

National Network To Prevent Birth Defects

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THE MEDICAL, ECONOMIC, AND ENVIRONMENTAL IMPACT OF 2,4-D

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Chemicals that challenge the health will be unprofitable to the nation, and will detract from the national productivity and growth. One reaches this conclusion because the health costs are simply so much larger than any other economic gain that a chemical could produce.

For example, the United States spends 10.7 percent of the entire Gross National Product, or \$387 billion per year in 1984, for medical care. It is an expenditure that dwarfs the total sales of all agriculture, forestry, and fisheries, which in 1982 accounted for \$84 billion in national product. It dwarfs synthetic organic pesticide sales, which were only \$4.7 billion in 1981, despite high federal research subsidies and direct subsidies.

Diseases of the aging process are America's most expensive medical problems. Rice and colleagues estimated that the medical and economic costs of cancer in 1980 totaled \$51 billion per year. The American Heart Association estimates heart disease, stroke, and arteriosclerosis to cost the nation \$51 billion a year in 1982, and the National Institute of Health estimates senility to cost \$40 billion a year. In 1982, Americans over the age of 65 were spending \$106 billion a year for hospital care.

Childhood diseases are also expensive. We estimate birth defect medical costs to total \$14 billion a year, as of 1980. Learning disabilities and mental retardation cost the nation considerably more than \$14 billion a year, if economic productivity costs are also included - in an age where education and working smart are essential.

Alternatives to Pesticides

The economic justification of taking health risks with pesticides diminishes even further in face of the widespread bankruptcy of farmers, and the need to cut back on chemical inputs to reduce costs, maintain competitiveness, and increase profit margin. Based on the results of years of research into alternative farming methods such as integrated pest management, many experts conclude that a large percentage (50 percent or more) of the use of synthetic organic pesticides represents economic waste to the nation because it increases farm costs without bringing farming advantages such as better control of pests.

In the case of homeowners and other users, exposure rates to hazardous pesticides can pose major health problems. Furthermore little national product is produced by cosmetic spraying of home plantings, and there are good alternatives. For example, the lawn is believed to be the easiest home planting to manage without any herbicide by experts who research alternatives.

THE CASE OF 2,4-D: WHEN HUMAN STUDIES BECOME AVAILABLE

As human studies become available on the health effects of various toxic substances, it is generally acknowledged that it

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becomes less necessary to rely on animal experiments to judge the safety of the chemical. Indeed, when significant and adverse health effects are found in people due to exposure to a pesticide, it means that the regulatory process which was designed to prevent human injury has failed to do its job.

Sufficient human studies as well as case studies are available for 2,4-D to be certain that the herbicide can cause serious health injuries after routine exposures. These human studies are in many cases reinforced by laboratory results with similar findings, but not in all cases. Differing human metabolism and inability to query laboratory animals about some symptoms produces some divergence in human and laboratory studies.

As Ruth Shearer wrote in 1981 about some of the acute effects of 2,4-D in humans:

"Acute effects of 2,4-D in human include headache, weakness and rapid fatigue, nausea and vomiting, diarrhea, burning eyes, sore throat with burning in the chest, and impaired senses of taste and smell. Delayed effects of acute exposure include numbness and pain in hands and feet, occasionally progressing to limb paralysis, and visual problems including diplopia. Residual effects include continued numbness and pain in limbs, chronic respiratory impairment, bleeding tendency including menstrual problems, concentration and memory problems, and hypersensitivity to non-physiologic chemicals. All of these have lasted for years and have been reported in cases of bystander exposure as well as user exposure.

Nearly all of these human symptoms are undetectable in laboratory rodents. Bleeding is detectable, however, and has been demonstrated in animals given high doses of 2,4-D and in fetal rats whose mother was given very low doses. Humans would be far more susceptible to such capillary injuries resulting from depletion of tissue ascorbic acid content because the test animals can synthesize ascorbic acid (Vitamin C) while human cannot. Research has shown that ascorbic acid is used up in the detoxification of organochlorine pesticides, and other studies have demonstrated that a 2,4-D family injury found at very low dose in rodents is depletion of ascorbic acid in spite of the fact that they are capable of replacing it by synthesis." (Belova and Sokolova, 1971)

The large number of laboratory studies showing internal bleeding in the animal and fetus are particularly important because of the many human reports complaining about the same problem. We will come back to this issue in looking at birth defects and abortions.

CANCER AND 2,4-D

In the United States, 22 percent of all deaths were from cancer in 1982, costing approximately \$51 billion a year. In a two step process of initiation and promotion, it really makes little difference from the viewpoint of medical costs whether the cancer is generated by initiation or promotion. Americans are already exposed to a wide range of initiators.

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A health approach that aims to reduce the medical costs of exposure to chemicals will look at the initiation and promotion of cancer as equals. A good example of how expensive cancer promotion can be is indicated by Blumer and Reich's paper on lead exposure to Swiss residents from gasoline. Removal of lead by EDTA chelation in high blood lead cases was found to reduce cancer deaths from 17 percent of the population to only 1.7 percent. In other words, at high dosages lead permits the full expression of latent cancers.

Farmers are also exposed to a wide range of cancer initiators, ranging from pesticides, to fertilizers, to viruses. Strange and Krupicka in 1984 noted the possibility that nitrogen fertilizers and the nitroso compounds generated from them, might explain some of the higher leukemia rates in mid-western farmers. Obviously, adding cancer promoters to such a situation will lead to problems.

The literature suggests that 2,4-D is both an initiator and promoter of cancer.

Non-Hodgkin's Lymphoma in Kansas Farmers Linked to 2,4-D

The recently published NCI study of Kansas farmers (Hoar et al and their cancers and pesticide use, is only the last of a series of human surveys linking 2,4-D and other chlorophenols to higher cancer rates.

In this case, a higher rate of non-Hodgkin's Lymphoma was found after 2,4-D exposure. It was significant that rates keyed to length of exposure and use of protective equipment. Farmers reporting exposure to 2,4-D for more than 20 days in any year had a 7.6 times greater risk of developing NHL as did nonfarmers. See table 1.

Previous human studies, largely from Scandinavia, have focused on soft tissue sarcoma, malignant lymphoma (including Hodgkin's Disease), nasal and nasopharyngeal cancer, with colon cancer used as a comparison. These are summarized in table 2. Balarajan and Acheson in a 1984 survey of soft tissue sarcomas in Britain, found that these sarcomas concentrate only in the category of farmer, farm manager, and market gardener, with a relative risk of 1.4.

We know from numerous studies of farmers that exposures to chemicals and to livestock and poultry will elevate cancers. Farmers tend to smoke and drink less than the population, which means that it is essential to be specific in comparing cancer rates with the general population, since lung cancer rates will be less - which accounts for such a large portion of cancer deaths.

What is most instructive about the Swedish and other phenoxy studies is that they key to cancer types that are relatively rare in the general population. Sharp elevation of rates in these rare cancers makes the case much stronger that 2,4-D does cause cancer in humans and probably initiates these cancers.

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1-D and Non-Hodgkin's
Lymphoma

Table 1. Non-Hodgkin's Lymphoma in Relation to Duration, Frequency, and Latency of 2,4-Dichlorophenoxyacetic Acid Use

	No. of Cases	No. of Controls	Odds Ratio (95% Confidence Interval)
Never farmed	37	286	1.0
Duration of use,* y			
1-5	3	16	1.3 (0.3, 5.1)
6-15	7	22	2.5 (0.9, 6.8)
16-25	8	15	3.9 (1.4, 10.9)
≥26	6	17	2.3 (0.7, 6.8)
χ for trend	3.560
P (one-tailed)	.0002
Frequency of use,† d/y			
1-2	8	17	2.7 (0.9, 8.1)
3-5	4	16	1.6 (0.4, 5.7)
6-10	4	16	1.9 (0.5, 6.7)
11-20	4	9	3.0 (0.7, 11.8)
≥21	5	6	7.6 (1.8, 32.3)
χ for trend	3.733
P (one-tailed)	.0001
First year of use‡			
1966 or later	5	21	1.9 (0.6, 6.0)
1956-1965	9	23	2.9 (1.1, 7.2)
1946-1955	8	24	2.1 (0.8, 5.6)
Before 1946	2	2	6.2 (0.6, 65.3)
χ for trend	3.561
P (one-tailed)	.0002

*Five controls had missing data.

