

RESIDUES IN THE ENVIRONMENT

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Soils

In monitoring surveys conducted by the Agriculture Research Services, USDA, six study areas revealed that soil residues of 2,4-D were minor. Only four soil samples (average concentration of 0.032 ppm) were positive for 2,4-D residue. In another survey, 99 soil samples were collected from wheat fields in 16 states with known histories of 2,4-D use. Analysis revealed only four samples contained measurable residues (0.751, 0.06, 0.05, and 0.04 ppm) (Kearney, 1970).

Water

Manigold and Schulze (1969) reported on an extensive survey of pesticides in water, conducted by the U. S. Geological Survey from October 1966 through September 1968. The survey was conducted at twenty sites on the major streams in the western United States and included the herbicide 2,4-D. Out of several hundred observations, 2,4-D was identified 26 times, ranging from 0.01 to 0.35 ppb. Norris (1971) stated that, in his investigations of stream contamination from spray projects on range and forest lands in Oregon, measurable concentrations occurred shortly after application but seldom exceeded 0.1 ppm.

Animal

A study of sheep and cattle fed a daily diet containing 2,000 ppm of 2,4-D had only 1 ppm or less in the muscle after 28 days of feeding (Clark, et al., 1975). The milk from cows grazing on pastures that were sprayed with 2,4-D esters, contained 0.01-0.09 ppm of 2,4-D during the first two days

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after spraying and lower amounts thereafter. When cows were put into the pastures four days after spraying, residues in milk were below 0.01 ppm (Klingman, et al., 1966).

In 1969, the Consumer and Marketing Service, USDA, analyzed 240 samples of red-meat fatty tissue for 2,4-D. These samples were taken at 44 different geographic locations in the continental United States. Results of this survey are shown in Table 2. According to this survey, 2,4-D residues in red meat do not appear to be significant in meat products currently marketed in the United States (Harvey, 1971).

Table 2. Residues of 2,4-D in Red Meat

Parts per Million 2,4-D	Number Samples	Percent
Negative	231	96.2
0.01-0.10	6	2.5
0.11-0.50	2	0.8
0.51-1.0	1	0.4
>1.0	0	0

Food

In a continuing program to monitor pesticide residues in food, the Food and Drug Administration, U. S. Department of Health, Education and Welfare, found a decreasing level of 2,4-D in food samples during the period 1964-1970, (Duggan and Corneliussen, 1972). The program, commonly known as the "total diet program", involves examination of food ready to be eaten. This investigation measures the amount of pesticide chemicals found in a "high-consumption" varied diet. The samples are collected in retail markets and prepared for

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consumption before analysis. Table 3 summarizes the data on 2,4-D for six years.

Table 3. Average Incident and Daily Intake of 2,4-D

Year	[T= < 0.001 mg]	
	Percent Positive Composite	Daily Intake (mg)
1965	4.2*	0.005
1966	3.0**	0.002
1967	1.7***	0.001
1968	0.6***	0.001
1969	0.3***	T
1970	0.3***	T

* 216 composites examined

** 312 composites examined

*** 360 composites examined

Investigations of the persistence of 2,4-D in the environment indicate that this herbicide is relatively short-lived. Likewise, examination of soil, water, animal tissue, milk and foodstuffs revealed low levels of 2,4-D residues, despite the extensive use of this herbicide in this country.

Based on the review of the above persistence and residue studies, it seems unlikely that 2,4-D would accumulate to significant levels as a result of its use in forestry management.

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ABSORPTION, DISTRIBUTION AND EXCRETION

Experimental Animals

Several investigators have studied the absorption, distribution and excretion of the herbicide 2,4-D with experimental animals. Reported studies indicate that the herbicides are readily absorbed from the gut and become widely distributed in the tissues. The major route of elimination of 2,4-D is via the urine, primarily as the parent compound and, to a much lesser extent, as a conjugate of the parent compound.

In rats, pigs, calves, and chickens, 2,4-D administered in doses of 50-100 mg/kg bw orally as salts was readily absorbed and eliminated mainly in the urine, with plasma half-lives varying from 3-12 hours (Erne, 1966 a,b). Pigs excreted 2,4-D in the urine primarily as the parent compound, but also as an unidentified acid hydrolyzable conjugate(s). In pigs and rats given oral doses of the butyl ester of 2,4-D the free acid and traces of esterified 2,4-D were present in the plasma, red blood cells, urine, and liver.

Khanna and Fang (1966) fed rats 1-100 mg of 2,4-D (^{14}C -label in either one or two positions of the side chain) and then monitored the expiratory gases, urine, feces, and various tissues for ^{14}C . No $^{14}\text{CO}_2$ was detected in the expiratory air. The rats excreted from 75.5 to 93.3 percent of the ^{14}C in the feces and urine within 144 hours (most within the first twenty-four hours after dosing). The rate of the excretion (expressed as percent of the dose) decreased as the size of the dose increased. The level of radioactivity in the tissues was maximum

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from 6-17 hours after dosing and then declined. A study of the intracellular distribution indicated that the soluble fraction contained more radioactivity than the nuclear, mitochondrial and microsome fractions. There was no significant difference in the distribution of ^{14}C in the various fractions when different dose levels were given. Chromatography studies indicated that most of the ^{14}C in the urine and tissues was as the parent compound. However, at least one unidentified metabolite was also present in the urine.

Clark, et al. (1964) administered a single oral dose of 2,4-D- C^{14} (acid form) to a sheep (dose 106.3 mg of 2,4-D, sheep weight 26.6 kg) and reported that approximately 96 percent of the ^{14}C was excreted in the urine with at least 1.4 percent in the feces (the expiratory gases were not analyzed for $^{14}\text{CO}_2$) within seventy-two hours. The level of ^{14}C in the blood reached a maximum 1.25 hours after dosing and rapidly declined (see Figure 4). Comparative chromatography and electrophoresis studies indicated that all of the ^{14}C in the urine was the free parent compound. The nature of the ^{14}C labeled compound(s) in the feces and tissues were not determined.

Lisk, et al. (1963) fed a steer 5 ppm of 2,4-D for one day; approximately 88 percent of the dose was eliminated in the urine as the parent compound within three days. However, the feces and tissues were not analyzed for the parent compound or metabolites.

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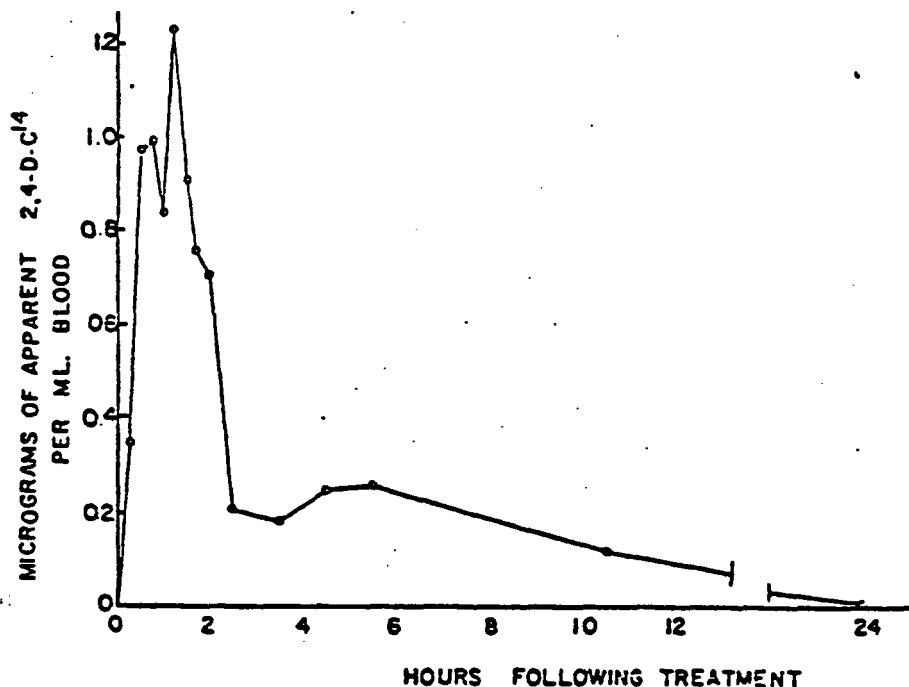


Figure 4. Appearance of C¹⁴ in the blood of a sheep after oral administration of 2,4-D-C¹⁴ (Clark, et al., 1964)

Humans

Feldman and Maiboch (1974) studied the percutaneous penetration of 2,4-D in man. Data were presented on the proportion of 2,4-D-C¹⁴ which was absorbed after application of 4 µg/cm² to the ventral forearm. Because ¹⁴C-metabolites were measured in the urine, it was necessary to determine the extent to which these metabolites appear in the urine after parenteral administration. All results were calculated as percent of the injected or applied dose. In the topical studies, the results were corrected for incomplete excretion. For example, if 50 percent of the test compound was excreted after I. V. administration, all values after topical administration were doubled. Urinary excretion of 2,4-D after I. V. administration was 100 percent

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after five days. Urinary excretion after topical administration of 2,4-D was 5.8 percent after five days. It appears that very little of the 2,4-D is absorbed through the skin. Skin absorption is incomplete because much of the applied chemical is lost from the skin surface by washing (subjects did not wash skin for twenty-four hours), evaporation or the gradual exfoliation of outer layers of the stratum corneum. Also, human skin appears to be a more effective barrier to penetration than that of certain small animals, at least for the quantities used in this investigation (Malkison and Rothman, 1962).

The pharmacokinetic profile of 2,4-D has been determined in five male volunteers (Saueroff, et al., 1976). After ingestion of a single 5 mg/kg oral dose, 2,4-D was eliminated from plasma in an apparent first-order process with an average half-life of 11.7 hours. All subjects excreted 2,4-D in the urine with an average half-life of 17.7 hours, mainly as free 2,4-D (82.3 %), with a smaller amount excreted as a 2,4-D conjugate (12.8 %).

Kohli, et al. (1974) studied the absorption and urinary excretion of 2,4-D acid in six subjects following oral ingestion (5 mg/kg administered in a gelatin with water). The 2,4-D was 99 percent pure. 2,4-D was determined as its ethyl ester by gas-liquid chromatography (g.l.c.). The absence of significant quantities of metabolites is based on a comparison of the g.l.c. profiles of blood and urine samples from individual volunteers before and after ingesting 2,4-D. In every case the only additional peak in chromatograms corresponded to the 2,4-D ethyl ester. Recovery experiments with 2,4-D

added to blood indicated a recovery of almost 95 percent.

Concentrations of 2,4-D in plasma, expressed in $\mu\text{g/ml}$, following administration of a single dose of 5 mg/kg, are given in Figure 5, which shows the curve from one individual and the mean curve of plasma concentration of six subjects as a function of time along with the standard error of determinations at each interval. Although there is a marked degree of individual variation, it would appear that the compound is absorbed fairly quickly; a significant amount of the compound was detected one hour after administration. The highest concentration of 2,4-D in plasma is reached in 7-24 hours, and then declines steadily. In general, the concentration reached in the plasma paralleled the amount excreted in the urine.

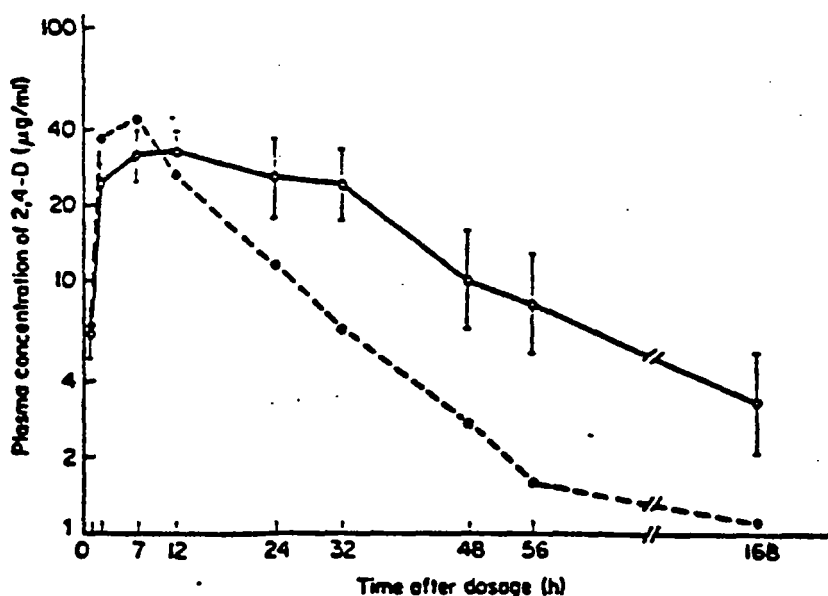


Figure 5. Plasma concentration of 2,4-D expressed after oral administration of a single dose (5 mg/kg) (Kohli, et al., 1974)

●----● Curve from one subject

○—○ Curve from six subjects, $\pm$ S.E.

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Studies of absorption, distribution, and excretion of 2,4-D in both animals and humans indicate that when this herbicide is ingested, it is rapidly absorbed through the gut and excreted, for the most part, in the urine. A large percentage is excreted as the parent compound and a lesser amount as a conjugate of the parent compound. However, it is evident in these studies that the investigators did not determine a total "mass balance". This may reflect, in the individual studies, one or more of the following shortcomings: (1) incomplete recovery by the methods used, (2) detected, but unidentified 2,4-D metabolites, and (3) incomplete examination of tissues, urine, and feces for the presence of 2,4-D or its metabolites.

Particularly lacking in the studies is information concerning the nature of 2,4-D metabolites. In some cases, no attempt was made to determine the presence of metabolites; in other studies, metabolites were noted but could not be identified. However, in one study, 2,4-dichlorophenol, a presumed 2,4-D metabolite, was identified in the liver and kidneys of sheep.

