determined by interview with subjects and next of kin. There was a strong association between STS and exposure to chlorophenoxy acetic acids (OR=5.3, 95% CI 2.4 to 11.5). Most subjects who were exposed to 2,4-D were also exposed to 2,4,5-T and TCDD, and the authors were unable to specify the risk related to use of 2,4-D alone. Eriksson and Hardell[136] later reported 110 cases of STS and 220 population controls in Sweden in which there was a strong association between STS and phenoxyacetic acid herbicides (OR=6.8, 95% CI 2.6 to 17.3). However, the risks related to 2,4-D were not examined. Because of the concurrent exposure to 2,4,5-T, TCDD, MCPA, mecoprop, and 2,4-DP (dichlorprop), the risks related to 2,4-D in this study are unknown.

Vineis[9] studied female rice weeders in northern Italy who were exposed to phenoxy acids. Interviews of subjects and next of kin were used to determine job titles, and exposures were inferred by chemical experts who had experience in agriculture. There was a moderate association between STS and exposure to phenoxy acid herbicides (OR=2.7, 95% CI 0.6 to 12.4). In a related ecological study in this same region of Italy, Vineis reported in 1991 incidence rates of HD, NHL, and STS.[90] Age-adjusted incidence rates for STS were higher in areas where 2,4-D and 2,4,5-T were detected in ground water or soil than in noncontaminated areas, but relative risks were not calculated. Neither of these studies provides information on the risks related to 2,4-D insofar as there was no population exposed in the absence of 2,4,5-T and (presumably) TCDD.

Other case-control studies have failed to find evidence of an association between STS and phenoxyacetic acid herbicides or 2,4-D specifically. Smith[137,138] found no clear association between STS and the use of phenoxyacetic acid herbicides (OR=1.3, 95% CI 0.6 to 2.5) in New Zealand and. Hoar[12] (described below under case-control studies of NHL), in a large study of 133 cases of STS and 948 general population controls

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in Kansas, reported no association with herbicide use (including 2,4-D) (OR=0.9, 95% CI 0.5 to 1.6). Hoar did not present results for 2,4-D alone, because the risk of STS did not increase with either the frequency or duration of herbicide use.[12]

Woods[139] reported no association of STS with phenoxyacetic acid herbicides (OR = 0.8, 95% CI 0.5 to 1.2) among 128 cases of STS and 694 population controls in Washington State. Although the investigators did not differentiate 2,4-D from other exposures in the analyses of STS, this was done for NHL, indicating their data were adequate to make such distinctions. Apparently, the risks related to 2,4-D were not examined further because the investigators found no increased risk of STS in association with either intensity or duration of exposure to phenoxy herbicides as a group.[97]

In 1992 Smith[140] reported the findings from a case-control study in which 30 cases of STS and 52 cases of lymphoma (10 HD and 42 NHL) were compared to 82 cancer controls and 82 population controls. Exposure to phenoxy herbicides was determined at interview by an occupational hygienist. STS was associated with 1 day or more of exposure to phenoxy herbicides (OR=2.0, 95% CI 0.5 to 8.0). No further details on the specific herbicides involved were given. As a result, this study is uninformative with respect to 2,4-D.

More recent case-control studies have also found conflicting evidence of an association between STS and exposure to 2,4-D. Kogevinas[132] performed a nested case-control study of STS using 11 cases and 55 controls derived from the IARC registry of workers exposed to phenoxy herbicides, chlorophenols, and dioxins.[122] Exposure to any combination of 2,4-D, 2,4-dichlorophenoxypropionic acid (2,4-DP) or 2,4-dichlorophenoxybutyric acid (2,4-DB) was associated with STS in a pattern showing dose response with increasing cumulative exposure. However, multivariate modeling in which 2,4-D, 2,4,5-T, and MCPA were all included produced appreciably lower odds ratios for 2,4-D (OR=1.4, 95% CI 0.1 to 15.8). In that model, both 2,4,5-T (OR=1.4, 95% CI 0.1 to 15.8) and MCPA (OR=7.3, 95% CI 0.3 to 172) were also associated with STS. These findings indicate that after controlling for correlated exposures, there was a weak, not statistically significant, association between 2,4-D and STS. This study has the advantage over the cohort study from which it is derived[122,123] insofar as it included incident cases as well as deaths due to STS and the exposure assessment was more detailed.