†One patient and ten controls had unknown frequency of exposure.

‡First available for use in 1942.

(Hoar et al)

Phenoxy Herbicides and
Cancers

Table 2. Risk Ratios (RR) in Cases Exposed to Phenoxy Acids or CP in Swedish Case-Control Studies Referred to in the Text

Cancer Type	Exposure		Reference
	Phenoxy Acids	High-grade Chlorophenols	
Soft-Tissue Sarcoma			
Northern Sweden	5.3	6.6	4
Southern Sweden	6.8	3.3 ^a	5
Malignant Lymphoma ^b	4.8	8.4	7
Hodgkin's Disease ^c	5.0	6.5	9
Nasal, Nasopharyngeal Cancer	2.1 ^d	6.7	10
Colon Cancer	1.3 ^d	1.8 ^d	12

^ap<0.01^bAn association was found with exposure to organic solvents, RR equals 3.1^cOrganic solvents, RR equals 3.0^dNot significant. For all other RR, p<0.001.(Adapted from Hurdell¹⁰)

(O'Brien)

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It is of particular concern in the case of 2,4-D, that the chemical is being used in the home and urban setting, as on the lawn. This exposes a much larger population, most of whom are not using protective equipment. In the Hoar study, excess cancer rates were found in farmers who used 2,4-D for even 1-2 days per year. (Table 1)

Animal Studies on Cancer

The laboratory studies are suggestive that 2,4-D has significant promotional capacity. For example, Archipov and Kozlova in 1974, reported 2,4-D to be a promoter of skin cancer in mice. Shearer notes that chlorinated catechols, a second-level degradation product, is also a co-carcinogen.

Shearer points out that the high incidence of tumors in the control animals of the American studies of 2,4-D, (that is the Hansen and Bionetic studies), makes it difficult to determine whether the higher cancer in 2,4-D treated animals was due to initiation or promotion.

Reuber's analysis of both studies show higher cancer rates, with the lymphoreticular system most sensitive to 2,4-D cancer in mice and rats, but other organs also showing increases. Shearer suggests that there may have been some cancer initiators in the testing laboratories, such as nitrosamines in the feed, that might explain the cancer rates in the control animals. Only a small amount of initiator is needed where there is a strong promoter.

In June 1986, the Environmental Protection Agency disclosed that 2,4-D had produced a rare brain tumor at high dose (40 mg/kg) in male rats.

Immune System and Cancers

Hardell suggested that the association between phenoxyacetic acid herbicides and Non-Hodgkin's Lymphoma might have biologic plausibility through the relationship between dioxin contaminants and the immune system. Cancer promotional properties of chemicals probably have immune system aspects in general, though the study of the immune system is still in its infancy. For example, available case studies show that the termite poison chlordane sharply reduces the numbers of natural killer cells, similarly to radiation, leading to higher rates of leukemia just like radiation

Very little information is available concerning the impact of 2,4-D and its associated dioxins, other contaminants, and breakdown products on the immune system. It has long been known that the TCDD dioxin can cause thymus atrophy in all mammalian species studied, and cause immunosuppression at levels too low to produce clinical or pathological changes, with the greatest impact from perinatal exposure.

The recent findings at the Quail Run Mobile Home Park in

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Gray Summit, Missouri that exposures to TCDD depresses immune response in humans confirms these laboratory studies. But, even here the entire range of immune response was not measured, such as natural killer cell levels. The Quail Run findings would suggest higher eventual rates of infection and auto-immune disease among the exposed population, as similar immune system depressions have produced in other populations. Less is known about the significance of abnormal T-cell ratios and loss of T-cell function to cancer rates. (See panel 2.)

For 2,4-D we will have to wait until adequate studies are completed.

MUTATION AND 2,4-D

The capacity of chemicals to cause mutation bears upon their capacity to initiate cancers or cause genetic based birth defects. Shearer concludes in 1981 from the literature at that time

"2,4-D causes point mutations in animal cells without liver activation, damages DNA in a manner similar to ionizing radiation, and stimulates mitosis. It does not cause chromosome breakage or nondisjunction."

Newer work changes this conclusion somewhat. A 1985 article by Turkula and Jalal finds that 2,4-D in cultured human lymphocytes causes a highly significant increase in sister chromatid exchanges at a 50 ug/ml dosage. Dosages of 100 and 250 ug/ml elevated SCE, but not significantly.

Table 3. Rates of sister chromatid exchanges in human lymphocytes exposed to 2,4-D (based on analysis of 50 cells for the control and each treatment)

Concentration µg/ml	Mean no. SCE per cell
DMSO	7.02
50	9.8/4.27**
100	8.32
250	8.36
t table†	2.68
F table‡	6.11***
df	3,∞
F table§	5.42***

** Significance at $P < 0.05$; *** $P < 0.001$

† Duncan's *t* value, which the treatment *t* value (to the right of the /) must equal or exceed to be statistically significant

‡ Value from ANOVA of sister chromatid exchanges from 2,4-D treatments

§ F table value for the corresponding *df*

The authors suggest that at the dosages higher than 50ug/ml, a high proportion of the cells may be so affected that they do not enter the division phase and fail to survive. They also suggest that the disparities among some of the 2,4-D mutation studies might be explained by Seiler's observation that 2,4-D may metabolize

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Panel 2

Some health effects associated with immune system depression
typical of TCDD dioxin exposures

TABLE 4.

Main experimental immunological diseases

	Effect of neonatal thymectomy	Effect of bursectomy
Spontaneous diseases		
New Zealand Black (mouse) disease	aggravates ^a	-
MRL/1 lupus	prevents ^b	-
BXSB lupus	aggravates ^c	-
Aleutian mink disease	not known	-
obese chicken thyroiditis	aggravates ^d	prevents ^e
Inducible diseases		
experimental allergic encephalomyelitis	prevents ^f	no effect ^g
lymphochoriomeningitis	prevents ^h	-

^aHowie and Helyer, 1966.

^bSteinberg et al., 1980.

^cSmith et al., 1983.

^dWick et al., 1970a; Welch et al., 1973.

^eWick et al., 1970b.

^fArnason et al., 1962; Jankovic and Isvaneski, 1963.

^gJankovic and Isvaneski, 1963.

^hRowe et al., 1963.

TABLE 5.

Relative dependence of infections on B and T cell function

	B ?	T
Bacterial infections	streptococci ^a staphylococci ^a pneumococci ^a <i>Hemophilus influenzae</i> ^a	<i>Mycobacterium tuberculosis</i> ^b <i>Salmonella</i> ^c <i>Treponema</i> ^b
Viral infections	enteroviruses (coxsacki) ^{b,c} togaviruses poliovirus ^a	herpesvirus (herpes simplex, cytomegalovirus, zoster) ^{a,c} pox virus (vaccine) measles ^a , mumps, influenza virus
Fungal infections		<i>Candida</i> ^a , <i>Monilia</i> ^a , <i>Cryptococcus</i> ^{a,b}
Parasite infections	malaria ^a trypanosomiasis	<i>Pneumocystis carinii</i> ^a , malaria ^a , <i>Aspergillus</i> leishmaniasis, Chagas disease

Data obtained on the following lines of evidence:

^a relative incidence in children with T or B cell immuno deficiency, or in adults with Hodgkin's disease (T cell deficiency) (Allison, 1972, 1973; Good et al., 1971).

^b high incidence of infections in ALS-treated mice (see Chapter 6).

^c protection by antibody (B cells) or sensitized cells (T cells) in mice irradiated or treated with high doses of cyclophosphamide (Allison, 1973).