The importance of identifying 2,4-D metabolites and studying their toxicity is illustrated by 2,4-dichlorophenol. Boutwell and Bosch (1959) found that when topically applying 0.3 percent dimethylbenzanthracene in benzene as an initiator (may induce tumors by itself or may be enhanced by or require the presence of another compound), and applying 20 percent (312 mg/kg) 2,4-dichlorophenol as the promotor (enhances, but does not induce tumors by itself), papillomas and carcinomas were

noted after thirty-nine weeks. Although this is not analogous to an environmental exposure to 2,4-D (eg. different route of exposure and presence of an initiator compound), it does illustrate the importance of recognizing that the toxicity of a metabolite may be as/or more important than the parent compound.

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ACUTE TOXICITY

There are two kinds of toxicity. Acute toxicity is the rapid response of organisms to a few large doses of a chemical received over a short period of time. Chronic toxicity is the accumulation of effects resulting from exposure over a long interval. Thus the nature of the response is determined by the magnitude and duration of the dose the organism receives.

Experimental Animals

The acute toxicity of 2,4-D in animals is considered because (1) animals are frequently used as models to indicate toxicity to humans and (2) it is important in evaluating potential herbicide effects in the context of an environmental statement. In reviewing the acute toxicity of 2,4-D, it should be kept in mind that the nature of the dose-response relationship varies with both the chemical and the organism. Also, there is some individual variation within a given species.

Figure 6 shows a generalized dose-response relationship for 2,4-D to several organism groups (Newton and Norris, 1976). This example shows that higher plants are the most sensitive organisms to 2,4-D. Clearly this is the basis for the use of 2,4-D as a chemical agent for selective control of vegetation.

A significant amount of the literature on the acute toxicity of 2,4-D to various animals is summarized in Table 4, (U.S.EPA, 1974).

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Figure 6 Typical dosage-response spectra for
2,4-dichlorophenoxyacetic acid for
five classes of organisms (Newton and Norris, 1976)

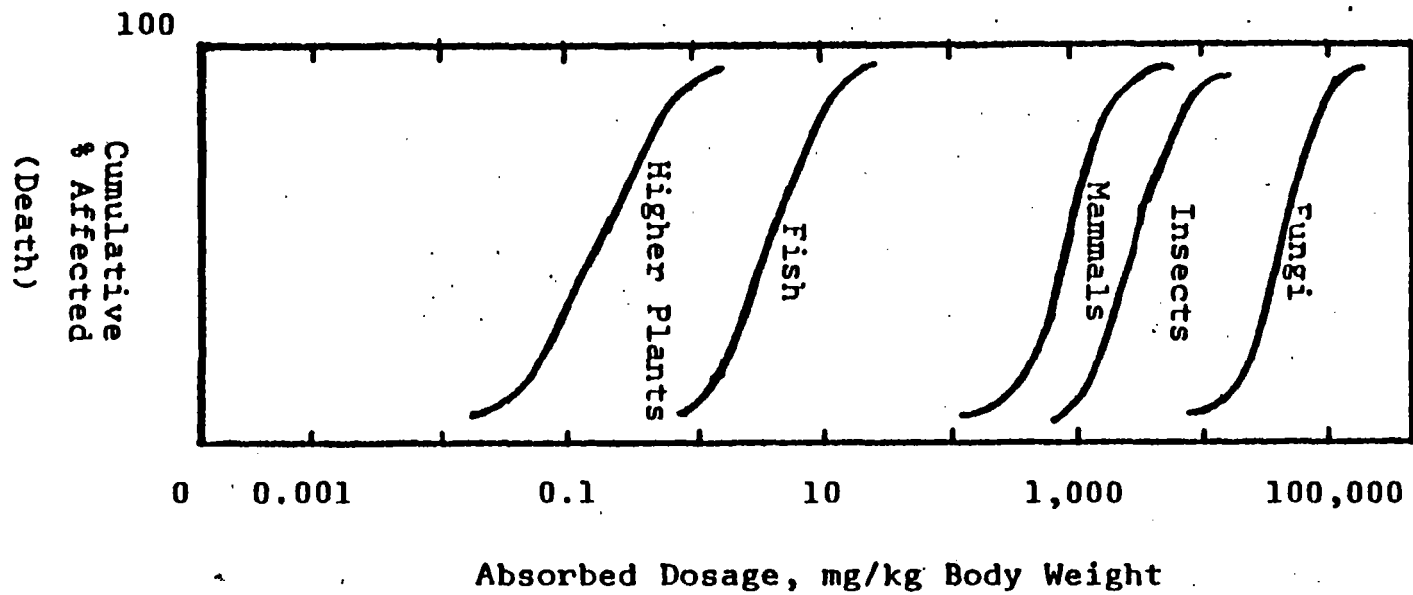


Table 4. Toxicity of 2,4-D
Birds, Fish and Invertebrate

Rat	Acute oral
Mouse	Acute oral
Rabbit	Acute oral
Dog	Acute oral
Guinea pig	Acute oral
Mule deer	Acute oral
Rat	Dietary, 2-yr
Dog	Dietary, 2-yr
Rat	Three-generation re- production
Cattle	Acute Oral 25 CDOD ³ 86 CDOD ³ 112 CDOD ³
Sheep	7 CDOD ³ 10 CDOD ³ 8 CDOD ³
Mallard	Acute oral Dietary, 5-day
Ring-necked pheas- ant	Acute oral Dietary, 5-day
Pigeon	Acute oral
Chicken	10 CDOD ³ 10 CDOD ³ 10 CDOD ³
Chorus frog tadpole	Acute, 24-hr
Bluegill	Acute, 24-hr
Rainbow trout	Acute, 24-hr
<u>Daphnia magna</u>	Acute, 48-hr
<u>Gammarus fasciatus</u>	Acute, 48-hr

Table 4 continued - notes

(Acid¹) to Mammals,
s (from EPA, 1974)

666 mg/kg	LD ₅₀	
375 mg/kg	LD ₅₀	
800 mg/kg	LD ₅₀	
100 mg/kg	LD ₅₀	
1000 mg/kg	LD ₅₀	
400-800 mg/kg	LD ₅₀	
1250 ppm	No effect	
500 ppm	No effect	
500 ppm	No effect	
250 mg/kg ⁴	Significant effect ²	
200 mg/kg ⁴	Significant effect ²	
100 mg/kg ⁴	Significant effect ²	
50 mg/kg ⁴	No effect	
500 mg/kg ⁴	Significant effect ²	
250 mg/kg ⁴	Significant effect ²	
100 mg/kg ⁴	No effect	
>1000 mg/kg	LD ₅₀	
>5000 ppm ¹	LC ₅₀	
472 mg/kg ¹	LD ₅₀	
>5000 ppm ¹	LC ₅₀	
668 mg/kg	LD ₅₀	
500 mg/kg ⁴	Significant effect ²	
250 mg/kg ⁴	Significant effect ²	
100 mg/kg ⁴	No effect	
100 ppm	LC ₅₀	
5 ppm	No mortality	
5 ppm	No mortality	0006043
>100 ppm	LC ₅₀	
3.2 ppm	LC ₅₀	

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1. There is very little variation in toxicity among the various salts and esters of 2,4-D in mammals and birds; however, certain esters are more toxic than acid to fish (1 ppm).
 2. Weight loss, reduced weight gain or illness.
 3. CPOD = consecutive daily oral doses each at the given dosage.
 4. Alkanolamine salts

Table 5 shows a range of LD₅₀'s and TLM's (summarized from the literature) for various groups of organisms for 2,4-D (from Norris, 1971).

Table 5. Acute Toxicity of 2,4-D (from Norris, 1971)

<u>Organisms</u>	<u>2,4-D</u>
Birds	
LD ₅₀ mg/kg	360-2000
Rodents	
LD ₅₀ mg/kg	375-800
Ruminants	
LD ₅₀ mg/kg	400-800
Other Mammals	
LD ₅₀ mg/kg	100
Fish	
TLM ppm ¹	1-60
Other Aquatics	
TLM ppm ¹	1-5

1. Forty-eight-hour median tolerance limit, i.e., the concentration of herbicide in water which will kill 50 per cent of an exposed population of aquatic organisms in 48 hours.

It can be seen that 2,4-D is generally less toxic to birds than to mammals. The toxicity to fish is greater than to mammals, but is highly variable. 2,4-D is absorbed after ingestion transported via the plasma, concentrated in the kidneys and rapidly

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eliminated in the urine (see section on Absorption, Excretion and Distribution). However, the dog has lower capacity to excrete 2,4-D, and as a result 2,4-D is about three times more toxic to dogs than to other test animals. 2,4-D is essentially nontoxic to insects and related organisms and is not significantly fungicidal or bactericidal (CAST, 1975).

A summary of symptoms of acute toxicity of 2,4-D to various organisms is given in an International Agency for Research on Cancer monograph, (IARC, 1977).

Symptoms of acute toxicity in mice, rabbits, guinea pigs, and rats are essentially similar. Some animals die suddenly, apparently from ventricular fibrillation; those that do not die immediately develop stiffness of the extremities, incoordination, lethargy, stupor, and coma prior to death. In mice acutely intoxicated with 2,4-D, dilation of the blood vessels of the lungs, liver and kidneys can be observed. Rats and guinea pigs administered lethal doses of 2,4-D exhibit congestion of the viscera and enlarged kidneys; microscopically, there is massive cloudy swelling of the proximal convoluted tubules with cast formation.

In dogs, toxic symptoms are often not present until six hours after oral administration of a lethal dose of 2,4-D; the animals become ataxic with progressive increase in spasm. Death appears to be due in most cases to hepatic congestion or to pneumonia. Pathological changes are limited to the gastrointestinal tract, lung and liver and follow the development of anorexia, weight loss and myotonia. Dogs exhibit evidence of liver damage more frequently than other animals.

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Acute toxic doses of 2,4-D produce fatty degeneration of the liver, spleen, kidney, and heart, and hemorrhagic gastroenteritis in chickens, and acute toxic doses have similar effects in sheep and cattle.

Human

The literature contains several descriptions of acute poisoning in man by 2,4-D. These include accidents and attempts at suicide. The exposures were quite high but varied within wide limits. Estimation of the fatal dose is difficult because in some cases the purity or the constituents of the commercial herbicide were not known, the magnitude of dermal exposure could only be guessed at, and in the case of exposure by ingestion, vomiting occurred.

Goldstein, et al. (1959) reported three cases of polyneuritis as a result of accidental exposure. Patient histories indicated that exposure to the herbicide 2,4-D preceded the development of the neuritis. The time relationship was such that it seemed reasonable that the herbicide caused the neurological disease. In each case severe sensory and motor symptoms necessitated hospitalization. In each case the disorder began some hours after the use of preparations of 2,4-D to kill weeds. Initial symptoms were nausea, vomiting, diarrhea, and headache. Symptoms of muscular weakness, swelling or aching of the feet and legs, with malaise and headache, persisted for 10-20 days. In one case, it is known that the individual spilled about 2 fluid ounces (60 cc) of a 10% solution of an ester of 2,4-D on his forearms without washing it off. All that is known about the exposure of the other two individuals is that their extremities were wetted with 2,4-D solution

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during spraying operations. The symptoms progressed through a period of days until pain, paresthesias and paralysis were severe. Disability was protracted and recovery was incomplete even after a period of years. Electromyographic examination supported the diagnosis of peripheral neuropathy.

Although it seems likely that the authors were correct in assuming that the 2,4-D caused the neuritis, they did not describe the details of manufacture or purity of the 2,4-D ester preparations. Therefore, it might be suggested that some other agent used in preparing or making a solution of the 2,4-D produced the neuritis and not the 2,4-D itself.

Berkley and Magee (1963) reported on a case of 2,4-D exposure to a farmer who repeatedly used his bare hands to correct plugging up of a weed sprayer. The farmer was using an aqueous solution of the dimethylamine salt of 2,4-D (40% solution). The individual's symptoms were a constant pricking of fingers, toes, mid-abdomen, upper chest, and anterior thighs. Hypersensitivity to touch and stiffness of the hands and knees were also noted. A diagnosis of primarily sensory, peripheral polyneuropathy was made and it was concluded the condition was probably produced by exposure to 2,4-D.

Seabury (1963) tentatively treated two patients suffering from coccidiosis by intramuscular or intravenous injection of the sodium salt of 2,4-D acid. One patient died of his disease, however, after having received no more than 40 mg. The other man received in the course of 34 days a total of 12.7 grams, beginning with very small doses, which were gradually increased. The last two doses were 2.0 and 3.6 grams. Towards the end of the course of treatment, various neurological signs and symptoms were noted including muscle weakness,

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fibrillary twitchings, and psychomotor retardation.

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Nielson, et al. (1965) described a case of fatal poisoning in man by 2,4-D, in which a 23-year-old farming student committed suicide with the dimethylamine salt of 2,4-D. The total amount of 2,4-D in the body was estimated to be no less than 6 grams. This corresponds to 80 mg/kg bw. However, this estimate of dosage was probably low due to loss of the chemical by vomiting. Death seems to have been preceded by convulsions and vomiting. Acute congestion of most organs was observed. Also, severe degenerative changes of the ganglion cells were found in the central nervous system.

Berwick (1970) describes a case of 2,4-D poisoning in a 46-year-old farmer who accidentally ingested approximately 30 ml of 2,4-D concentrate. The patient exhibited fibrillary twitching, paralysis of intercostal muscles, myotonia, and muscle weakness. There was evidence of generalized skeletal muscle damage as indicated by marked elevation of serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, lactic dehydrogenase, aldolase, and creatine phosphokinase levels. The constituents of the herbicide involved in this poisoning were known. Laboratory tests, the patient's elevated symptoms, and toxicological knowledge of this commercial herbicide ruled out toxicological response by the patient to the constituents other than 2,4-D. By calculation it would appear that the patient ingested 7,200 mg of 2,4-D acid. The patient's weight was 65 kg (143.3 lbs.) and he, therefore, ingested 110 mg-2,4-D/kg bw.