In summary, the two early studies by Hardell and colleagues that showed strong associations between STS and phenoxyacetic acid herbicides led to more rigorous studies that in the aggregate have shown weakly positive to weakly negative associations. The studies that have collected detailed exposure information regarding 2,4-D specifically have reported either no association with STS,[12,139] or a weak and not statistically significant association.[132] The studies in which significantly increased risks of STS were observed had concurrent exposure to 2,4,5-T and TCDD, and no attempt was made to control for these factors.

E. Case-Control Studies of Non-Hodgkin's Lymphoma (Summarized in Table 3)

Hoar in 1986[12,141] reported on 170 cases of NHL and 948 general population controls in Kansas who were interviewed regarding farming practices and pesticide use. Next of kin interviews were conducted for approximately half of the subjects, who were deceased. The investigators reported that annual days of herbicide use were significantly related to NHL risk, with risk increasing to more than seven-fold for persons using herbicides more than 20 days per year. The use of 2,4-D only (eliminating 2,4,5-T users) was associated with NHL (OR=2.6, 95% CI 1.4 to 5.0). The investigators were unable to specify the dates and frequency of use of 2,4-D specifically. This study indicates a moderate association between NHL and 2,4-D use, but had limited information on risks associated with 2,4-D alone.

In 1990[91,142] Zahm reported a study in eastern Nebraska in which 201 white males with NHL and 725 controls were interviewed by telephone. Eighty of the cases were deceased: they were matched to deceased controls, and next-of-kin interviews were conducted for these subjects. Specific information was collected on the duration and frequency of 2,4-D use. No excess risk was found for those subjects ever having worked or lived on a farm, but the men who mixed or used

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TABLE 3
Case-Control Studies of Non-Hodgkin's Lymphoma

Study/year	Cases/controls	Exposures	Odds Ratio (95% CI)
Hoar, 1986 [12,141]	133 male cases and 948 general population controls in Kansas	Phenoxyacetic acids (2,4-D and 2,4,5-T)	2.6 (1.4-5.0)
Zahm, 1990 [91,142]	201 male cases and 725 population controls in Nebraska	Ever handled 2,4-D (excluding subjects who also handled 2,4,5-T)	1.5 (0.8-2.6)
Cantor, 1992 [143]	622 male cases and 1245 population controls in Iowa and Minnesota	Ever mixed or used 2,4-D	1.2 (0.9-1.6)
Woods, 1987 [139]. Woods, 1989 [97]	576 male cases 694 population controls in Washington State	2,4-D specifically	0.7 (0.4-1.3)
Pearce, 1986, 1987, 1989 [150,152,156]	183 male cases and 338 cancer controls in New Zealand	Phenoxy herbicides	1.0 (0.7-1.5)
Smith, 1992 [140]	52 cases (NHL and HD combined), 82 other cancer controls, and 82 population controls in Australia	Phenoxy herbicides or chlorophenols	2.7 (0.7-9.6)
Kogevinas, 1995 [132]	32 cases and 158 controls from cohort of European workers exposed to phenoxy herbicides, chlorophenols, and dioxins	Any combination of 2,4-D; 2,4-DP; or 2,4-DB	1.1 (0.5-2.7)
Hardell, 1994 [153]	105 male cases and 305 population controls in Sweden.	Phenoxyacetic acids (2,4-D; 2,4,5-T; and TCDD).	5.5 (2.7-11.0)
Hardell, 1999 [154]	404 cases and 741 population controls in Sweden.	2,4-D and 2,4,5-T	1.3 (0.7-2.3)