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differently, to produce in some cases a herbicide-protein transport complex that is more potent biologically than free 2,4-D, or to produce through hydroxylation inactive metabolites.

In 1979, Seiler reported on his findings that 2,4-D and other phenoxy herbicides caused inhibition of testicular DNA synthesis as noted by the table below. 2,4-D at 200 mg/kg produced a 29 percent inhibition, which is relatively mild compared to the MCPA. Seiler called for more cancer tests, based upon these findings.

RESULTS and DISCUSSION

Of the five phenoxyacids tested four yielded positive results, i.e. they depressed thymidine uptake significantly. Only 2,4-DP was not significantly positive (see Table 1). As there exists a high correlation between inhibition of testicular DNA synthesis and carcinogenicity by a chemical agent, the question arises immediately, whether phenoxyacids should be suspected of carcinogenic activity.

TABLE 6.

Inhibition of testicular DNA synthesis by various phenoxy acids

Compound	Concentration (mg/kg)	Inhibition (%)	p <
2,4-D	200	29	0.05
2,4-DP	200	14	-
2,4,5-T-acid	200	39	0.05
2,4,5-T-isooctylester	400	44	0.01
	200	31	0.05
	100	10	-
	50	1	-
MCPA	200	54	0.01
MCPP	200	60	0.01

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Seiler's review of the literature on the mutation properties of the phenoxy acids other than 2,4,5-T, in 1978, concluded that the phenoxy acids do influence nucleic acids and their synthesis, are weak mutagens in many different test systems, though there were some negative tests. He concludes that exposure to people handling the material would pose the most risk, noting the findings of Yoder of chromosome breakage in people exposed during the spray season, frank mutations in fruit flies, and increased reports of cancers in workers. Seiler concludes:

"Thus these compounds are not the absolutely harmless and innocuous substances as which they have been described..."

Like Turkula and Jala, Pilinskaya in 1974 also found positive results in human lymphocyte cultures, with .002 to 50 ug/ml dosages. Only at the lowest levels were no effects found, with no further increases in damage noted above .2 ug/ml. Chromatid type aberrations prevailed over chromosome at a 4 to 1 ratio. Ahmed's study of SV-40 transformed human fibroblast repair synthesis found 2,4-D to act similarly to radiation.

Yoder found chromatid gaps and breaks in workers to follow the spray season in Idaho, with mean number of chromatid breaks rising more than four fold, and also the maximal number of aberrations scored in a single person (25 cells) rising from 3 to 6. 2,4-D and amitrole were the two most frequently used herbicides

Confirming these studies is a Russian study (Belova and Soklov 1971, showing a loss of fertility in both sexes of rats after relatively low dosages of 2,4-D butyric acid (a herbicide in the 2,4-D family). Impaired fertility was also found in the first generation progeny.

In the third generation, there was a 12 percent incidence of hairless and a 15 percent incidence of dwarf young among the newborn rats, indicating induction of recessive mutations in the germ cells of the treated grandparents.

BIRTH DEFECTS, SPONTANEOUS ABORTIONS, REPRODUCTIVE PROBLEMS AND 2,4-D

In August 1979, a group of women from Tidewater, Oregon wrote a letter to the Environmental Protection Agency to complain about a series of miscarriages, after the U.S. Forest Service sprayed 2,4-D and Tordon 101 (2,4-D and picloram), by aerial application. There were some other symptoms:

"...Between May 25 and June 2, three of the only five women known to be pregnant in the valley had spontaneous abortions. All three women were treated by physicians and were in the first trimester of pregnancy. The two surviving pregnancies were in the later stages of gestation... All three women live within one mile of heavily sprayed units.

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Since May 12, the health of the population of our valley has undergone profound and disturbing changes. Chief among these has been the incidence of respiratory illness and intestinal disorders in almost every household. Several women experience uterine hemorrhaging not associated with pregnancy. Children and adults suffered bleeding gums, bloody noses, and a number of women suffered from bacterial vaginal infections. Ten children and three adults have suffered an undiagnosed illness characterized chiefly by high fever; two children and two adults had undiagnosed rashes that doctors were unable to explain, and on July 9 occurred one near-fatal case of meningococcal meningitis in a two-year-old who is still hospitalized..."

Numerous other cases of spontaneous abortion associated with 2,4-D exposure were reported, as well as other similar symptoms such as bleeding. In April 1980, a group of women from Ashford, Washington for example, also wrote to E.P.A. as noted in Panel 3. A group of factory reports note similar symptoms such as bleeding among workers.

Ruth Shearer, as already noted, attributes the bleeding to vitamin C depletion related to the metabolism of 2,4-D, which happens also in numerous laboratory animal studies despite the capacity of these animals to manufacture their own ascorbic acid.

Depletion of vitamins can also be a source of birth defects such as neural tube defects. Smithell and colleagues in three human studies find that depletion of folate, vitamin C and riboflavin is associated with mothers who have given birth to neural tube deformed children, and that simple vitamin supplementation can reduce future neural tube rates from 5 percent to 1 percent. 2,4,5-T has been shown to cause neural tube birth defects, but little seems to be known about 2,4-D and human pregnancies outside of the many reports that have been received.

The Environmental Protection Agency undertook the Five Rivers Health Study to investigate the reports of human fetal abortions in Oregon, but never issued a report. Correspondence presented in the court case, Merrell vs. Block, suggests government awareness of a problem. Dr. Barbara Wood of the Health Department of Lincoln requested a delay in fall aerial spray due to the preliminary results of the Five River Health Study that noted health histories confirming the symptoms of bleeding and abortions.

The ban on herbicide use by federal agencies in Oregon and aerial spray of herbicides nationally has reduced exposures to 2,4-D in spray areas where there are significant populations, and reduced the number of adverse health reports.

Laboratory Findings About Developmental Toxicology

Shearer reviewed the few studies available on developmental toxicity, and concluded that 2,4-D does cause malformation, malfunction particularly through internal bleeding, growth retardation and lethality. Panel 4 summarizes her conclusions in 1980. 2,4-D easily crosses the placenta.

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Panel 3

Letter to E.P.A. from Ashford, Washington Complaining About
Health Effects from 2,4-D Spray Drift, April 1980

"In early autumn of 1979, Ashford had eight pregnant women, a ninth lived thirteen miles away but traveled the common road through Ashford, and a tenth pregnant woman was a roadside mail handler... From Sept. 1979 through March 11, 1980, eight of these ten women suffered miscarriages... Two of the miscarriages were determined to most closely resemble a hydatidiform mole, although one of these two was atypical of a true mole. (The lab at Duke University was not 100% certain, as it met one of the three criteria but not fully the other two). A third miscarriage was a deformed fetus, and the others were lost too early to determine any deformation if it existed..."

The women noted similar effects in animals of the area, and attributed the health problems to timber and highway spraying with 2,4-D.

Worker Reports With Similar Medical Problems

- AU - Elina VA
AA - Ufim. Inst. Gig. Profzabol., Ufa, USSR
TI - Effect of products of organochlorine herbicide production on specific functions of the female body
S - CA/087/106184Z
SO - Gig. Tr. Sostoyanie Spetsificheskikh Funkts. Rab. Neftekhim. Khim. Prom-sti.; 1974:187-90
LA - Russ
AB - CBAC COPYRIGHT: CHEM ABS Workers of organochlorine herbicide prodn. of the 2,4-D family, are exposed to chlorinated hydrocarbons in concns. exceeding max. admissible concns. (MAC). (94-75-7 2,4-D) Substantial impairment of menstrual and child-bearing function arise manifested as higher rate of miscarriages, premature births, toxicosis of second half of pregnancy, and the menace of miscarriages during whole pregnancy period. Sanitary-hygienic recommendations are discussed.