A case of fatal human ingestion of 2,4-D is reported by Dudley and Thapar (1972). An elderly man with senile dementia died 6 days after ingestion of a large amount of 2,4-D (approximately 1 pint in

a kerosene-like solvent). Death was presumed to be due to ventricular fibrillation induced by the cardiac muscle irritability associated with 2,4-D ingestion. Tissue concentrations in various organs were as follows: blood 57.60 ppm; brain 93.40 ppm; kidney 193.35 ppm; liver 407.87 ppm; and muscles 117.50 ppm. An autopsy of the patient revealed wide-spread plaques and acute demyelination in all parts of the brain. These perivascular plaques resemble those formed by multiple sclerosis and certain toxins, such as arsenic and carbon monoxide. The authors suggest that it is possible 2,4-D or one of its metabolites can induce demyelination.

In summary, the data from the above reports are variable and incomplete. However, ingestion of relatively large doses of 2,4-D does present the clinical triad of gastroenteritis, skeletal and cardiac myotonia, and central nervous system depression, which are the same symptoms observed in 2,4-D exposures to animals. Incidents of peripheral neuropathy following the use of a 2,4-D spray and exposure have also been observed.

An LD_{50} for humans cannot be accurately determined but can be estimated for the purposes of illustrating the nature of the acute toxicity of 2,4-D to humans. Hill and Carlisle (1947) have estimated an LD_{50} for humans extrapolated from their animal data.

"Assuming that man is no more resistant or susceptible than the rabbit or monkey-the largest estimated tolerated dose for a 75 kilogram man would be 15 grams (200 mg/Kg). With the exception of the monkey, all laboratory animals used lacked the vomiting reflex, so that they were unable to relieve themselves of irritating materials by vomiting. The experiments conducted on monkeys indicate that the material is a gastric irritant in large doses, so that the possibility of acute poisoning in humans would seem relatively remote, because of the large dose which man could presumably tolerate. Assuming that man is no more susceptible than the most susceptible animal tested, the mouse, then the calculated LD_{50} for man would amount to approximately 28 grams or 1 ounce."

CHRONIC TOXICITY

Animal

Rats fed 1,000 ppm of 2,4-D in their diet for one month showed no signs of toxic effects (Hill and Carlisle, 1947). No adverse effects were noted in young female rats fed 100 and 300 ppm of 2,4-D in their diet for periods up to 113 days, while those given 1,000 ppm over the same period had increased mortality, depressed growth rate, and slightly cloudy swelling of the liver. Animals fed 3,000 or 10,000 ppm of 2,4-D in their diet were sacrificed after twelve days because of food refusal and rapid weight loss. Increased liver and kidney weights were noted (Rowe and Hymas, 1954).

Rabbits were dermally exposed (intact and abraded skin) to three commercially available formulations of 2,4-D (the dimethylamine salt and the isooctyl and butyl esters). Doses of 15 ml were applied five times weekly for three weeks at two concentrations, 0.626% and 3.13% (the dimethylamine salt was diluted in water and the esters in either oil or water). There were no significant adverse effects upon the following parameters attributable to 2,4-D: (1) body weight, (2) survival, (3) hematologic values, (4) clinical chemistry, and (5) organ/body weight ratios (Kay, et al., 1965).

Subacute intoxication was produced in dogs by the daily administration of 25 mg/kg bw (intravenously) over a six day period with the development of liver damage (Hill and Carlisle, 1947). However, no adverse effects related to 2,4-D administration were observed when groups of three male and three

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female beagle dogs were fed 10, 50, 100, or 500 ppm of 2,4-D in their diet (96.6% pure, with no detectable dioxin content) for two years starting at 6-8 months of age. Twenty-eight dogs that survived the two-year period were clinically normal (Hansen, et al., 1971).

No adverse effects were seen in cattle and sheep with an intake of 50 mg/kg bw and 100 mg/kg bw respectively of two formulations of 2,4-D (the alkanolamine salt and the propylene glycol butyl ether ester). The doses were administered for 112 days to cattle and 481 days to sheep (Palmer and Radeleff, 1964).

Young pigs treated with 50, 100, or 200 mg/kg bw of commercial triethanolamine or butyl ester of 2,4-D, for varying intervals up to 103 days, exhibited symptoms of intoxication and pathology analogous to those seen in laboratory animals. Clinical signs of anorexia and retarded growth were found in one animal given fifty-one doses of 50 mg/kg bw triethanolamine salt over 103 days. Pigs fed 500 ppm of the triethanolamine salt of 2,4-D in their diet for up to twelve months developed locomotor disturbances of increasing severity after about one month. Animals sacrificed after 2-12 months had normal organ weights and no gross pathological changes. Clinico-chemical observations included lowered hematocrit and hemoglobin values, reduced albumin and albumin:globulin ratios, and elevated glutamic-oxaloacetate transaminase in the treated animals (Bjorklund and Erne, 1966).

Human

In a study of 292 persons (248 men and 44 women) engaged in manufacture of the amine salt and butyl ester of 2,4-D, with exposure ranging from under five years to 6-10 years (for 194 and 98 persons, respectively), 63% of these workers complained frequently of weakness, rapid fatigue, headache or vertigo. About 20% had disturbances of the cardiovascular system (mainly hypotension and bradycardia). Various liver dysfunctions were found and were more pronounced in workers with longer exposures to the herbicides (Bashirov, 1969).

In a brief paper, lacking numerical data and many important details, Festisov (1966) describes some results of health examinations on 105 workers engaged in the production of 2,4-D including salts and esters, and on forty-five persons engaged in aerial spraying of 2,4-D herbicides in agriculture. Symptoms, which were reported and which appeared to increase with the degree of exposure, were headaches and fatigue at the end of the workday, loss of appetite, pains in the stomach and liver, and occasionally symptoms in the upper respiratory tract. Impairment of taste sensitivity was noted in some cases. The symptoms usually disappeared by the next morning. No examinations on comparable control populations are mentioned. The concentration of the chemical in the air of the factory was extremely high, containig up to 28-44 mg/m³.

In a similar study, Radionov, et al. (1967) reported on symptoms manifested by several groups of workers whose duty

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it was to thin-out and weed maize fields, the day following or, in some cases, several days after the treatment of the fields with 2,4-D. The formulations used were the sodium, amine and dimethylamine salts of 2,4-D. Dosages ranged from 1.5-3 kg/hectare. Workers complained (usually within one hour of beginning work) of headache, vertigo, nausea, weakness, irritation of the eyes and the nasopharyngeal mucosa, burning sensation of the skin, and substernal pain. Occasionally, some workers vomited. The workers usually recovered within a few days. No permanent damage was noted. One point of interest is that dry weather seemed to aggravate the situation. Under these conditions, more dust is generated and the plants and upper strata lack the moisture which would partially prevent atomization of the herbicide in the air.

In a report on 220 workers exposed in a manufacturing plant to a concentration of 30-40 mg/day of 2,4-D for periods ranging from 0.5-22 years, Johnson (1971) stated that no "meaningful" differences were noted when clinical results on these workers were compared to those obtained on a control population of 4,600 men not exposed to 2,4-D. However, the clinical tests were not specified and no supporting data were provided. No chromosomal effects were noted in ten workers whose chromosomes were karyotyped.

These health studies of people occupationally exposed to 2,4-D generally have serious shortcomings that limit their usefulness. All of the available studies are cross-sectional; the exposed populations were examined only once or, in some cases, twice.

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No longitudinal studies, in which the same persons are observed at regular intervals over longer periods of time, have been made. Thus, temporary and also delayed effects may have been overlooked. There is, however, no evidence for delayed effects in the animal experiments. In spite of these shortcomings, the fact that three of the studies reported similar symptoms in exposed human populations is sufficient to suggest that chronic exposure to high concentrations of 2,4-D can produce adverse health effects in humans.

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TERATOGENICITY

An agent or chemical is considered as teratogenic when it causes developmental disturbances in the embryo resulting in congenital malformations. If an agent kills the embryo, it is said to be embryocidal, and if it produces tissue damage (not necessarily resulting in malformation), it is embryopathic. The term embryotoxic will refer to any harmful effect on the embryo, or fetus.

Schwartz, et al. (1971) fed 2,4-D acid at levels up to 87.5 mg/kg/day (maximum tolerated dose), equimolar doses of propylene glycol butyl ether ester of 2,4-D up to 142 mg/kg/day, and isooctyl ester of 2,4-D up to 131 mg/kg/day to rats (Sprague-Dawley), on days 6-15 of gestation, the time when the rat embryo is most sensitive to teratogenic agents. Embryotoxic responses were seen including edema, delayed ossification, decreased fetal body weight, and wavy ribs. However, no genuine teratological effects were seen even at the highest dosages. The highest level of esters decreased viability and lactation in the mothers, but had no effect on the growth and development of the offspring.

Khera and McKinley (1972) in prenatal studies on Wistar rats showed that 2,4-D induced embryotoxic effects and increased the incidence of skeletal anomalies after single oral doses of 100-150 mg/kg/day on days 6-15 of gestation. At the highest dosage of 150 mg/kg/day, the isooctyl ester, and butyl ester, and butoxyethynol and dimethylamine salts of 2,4-D were all associated with significantly increased teratologic incidence. The butyl and isooctyl esters also tended to decrease fetal weight.

At a lower dosage, 2,4-D, and its salts and esters induced no apparent harmful effects.

Collins and Williams (1971) found in the progeny of hamsters treated with three commercial samples of 2,4-D at levels up to 100 mg/kg/day on day 6-10 of pregnancy, occasional anomalies of the fused rib type. However, the percentages were not significantly different from that of the control population. Fetal viability decreased significantly at the higher dose levels, but again was not clearly dose-related.

Sprague-Dawley rats were given 1,000 mg/l 2,4-D in their drinking water during pregnancy and for a further 10 months, 2,4-D was also administered to the second generation for up to 2 years. Pregnancy and parturition were normal; litter size was not significantly reduced, and no malformations were noted in the young. Except for retarded growth and increased mortality in the second generation, no unequivocal clinical or morphological changes were seen (Bjorklund and Erne, 1966).

Female rats (10 per group) were fed 2,4-D at levels up to 2,000 mg/kg of diet for 95 days and then mated with untreated males and continued on their respective diets through gestation and lactation. Pups born to females fed the highest level were small at birth; 94% died before weaning; some deaths also occurred in pups of rats fed the lower level (1,000 mg/kg) (Gaines and Kimbrough, cited in Hansen et al., 1971).

In a three-generation study, Osborne-Mendel rats were fed 100 or 500 ppm of diet 2,4-D that was 96.7% pure, with no detectable (≤ 1 ppm) TCDD. No adverse effects were noted (fertility, mean litter size or viability of pups). However, diets containing 7057

1,500 ppm 2,4-D, while apparently affecting neither the fertility of either sex nor litter size, sharply reduced the percentage of pups that survived to 21 days of age and depressed the weights of these weanlings (Hansen, et al., 1971).

When 2,4-D was administered at a concentration of 500 ppm of diet during the entire pregnancy of a sow, anorexia was observed. The piglets were clearly underdeveloped and apathetic and did not willingly suck. Ten of the 15 newborn piglets died within 24 hours. No malformations were noted in the dead piglets. Continued feeding of 500 ppm of diet to the survivors until they were 8 months of age caused marked growth depression, persistent anemia and moderate degenerative changes of liver and kidneys (Bjorklund and Erne, 1966).

A study that attempted to simulate field conditions for spraying with 2,4-D and to evaluate the effect on pheasant eggs and development of chicks was done by Lutz-Ostertag and Lutz (1970). A high mortality rate and morphological alterations were observed in most of the surviving embryos, and 50% of surviving chicks were sterile.

Gyrd-Hansen and Dalgaard-Mikkelsen (1974) studied the effect of 2,4-D on the hatchability of hens (leghorn) eggs and the viability of the chicks, both by injecting the herbicide into the yolk and by immersing the eggs into solutions of the herbicide. A pure compound containing 99.5% 2,4-D as the dimethylamine salt and a commercial product containing about 93% 2,4-D as the dimethylamine salt were used in the investigation. Dose levels in the injection experiments ranged from 0.1 to 10.0 mg/60g egg.

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In the immersion experiments, eggs were soaked in either 10 or 50 g/l aqueous solutions of 2,4-D. In the injection experiments, hatchability and viability were reduced at the 2-mg-and-above level. 2,4-D injected into the yolk exhibited both embryotoxic and teratogenic properties at high dose levels. However, immersion in a 1% 2,4-D solution had no effect and a 5% solution showed only a moderate effect on the hatchability of the eggs and the viability of the chicks. The 1% immersion level corresponds to the levels used in spraying operations, however, in the immersion experiment, the entire surface of the egg is exposed. The authors state that their investigations show that 2,4-D has little effect on hen eggs after immersion. This is in contrast to the conclusions from the Lutz-Ostertag and Lutz study.

Verrett (1970) reported that 2,4-D produced fetal anomaly and chick edema syndrome following injection into the yolk sac. Eggs were injected with 2.5 mg 2,4-D/egg either prior to incubation or at the fourth incubation day (96 hours), the latter being a time at which the embryo is more sensitive to some teratogenic agents. 2,4-D did not show any particular acute toxicity to the embryo when treatment was pre-incubational; however, occurrence of abnormal embryos was high. Treatment at 96 hours resulted in higher toxicity and also a high percentage of abnormal embryos. The results from egg injection studies are difficult to interpret due to the extreme sensitivity of this test procedure.

The results of the teratogenesis studies in animals with 2,4-D were variable. The studies with birds presented conflicting data. One study that simulated environmental spraying conditions

resulted in a significant teratogenic effect on pheasant eggs. However, a similar immersion study with chicken eggs had no effect. Egg injection studies also produced teratogenesis. These studies are not particularly applicable to a human exposure because a human embryo would not be exposed in this manner and also because of the greater degree of protection afforded the human embryo by its mother. However, these studies do indicate a possible ecological impact on bird wildlife as a result of spraying 2,4-D in forests.