2,4-D had a slightly excess risk (OR=1.5, CI 0.9 to 2.5). Essentially the same results were found after excluding from the analyses subjects who also used 2,4,5-T (OR=1.5, 95% CI 0.8 to 2.6). Those men who mixed or used 2,4-D for more than 21 days per year had a higher risk (OR=3.3, CI 0.5 to 22), based on three cases. There was a significant trend in risk (p = 0.051), with increasing number of days/year of use of 2,4-D. However, an adjustment for organophosphate exposure lowered the risk estimates for 2,4-D in every category of exposure. Exposure to 2,4,5-T was strongly associated with NHL (OR=6.4 among men exposed 6 to 20 days/year, based on four cases and two controls; no confidence interval is given by the authors). The association between 2,4-D and NHL was stronger among persons with proxy interviews (OR=2.4 for subjects with 20+ days/year of exposure) than among self respondents (OR=1.4 for subjects with 20+ days/year of exposure). This study supports the conclusion that 2,4-D exposure is moderately associated with risk of NHL. Although none of the stratum specific risk estimates was statistically significant, the data showed increasing risk with increasing days/year of exposure. Methodological concern exists regarding the discrepancy in risks between proxy and self-respondents because proxy respondents, as a class, appear to report greater exposure.

In Iowa and Minnesota, Cantor[143] conducted a study of pesticides and other agricultural risk factors for NHL. Of NHL, 622 white male cases and 1245 controls were included. A small increase in risk was seen for those who ever mixed or used 2,4-D (OR=1.2, CI 0.9 to 1.6). There was no difference in risk by historic period or by use/nonuse of protective equipment. Information on the frequency of use of 2,4-D among the Iowa respondents, reported in a separate letter,[144] showed no association with days of use per year (OR=0.6, CI 0.3 to 1.3 for 1 to 4 days per year, OR=0.4, CI 0.2 to .09 for 5 to 9 days per year, OR=1.1, CI 0.5 to 2.4 for 10 or more days per year). The authors considered their findings to be very weak evi-

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dence either for or against a causal association of NHL with 2,4-D exposure. Further analyses of these data by Olsen et al.[145] indicated that data from the proxy respondents gave substantially higher odds ratios for NHL at every level of frequency of use than data from the self-respondents. This and other studies of occupational exposures suggest that data from proxy respondents may give different risk estimates than those from self-respondents,[146,147] and that the reliability of proxy interviews may be lower than of self-respondents.

In 1993, Hoar and colleagues[148] combined the cases of NHL from studies in Kansas, Nebraska, and Minnesota–Iowa and examined the risks of NHL related to atrazine. Although a significant association was initially found, after adjustment for the use of 2,4-D and organophosphate insecticides, the odds ratio for atrazine was reduced to 1.2 (95% CI 0.9 to 1.7). Hoar also reported the results among Nebraska women in a separate analysis in 1993[149] in which she found that handling of herbicides was not associated with NHL (OR = 1.2, 95% CI 0.3 to 4.2), while handling of organophosphate insecticides was (OR=4.5, 95% CI 1.1 to 17.9). It is difficult to reconcile this series of reports with respect to the risks from 2,4-D alone, insofar as in some settings the risks from 2,4-D are confounded by organophosphate exposures, and in some settings they are not.

Woods[139] reported no association of NHL with 2,4-D exposure (OR=0.7, 95% CI 0.4 to 1.3) among 576 male cases and 694 population controls in Washington State. In 1989, Woods[97] further examined risks related to 2,4-D among farmers in the previous study. Farmers who used 2,4-D regularly were not at increased risk of NHL (OR = 0.68, 95% CI 0.3 to 1.4). Similar results were found for 2,4,5-T. Woods concluded that 2,4-D and 2,4,5-T appeared not to independently increase risk of NHL, but might interact with risks due to other agricultural chemicals

In New Zealand, several studies were conducted in the mid-1980s on the relationship between phenoxyacetic acid herbicides and NHL. The primary chemical used in 1950 to 1980 was 2,4,5-T, and not 2,4-D. Pearce et al. reported three studies[150-152] during this time period using 183 men with NHL and 338 controls from the New Zealand cancer registry. No association was found (OR=1.0, CI 0.7 to 1.5) for exposure to phenoxy herbicides. There was no clear dose response relationship with days of exposure per year.