79-2080. Bezuglyi, V. P.; Fokina, K. V.; Komarova, L. I.; Sivitskaia, I. I.; Il'ina, V. I.; Gorskaia, N. Z. (Inst. Toxicol. & Hyg. Pestic. Polym. & Plast., Kiev, USSR) Klinika ot-dalennykh posledstviiv ostrogo otravleniia 2,4-dikhloro fenoksiusnoi kislotoi. [Clinical manifestations of long-term sequel of acute poisoning with 2,4-dichloro phenoxyacetic acid.] *Gig. Tr. Prof. Zabol.* (3): 47-48; 1979. (Russian)

A group of 11 female field workers who had developed symptoms of acute poisoning after exposure to the herbicide 2,4-dichloro phenoxyacetic acid (2,4-D), were followed-for 2 yr. At the initial examination the patients complained of periodic headache, vertigo (7), fatigue, numbness and pain in legs and arms, irritability (5) and partial

amnesia (2). All patients had cardiac pain, six patients featured palpitation and five had marked dyspnea. Within 1-1.5 mo of poisoning 9/11 patients developed oligomenorrhea (in 7 women the menstrual cycle normalized within 5-6 mo). Six patients had mono- and lymphocytosis, while all patients had statistically significant decreases in the activity of a series of oxidative enzymes of the peripheral blood leukocytes. Two patients had chronic toxic hepatitis, 9 developed encephalopolyncuritis, myocardiodystrophy and vascular dystonia, and 8 patients had chronic conjunctivitis.

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Shearer's Conclusions About 2,4-D and Developmental Toxicity

2. Conclusions

The four manifestations of developmental toxicity have all been demonstrated in animals treated with 2,4-D or its esters or amines.

Malformation: skeletal at high dose (60 mg/kg/day or above), peripheral circulatory system distended at low dose (0.1 mg/kg/day) and after single high dose (1/2 LD₅₀), eye anomalies at 100 mg/kg/day.

Malfunction: subcutaneous edema at 12.5 mg/kg/day and above, hemorrhage into soft tissues and body cavities from 50 mg/kg/day to 0.5 mg/kg/day.

Growth retardation: prenatal at 0.5 mg/kg/day and above. Postnatal after 50 mg/kg/day or when treatment continued during lactation.

Lethality: pre-implantation not reported. Post-implantation at 100 mg/kg/day and above, or after a single high dose (1/2 LD₅₀). Postnatal in progeny of rats fed 150 mg/kg/day, or in a pig fed 500 ppm.

The above summary includes both oral and intraperitoneal treatment. 2,4-D is rapidly and completely absorbed from the gastrointestinal tract and is not metabolized in animals, so the serum concentrations should be similar by the two routes. Erne, 1966, has demonstrated the ease of placental transfer of 2,4-D in the pig. 2,4-D also rapidly penetrates the placenta in rats; 24 hours after a single dose, 16.8% of that dose remains in the uterus, placentas, fetuses, and amniotic fluid (Fedorova and Belova, 1974).

The effect of 2,4-D on the circulatory system was synergistic with that of its microbial breakdown product, 2,4-dichlorophenol. When the customary 100-fold safety factor is applied to the effective dose (Wilson, 1973, p. 156), the acceptable tolerance is equivalent to a 50 kg woman drinking 40 ml of treated water (2.5 ppm) daily during early pregnancy at a time when 50% of the 2,4-D has been degraded to 2,4-dichlorophenol. The situation is not quite that simple, however, because breakdown continues to other untested compounds, and part of the 2,4-D would be degraded in plants where 2,4-dichlorophenol is not part of that pathway (Ashton and Crafts, 1973).

Many of the studies reported here were done in other countries, raising the question of the similarity of synthesis and contaminants. No studies indicated that the synthesis and purity of these products is different elsewhere. 2,4-D caused developmental toxicity in all four species tested, including studies done in four countries. It is interesting to note that the hemorrhaging found in all of the Russian rat studies using low doses was not found in any of the high dose American studies. This may be a strain difference in rats, or a difference in the protocols of observation.

Shearer, 1980

The Environmental Protection Agency summary of the literature is particularly interesting in showing the same internal bleeding (edema) and hemorrhaging problem in many laboratory animal experiments where 2,4-D was the pesticide under study.

One of the more interesting studies is that of Konstantinova in 1976, showing a synergistic interaction of 2,4-D and its microbial breakdown product, 2,4-Dichlorophenol. Significant effects were shown at a dosage of only .1 mg/kg/day.

"...the action of 2,4-D alone in the highest dose tested (50 mg/kg) produced an increase in the overall number of defective fetuses...for the most part embryos with hemorrhages of varying degree and localization (primarily in the thoracic and abdominal cavities, liver and soft tissue...)... The administration of 2,4-Dph (breakdown product of 2,4-D) alone to the pregnant rats in the highest of the tested doses (1 mg/kg) also increased the total number of defective fetuses... due entirely to hemorrhaging in the organs and tissues... At the same time, the combined administration of the lowest dose of 2,4-D and 2,4-Dph (.1 and .1 mg/kg) which did not produce an effect when administered separately, increased the number of fetuses with hemorrhaging cavities, organs, and soft tissues..."

The laboratory animals are bleeding, just like the humans who have complained in spray areas, and there appears to be birth defects by a mechanical type of action and membrane damage. Doses are very low in the combined test.

Schwetz et al in 1971 found that internal bleeding in fetal rats occurred at 12.5 mg/kg/day with 2,4-D. Shearer notes that with a factor of 100 for safety, a pregnant woman would have to drink only 1/6 cup a day from a lake treated for weeks with 2,4-D.

As already noted, frank mutations were shown by Belova and Soklova to occur in laboratory animals after exposure to 2,4-D butyric acid. A number of studies show skeletal and eye defects to occur where dosages are close to maternal toxicity. But, malfunction of the circulatory system is seen after very low dosages.

Finally, Diane Courtney's 1975 study of CD-1 mice showed that 2,4-D could produce cleft palates, as well as affecting fetal weight and prenatal development. It was found that: "In general the greatest effects of 2,4-D were produced by low doses administered over long time periods." When 2,4-D was administered with corn oil, the major effect was on fetal weight, and when administered with DMSO, fetal mortality increased.

Farm Animal Studies and Reports

Similar effects and also adverse effects on fertility have been reported to use in goats, horses, and other farm animals.

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There is at least one farm animal study, showing increases in spontaneous abortion, sterility, and decrease of fertility of male sheep grazed on 2,4-D sprayed pastures. We are told that farmers are advised not to graze right after spray with 2,4-D because of these problems.

"...As a result of our farm experiments, it was established that butyl 2,4-D had a particularly harmful effect on animals (sheep) grazed on sprays pastures on consuming feed from these pastures during the first ten days after spraying with this herbicide. This effect manifested itself in spontaneous abortions, mummification of the fetuses, high sterility, a large number of stillborn lambs, and a decrease in the sexual activity of the males and the quality of the sperm. Therefore, in order to prevent the harmful effect on the reproductive functions of animals, the grazing of all species of animals on pastures sprayed with herbicides should be prohibited during the first 20 days after spraying, with an increase in the quarantine period to 45 days for the suckling offspring." (Sadykov, 1972)

NEUROLOGICAL EFFECTS OF 2,4-D IN ADULTS

Agents that have adverse effects on the neurology of adults often have even more severe effects on the fetus and infant. We will look at the issue of learning disabilities and retardation later.

A series of cases of severe peripheral neuropathy due to skin exposure to 2,4-D led to a Hazard Alert being issued by the California Department of Health Services in June 1980. A number of other cases has also been reported.

The Department notes that "a number of points favor the role of 2,4-D as a primary neurotoxin". It was noted that the mechanism was not known, though many neurotoxins interfere with an essential nutrient such as Vitamin B6.

The Department recommended a change in the label of 2,4-D, including the words: "Permanent Nerve Damage May Result After Skin Contact".

Possible linkage of 2,4-D with cropduster crashes in the middle West was noted by Mounce and Savage in 1973. In severe cases of exposure to 2,4-D as in suicide, demyelination of the nerves were noted.