In studies of mammals, which are more applicable to humans because of similar routes of exposure to the embryo, teratogenic effects are observed but only at doses that approach maternal toxicity. The phenomenon of teratogenesis, unlike carcinogenesis and mutagenesis is thought to have a "no-effect" level, that is a threshold below which no teratogenic response is observed. It is apparent from the studies of mammals that this threshold is very high and is in all probability considerably above the level of any potential environmental exposure (see section : Comparison of Estimated Maximum Intake of 2,4-D and Acceptable Daily Intake). Therefore, it is very unlikely that levels of 2,4-D used in forestry management would produce teratogenesis in humans.

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MUTAGENICITY

2,4-D was negative in the rec-assay test (Shirasu, 1975). The rec-assay is believed to give an indication of reparable DNA damage; it is a simple method capable of detecting DNA-damaging capacity by analyzing differences in growth sensitivities of H17 Rec⁺ and M45 Rec⁻ mutant cells of Bacillus subtilis.

2,4-D was also not mutagenic in reverse mutation systems (Anderson, et al., 1972; Shirasu, 1975; Shirasu, et al., 1976; and Zetterberg, et al., 1977). The reverse mutation systems employed were the histidine-requiring mutants of Salmonella typhimurium [Ames test (TA1535, 1536, 1537, and 1538)] and two tryptophane-requiring mutants of Escherichia coli WP2 hcr⁺ and WP2 hcr⁻.

Zetterberg, et al. (1977), using host-mediated assays with S. typhimurium strains TA1530 or TA1531 or with S. cerevisiae D4, observed no mutagenic effects when adult male mice were given 6 mg 2,4-D (200 mg/kg) by gavage.

2,4-D did not increase dominant lethal mutations in mice when given as a single i.p. injection of 125 mg/kg bw, or when given orally on five successive days for a total dose of 75 mg/kg bw (Epstein, et al., 1972).

No increase in the number of recessive lethals was observed when 2-day-old adult male Drosophila melanogaster flies were fed 4.5 or 9.0 mM 2,4-D in sucrose (Vogel and Chandler, 1974).

The above investigations have concluded, within the limits of the sensitivity of the tests employed, that 2,4-D is not mutagenic. However, there are several studies that indicate

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that 2,4-D may possibly have mutagenic properties.

Commercial 2,4-D tested for induction of mitotic gene conversion in a diploid strain of the ascomycete Saccharomyces cerevisiae showed weak mutagenic activity when compared to known mutagens. However, the treatment concentration was very high (1,000 ppm) and survival rate of the yeast cells was only 22% (Siebert and Lemperle, 1974). Mitotic recombination in S. cerevisiae D5 was also increased by 2,4-D (300 µg/ml) (Zetterberg, et al., 1977).

Treatment of cultured human lymphocytes with 2.5×10^{-7} M (0.02 µg/ml) 2,4-D increased the number of chromatid aberrations and, to a lesser extent, of chromosomal aberrations. In mice, toxic concentrations (100-300 mg/kg bw) of 2,4-D administered as a single oral dose significantly increased the frequency of aberrant metaphases (2-4 fold) in lymphocytes; single fragments were the primary aberration (Pilinskaya, 1974, cited in IARC, 1977).

In terms of human relevance, the above mutagenic studies can be categorized as submammalian and mammalian systems, (See Table 6 for classification and results). The relevance of data obtained from submammalian test systems is uncertain in view of factors such as cell uptake, metabolism, detoxification dosage and method of administration. Mammalian systems entail fewer of these limitations and may be considered more useful for providing evidence of a potential mutagenic hazard to humans.

Table 6 Classification and Results of the Mutagenicity Studies Reviewed

<u>Submammalian</u>		<u>Mammalian</u>	
Rec-assay		Host mediated assay	
<u>B. subtilis</u>	(-)	<u>S. typhimurium/mice</u>	(-)
		<u>S. cerevisiae</u>	(-)
Reverse mutation			
<u>S. typhimurium</u>	(-)	Dominant lethal	
<u>E. coli</u>	(-)	mice	(-)
Recessive lethal		Cytogenetic test	
<u>D. melanogaster</u>	(-)	Human lymphocytes (in-vitro)	(+)
		Mouse lymphocytes (in-vitro)	(+)
Gene conversion			
<u>S. cerevisiae</u>	(±)		
Mitotic recombination			
<u>S. cerevisiae</u>	(±)		

(-) Negative

(+) Positive

(±) Weak Activity

Except for the gene conversion and recombination studies, which showed some weak activity, the submammalian systems were negative. Mammalian systems were negative, except for the human and mouse lymphocyte studies. A positive result in this test system is of concern, because mammalian tests are more relevant in assessing the potential hazard to humans than submammalian tests. However, these positive results are not sufficient evidence to conclude that 2,4-D will produce mutagenic disorders in humans at levels normally encountered.

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CARCINOGENECITY

Oral Administration - Animals

The Bionetics Research Laboratories under contract with the National Institute of Health carried-out a large-scale study designed to screen selected pesticides (including 2,4-D) and industrial compounds for tumorigenicity in mice. A summary of the results of the oral administration portion of this investigation is reported by Innes, et al., (1969).

Groups of mice were orally administered maximum tolerated doses (duration of exposure was 7 days to 18 months) of commercial 2,4-D acid and several of its esters (see Table 7 for the compounds and the dose regime used). Tumor incidences of the treated groups were compared with those observed among groups of 79, 87, 90 and 82 control mice, which had either been untreated or had received gelatin only. Results of the experiment indicated that mice treated with 2,4-D compounds listed in Table 7 did not have a statistically significant elevation of tumor incidence of any type of tumor in any sex-strain subgroup or combination of groups.

The Food and Drug Administration studied the effects of long term feeding of 2,4-D on rats (Hansen, et al., 1971). Groups of 25 male and 25 female 3-week-old Osborne-Mendal rats were fed for 2 years on diets containing 0, 5, 25, 125, 625, or 1,250 ppm of 2,4-D (free acid, 96.7% pure) in the basal diet. The 2,4-D contained no detectable levels of dioxin compounds; the limit of sensitivity of the method of analysis was 1 ppm. Results of this study indicated that the total number of rats with malignant tumors were 6, 8, 7, 7, 8, and 14 in the control and in the 5, 25, 125, 625, and 1,250 ppm groups, respectively.

Table 7 2,4-D Dose Regime (from Innes, et al., 1969)

<u>Compound</u>	<u>Purity of Compound</u>	<u>Strain of Mice</u>	<u>No. of Mice</u>	<u>Daily Dosage mg/kg</u>	<u>Vehicle</u>	<u>ppm</u>
1. 2,4-D acid	90%	(C57BL/6xC3H/Anf)F, (C57BL/6xAKR)F,	18m, 18f 18m, 18f	46.4	0.5% gelatin	149
2. 2,4-D acid	90%	"	"	100	"	323
3. 2,4-D Isopropyl ester	99%	"	"	46.4	"	111
4. 2,4-D Butyl ester	99%	"	"	46.4	"	149
5. 2,4-D Isooctyl ester	97%	"	"	46.4	"	130

Notes

1. Used during stomach intubation only (days 7-28 age).
2. Dosage in diet ad libitum (after 28 days of age).

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The authors state that from the pathological interpretation of the tumor incidence, it is apparent that the tumors were not "target organ" types and they were randomly distributed types normally found in aging Osborne-Mendel rats. In addition, the number of animals surviving the two year study did not differ from group to group, whereas with a carcinogenic substance, one would expect fewer survivors in the high dose group. When the tumor incidence was analyzed, a statistical increase ($P < 0.05$) of malignant tumors occurred in male rats fed 2,4-D at 1250 ppm (the highest dose), and a trend toward increased tumor formation with log dose in female rats was noted. Despite the statistical calculations on tumor incidence, it is the author's opinion that the pathological interpretation indicates that a carcinogenic effect by 2,4-D has not been shown.

Another interpretation of this study has been offered by Rueber (1976), an independent pathologist, who reviewed the data for the U. S. Senate Subcommittee on Administrative Practice and Procedure. He concluded that the data suggested that the tumors were of a "target organ" type and that the statistical interpretation of the data verifies that "2,4-dichlorophenoxyacetic acid is carcinogenic in rats".

Subcutaneous Administration - Animals

The Bionetics Research Laboratories also tested the tumorigenicity of 2,4-D and several of its esters in mice with subcutaneous administrations of the herbicide.

Groups of mice, 18 male and 18 female (C57BL/6xC3HAnf)F mice, and 18 male and 18 female (C57BL/6xAKR)F mice, were given

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single subcutaneous injections of 215 mg/kg bw 2,4-D (90% pure) in dimethyl sulphoxide on the 28th day of life and observed up to 78 weeks of age, at which time 16, 17, 18 and 18 mice in the four groups, respectively, were alive. Tumor incidences were compared with those in groups of 141, 154, 161, and 157 controls that were either untreated or were injected with dimethyl sulphoxide, 0.5% aqueous gelatin or corn oil. The tumor incidence in any group or combination of groups was not significantly different from that in controls ($P > 0.05$). No increase in the incidence of tumors was observed in similar groups of mice treated with single s.c. injections of 215 mg/kg bw butyl or 100 mg/kg bw isopropyl esters of 2,4-D (both 99% pure). Of mice treated with 21.5 mg/kg bw isooctyl ester of 2,4-D (97% pure), 5/17 females of the second strain developed reticulum-cell sarcomas ($P = 0.01$) (NTIS, 1968).

Humans

Axelsson and Sundell (1974) reported that in an epidemiological investigation of tumor incidence and mortality among Swedish railroad workers, exposed to different herbicides, showed a twofold excess of all cancers, as compared with the national average. The situation is difficult to evaluate because of the combined exposure of many workers to more than one herbicide. The excess cancer appears to be due to exposure to 3-amino-1,2,4-triazole (amitrole). Those subgroups that had been exposed to phenoxy acids (2,4-D and/or 2,4,5-T) had about normal tumor incidence (5 cancers at all sites observed versus 2.8 expected).

Comments on Carcinogenicity Data

The International Agency for Research on Cancer has reviewed and evaluated studies on the carcinogenicity of 2,4-D, including those reported above (IARC, 1977). IARC initiated a program in 1971 to evaluate the carcinogenic risk of chemicals to man. IARC is supported in part by the National Cancer Institute of the United States and is regarded by government authorities as a source of expert, independent scientific opinion on environmental carcinogenesis. The IARC comments on the carcinogenicity of 2,4-D are as follows:

Animal data. 2,4-D and several of its esters were tested in rats and mice by oral administration and in mice by subcutaneous administration. All of these studies had limitations, due either to inadequate reporting or to the small number of animals used. Therefore, although increased incidences of tumors were observed in one study in which rats received 2,4-D orally and in another in which mice received its isooctyl ester by subcutaneous injection, no evaluation of the carcinogenicity of this compound could be made.

Human data. The results of the single cohort study of a small number of workers exposed to various herbicides, including 2,4-D, 2,4,5-T and 3-amino-1,2,4-triazole (amitrole), are not sufficient to evaluate the carcinogenicity of 2,4-D to man.

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COMPARISON OF ESTIMATED MAXIMUM INTAKE OF 2,4-D
AND ACCEPTABLE DAILY INTAKE

Estimate of Exposure

The 1977 herbicide monitoring program in the Chippewa and Superior National Forests of Minnesota was done in part to determine if there were any adverse impacts on the water quality and the wildlife in these forests. It did not directly address the question of human health impact from exposure to 2,4-D, as a result of the conifer release spraying project, to people living in or near the forests or the people using the forests (St. MN., 1977).

Exposure to 2,4-D would logically occur through the food chain to the hunter, fisherman, gardener, and foraging naturalist. Although, at this point in time, it is difficult to accurately determine the level of exposure and any associated health effects, an estimation of 2,4-D intake for a "maximally exposed individual" can be calculated using wildlife monitoring and water quality data.

A "maximally exposed individual", for the purpose of this calculation, is assumed to be an adult male whose total diet is derived from the forest habitat and the forest surface waters. Dietary intake is based on data for the "standard man" (70 kg bw), (U.S. HEW, 1970). The total non-fluid daily intake for a "standard man" is approximately 1600 grams and daily fluid intake is approximately 2000 grams.

The data available are 2,4-D levels in the kidneys and livers of small rodents (e.g., ground squirrels, chipmunks, shrews, voles, and mice) and birds (e.g., sparrows, flycatchers, warblers, etc.) from the U. S. Forest Service 1977 monitoring program in Chippewa

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National Forest. Specimens were collected before and after a typical conifer release spraying episode. The wildlife monitoring data from the Superior National Forest, collected by the Minnesota Department of Natural Resources, were not used in the exposure estimation because of a lack of positive data. Water quality data is available for both forests before and after conifer release spraying from the monitoring programs of both the Minnesota Pollution Control Agency and the U. S. Forest Service.

It is assumed that the non-fluid portion of the dietary intake of the "maximally exposed individual" consists entirely of animal tissue. Vegetables, fruits, etc., are not considered in the non-fluid portion of the diet, although 2,4-D levels on their surfaces might initially be higher than that found in animal muscle tissue. However, it is likely that these foods would be washed before being eaten, reducing the exposure from this source to something which is in all probability less than the exposure from animal tissue. The individual's non-fluid dietary exposure to 2,4-D is calculated by multiplying the mass of the non-fluid diet by the projected animal tissue 2,4-D concentration. The projected tissue concentrations were calculated using data from an animal study in which kidney, liver, and muscle tissue levels of 2,4-D were determined after exposure to a diet containing 2,4-D. The animal study chosen (Erne, 1966a) involving feeding rats and chickens 1000 ppm of 2,4-D amine in their drinking water for two months. At the end of this time, the animals were sacrificed and various tissues were analyzed for 2,4-D content. From this data, a ratio of 2,4-D concentration in the liver tissue to muscle tissue can be developed for both rats and chickens. These

ratios are then applied to the average 2,4-D concentration found in the liver tissue of the mammals and birds, which were analyzed in the U. S. Forest Service's Chippewa wildlife monitoring project. This gives the estimated maximum concentration of 2,4-D in the muscle tissue of these mammals and birds. This concentration represents a maximum value because it is calculated from measured concentrations in animals collected at a time (three days after spraying) that theoretically has allowed 2,4-D levels in the animal tissue to reflect the maximum concentration resulting from spraying.