The Smith study described above[140] reported the findings from a case-control study in which 52 cases of lymphoma (10 HD and 42 NHL) were compared to 82 cancer controls and 82 population controls. Exposure to phenoxy herbicides was determined at interview by an occupational hygienist. Malignant lymphomas (not broken down by NHL or HD) were associated with 1 day or more of exposure to phenoxy herbicides (OR=2.7, 95% CI 0.7 to 9.6). No further details on the specific herbicides involved were given. As a result, this study is uninformative with respect to 2,4-D.

The Kogevinas study described above[132] included 32 cases of NHL and 158 controls. The study provided no clear evidence of an association with 2,4-D exposure (OR=1.1, 95% CI 0.5 to 2.7 for exposure to any combination of 2,4-D, 2,4-DP, or 2,4-DB).

In 1981, Hardell [5] reported on the relationship between exposure to phenoxyacetic acids or chlorophenols and malignant lymphoma in Sweden. The study involved 60 subjects with Hodgkin's lymphoma, 109 with non-Hodgkin's lymphoma, and 338 controls from the general population. An increased risk was found with exposure to phenoxyacetic acid herbicides (OR=4.8, CI 2.9 to 8.1). Results were not reported separately for Hodgkin's disease and non-Hodgkin's lymphoma. In 1994, Hardell reported results separately for 105 cases of NHL[153] derived from his earlier studies. Phenoxyacetic acid herbicides were strongly associated with NHL (OR=5.5, 95% CI 2.7 to 11), but almost all cases had been exposed to 2,4,5-T combined with other materials. Exposure to 2,4-D alone was uncommon (three cases and one control) and was associated with a 13-fold risk (95% CI 1.2 to 360). Exposure to MCPA alone was also strongly associated with NHL (OR = infinite, based on four cases and zero controls).

In 1999, Hardell reported on a new study of 404 cases and 741 controls[154] in which phenoxyacetic acid herbicides were again associated with NHL. However, risks had decreased substantially since the earlier reports, and there were no subjects who had

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exposure to 2,4-D alone. Exposure to 2,4-D and 2,4,5-T together was weakly and not significantly associated with NHL (OR=1.3, 95% CI 0.7 to 2.3). There was no evidence of dose response based on the number of days exposed: subjects with greater than 30 days total exposure were at lower risk (OR=1.0, 95% CI 0.4 to 2.2) than were subjects with less than 30 days exposure (OR=1.7, 95% CI 0.8 to 3.3). Of interest, this study reported a moderate association of NHL with MCPA (OR=2.7, 95% CI 1.0 to 7.0) with increasing risk with increasing days of MCPA exposure (OR=4.1, 95% CI 1.0 to 17 for subjects with more than 26 days of exposure). This series of reports provides dramatically inconsistent results across studies that do not have any evident explanation.

In 1999, Garabedian reported results from a case-control study of 995 cases of NHL and 1783 matched controls derived from eight population-based cancer registries in the U.S.[155] Self-reported exposures to phenoxy herbicides were found to be less frequent among cases than among controls (4.92% vs. 5.55%, respectively) and were not significantly different.

In summary, the case-control studies of NHL give conflicting results. The early report of Hoar from Kansas that showed a 2.6-fold association among subjects exposed to 2,4-D was followed by a series of studies that indicated weak and nonsignificant associations in Nebraska and Minnesota/Iowa, an absence of association in women, and stronger associations among proxy respondents than among self-respondents. The two largest studies, both of which examined risks related to 2,4-D alone, showed no association between NHL and 2,4-D. Two other studies showed no association between NHL and mixtures of 2,4-D and 2,4,5-T. Overall, these studies are inconclusive with respect to whether NHL is associated with 2,4-D exposure.

F. Case-Control Studies of Hodgkin's Disease (Summarized in Table 4)

A number of the studies reviewed above contain information on malignant lymphomas but were not analyzed separately for HD and NHL. These studies are not discussed further here. The studies presented below contain information on HD and phenoxy herbicides specifically.

The study by Hoar,[12] discussed above, included 121 cases of Hodgkin's disease and 948 controls in Kansas and reported no association between phenoxyacetic herbicides and Hodgkin's disease (OR=0.9, 95% CI 0.5 to 1.5).