Loss of Nerve Conduction Velocity in Adults

Of even greater concern than the number of extreme cases is the report of Raymond Singer et al in 1982, concerning the loss of nerve velocity in 56 workers employed in the manufacture of 2,4,5-T and 2,4-D. As the table below shows, there was a slowing of conduction in median motor, median sensory, and sural nerves - a change that held up after controlling for alcohol and other neurotoxic agents. Duration of employment was significantly correlated.

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The sural nerve has a long fiber length, less myelination, and small diameter, and has been shown by other studies to be susceptible to disruption of normal nervous tissue function and metabolism.

NCV AND EXPOSURE TO PHENOXY HERBICIDE

TABLE 7.
MEAN NERVE CONDUCTION VELOCITIES OF STUDY VERSUS CONTROL GROUPS^a

Nerve	Group	N	Mean Z value	SD	t	Prob. t (one-tailed)
Median motor	Study	44	0.11	1.17	2.29	0.01
	Control	25	0.92	1.02		
Median sensory	Study	44	-0.23	1.06	1.01	0.15
	Control	23	0.04	0.81		
Sural	Study	41	-2.11	1.17	4.58	0.0001
	Control	20	-0.52	1.62		

^a Based upon Z values which represent the velocity expected on the basis of age subtracted from the temperature corrected observed velocity, divided by the standard deviation. Nine subjects with possibly significant previous exposure to neurotoxic agents were removed.

It was noted by the authors that although dioxins were involved here, the significant findings may also be due to 2,4-D. The study suggests that exposures to 2,4-D that do not involve gross neuropathies can produce a general loss of vitality of an exposed population and loss of a range of nerve function.

While Dow maintains that their laboratory studies do not show neuropathy in laboratory animals, when so many human examples are available, we really do not have to guess anymore about the problem.

Laboratory Studies

There are a number of interesting laboratory findings. Elo et al reported that 2,4-D exposure impaired the functioning of the blood-brain barrier in rats during poisoning, in that blood cells appear in the cerebrospinal fluid as a result of capillary injuries.

Desi et al reports that several effects occur in laboratory rats, cats, and dogs:

1. There is an inhibition of cerebral electrical activity in acute and chronic 2,4-D exposures, with severe damage to higher nervous activity occurring, as measured by conditioned reflex experiments;
2. This occurs without obvious structural changes in nerve cells;

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3. Spinal cord damage may be responsible for paralysis in extremities;
4. It must be assumed that human subjects may suffer milder disturbance from smaller doses in function of the nervous system.

In summary, it needs to be pointed out that chemicals that cause a debilitation of nervous system response in adults and a loss of vitality will have some significantly adverse economic effects for the nation.

■ LEARNING DISABILITIES AND 2,4-D

It has long been known that the phenoxy acids interfere with the turnover rate and distribution of thyroid hormones (Florsheim et al, 1963). 2,4-D is known to enhance the incorporation of radioiodine into the thyroid gland (Kiltgaard et al, 1951 and Florsheim and Velcoff, 1962) and competes with thyroxine for binding to plasma carrier proteins.

Chemical exposures that cause hyper- or hypo-thyroidism have been shown to lead to learning disabilities and in extreme cases to mental retardation, where exposure to that chemical takes place either during pregnancy or during early childhood. For example, as Sjoden and Soderberg noted:

"...It is, therefore, obvious that all procedures that induce endocrine disturbances (of hormone levels, distribution or tissue response) in utero or shortly after birth may be followed by permanent defects in physiological parameters and behavior. Such effects are easily overlooked by classical teratologists."

Sjoden and Soderberg's experiments found that the phenoxy herbicide 2,4,5-T had some significant effects on thyroid function.

"...However, we are already justified in claiming that 2,4,5-T has permanent effects on the thyroid, inducing increased thyroid activity at birth; although a steeper fall in activity is observed with advancing age in treated than in control animals... In this way, treated animals develop hypothyroidism, and 2,4,5-T thus accelerates the rate of aging of this physiological function. Aging of the thyroid system has also been found in man. (Wahlin et al, 1975) The effects of 2,4,5-T on thyroid activity shows a sexual dimorphism, having a stronger reaction in females than in the males. This is of interest in view of the well-known excess morbidity among women in relation to thyroid and to manic-depressive diseases."

The authors' laboratory studies found the following effects:
1. behavioral teratology in rats from a single prenatal exposure to 2,4,5-T towards the first week of pregnancy - leading to a long-term change in behavioral and learning functions well into adult age of the offspring, as measured by swimming maze tests and conditioning active avoidance tests; (Dose was 100 mg/kg on the 8th day), 2. strong effect on taste aversion at dosages

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above 15 mg/kg, and higher order conditioning of taste aversion; 3. transient inhibition of food and water intake and widespread change in electrolyte distribution, with strongest effect on brain and kidney; 4. enhancement of the transport of tryptophan into the brain; 5. offspring of 2,4,5-T treated animals showing changes in weight development, thyroid activity, and brain serotonin, which correlated with behavioral changes.

In summary, while exhaustive testing of this nature has not been done for 2,4-D, we can expect in view of its thyroid activity and similar chemical structure to be a strong candidate as a learning disability agent in animals and humans.

The Dioxin and Liver Enzyme Issue

In our review of the literature, we have found that chemicals that induce liver enzymes as a class appear to produce learning disabilities. For example, TCDD dioxin is a strong liver enzyme inducer, and also has been shown to cause hypothyroidism. (Rozman shows that the wasting syndrome is modulated by the thyroid.) PBB's cause liver enzyme induction and hypothyroidism as another example. The 2,4-D dioxins may act similarly on liver induction.

Alcohol and phenobarbital are examples of liver enzyme inducers that have been shown to cause learning disabilities in human children exposed in utero, as is PCB's.

Furthermore, induction of liver enzymes during pregnancy has been shown to cause infertility in the offspring. A good example is phenobarbital, used in epilepsy treatment, which causes both learning disabilities and infertility in both male and female animals. The learning disabilities are confirmed in human children and there are indications of infertility in humans as a result of phenobarbital exposure in utero.

Microneuronal Hypoplasia

Joseph Altman has looked at one of the mechanisms of learning disabilities, which is depletion of the microneurons, when exposure to a substance takes place late in pregnancy or early childhood as through contaminated milk. In contrast, early toxic exposures that deplete the macro or meso-neurons can lead to profound retardation and motor difficulties.

Hypo- and hyper-thyroidism and liver enzyme inducers can produce these neuron deficits. And in summary, 2,4-D is a strong candidate as a chemical that will produce learning disabilities where exposure takes place during pregnancy or in early childhood. Furthermore, thyroid malfunctioning can affect the myelination of the brain in children. Dudley in 1972, reported extensive demyelination of the brain in the case of a man who died from ingested 2,4-D - a case that resembled multiple sclerosis. As is so often the case, where serious neurological problems are found in the adult, similar effects may be found in the child at much lower dosages.

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OTHER HEALTH ISSUES AND FIELD SURVEYS

Heart Disease and Stroke

Little information seems available concerning the effect of 2,4-D on heart disease and stroke. The capacity of the chemical to damage the capillaries and cause internal bleeding would make it a candidate for stroke.

PCB's with its dioxins and dibenzofurans is known to elevate blood pressure and increase cholesterol levels - making that chemical a heart disease candidate. Possibly the dioxins and fura in general may have similar effects.

Field Studies

Besides the reports from Alsea, Oregon and Ashford, Washington we have also two acute health effects surveys from Canada and North Carolina. As is noted on the next page, farmers in Saskatchewan found 2,4-D to be their most difficult chemical from the viewpoint of health, with cumulative symptoms from one season to the next leading farmers to stop spraying and contracting out. Nausea to skin rashes were reported as can be seen.

A just completed study from North Carolina looks at the symptoms of 85 people exposed to 2,4-D and Tordon 101 spray drift from Boise Cascade timber tracts.