To use these concentrations to estimate the 2,4-D intake for the "maximally exposed individual" requires the assumptions that (1) the liver to muscle 2,4-D ratio for rats and chickens, as measured in laboratory experiments, does not differ by orders of magnitude from the liver to muscle 2,4-D ratio for the small rodents and songbirds which were collected as part of the Chippewa wildlife monitoring program, and (2) the liver to muscle 2,4-D ratio for the small rodents and songbirds does not differ drastically from the liver to muscle 2,4-D ratio for the large mammals and birds, such as the rabbit, deer, grouse, etc., which would actually comprise the diet of the "maximally exposed individual".

The calculation for the mammal muscle tissue is as follows:

- (1) Liver: muscle ratio in rats from the laboratory animal study = 3.6:1.
- (2) Average 2,4-D concentration in the liver tissue of twenty-six mammals from Chippewa National Forest = 1.19 ppm.

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- (3) Estimated 2,4-D concentration of muscle tissue of Chippewa mammals = $1.19 \text{ ppm} / 3.6 = 0.33 \text{ ppm}$.

The calculation for the bird muscle tissue is as follows:

- (1) Liver: muscle ratio in chickens from the laboratory animal study = 5:1.
- (2) Average 2,4-D concentration in the liver tissue of eight birds from Chippewa National Forest = 0.48 ppm.
- (3) Estimated 2,4-D concentration of muscle tissue of Chippewa birds = $0.48 \text{ ppm} / 5 = 0.10 \text{ ppm}$.

Assuming that the non-fluid portion of the diet consists of one-half mammal muscle tissue and one-half bird muscle tissue, then the average 2,4-D concentration in animal muscle tissue consumed is 0.22 ppm; therefore, exposure of 2,4-D to the "standard man" from non-fluid food intake is:

$$(1600 \text{ grams/day}) (0.22 \text{ } \mu\text{g 2,4-D/gram muscle}) = 352 \text{ } \mu\text{g 2,4-D/day}$$

The intake of 2,4-D through the fluid portion of the diet was determined by using the average 2,4-D concentration found in water samples taken twenty-four hours after spraying. The twenty-four hour values were used because the concentrations of 2,4-D in the water appeared to peak at that time. Only the Minnesota Pollution Control Agency water quality data were used because the detection was lower and the program provided data twenty-four hours after spraying. The Minnesota Pollution Control Agency program included data from both Chippewa and Superior forests with data from both forests being averaged for this calculation.

The average twenty-four hour 2,4-D level in water at all sites in both forests was 0.42 ppb; therefore, assuming that the total intake of fluid consumed by the "maximally exposed individual" is forest surface water, the exposure is calculated as follows:

(1) Fluid intake = 2 liters/day

(2) Concentration of 2,4-D in water = 0.42 $\mu\text{g/l}$

(3) 2,4-D intake from the fluid portion of the diet =
 $(2 \text{ l/d})(0.42 \text{ } \mu\text{g/l}) = 0.84 \text{ } \mu\text{g 2,4-D/day.}$

Then the total dietary intake of 2,4-D is:

352.0 $\mu\text{g 2,4-D/day}$ (non-fluid intake)

+ 0.84 $\mu\text{g 2,4-D/day}$ (fluid intake)

352.84 $\mu\text{g 2,4-D/day}$ (total intake)

This is approximately 0.35 mg of 2,4-D/day. The contribution from the water portion of the diet is seen to be negligible.

For the 70 kg "standard man" the intake per unit of body weight is:

$$\frac{0.35 \text{ mg 2,4-D/day}}{70.0 \text{ kg}} = 0.005 \text{ mg 2,4-D/kg bw/day}$$

Earlier, it was indicated that exposure to 2,4-D would probably occur to an individual eating fish taken from bodies of water within the area impacted by spraying. The contribution of fish to the non-fluid portion of diet is judged to be negligible and was not considered in the estimation of 2,4-D exposure. Fish are not likely to accumulate 2,4-D over the concentration in the water (Smith and Isom, 1967 and Schultz, 1973), and since the water quality indicate that the 2,4-D levels in the forest waters are very low, the level in fish tissue would be negligible in comparison to the level estimated in the muscle tissue of mammals and birds. Therefore, excluding any contribution of 2,4-D from fish to the non-fluid portion of the diet actually maximizes the estimated 2,4-D intake.

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FAO/WHO Allowable Daily Intake

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The Food and Agriculture Organization of the United Nations and the World Health Organization have jointly studied and evaluated possible hazards to people arising from the occurrence of residues of pesticides in foods. From these efforts, they have, in some cases (including 2,4-D), been able to establish an acceptable daily intake (ADI) for humans. The ADI is expressed as milligrams per kilogram body weight (mg/kg bw). Vettorazzi (1975), in discussing the ADI, states that:

"the concept is based on the widely accepted fact that all chemicals are toxic, but their toxicities vary markedly, not only in nature, but also in the amount that is required to produce signs of toxicity. The figure (mg/kg bw) is indicative of the amount of a chemical that might be ingested daily even over a lifetime, without appreciable risk to the consumer. 'Without appreciable risk' is taken to mean the practical certainty that injury will not result after a lifetime exposure".

To establish an ADI for a pesticide, the FAO/WHO evaluates data from long-term studies in animals, observations on humans, and other pertinent toxicological data. From this, they determine a "no-effect level", which is that daily dose that produces no indication of toxic effects in the test animals or human subjects. Then, in order to extrapolate to a safe level for human intake, a safety factor is generally applied. No hard-and-fast rule is established with regard to the magnitude of the safety factor. Although the widely accepted figure of 100 is often employed, in practice, this factor has varied from ten to several hundred.

The FAO/WHO has established the maximum ADI for 2,4-D at 0.3 mg/kg bw. A summary of the "no-effect level" and other

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elements that have been chosen by the FAO/WHO as a basis for the ADI of 2,4-D is given in table 8 .

Table 8 : Summary of Toxicological Data
(from Vettorazzi, 1975)

Compound	2,4-D
Animal species	Rat
Kind of toxicological test	Two year
Levels tested	0, 5, 25, 125 625, 1250 ppm
Levels causing no toxicological effects	625 ppm in the diet (31 mg/kg bw)
Safety factor employed	>100
Maximum acceptable daily intake (ADI) mg/kg bw	0.3
Brief indication of effects	Macrocystosis; slight polychromasia, and hypochromasia
References	Hansen, et al., 1971
Remarks	"An ADI for man was established on the 2-year feeding study in the rat."

Comparing the Estimated Exposure to the ADI

When comparing the estimated 2,4-D exposure of a "maximally exposed individual" in the northern Minnesota forests to the maximum acceptable daily intake, several things are apparent. First, the estimated exposure is approximately sixty times less than the ADI (0.005 mg/kg bw vs. 0.3 mg/kg bw). Since the ADI has a hundred fold safety factor, the estimated exposure is approximately 6,000 times below the "no-effect level" measured in the rat study.

Based on this comparison alone, there appears to be little potential for an adverse health effect to the "maximally exposed individual". This conclusion is further supported by the fact that the projected exposure for the hypothetical individual living in the forest was the "worst case" exposure. In reality, the actual exposure, even if it ever reached the calculated maximum level, would decline quickly to a much lower level, because 2,4-D is rapidly degraded in the environment. What we have done, in essence, is to compare a short term 2,4-D intake to an ADI, which is meant to be used for a lifetime exposure.

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CONCLUSIONS AND RECOMMENDATIONS

Conclusions

Various possible adverse health effects resulting from exposure to 2,4-D have been examined, including acute toxicity, chronic toxicity, teratogenicity, mutagenicity, and carcinogenicity. A review of the literature of the toxicology of 2,4-D, the data from the 1977 monitoring programs of the Chippewa and Superior National Forests, and the calculation of the estimated 2,4-D exposure to a "maximally exposed individual", supports the conclusion that, although certain adverse health effects are not likely to occur, there is significant doubt about some areas of the toxicology of 2,4-D which precludes an absolute assumption of safety relating to its use in forestry management.

The adverse human health effects that do not seem likely to occur as a result of exposure to 2,4-D, as it is used in forestry management, include:

1. Acute Toxic Response. Although accidental poisonings involving 2,4-D have occurred, the dose levels were very high. Numerous studies in animals indicate that acute toxicity occurs only at high doses and it has been estimated that the LD₅₀ for man is approximately one ounce of 2,4-D.
2. Chronic Health Effects. Chronic health effects, excluding mutagenicity and carcinogenicity resulting from 2,4-D exposure have been observed in both animals and humans. Effects in humans have been associated with long-term occupational exposure to high concentrations of 2,4-D. Symptoms of chronic toxicity include gastritis, loss of appetite, headache, vertigo, weakness, and disturbances

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of the cardiovascular and respiratory systems. Although chronic health effects can occur, it is unlikely that exposure to an individual living in a spraying area would result in such effects since the exposure would be of short duration. However, acute and chronic health effects could be of concern to the applicator.

3. Teratogenesis. Considerable concern has been expressed over the possibility of a teratogenic response as a result of exposure to 2,4-D. Based on a comparison of animal teratogenicity studies and the estimated maximum exposure resulting from the use of 2,4-D in forestry, it is expected that 2,4-D would not produce teratogenesis in humans. Teratogenesis observed in experimental animals (mammals) was only produced at dose levels that approached the level of maternal toxicity. The levels at which this effect began to appear in mammals are at least one-hundred fold above the ADI, and are approximately five-hundred fold above our estimated exposure to a "maximally exposed individual".

Although reasonably definite conclusions can be drawn with regard to the above three areas, there remain questions relating to the toxicology of 2,4-D which prevent the assumption that the use of 2,4-D in forestry is completely safe. Such an assumption will require further definitive research in the following areas:

1. Mutagenicity. The results of the mutagenicity studies present conflicting results making it difficult to conclude that 2,4-D is not mutagenic in humans. The fact that at least one study has found that 2,4-D produces aberrations in the chromosomes of human lymphocytes at low dose levels is cause for concern.

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2. Carcinogenicity. The results of the carcinogenicity studies are also inconclusive. Only a limited number of studies have been done, the results of which have been subject to conflicting interpretation. An adequate assessment of the carcinogenic potential of 2,4-D will require further studies involving large numbers of animals of several species.

3. Contaminants and Metabolites of 2,4-D. It is now known that the production of 2,4-D, at least theoretically, will not result in its contamination by the very toxic compound tetra-dioxin. However, hexa-dioxin has been identified in commercial 2,4-D and although not nearly as toxic as tetra-dioxin it has been shown to produce a toxic reaction in animals. Other contaminants have also been identified in commercial 2,4-D, but little or nothing is known of their toxic properties.

Several studies have examined the absorption and excretion of 2,4-D. These studies indicate that 2,4-D is rapidly absorbed through the gut and excreted in the urine mainly as the original compound. Although these studies are able to account for a large percentage of ingested 2,4-D in the urine and feces of test animals and human volunteers, there is still a small fraction which is not excreted as the original 2,4-D compound. The same studies have revealed the presence of several metabolites of 2,4-D in the urine including 2,4-dichlorophenol, a suspected carcinogenic promoter.

4. Environmental and Wildlife Monitoring. The 1977 monitoring program in the Chippewa and Superior National Forests did not provide the type and amount data necessary to adequately assess the extent of 2,4-D exposure to humans. A more complete risk assessment

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will require more data from the human food chain (e.g., rabbit, deer, fish, grouse, vegetation, and water).

5. Acceptable Daily Intake. The ADI, as was explained earlier, is based on a "no-effect level" observed in an animal study and an arbitrary safety factor of 100. It is possible that some health effects, such as carcinogenicity or mutagenicity, may not manifest themselves in the particular species or at the particular dose level used in the study. If future studies on several species of animal indicate that 2,4-D is mutagenic or carcinogenic, a more conservative approach to the establishment of an ADI will be required.

These concerns leave some doubt as to the safety of 2,4-D. The available scientific data suggests that 2,4-D is possibly a weak carcinogen or mutagen. However, even if 2,4-D is carcinogenic or mutagenic the risk of the development of cancer or mutagenic disorders in an individual is small at levels of exposure which are approximately that of the "maximally exposed individual". As a matter of fact the risk to such an individual is most likely not high in comparison to that which we face daily from the thousands of untested, possibly carcinogenic or mutagenic, chemicals used by society.

If the population exposed to 2,4-D residues at the estimated maximum level numbered in the tens of thousands, there would be cause for more serious concern since low level exposures to carcinogens or mutagens in large populations may produce disease. However, the population exposed to such levels as a result of the use of 2,4-D in forestry management in Minnesota is very small.

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The small size of the population coupled with the low level of risk to an individual make it difficult to conclude that there is a reasonable chance of disease occurring as a result of spraying. However, it is equally difficult to conclude that 2,4-D is absolutely safe.

Recommendations

In the absence of clear evidence that 2,4-D poses no threat to the public's health, a prudent policy governing the use of 2,4-D should provide, (1) assurances that exposure is minimized for residents, workers, and persons participating in all activities in spray areas and (2) for the acquisition of sufficient information which, coupled with future toxicological research, will allow a more complete assessment of health risk. Such a policy should include as a minimum the following:

1. Environmental and Wildlife Monitoring Program. The program should be implemented in areas where herbicides are used for forestry management and should provide data on 2,4-D concentrations in the human food chain. Of course the program can be designed to address concerns relating to the ecological impact of the use of 2,4-D also.
2. Human Health Studies. Limited studies of human populations exposed to herbicide spraying should be done. This might include, for example, analysis of blood and urine samples for the presence of 2,4-D or 2,4-D metabolites.