Persson [85] in 1993 reported on 31 cases of HD and 204 controls who completed mailed questionnaires regarding occupational exposures. Subjects who reported occupational exposure to herbicides in farming or forestry were considered to have phenoxy herbicide exposure. Phenoxy herbicides were strongly associated with HD (OR=7.4, 95% CI 1.4 to 40) in logistic regression models. No effort was made to determine the identity of the phenoxy herbicides. Insofar as other sources support indicate that MCPA is the predominant agricultural herbicide used in Sweden[1] and that 2,4,5-T has been the most widely used herbicide in Swedish forestry,[99,113] this finding appears to be uninformative with respect to 2,4-D.

In summary, there is no reliable evidence from case-control studies that HD is associated with 2,4-D exposure.

IV. CANINE EPIDEMIOLOGY STUDIES

Hayes and colleagues reported in 1991 a case control study of canine malignant lymphoma in which dogs with lymphoma (n=491) were individually matched on age to dogs with other malignancies (n=479) and to dogs with other nonma-

TABLE 4
Case-Control Studies of Hodgkin's Disease

Study/year	Cases/controls	Exposures	Odds Ratio (95% CI)
Hoar, 1986 [12]	121 male cases and 948 general population controls in Kansas	Phenoxyacetic acids (2,4-D and 2,4,5-T)	0.9 (0.5-1.5)
Persson, 1993 [85]	31 cases and 204 population controls in Sweden	Phenoxy herbicides, including 2,4,5-T and MCPA	7.4 (1.4-40)

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lignant conditions (n = 466).[43] The study found a weak association between 2,4-D exposures and lymphoma (OR=1.3, 95% CI 1.04 to 1.67). The principal issue in the interpretation of the Hayes study, its criticisms, and reanalyses[44,157-159] is the reliability of the exposure assessments. The measurements of exposure are surrogates for measures of internal dose, of which there were none in any of these reports. The original Hayes study found no significant association between canine lymphoma and any category of commercial lawn chemical treatment or any single category of owner applied 2,4-D. It did find, however, a significant trend for increasing odds ratios with the number of owner applications of 2,4-D. In contrast, Hayes collected but did not present information on the odds ratios associated with the dog having access to the treated areas within 3 days of application. These data, presented by Kaneene,[44] showed that the odds ratio was lower among dogs with access to the treated areas than among those without access. The interpretation of increased relative risk associated with owner applied 2,4-D in the original Hayes paper must also include consideration of the findings from the original data that the dogs' access to the treated areas was associated with reduced relative risk of lymphoma. It should also be noted that the Hayes study found no evidence of increasing relative risk with increasing duration of 2,4-D application by the owner.

Thus, three of the four measures of exposure used by Hayes (number of commercial lawn treatments per year, proportion of times the dog had access to the treated areas, and duration of owner application of 2,4-D) showed no relationship to lymphoma. Although the odds ratio increased with the number of owner applications of 2,4-D, there was no attempt to simultaneously adjust for the probability of exposure as could easily have been done using logistic regression, and thus it is unclear whether the association represents dose or some as yet unrecognized covariate associated with 2,4-D exposure.

Kaneene and colleagues reassessed the original questionnaire responses to determine which lawn and garden products contained 2,4-D, based on expert knowledge of product formulations. This reassessment led to substantially different numbers of dogs in the various exposure categories than in Hayes' original assessment. Of particular note, in Hayes' original data the highest odds ratio was associated with owner application of 2,4-D and commercial lawn treatments (OR=1.9, 95% CI 0.88 to 4.14). Kaneene's reassessment of this group led to a substantially lower estimate (OR=1.1, 95% CI 0.64 to 1.87), which did not support the Hayes estimate. In summary, the exposure estimates on which the evidence of an association between 2,4-D and lymphoma is based in the Hayes study appear not to be substantiated, whereas alternative 2,4-D exposure estimates provide no clear evidence of an association with lymphoma. Moreover, because small increases in odds ratios (as originally reported) are susceptible to small biases and confounding, cautious interpretation of these findings is appropriate.