A statistically significant increase in respiratory problems was found among people receiving the spray drift, along with a number of other symptoms presented in the table. Adjustments for age, sex, race, smoking status and education did not alter these findings, and the symptoms were also associated with increased exposure, in that the reactors remained in the spray drift area for a longer time.

Dioxins

The production of chemicals contaminated with dioxins needs to be discouraged, even if the dioxins are ostensibly removed to some degree by the manufacture process. The manufacturer still has to destroy the dioxins removed from the chemical, and there is an additional problem of dioxin production during the distribution and use phase. For example, burning of sprayed areas will generate dioxins.

It appears that most Americans now have dioxins in their fat at time of death, and human milk has become increasingly contaminated with dioxins, as has fish and some other food products.

The dioxin issue is sufficient cause by itself to discontinue the production of 2,4-D. The enclosed summary of the dioxin issue with regard to 2,4-D by Pollution Probe of Ottawa is enclosed.

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Panel 5

Most Americans become exposed to dioxins during their life.

Table 8.-Comparison of the Levels of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Parts per Trillion) in Adipose Tissue of Exposed and Control Groups

Variable	Controls	Exposed			
		Total	Recreational	Residential	Occupational
N	57	39	8	16	15
Arithmetic mean	7.4	79.7	90.8	21.1	136.2
Median	6.4	17.0	23.5	14.5	24.7
Range	1.4-20.2	2.8-750	5.0-577	2.8-59.1	3.5-750
Geometric mean	6.4	21.8	24.8	15.3	29.8
Mean age, y (SD)	52.6 (15.7)	44.3 (13.7)	42.1 (14.7)	39.7 (14.9)	50.3 (9.8)
% Men	35.1	61.5	37.5	43.8	93.3

Table 9.-Comparison of the Adipose Tissue Concentrations of TCDD in Populations With No Known TCDD Exposure*

Source of Specimens	N	Mean, Parts per Trillion	Range, Parts per Trillion
Present study: elective surgical patients in Missouri	57	6.4†	1.4-20.2
Autopsy specimens from Ohio ¹¹	6	...	5-12
Autopsy specimens from St Louis ¹² and Canada ⁷ and adipose from veterans ¹³	61‡	7.5	1-15
Autopsy specimens from sudden deaths in St Louis ¹⁴	35	7.2†	...
Autopsy specimens from Georgia and Utah ¹⁵	35	7.1†	2.7-19.0

*TCDD indicates 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

†Geometric mean.

‡Combination of results from references 7, 12, and 13. Three results from persons known to have had exposure to 2,4,5-trichlorophenol were excluded.

Dioxin Levels—Patterson et al

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Damage to Other Crops and the Environment

Numerous problems with 2,4-D drift and vegetation damage have been presented. The case of serious damage to grapes in Washington State after long distance drift from wheat fields in Oregon is an unsolved issue. It is fair to say that grapes are a more expensive crop than wheat, and we can expect that 2,4-D probably diminishes the total agricultural product in this case.

Damage to sunflowers and cotton are other examples.

Damage to aquatic weeds from herbicide runoff in the Chesapeake Bay has proven to be a serious problem, and causes a significant decline in fishing resources and the prosperity of the fishing industry. Here is another example of a reduction of economic produce from drift and run-off.

Dioxin and PCB's contamination of the rockfish of the Chesapeake Bay is believed to be a major factor in the sharp decline in populations - leading to fishing moratoriums of recent years.

CONCLUSION

While our judgement must be qualitative at this time, there is very good reason to conclude that 2,4-D is probably a net loser to the national economy in view of the significant health and environmental problems associated with the herbicide. One could presume against the further use of 2,4-D solely on the basis of it being a precursor and source of dioxins, since Americans have become so contaminated with dioxins over the past years.

However, even without this issue of dioxins, we think that there are sufficient adverse health and environmental effects of 2,4-D, even in a form purified of dioxins, to conclude that the national economy is probably made poorer because of the chemical

APPENDIX VII.0

HEALTH EFFECTS OF 2,4-D

The following letter, reprinted here for the information and interest of the reader, was supplied to the panel in reply to a request for information on health effects of phenoxy herbicides.



PRAIRIE INSTITUTE OF ENVIRONMENTAL HEALTH
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S4P 2M7

Phone: 523-5644
523-5645

November 15, 1976.

HEALTH EFFECTS OF 2,4-D

- 1. As far as I am aware there are no reliable statistics relating to the health effects of 2,4-D usage in Saskatchewan, where, in 1971 it was estimated that 70% of the cultivated acreage of the province was sprayed with the herbicide in a year.
- 2. A small unidentified number of persons, mainly children, have been hospitalised with acute poisoning, circumstances unknown.
- 3. Because of the widespread use of the herbicide 2,4-D and because no mechanism existed in Saskatchewan which identified agricultural chemical poisoning, a general question was included in a questionnaire used in 1969,1970 as part of a field survey of respiratory diseases and effects amongst farmers and grain elevator operators

Q. 78. Have you ever had any ill effects from working with any agricultural chemical yes no

IF YES

specify the chemical product _____
describe the circumstances _____
what were the effects _____

- 4. 20% of 3,300 farmers and grain elevator operators surveyed, responded yes to the question. Whilst the question was a general one, certain conclusions were drawn from it
 - a) farmers found 2,4-D the most troublesome chemical they used (it is also the most widely used)
 - b) symptoms were confined to the season (or time) of spraying and were similar amongst farmers who complained of health effects
 - 1) nausea, loss of appetite, loss of weight, occasional vomiting during the spraying season.
 - 2) a skin rash in a small number of persons.
 - 3) the symptoms of one year often worse than the year before leading to a significant number of farmers having to stop spraying themselves and contracting the spraying out.
- 5. The conclusions drawn from the questionnaire are supported whenever health and safety problems are identified and discussed at farmer/rural meetings
- 6. The significance of these observations in relation to long term effects is unknown; it appears to me that some farmers develop a sensitivity to the effects of 2,4-D (not necessarily the same thing as an allergy) and that this sensitivity is enhanced with repeated exposure over time.

C. A. R. Dennis

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Symptoms of North Carolina Residents Injured by 2,4-D and Tordon 101 Spray Drift, (Tolbert)

Table 15. Association of Each Symptom Queried with Exposure: Results of Crude Analysis (Continued)

<u>Symptom</u>	<u>Observed Among Exposed</u>	<u>RR</u>	<u>95% CI</u>	<u>P-Value</u>
Fatigue	9	2.1	(0.8, 5.2)	0.089
Breaking fingernails	5	3.1	(0.8, 12.7)	0.100
Headaches	10	1.9	(0.8, 4.3)	0.109
Chest pain	4	3.7	(0.7, 20.0)	0.113
Asthma	2	9.3	(0.4, 191.6)	0.120
Hair loss	3	5.6	(0.6, 53.1)	0.123
Swollen eyes	6	2.2	(0.7, 7.1)	0.141
Lack of appetite	5	2.3	(0.6, 8.5)	0.165
Blood in urine	3	2.8	(0.5, 16.5)	0.231
Bleeding gums	2	3.7	(0.3, 40.7)	0.279
Burning on breathing	2	5.6	(0.2, 135.5)	0.348
Easy bruising	1	5.6	(0.2, 135.5)	0.348
Fainting	1	5.6	(0.2, 135.5)	0.348
Burning on urination	1	5.6	(0.2, 135.5)	0.348
Aching joints	1	0.8	(0.3, 2.4)	0.494
Seizures	0	--	--	--

Table 15. Association of Each Symptom Queried with Exposure:
Results of Crude Analyses