The Minnesota Department of Health is currently planning to establish an Environmental Pathology Laboratory which could perform specialized studies on biological specimens from people exposed to 2,4-D. This laboratory would be capable of providing highly sophisticated and very valuable studies involving, for example, the

analysis of urine for the presence of mutagenic substances.

The more conventional forms of epidemiology, i.e., measuring disease incidence in the exposed population, should also be conducted if sufficiently large exposed populations can be identified.

3. Herbicide Analysis Program. The herbicides used in forestry management should be routinely analyzed for contaminants prior to application. The toxicology of 2,4-D is, to some degree, known; however, studies have indicated that contamination of commercial 2,4-D does occur and it is conceivable that contaminants such as the dioxins could have a serious adverse impact on human health. A policy relating to the use of contaminated herbicides should also be established.

4. Physical Control of Exposure. Regulations providing strict control on overspraying, drift, limited access to spray areas, posting of warnings and protection of applicators should be established to minimize human exposure.

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2,4-D
IN THE
URBAN AND SUBURBAN ENVIRONMENT
AND
HUMAN HEALTH

E.C. PACKEE, PH.D.

Presented to the Nanaimo Parks and Recreation Commission

Bowen Park Complex

March 29, 1979

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FORWARD

"2,4-D in the Urban and Suburban Environment and Human Health" was prepared as a private contribution for a meeting called to review the use of 2,4-D by the governmental agencies of the city and school district of Nanaimo. The information presented in the report is equally valid for forestry uses.

Of major concern in forestry is the exposure of the applicator to 2,4-D. Since no substance, natural or artificial, known to man is absolutely safe under all conditions, it is essential to think in terms of risk or hazard; in the purest sense of the word, no substance is safe! Therefore, it is commonsense to minimize unnecessary exposure to a substance. For 2,4-D this means good personal hygiene and use of protective equipment as necessary must be enforced.

In reading this report, which was orally presented, be certain to refer to the appropriate visuals which are attached. A number indicated as follows, (4), refers to visual number 4.

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1. 2,4-D was developed for chemical warfare.
2. 2,4-D has been shown to cause birth defects and cancer in Vietnam.
3. Because 2,4-D belongs to the phenoxy herbicide group it has the same contaminants and physiological effects - the family likeness syndrome.
4. 2,4-D accumulates in the environment and mammalian tissue.
5. The South Okanagan Environment Coalition's "'The Other Face of 2,4-D...' stands up to rigorous scientific scrutiny," is the best scientific document on 2,4-D and is fair.

Lethal Toxicity to Humans

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2,4-D and Carcinogenicity

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2,4-D IN THE URBAN AND SUBURBAN ENVIRONMENT
AND HUMAN HEALTH

Obviously, this meeting is the result of the division of the public and, to a lesser degree, scientists over the safety and benefits of 2,4-D, one of the phenoxy herbicides. As in any controversy, the opposing parties include both reasonable and unreasonable people and individuals with vested interests or personal ambitions. Because of the use and abuse of scientific and pseudo-scientific jargon, hogwash and whitewash, and publicity generated by both sides, sincere citizens have become confused, are concerned, and are clamoring for action.

Furthermore, there are fundamental philosophical differences over herbicide usage. At one extreme are those who consider inserting any synthetic chemical into the environment as fundamentally wrong, regardless of benefits and proven safety. At the other extreme are those who are unable to accept any suggestion that some chemicals, although used successfully and with no apparent problems in the past, might actually constitute a hazard which is only becoming evident now.

As a scientist, I deal with theories, hypotheses, and facts. Decisions must be based on supported hypotheses or facts. The

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facts are found in juried journals and reports. (1) The news media is rarely a source of reliable scientific facts. This illustration (2) provides examples of sources for scientific facts. Regardless of the source, however, the questions raised by the media and the public deserve an answer - I am part of the public and I, too, want answers. (3)

Before discussing the safety aspects of 2,4-D, I would like to dispel some misconceptions. (4) This will greatly reduce the time needed for discussion.

1. 2,4-D was not developed as a weapon of war (5)

Shortly after the turn of the century researchers were attempting to synthesize plant growth stimulating substances; such work is continuing today. In August 1941, Dr. Kraus, a University of Chicago botanist, suggested to two former graduate students that they investigate the plant-killing aspects of growth stimulators. They obtained various substances, one of which was 2,4-D. In 1942, recognizing the crop-killing potential of growth-regulating substances, Dr. Kraus advised the National Academy of Sciences about the potential dangers of biological warfare. It was not until 1944 that herbicide research was included in the research program at Camp Dietrick (Peterson 1967; Davis 1979).

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2. 2,4-D has not been shown to have caused birth defects or cancer in Vietnam.

2,4-D was always used in mixture (6) with either 2,4,5-T as agents orange or white or with picloram as agent purple (Council for Agricultural Science and Technology 1975; Whiteside 1970). Thus it is impossible to attribute the birth defects to 2,4-D or 2,4,5-T or picloram specifically. Follow-up research on agent orange indicated that the 2,4,5-T component was highly contaminated with TCDD (Council for Agricultural Science and Technology 1975; Whiteside 1970) a known teratogen.

Agent orange was applied at 5 to 10 times normal levels used for agriculture in North America (Council for Agricultural Science and Technology 1975); Whiteside (1970) states 13 times. Many areas were retreated. The estimated amount of TCDD distributed in South Vietnam is 120 to 165 kg. Dr. William Wells, Acting Director, Special Pesticide Review Division, Office of Pesticide Programs, U.S. E.P.A., Washington, D.C., assures me that the major concern about the phenoxy herbicides to which 2,4-D and 2,4,5-T belong is the TCDD contaminant. Costle's (1979a and 1979b) recent decision and emergency suspension orders regarding 2,4,5-T and 2,4,5-TP which state, "It is reasonable to assume that the adverse human reproductive effects observed in Alsea which have been attributed to low-level exposure to 2,4,5-T are due primarily to the TCDD in the

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2,4,5-T," support the concern over TCDD. Even Ton That and associates (1973) attribute increased liver cancer to herbicides "containing TCDD"! TCDD is not present as a contaminant or by-product of 2,4-D (I.A.R.C. 1977a and 1977b).

3. Because a chemical belongs to a particular family of chemicals or only varies by one molecule, it does not follow that it behaves in all cases like the similar compounds.

For example, H_2O and H_2S vary by only one atom, but we all know that water and hydrogen sulfide are vastly different. Similarly, ethanol and methanol are alcohols, but the former is grain alcohol and the latter wood alcohol. Because 2,4-D and 2,4,5-T belong to the same family, the chlorophenoxys, it does not mean that they are produced the same way. 2,4-D is produced from dichlorophenol and 2,4,5-T is from trichlorophenol. The former precludes production of (7) TCDD but not DCDD; the latter includes production of TCDD as a by-product. The use of the word dioxin is misleading, it denotes a family of compounds called chlorinated dibenzodioxins. The point is - oversimplification or generalizations can lead to erroneous conclusions; this is demonstrated in the following table (8) - quite a difference in the survival of OCDD and DCDD treated animals. Reports (Warnock and Lewis 1978) that hexa, hepta, and octachlorodibenzo-para-dioxins are contaminants are unsubstantiated; however, I must note that Woolson and associates (1972)

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reported finding less than 10 ppm of a hexachlorodibenzo-*para*-dioxin in one of the 28 samples of 2,4-D; this observation has never been duplicated, and all chemists whom I have queried believe the contaminant entered the 2,4-D after production. Also, the "International Conference on Chlorinated Phenoxy Acids and Their Dioxins" (Anonymous 1977) concluded that the only dioxin found in phenoxy herbicides which is of environmental concern is TCDD.

4. 2,4-D does not accumulate in the environment or mammalian tissues.

2,4-D is readily absorbed by plant tissues and translocated generally in the direction of food sinks principally at the active growing points of shoots and roots (Crafts 1964).

On reaching the soil, 2,4-D is adsorbed and bound to soil particles and is retained in the upper part of the soil profile (Council for Agricultural Science and Technology 1975). Once bound, 2,4-D does not leach into groundwater nor does it move in significant quantities in surface runoff (Sheets et al. 1972; Manigold and Schultze 1969). In or on the soil 2,4-D is immediately attacked and broken down by soil organisms (Audus 1969; Kaufman and Kearny 1976). Generally, 90% or more is degraded within 35 days of application (Norris 1970; Altom and Stritzke 1973); formulation does not affect rate of decomposition (Norris and Greiner 1967).

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All available data suggests that 2,4-D entering streams will be lost by volatilization, adsorption to sediment particles, absorption by biota, microbial degradation and decomposition by sunlight (Tutass 1966; Tutass and Crosby 1965; Aly and Faust 1964; Schultz and Harman 1974).

A portion of herbicide material will be lost to the atmosphere through drift or volatilization. In areas of heavy agricultural spraying, maximum average 24-hour concentrations of combined droplets and vapor were $0.123 \mu\text{g}/\text{m}^3$ with an absolute maximum concentration of $2.65 \mu\text{g}/\text{m}^3$. By comparison the U.S.S.R. acceptable ceiling concentrations are $1 \text{ mg}/\text{m}^3$ (I.A.R.C. 1977); thus the levels in eastern Washington are 8130 and 377 times below the acceptable U.S.S.R. value which is only 1/10 of that of the U.S. or West Germany. Vapor/droplet levels due to parks and playfield treatment in Nanimo would never reach the levels found in those agricultural areas. 2,4-D in the atmosphere will break down in sunlight or will be washed out by precipitation.

If 2,4-D were to be absorbed and become well distributed throughout an animal's body, does it persist or bioaccumulate? First, how does a substance get into an organism? (9) Skin absorption, inhalation, and ingestion. Once in the body it can be transported to a number of body components.

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Note that in many cases there are one-way routes or possibly two-way routes. The two-way routes don't always guarantee the return to body fluids. Now let's look specifically at 2,4-D.

The amine and alkali salts of 2,4-D are readily absorbed and completely distributed in the body of calves, pigs, rats and chickens; 2,4-D ester is incompletely absorbed and reaches only a low level in the body fluids and tissues. Highest tissue levels are commonly found in the liver, kidneys, spleen and lungs; these tissue levels can exceed the levels found in the body fluids. Penetration of 2,4-D into placental tissue of pigs is a matter of record; however, there is little or no evidence of penetration into adipose tissue or the central nervous system (Bjorklund and Erne 1966; Leng 1977). Traces of orally administered 2,4-D (50 ppb or 0.05 mg/kg of body weight) were detected in the milk of lactating rats for six days; also within 24 hours of treatment about 17 percent of the dosage was found in the uterus, placenta, fetus and amniotic fluid (Fedorova and Belova 1974). However, detectable residues did not appear in the milk of cows consuming up to 300 ppm of 2,4-D in the diet for two to three weeks (Clark et al. 1975; Leng 1972 and 1977). Since the fetus is an integral part of the mother's body, physiological processes of the mother are also active in the fetus.

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Noting the two-way street symbol for tissue/bone/brain, liver and blood cells compartments, there is a potential pathway for the removal of the 2,4-D from these compartments. (10) In reality, the mammalian system does eliminate 2,4-D. In fact elimination of 2,4-D from the body of mammals is quite rapid. The body fluid half-life is about 3 hours in rats, 8 hours in calves (also chickens) and 12 hours in pigs; tissue half-life values range from 5 to 30 hours (Way 1969). The rate of elimination appears to be dosage dependent (Way 1969; I.A.R.C. 1977). The major route of excretion is in the urine with minor amounts in the feces (Way 1969). A 4 mg/kg dose of 2,4-D, the maximum daily dose likely to be ingested from grazing pasture, fed to sheep was excreted within 72 hours, in excess of 98 percent was via kidneys and only 1.5 percent was present in the feces (Clarke et al. 1964).

In support of this is the work of Sauerhoff and associates (1977); five male human volunteers (29 to 40 years of age) ingested 5 mg/kg of analytical grade 2,4-D acid. Within 24 hours 16.8 to 39.1 percent of the 2,4-D as both the free compound and conjugate had been excreted; after 144 hours an average in excess of 90 percent had been excreted with the range of recovery being 87.6 to 106.3 percent. No explanation of the 106.4 percent figure is given, but it can be assumed to be analytical error with regards to precision. The half-life value for clearance from body fluids

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was 11.6 hours. Kohli and associates (1974) calculated a half-life for excretion of 33 hours. Thus, there is absolutely no evidence to support the fear that 2,4-D will accumulate in children and create problems in later life.

5. The South Okanagan Environment report is not the best scientific document on 2,4-D. (11)

Let's not kid ourselves about this red herring. It wouldn't rate a passing grade in any reputable science class; it might make it in a creative writing course. It is full of unsubstantiated claims, gross misinterpretations of scientific reports, misrepresentations of expertise, half-truths, and deliberate attempts to mislead. It is biased. In fact, this report is so unscientific, it really warrants no further discussion.

Lethal Toxicity to Humans

Acute toxicity of 2,4-D is low to moderate. (12) The Merck Therapeutics Index states, "Clinical reports of 2,4-D poisoning are rare and show no consistent pattern." Less than a dozen deaths have been related to 2,4-D; most were confirmed suicides. Kraus reported on individual ingestion of 500 mg/day for 21 days; he reported no ill effects (Mitchell et al. 1946; I.A.R.C. 1977). Sauerhoff and associates (1977) reported on five males who ingested 5 mg/kg of body weight (70 kg person ingested 350 mg and a 90 kg person ingested 450 mg); again no ill effects. Seabury (1963) treated two patients at Louisiana State University

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School of Medicine with terminal cases of disseminated coccidioidomycosis, a fungal infection, with 2,4-D. One patient received about 16.3 g of 2,4-D over a 34-day period; an individual dose of 2 g (37 mg/kg of body weight) produced no symptoms of toxicity; however, a dose of 3.6 g (66 mg/kg of body weight) caused intoxication symptoms. The likelihood of a person, even a child, receiving a dose similar to the above examples from the Park's or School Board's programs is essentially nil!