The doses of 2,4-D received by dogs in the Hayes study must also be considered with reference to experimental studies of 2,4-D carcinogenicity. The worst-case lifetime dose of 2,4-D a dog would have received from contact with treated lawns has been estimated at 126 mg.[158] This dose is 1.5% of the total dose (ca. 90 g) given to beagle dogs in a chronic feeding study that found no evidence of carcinogenicity[160] and is approximately two orders of magnitude below the total dose given in another chronic feeding study in beagles that found no evidence of carcinogenicity.[42] This inconsistency does not favor a causal interpretation of the weak association found in the Hayes study.

SUMMARY

Epidemiology studies in human cohorts provide scant evidence that supports a conclusion that exposure to 2,4-D is associated with STS, NHL, or HD. A number of the studies reviewed were based on careful assessments of exposure, and those that differentiated 2,4-D from other exposures (2,4,5-T and TCDD, in particular) provided a consistent picture that 2,4-D exposed populations were either not at increased risk of these cancers or that the estimated risks were low and that the data were also compatible with there being no association. The cohort studies also allowed assessments of the risk of a wide range of

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other cancer and non-cancer endpoints and showed no consistent evidence of increased risk of any other cancer type or cause of death associated with exposure to 2,4-D.

The case-control studies varied in the quality of the exposure assessments to 2,4-D. Many made no assessment beyond the determination of herbicide or phenoxy herbicide exposure. Furthermore, a number of studies relied to a considerable extent on proxy interviews to establish exposure. Proxy interviews to establish detailed chemical exposure histories are believed to be less reliable than other methods for determining exposure, such as direct interviews, expert reviews of reported exposures, and measurements of exposure.[161-169] Consequently, the studies that relied heavily on evidence derived from proxy interviews should be viewed as less reliable than those that ascertained exposure by more reliable methods. It is appropriate to recognize that, by definition, canine epidemiology studies are based on proxy interviews and that little, if anything, is known about the reliability of exposure assessments in this setting.

The case-control studies do not support a conclusion that 2,4-D is causally associated with soft tissue sarcoma. Although a small number of studies suggested increased risks, the exposure assessments in those studies did not adequately address potential confounding by exposure to other agents. Other studies of STS do not indicate any association with 2,4-D. The case-control studies of NHL give a conflicting picture. The early report of a moderate association between NHL and 2,4-D has been followed by a series of studies showing either weak or no association, and by suggestions that confounding and response bias may explain some of the positive findings. There is no reliable evidence from case-control studies that HD is associated with 2,4-D exposure. The case-control studies in dogs do not provide reliable evidence of an association between 2,4-D exposure and canine malignant lymphoma.

The available data from animal studies of acute, subchronic, and chronic exposure to 2,4-D, its salts, and esters show clear and unequivocal lack of systemic toxicity by any route of administration at doses that do not exceed 50 mg/kg, a dose that saturates renal clearance mechanisms. Similarly, offspring of treated does and dams show mild to moderate alterations in skeletal development only in the presence of overt maternal toxicity. At high doses, 2,4-D damages the liver and kidney. Signs of systemic intoxication may also be produced by the application of large doses of 2,4-D to the skin.

Animals exhibiting neurologic sequelae of exposure to 2,4-D are invariably given doses that would be extremely unlikely in the environment or in the workplace in the absence of a spill or accident. Although myotonia and alterations in gait and behavioral indices are consistent findings, the mechanisms underlying neurobehavioral outcomes are due to overwhelming levels of 2,4-D. Alterations in the neurologic system of experimental animals are not observed with the administration of doses of 2,4-D in the microgram/kg/day range, akin to ambient environmental levels or even those absorbed from contact with freshly sprayed lawns or vegetation. It is unlikely that 2,4-D has any neurotoxic potential at doses below those required to induce significant systemic toxicity.

Despite several thorough *in vitro* and *in vivo* studies, no experimental evidence exists supporting the theory that 2,4-D or any of its salts and esters are capable of damaging DNA under physiologic conditions. The lack of spontaneous or metabolic reactive intermediates renders 2,4-D and its metabolites improbable candidates as carcinogens. Likewise, there is no evidence that 2,4-D in any of its forms activates or transforms the immune system even after prolonged exposure to high doses.

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