Symptom	Observed Among Exposed	RR	Precision-Based 95% CI	Fisher's Exact Test P-Value
Cough	13	12.2	(2.8, 52.6)	0.000
Difficulty breathing	13	12.2	(2.8, 52.6)	0.000
Sinus congestion	10	6.2	(1.8, 22.0)	0.002
Runny nose	9	8.4	(1.9, 38.1)	0.002
Swollen glands	6	11.2	(1.4, 91.7)	0.008
Skin peeling	4	16.7	(0.9, 307.3)	0.014
Wheezing	6	5.6	(1.2, 27.2)	0.023
Dizziness	6	5.6	(1.2, 27.2)	0.023
Blurred vision	9	2.8	(1.0, 7.6)	0.036
Nausea	7	3.3	(1.0, 10.9)	0.045
Hay fever	4	7.5	(0.8, 65.9)	0.051
Constipation	4	7.5	(0.8, 65.9)	0.051
Vomitting	5	4.7	(0.9, 23.6)	0.052
Skin rash	9	2.4	(0.9, 6.2)	0.059
Burning eyes	8	2.5	(0.9, 7.0)	0.068
Upset stomach	7	2.6	(0.9, 8.0)	0.077

c) (Warnock, 1980)

"In September 1978 the Alberta Cancer Registry announced the results of a survey of bladder cancer in that province. Farmers constituted 43% of all patients with bladder cancer, even though they made up only 18% of the total male population in that province. Dr. Michael Grace, the Director of the registry, suggested that the farmers' exposure to herbicides, pesticides and seed treating chemicals, in combination with ammonium nitrate fertilizer, is behind the high cancer rate. The primary pesticides to which Alberta farmers are exposed are 2,4-D and MCPA"

d) Summary:

For a critical analysis of every known cancer experiment on 2,4-D, see the report by Shearer (Appendix). The animal studies are strongly suggestive although not conclusive that 2,4-D causes cancer. The primary breakdown product, 2,4-dichlorophenol, appears to be carcinogenic (especially as a promoter, i.e. when another initiator is present.) Human epidemiology studies can never be conclusive when more than one chemical is used (which is almost always the case). The positive findings in herbicide studies should then act as a warning signal that 2,4-D may be carcinogenic in humans.

DIOXIN AND 2,4-D (From Wright)

~~PROCESSES~~ 5. Are dioxins present in, or formed from, 2,4-D?

a) Recent data from Health and Welfare Canada (Cochrane et al, 1980) have demonstrated the existence of a variety of dioxins in 2,4-D. "Eight out of nine esters and four out of seven amine samples were found to contain di-, tri-, and tetra-chlorodibenzo-p-dioxins." The esters showed unexpectedly high concentrations of dioxins, ranging from 1 ppm (total) up to 7 ppm (total). Amine dioxin concentrations ranged from 0-0.8 ppm. No 2,3,7,8- dioxin was found. The highest concentration species reported was the 2,7-(or 2,8-) dioxin.

b) Dioxins can form in unexpected ways. Millions of chickens died of "chick edema factor", discovered to be caused by hexachloro-dioxin. It was believed that the dioxin came from vegetable oil derived from 2,4-D treated corn (Crossland and Shea, 1973).

- c) Dioxins can form by heating or burning of vegetation sprayed with 2,4-D. Although few controlled experiments of this kind have been done with 2,4-D, the chemistry is sufficiently understood that this point is generally accepted. In manufacturing, the temperature is kept as low as possible for exactly that reason. Also, dioxin formation has been demonstrated from burning chlorophenols (Rappe and Markland, 1978), (Nelsson et al, 1974) and vegetation sprayed with 2,4,5-T (Stehl and Lamparski, 1977).
- d) It is possible that dioxins can be formed by the action of sunlight on 2,4-D (Akermark, 1978). More studies need to be done in this area, but the coupling of two molecules of dichlorophenol can yield an isomer of dioxin, especially under alkaline conditions.
- e) The range of toxicities of the 75 possible dioxins varies widely. The most toxic 2,3,7,8-isomer has not been found in 2,4-D. However, their chemical structure suggests that they are resistant to breakdown, and being fat soluble, may deposit in the liver, potentially acting as a cumulative poison. The dioxins tested so far in mice and guinea pigs produced similar clinicopathologic symptoms as TCDD, at difference dose levels (McConnel, 1978)
- f) the 2,7-dioxin, apparently the most prevalent in the 2,4-D esters, causes defects in the heart muscle of rats at the low dose level of 1-2 mg/kg (Khera and Ruddick, 1973).
- g) Summary: There is enough evidence on dioxin contamination of 2,4-D, or formation from 2,4-D, to indicate considerable caution in its use. The chemistry of the formation of dioxins under laboratory conditions is fairly well understood, but environmental studies of dioxin formation are just beginning. Any form of heating of 2,4-D, short of high temperature (greater

than 800°C) incineration, should be avoided. Also, dioxins form more rapidly under alkaline conditions.

V. CONCLUSIONS

Increasing concern about the safety of 2,4-D has led to discontinuation of its use in numerous school boards in Ontario and in the cities of Toronto and Ottawa. 2,4-D has been shown to cause birth defects and mutations in animals and is suspected of causing cancer. Occupational exposure of sprayers and farmers has led to a variety of reported symptoms, the most serious being paralysis. Dioxin contamination of commercial products has been shown and in addition, formation of dioxins from 2,4-D via environmental processes is possible.

Practices of using herbicides on lawns are primarily cosmetic. While there are serious doubts on the safety of 2,4-D, both for the short and long term health of sprayers and of those who use the parks, the most reasonable course of action is to continue to suspend herbicide use in these areas. Introduction of any alternative herbicide should not be begun without a thorough safety analysis and public discussion.

VI. RECOMMENDATIONS

1. That the City of Ottawa continue its suspension of all herbicide spraying programs.
2. That fertilization, aeration and reseeding programs with hardy grasses be tried in selected areas on an experimental basis, with costs being estimated for large-scale application.
3. That the quality of lawns be monitored and reported on yearly to the Environmental Advisory Committee.

- Ahmed, Farid, E. et al, "Pesticide induced DNA damage and it's repair in cultured human cells", *Mutation Research*, Vol. 42, pp. 161-174, (1977)
- Altman, Joseph, "An animal model of minimal brain dysfunction: Microneuronal hypoplasia", in Catherine Caldwell Brown, editor, Childhood Learning Disabilities and Prenatal Risk. Pediatric Round Table 9, Johnson & Johnson, Skillman, New Jersey, 08558, (1983)
- Archipov, G.N. and I.N. Kozlova, "Study of the carcinogenic properties of the herbicide amine salt of 2,4-D", *Voprosy Pitaniya*, Vol. 5, pp. 83-84, (1974)
- Bach, J.F. and T.B. Strom; "The mode of action of immunosuppressive agents", *Research monographs on immunology*, Vol. 9, Elsevier, New York: (1985)
- Balarajan, R. and Ed Acheson, "Soft tissue sarcomas in agricultural and factory workers", *Journal of Epidemiology and Community Health*, Vol. 38, pp. 113-6, (1984)
- Belova, R.S. and L.A. Sokolva, "Toxicolog. Evaluation of the herbicide 2,4-D & Butyric Acid from the viewpoint of food sanitation", *Gigiena I Sanitariya*, Vol. 36, pp. 211-5, (1971)
- Blaska, David, "U.W. researchers say 2,4,5-T may impair immunity", *Capital Times*, Aug. 21, 1981
- Blumer, W. and Th. Reich, "Leaded gasoline- a cause of cancer", *Environment International*, Vol. 3, pp. 465-71, (1980)
- Courtney, K., Diane, "Prenatal effects of herbicides: evaluation of the prenatal development index", Presented in Part at 15th annual meeting of Teratology Society, May 11-15, 1975, Philadelphia. U.S. E.P.A. Research Triangle Park, N.C.
- Czuczwa, Jeane, and Ronald A. Hites, "Airborne dioxins and dibenzofurans: sources and fates", *Env. Sci. Techn.* Vol. 20, No. 2, (1986)
- Dennis, C.A. R., "Health effect of 2,4-D", *Prairie Institute of Environmental Health*, Regina, Saskatchewan, Nov. 15, 1976
- Desi, I. et al, "Nervous system effects of a chemical herbicide", *Archives of Environmental Health*, Vol. 4, No. 1, pp. 95-102, (1962)
- Epidemiological Studies Laboratory, (Hazard Alert System), State of California, Department of Health Services, 2,4-Dichlorophenoxy acetic acid: Evaluation of human health hazards. June 16, 1980
- Florsheim et al, "Some effects of 2,4-dichlorophenoxy acid in thyroid function in the rat..." *Endocrinology*, vol. 71, pp. 1-6, (1962) and vol. 72. pp. 327-333, (1963)
- Grady, Denise, "The Health care crisis", *Discover*, Vol. 7, No. 5, May 1986
- Hansen, W.H. et al, "Chronic toxicity of 2,4-D in rats and dogs", *Toxicology and Applied Pharmacology*, Vol. 20, pp. 122-129, (1971)
- Hoar, Sheila, et al, "Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma", *JAMA*, Vol. 256, No. 9, Sept. 5, 1986
- Hoffman, Richard, E. et al, "Health effects of long-term exposure to 2,3,4,8-Tetrachlorobenzo-p-Dioxin", *JAMA*, Vol. 255, No. 15, April 18, 1986
- Kallen, Bengt, and Gunnar Thorbert, "A study of pregnancy outcome in a small area around a chemical factory and a chemical dump", *Env. Research*, Vol. 37, pp. 313-19, (1985)
- Khera, K.D. and J.A. Ruddich, *Adv. in Chemistry Ser.*, Vol. 120, No. 70, (1973)