Sublethal Toxicity to Humans

Sublethal effects of 2,4-D in humans is dependent upon the dose; the greater the dose the more serious the symptoms. Data suggest that the sublethal effects of 2,4-D are temporary. One apparent exception to this is the case of a 37-year-old Russian woman who suffered acute poisoning because of non-observance of hygienic and sanitary labor conditions (Kaskevich and Soboleva 1978). This woman continues to be disabled three years later; the authors state that observation has revealed the progressive course of the pathological process. Careful review of a translation suggests there is an element of doubt that the herbicide caused the entire problem.

Symptoms of 2,4-D poisoning such as fibrillary twitching and muscle paralysis have been reported following ingestion of large quantities (Berwick 1970; Seabury 1963; Gesselin et al. 1976) or excessive dermal exposure (Goldstein et al. 1959). Numbness and aching of feet and hands and partial paralysis for several

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months have resulted from excessive dermal exposure (Goldstein et al. 1959; I.A.R.C. 1977). In all cases, large doses were involved.

More typical symptoms of 2,4-D include fatigue, weakness, dizziness, loss of appetite, nausea, vomiting and diarrhea. "Protracted inhalation of spray is likely to irritate the nose, eyes, throat and bronchi causing disagreeable local burning sensations and coughs." (U.S. E.P.A. 1977). Sare (1972) reported that spray operators experience headaches and double vision. Dennis (1976) conducted a questionnaire survey of farmers and grain elevator operators in Saskatchewan.

"Twenty percent of 3330 surveyed reported that they had experienced ill effects from working with agricultural chemicals, 2,4-D apparently being the most troublesome. Symptoms were generally confined to the season or time of spraying, and were similar among those affected. They included nausea, loss of appetite, weight loss, and occasional vomiting. A small number reported a skin rash. The symptoms observed one year were often more extreme than those observed in previous year(s), requiring a number of farmers to contract out their spraying to other operators. This report suggests a possible development of sensitivity to the spray with repeated exposure." (National Research Council of Canada 1978).

Assouly (1951) reported that workers employed in the production of an ester of 2,4-D developed symptoms of drowsiness, loss of appetite, neuralgic pain in the stomach or the forward walls of the abdomen, increased salivation, a sweet taste in the mouth, a sensation of drunkenness, heaviness of the legs, and excessive acuteness of the sense of hearing. Symptoms noted above are similar to exposure to some petroleum solvents (Browning 1965)

(and products. Seabury (1963) questions whether the symptoms identified by Assouly were related to the 2,4-D acid or to the chemicals used in the process of esterification. He states, "Certainly a sweet taste in the mouth with sialorrhea [heavy salivation] suggests the symptoms were related to the chemicals used in esterification." Unfortunately, there are no adequate epidemiological studies to clarify the point. The Saskatchewan study has not been submitted for peer review. Except for the rash, the symptoms are firmly believed to be of minor consequence and transitory in terms of applications within the urban/suburban setting.

(If the rash is chloracne, then there is a problem and a need for real concern. However, all evidence indicates that the rash is not chloracne. The chloracne issue must be reviewed in depth since the South Okanagan Environmental Coalition Report suggests or states in numerous places that the phenoxy herbicides produce chloracne. Warnock and Lewis (1978) state "there is evidence that all the phenoxy herbicides produce chloracne, even 2,4-D and 'purified' 2,4,5-T." They state, "Poland and his colleagues found chloracne among workers in plants manufacturing 2,4-D and 2,4,5-T,..." They also state,

"Two doctors have reported treating more than 40 cases of chloracne contracted by workers in plants engaged in the synthesis of 2,4-dichlorophenol and 2,4,5-trichlorophenol. There was some question as to whether TCDD exposure (from the making of 2,4,5-T) was responsible for the chloracne in all cases."

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No reference is provided for the above "two doctors."

Finally they refer to a report by Dr. M.Kay of the U.S. Public Health Service who tested commercial preparations of 2,4-D and 2,4,5-T through open patch skin tests on his own arms. They state, "... both induced chloracne on his arm (Bleiberg and Brodtkin, 1964)."

Careful review of the report by Poland and colleagues (1971) suggests that the chloracne was associated with the manufacture of 2,4,5-T; however, it was statistically impossible to correlate the chloracne with any job location within the plant since the workers commonly worked in more than one location. Their comments on chloracne are completely concerned with 2,4,5-T, trichlorophenol, and TCDD (the last, a known and severe acnegenic agent). They also state, " Although the structures of 2,4-D and 2,4,5-T (...) differ only by one chlorine, the commercial syntheses of the two compounds are dissimilar," and, "In 2,4-D production there is no formation of the TCDD." There was only one manufacturing plant involved in this study. Warnock and Lewis (1978) leave the impression that several plants were involved and it can be construed from their wording that at least one only manufactured 2,4-D.

Since no specific reference is available for the second reference of Warnock and Lewis (1978) to chloracne in manufacturing plants, a review of the pertinent literature was made. I.A.R.C.(1977b) made no reference to chloracne in their discussion of 2,4-D. However, they gave extensive coverage to chloracne in their

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discussions of 2,4,5-T (I.A.R.C. 1977c) and the chlorinated dibenzodioxins (I.A.R.C. 1977a). The National Research Council of Canada (1978) makes no reference to a relationship between chloracne and 2,4-D. In an attempt to determine specifically if 2,4-D was related to chloracne of workers employed in its manufacture, Dow Chemical Canada Limited, a major Canadian producer of phenoxy herbicides was queried. Dr. H.B. Wallis, M.D., Dow's Corporate Medical Director replied, "To the best of my knowledge and belief no Dow Chemical of Canada employee associated with the production and/or formulation of Dow 2,4-D SIC Acid has ever developed signs suggestive of Chloracne" (Wallis 1978). Dow chemical, U.S.A. also reports a no-incidence status (Carney 1978). If chloracne were caused by 2,4-D, undoubtedly the Therapeutics Index (Gesselin et al 1976) would have mentioned such a relationship. Also the U.S. E.P.A. (1977) makes no specific comment about chloracne; the U.S. E.P.A. simply states, "Irritation of the skin follows excessive contact with many chlorophenoxy compounds."

The chloracne incident reported by Bleiberg and Brodtkin (1964) is interesting in that it is contrary to experience and more recent research results. Although I have not exhausted the literature search, I am convinced that 2,4-D is not a cause of chloracne.

In conclusion, sublethal effects of 2,4-D as used in an urban/suburban area will be of a minor and transitory nature and do not pose a serious hazard to the public.

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2,4-D and Carcinogenicity

Before discussing 2,4-D specifically, it is necessary to review a few definitions and concepts concerning cancer(13). It is obvious that cancer and carcinogenicity have different meanings for different people. The next table (14) lists some substances that are known to be carcinogenic. Note tobacco on the list. The long term trend of cancer, exclusive of lung cancer, in North America, is downward. If lung cancer is included in the average, the trend is upward and we know that there is a cause and effect relationship between tobacco and lung cancer.

Looking specifically at 2,4-D, all scientifically acceptable attempts to demonstrate that 2,4-D causes cancer have failed or are considered "inconclusive". Innes et al (1964) screened 120 compounds for tumourgenic properties in mice; 2,4-D as the acid, the isopropyl ester, the butyl ester, and the isooctyl ester were classed as "Experimental compounds which did not cause a significant increase in tumours after oral administration". Despite statements by many environmentalists, toxicologists and statisticians, these conclusions still stand as valid.

Hansen and associates (1971) fed groups of 25 female and 25 male rats 0, 5, 125, 625, and 1250 ppm of 2,4-D acid in the basic diet. They also investigated the effects of 0, 100, 500, 1500 ppm of 2,4-D through three generations of rats. The tumour incidence found in the rats is given in this table (15). Their conclusions, "from the pathological interpretation of the tumour

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incidence it is apparent that the tumours were not 'target organ' types and they were randomly distributed types normally found in aging Osborne-Mendel rats. In addition, the number of animals surviving the 2 year study did not differ from group to group, whereas with a carcinogenic substance one would expect fewer survivors in the high dose group." They concluded "the raw data, however, support the pathological interpretation that a carcinogenic effect has not been shown." Several persons have disputed this conclusion. A review of peer opinions is desirable.

I.A.R.C. (1977) commenting on this report states, "Therefore, although increased incidences of tumours were observed in one study in which rats received 2,4-D orally, no evaluation of the carcinogenicity of this compound could be made" when considered in the light of other data. The U.S. National Cancer Institute determined that the above study "presented no convincing evidence of carcinogenicity" (Johnson 1978). The U.S. National Center for Toxicological Research evaluated the statistical analysis and found the data suggestive of positive evidence of carcinogenicity (Johnson 1978). The Center also felt that "the data demonstrated the potential for other chronic health effects which were not evaluated by the researchers." A consultant for the Cancer Assessment Group of the U.S. E.P.A. "informally reported that he felt the data presented in the study indicated positive evidence that 2,4-D is a

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carcinogen," however, the Cancer Assessment Group (CAG), itself, "has neither formally or informally reviewed the study in question" (Johnson 1978). Johnson (1978) states, "Therefore neither CAG nor EPA has taken a position on whether 2,4-D is or is not a carcinogen."

In contrast to the above, Warnock and Lewis (1978) state "The F.D.A.'s study revealed that 2,4-D caused malignant tumours in male and female rats tested: he concluded that "2,4-dichlorophenoxyacetic acid is carcinogenic in rats." "He" is Dr. Melvin Reuber, "the consultant to CAG". Officially, the "informal review" attributed to CAG was never conducted."

"Reuber's review was conducted totally independent from CAG. CAG never authorized the review, and they have no records on it. Just recently when shown the review, "_____ " indicated they could not comment, or support, its content" (Lambert 1978).

Also, Warnock and Lewis (1978) state, "Research by the Biometrics Research Laboratory (1967) and the U.S. Food and Drug Administration (1963) demonstrates that 2,4-D causes malignant tumours in laboratory rats and mices." The Biometrics Research Laboratory is the report of Innes and associates (1969) and the U.S. Food and Drug Administration study is the report of Hansen and associates (1971) which have just been reviewed above.

The conclusion, 2,4-D does not pose a demonstrated cancer threat to the citizens of Nanaimo.

It is worth looking at the Hansen et al. (1971) data once again. Experimental design dictates enough animals, doses, and controls. Note that even the control animals have tumours. To evaluate such data requires an appropriate statistical design which includes a control; the control accounts for background noise.

2,4-D and Mutagenicity

A mutation is an inheritable change in a chromosome (Watson 1976). Emphasis is on the word "inheritable." For an agent to be considered a mutagen, the change must be passed on to the next generation!

2,4-D was demonstrated to be non-mutagenic in Escherichia coli and Salmonella typhimurium (Anderson et al. 1972; Nagy et al. 1975; Zetterberg et al. 1977). A test involving Bacillus subtilis believed to give an indication of reparable DNA damage proved negative, thus suggesting that 2,4-D does not damage DNA (Shirasu 1975). Serum from 2,4-D orally dosed rats had no mutagenic effect on Salmonella typhimurium (Styles 1973). Vogl and Chandler (1974) demonstrated no mutagenic activity of 2,4-D in male Drosophila melanogaster flies. Epstein and associates (1972) found that a total of 75 mg/kg of body weight of 2,4-D given over a 5 day period did not increase dominant

lethal mutations in mice; single injection of 125 mg/kg of body weight also had no effect. Injection of 100 mg/kg of body weight of 2,4-D did not increase the micronuclei of mouse bone marrow erythrocyte (hemoglobin-rich blood) cells; the compound did, however depress slightly mitotic activity (Jensen and Renberg 1976).

Using cell culture techniques and experimental methods not widely recognized nor readily interpretable Ahmed and associates (1977a) demonstrated that 2,4-D can produce DNA damage in human fibroblast cells; however, the cells were able to repair the damage. They have also shown that 2,4-D fluid acts as a weak mutagen of a specific cell line derived from the lung of a male hamster; they suggest that this approach, if coupled with other assays, might be used as a prescreen for mutagens (Ahmed et al. 1977b). In essence, it is not known whether Ahmed and associates work has practical application. For example, how does one relate the artificial cell culture technique to the way the cell behaves in the body and how the physiological processes of the body effect the cell?

Several studies have referred to chromosomal aberrations (breakage, pairing of fragments, inverted linkage of fragments) in animals (Shaw 1970; Bongso and Basrar 1973) and even in humans (I.A.R.C. 1977; Golberg 1971). Some clastogens (chromosome aberration causing agents) are presented in this table (16).

(In all of the clastogen positive studies involving 2,4-D, none have concluded that 2,4-D causes mutations in animals or bacteria! The reason for mammals being: mammalian systems have defense mechanisms to prevent the damage from being passed onto succeeding generations, for example, cells can repair the damage, damage may prevent the cell from reproducing, the cell may die, the cell may be killed by natural antibodies.

Because 2,4-D acts as a plant growth regulator it can be assumed that it is a plantclastogen and/or mutagen. It does not follow that if an agent causes mutations in plants, that it will cause mutations in animals. If such were the case, there would be no need to test with laboratory animals.

(Before concluding, it is worth looking at the three generation rat study of Hansen and associates (1971) (17). Three generations of rats fed a diet containing 2,4-D and no genetic abnormalities were mentioned.

All evidence demonstrates that 2,4-D is not a mutagenic agent in mammals.

2,4-D and Embryotoxicity

(Karnofski's Law (18) "Any drug administered at the proper dosage, at the proper stage of development, to embryos of the proper species, will be effective in causing disturbances in embryonic development" (Wilson 1972). The law holds true for many other, if not all, types of chemicals. This (19) is a very incomplete

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list of products or substances known to have embryotoxic effects, in this birth defects, on at least one species of laboratory mammal.

Embryotoxic effects of a chemical are manifested in many ways: spontaneous abortion or miscarriage, stillbirth, decreased fetal weight, deformities, wavy ribs, and immature (soft) bones. Agents causing birth defects are called teratogens.