- Kiltgaard, H.M. et al, "Inhibition of thyroxine action by iodinated phenoxy acids", Endocrinology, Vol. 48, pp. 525-533, (1951)
- Konstantinova, T.K. et al, "The embryonic effect of the dissociation products of herbicides based on 2,4-D", Gigiena I. Sanitariya, No. 11, pp. 102-5, (1976)
- Mattsson, Joel, L. et al, "Neurotoxicological examination of rats dermally exposed to 2,4-D amine for three weeks", Neurobehavioral Toxicology and Teratology, Vol. 8, pp. 255-63, (1986)
- Mattson, Joel, L. et al, "Lack of neuropathological consequences of repeated dermal exposure to 2,4,-D acid in rats", Fundamental and Applied Toxicology, Vol. 6, pp. 175-181, (1986)
- Merrell, Paul vs. J.R. Block et al, U.S. District Court for District of Oregon, Civil No. 81-6138-E, Memorandum in support of plaintiff.
- Mounce, M. and E.P. Savage, "The epidemiology of aerial application in the High Plains, 1966-1969", Agricultural Aviation, Vol. 15, No. 4. pp. 105-112, (1973)
- Northwest Coalition for Alternatives to Pesticides, (NCAP), 2,4-D. P.O. Box 1393, Eugene, Oregon 97440, \$9
- O'Brien, Mary, H. "Those Swedish Studies by Hardell: phenoxy herbicides, chlorophenols, and cancer", NCAP News, Spring 1984
- Patterson, Donald, G., Jr., "2,3,7,8-Tetrachlorobenzo-p-dioxin levels in adipose tissues of exposed and control persons in Missouri", JAMA, Vol. 256, No. 19, Nov. 21, 1986
- Pesticide and Toxic Chemical News, "2,4-D produces rare brain tumor in male rats, E.P.A. officials note", June 25, 1986
- Pitinskaya, M.A., "Cytogenetic effect of the herbicide 2,4-D on human and animal chromosomes", Tsitolagiya i Genetika, Vol. 8, No. 3, pp. 202-6, (1974)
- Reuber, Melvin, "Preliminary review of some oncogenicity studies for 2,4-D", U.S. Senate Judiciary Committee Report on the E.P.A. and Regulation of Pesticides December 1976
- Reuber, Melvin, "Re-review of slides of Bionetics study", From E.P.A. Review of the Literature on 2,4-D, (1979)
- Rice, D.P. et al, "Health Care Financ. Review, Vol. 7, pp. 61-80, (1985)
- Rozman, K. et al, "Thyroid hormones modulate the toxicity of 2,3,7,8- Tetrachloro-dioxin-p-Dioxin (TCDD), Journal of Toxicology and Environmental Health, Vol. 16, pp. 481-91, (1985)
- Sadykov, R.E., "The effect of butyl 2,4-D treatment of pastures on the reproductive functioning of sheep", Zhivotnovodstvo (Animal Breeding), Vol. 34, No. 1, pp. 73-4, (1972)
- Schumacher, Mary, Catherine, "Farming occupations and mortality from Non-Hodgkins Lymphoma in Utah", J. of Occupational Medicine, Vol. 27, No. 8, Aug. 1985.
- Schwetz, B.A. et al, "The effect of 2,4-D and esters of 2,4-D on rat embryonal, foetal and neonatal growth and development", Food, Cosmetic Toxicol., Vol. 9, pp. 801-17, (1971)
- Seiler, J.P., "Phenoxyacids as inhibitors of testicular DNA synthesis in male Mice", Bull. Env. Contam. and Toxicol., Vol. 21, pp. 89-92, (1979)
- Seiler, J.P., "The genetic toxicology of phenoxy acids other than 2,4,5-T", Mutation Research, Vol. 55, pp. 197-226, (1978)

19782 17195

- Shearer, Ruth, W. and Mark Halter, Literature Reviews of Four Selected Herbicides: 2,4-D, dichlorobenzil, diquat, and endotal", Municipality of Metropolitan Seattle, p. 1-34, January 1980
- Shearer, Ruth, W. "Toxicology of 2,4-D", April 24, 1981
- Shearer, Ruth, W., Affidavit in Superior Court of Washington for Thurston County, July 2, 1982
- Singer, Raymond, et al, "Nerve conduction velocity studies of workers employed in the manufacture of phenoxy herbicides", Environmental Research, Vol. 29, pp. 297-31, (1982)
- Sjödén, P.O. and U. Söderberg, "Phenoxyacetic Acids, sublethal effects", in C.Ramel, editor, Chlorinated Phenoxy Acids and Their Dioxins, Ecol. Bull., Vol. 27, pp. 149-164, Stockholm, (1978)
- Smithells, R.W. et al, Archives of Diseases in Children, Vol. 51, (1976), The Lancet, Feb. 16, 1980, The Lancet, May 7, 1983
- Strange, Marty and Liz Krupicka, "Farming and Cancer", in Center for Rural Affairs, It's Not All Sunshine and Fresh Air, CRA, Box 405, Walthill, Nebraska 68067, April, 1984, \$5
- Tolbert, Paige, Elizabeth, "Retrospective cohort study of a community exposed to herbicides - an investigation of perceived health effects", Masters of Science in Public Health technical report, U. of North Carolina, Chapel Hill, (1986)
- Turkula, T.E. and S.M. Jalal, "Increased rates of sister chromatid exchanges induced by the herbicide 2,4-D", Journal of Heredity, Vol. 76, pp. 213-4, (1985)
- U.S. Environmental Protection Agency, Industrial Environmental Research Laboratory, Dioxins, Vol. 1, Sources, Exposure, Transport, and Control. EPA/600/2-80-156, June 1980
- U.S. Statistical Abstract
- U.S. E.P.A., Review of literature on 2,4-D, (1979-80?)
- Vital Statistics, 1982
- Wright, James, S. and Virginia Salares, Health Effects of 2,4-D, Presentation to the City of Ottawa, March 26, 1981, Pollution Probe, Ottawa
- Yoder, J. et al, Mutation Research, Vol. 21, pp. 335-40, (1973)
- Elo, Heikki and Ylitalo, Pauli, "Substantial increase in the levels of chlorophenoxyacetic acids in the CNS of rats as a result of severe intoxication", Acta Pharmacol. et Toxicol. Vol. 41, pp. 280-4, (1977)