There is no evidence that 2,4-D causes spontaneous abortions, miscarriages, or stillbirths. There is no suggestion in the current scientific literature that even suggests such a hazard exists. We must remember that at least one conception in seven results in a spontaneous abortion. I believe that it is valid to say that 2,4-D is no hazard in terms of spontaneous abortion.

Hansen and associates (1971) data suggest that reproductive function of rats in the three generation study was not altered by the 500 and 1000 ppm 2,4-D diet. However, percentage of pups surviving to weaning and weanling weight was decreased by 1,500 ppm of dietary 2,4-D. There is no likelihood that a person would consume such a level in a normal or even fad diet.

We now can look at teratogenicity. Most work has been done with rats and mice, hamsters, guinea pigs, monkeys, and livestock. Dost (1978) concludes that sheep apparently are not subject to 2,4-D induced birth defects.

Mice, (20) contrary to environmentalists, and some biologists, are highly sensitive to many chemicals and drugs. Laboratory mice have a great propensity for a specific defect called cleft palate. (21) This lists only some of the agents known to cause birth defects in mice. This certainly questions the use of mice for teratogenicity studies.

Schwetz et al. (1971) determined that 2,4-D at the higher daily doses (75 mg/kg as 2,4-D, 75 mg/kg as 2,4-D propylene glycol butyl ester; 87.5 mg/kg as 2,4-D isooctyl ester), levels just below the maternal toxic dose, caused decreased fetal weight, subcutaneous edema, delayed bone ossification, and wavy ribs. Khera and McKinley (1972) observed wavy ribs or fused sternum in rats associated with 2,4-D doses as low as 25 mg/kg/day. 2,4-D at doses of 100 mg/kg/day through days 6-10 of pregnancy caused a low incidence of anomalies, usually fused ribs. A woman weighing 50 kg would have to consume 5000 mg or 5g of 2,4-D for at least 5 days of her pregnancy; cutting this to half begins to approach a dose that is non-lethal (based on Seabury's observations). Levels involved are well above levels one could ever anticipate a person receiving without knowing.

Summary

There is no evidence to suggest that 2,4-D as used by Parks or School Board employees is a hazard to the public of Nanaimo.

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In conclusion there are many of us, like the local Council of Women, who are genuinely concerned for the well-being of our children. Too often we become emotionally involved and have not or cannot make an objective evaluation of the data or even accept new data. It is unfortunate that there are individuals and groups who, for whatever reason, attempt to subvert this genuine concern. 2,4-D and its supporters have been vilified; the benefits of 2,4-D to us and future generations have been ignored. The prime achievement of these vilifiers has been to confuse and frighten the public. Like cancer, confusion and fright will spread and destroy.

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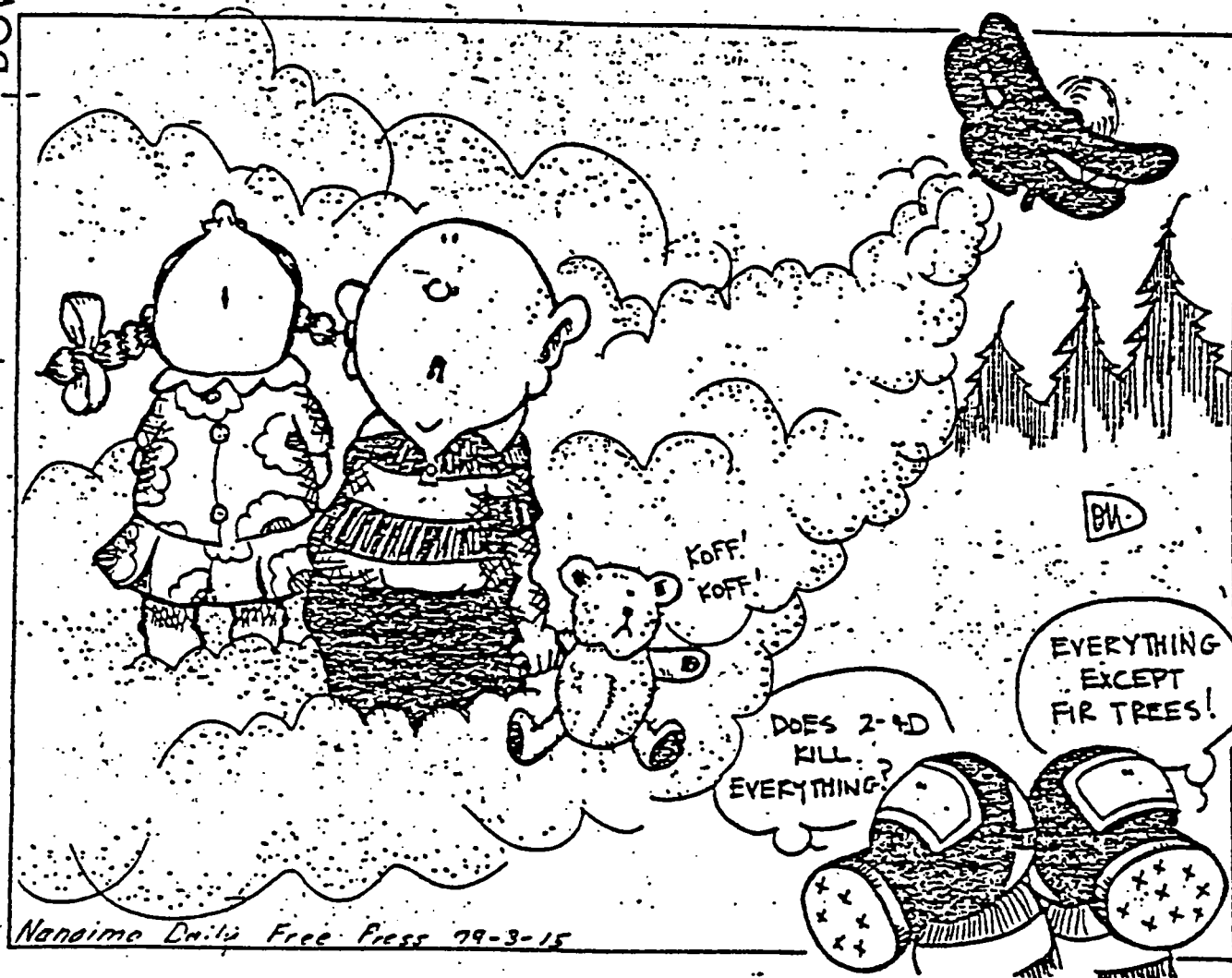
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/ECP
April 5, 1979

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An example of misleading editorializing by the press;
lack of objectivity and truthfulness.

ECOLOGICAL

FORMS OF LIFE IN RELATION TO ENVIRONMENT

OFFICIAL PUBLICATION OF THE
ECOLOGICAL SOCIETY OF AMERICA

ON THE
EVALUATION OF THE CARCINOGENIC RISK
OF CHEMICALS TO MAN:

Fumigants, the Herbicides 2,4-D and 2,4,5-T,
Chlorinated Dibenzodioxins and
Miscellaneous Industrial Chemicals

Volume 15

This publication represents the views of an
IARC Working Group on the
Evaluation of the Carcinogenic Risk of Chemicals to Man
which met in Lyon,
8-15 February 1977

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SCIENCE

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

Canadian Journal of Zoology

AGRONOMY JOURNAL

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Volume 68

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Volume 52 • Number 1
January 1974

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QUESTIONS FOR WHICH I SEEK ANSWERS AS A
FOREST ECOLOGIST AND POSITIVE ENVIRONMENTALIST

- . What effect will 2,4-D have on the function and specific components of the ecosystem?
- . What are the risks of 2,4-D in terms of: lethality, carcinogenicity, teratogenicity, mutagenicity, abortagenicity, embryotoxicity?
- . What are the hazards to man, animals and plants when 2,4-D is used normally?
- . What are the benefits and costs to society of the use of 2,4-D?
- . What are the alternatives?

MAJOR MISCONCEPTIONS CONCERNING 2,4-D

1. 2,4-D was developed for chemical warfare.
2. 2,4-D has been shown to have caused birth defects and cancer in Vietnam.
3. Because 2,4-D belongs to the phenoxy herbicide group it has the same contaminants and physiological effects - the family likeness syndrome.
4. 2,4-D accumulates in the environment and mammalian tissues.
5. The South Okanagan Environment Coalition's claim that "'The Other Face of 2,4-D' stands up to rigorous scientific scrutiny," is the best scientific document on 2,4-D and is fair.

(3a)

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DISCOVERY AND DEVELOPMENT OF 2,4-D

- 1880-1890 Darwin discovered plant growth toward light governed by tip.
- 1926 Frits Went discovered "auxin," a growth promoter.
- 1934 F. Kōgl discovered Indoleacetic acid (IAA), a growth promoter, in plant tissues.
- 1941 R. Pokorny reported 2,4-D and other chlorophenoxyacetic acids.
- 1941 Dr. E.S. Kraus suggested that growth stimulators be looked at for plant-killing ability.
- 1942 Dr. Kraus aware of crop-killing potential of growth regulators; advised U.S. National Academy of Sciences.
- 1943 Dr. Kraus reported formally to National Academy of Sciences on herbicides.
- 1944 U.S. Army, Camp Dietrick, herbicide research begun under direction of Dr. Kraus.
- 1944 Mrs. Fanny-Fern Davis began testing 2,4-D on turf (golf courses and parkways).
- 1944 2,4-D used on German grain field (unsuccessfully) to destroy alcohol source for V-2 rockets.
- 1945 Japan already producing 2,4-D commercially.

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1946 2,4-D introduced to North American farmer.

1968 U.S. 2,4-D production 36,000,000 kg.

1970 U.S. 2,4-D production 20,000,000 kg.

1974 U.S. 2,4-D production 27,000,000 kg-used as follows:

	<u>%</u>	<u>Million kg</u>
- wheat and small grains	31	8.4.
- corn and grain sorghum	26	7.0
- pasture and range	25	6.8
- industrial and commercial	9	2.4
- lawns and turf	5	1.4
- aquatic weed control	3	0.8
- rice and fruit	1	0.3

1975 Japanese 2,4-D production 511,000 kg.

European production (western) 3,000,000 to 30,000,000 est.

European production (eastern) <10,000,000 kg est.

HERBICIDE FORMULATIONS USED IN VIETNAMBY U.S. MILITARY^{1/}

<u>Formulation</u>	<u>Millions of Gallons (1965-1971)</u>	<u>Herbicides</u>	<u>Ratio</u>	<u>Conc., lb/gal</u>
Agent Orange	11.22	2,4-D:2,4,5-T	1:1	4 + 4.6
Agent White	5.24	2,4-D:Picloram	4:1	2 + 0.54
Agent Purple	-	2,4-D:2,4,5-T	1:1	-
Agent Blue	1.12	Cacodylic Acid		3.1 (1.7 lb is arsenic)

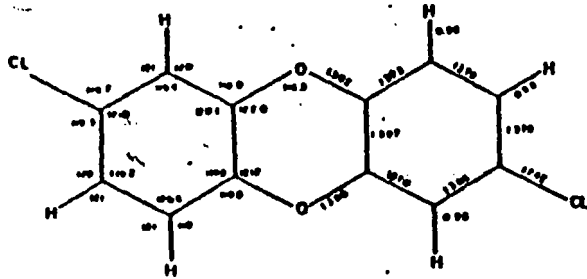
(Note: Agent Purple replaced by Agent Orange in 1964).

^{1/} From Council for Agricultural Science and Technology.
1975. Effects of herbicides in Vietnam and their
relation to herbicide use in the United States.
C.A.S.T. Report No. 46. 13 p.

PARTIAL LIST OF COMPOUNDS OF THE DIOXIN FAMILY

(Theoretically 75 isomers are possible - Blair 1973)

DCDD (May be in 2,4-D)



1-Chlorodibenzo-para-dioxin

2-Chlorodibenzo-para-dioxin

1,3-Dichlorodibenzo-para-dioxin

1,6-Dichlorodibenzo-para-dioxin

2,3-Dichlorodibenzo-para-dioxin

2,7-Dichlorodibenzo-para-dioxin DCDD

2,8-Dichlorodibenzo-para-dioxin

1,2,4-Trichlorodibenzo-para-dioxin

2,3,7-Trichlorodibenzo-para-dioxin

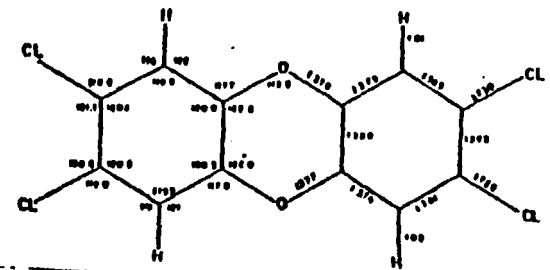
1,2,3,4-Tetrachlorodibenzo-para-dioxin

1,2,3,8-Tetrachlorodibenzo-para-dioxin

1,3,6,8-Tetrachlorodibenzo-para-dioxin

1,3,7,8-Tetrachlorodibenzo-para-dioxin

TCDD (Not in 2,4-D)



2,3,6,7-Tetrachlorodibenzo-para-dioxin

2,3,7,8-Tetrachlorodibenzo-para-dioxin TCDD

1,2,3,7,8-Pentachlorodibenzo-para-dioxin

1,2,4,7,8-Pentachlorodibenzo-para-dioxin

1,2,3,4,7,8-Hexachlorodibenzo-para-dioxin

1,2,3,6,7,8-Hexachlorodibenzo-para-dioxin

1,2,3,6,7,9-Hexachlorodibenzo-para-dioxin

1,2,3,7,8,9-Hexachlorodibenzo-para-dioxin

1,2,4,6,7,9-Hexachlorodibenzo-para-dioxin

1,2,3,4,6,7,8-Heptachlorodibenzo-para-dioxin

1,2,3,4,6,7,8,9-Octachlorodibenzo-para-dioxin OCDD

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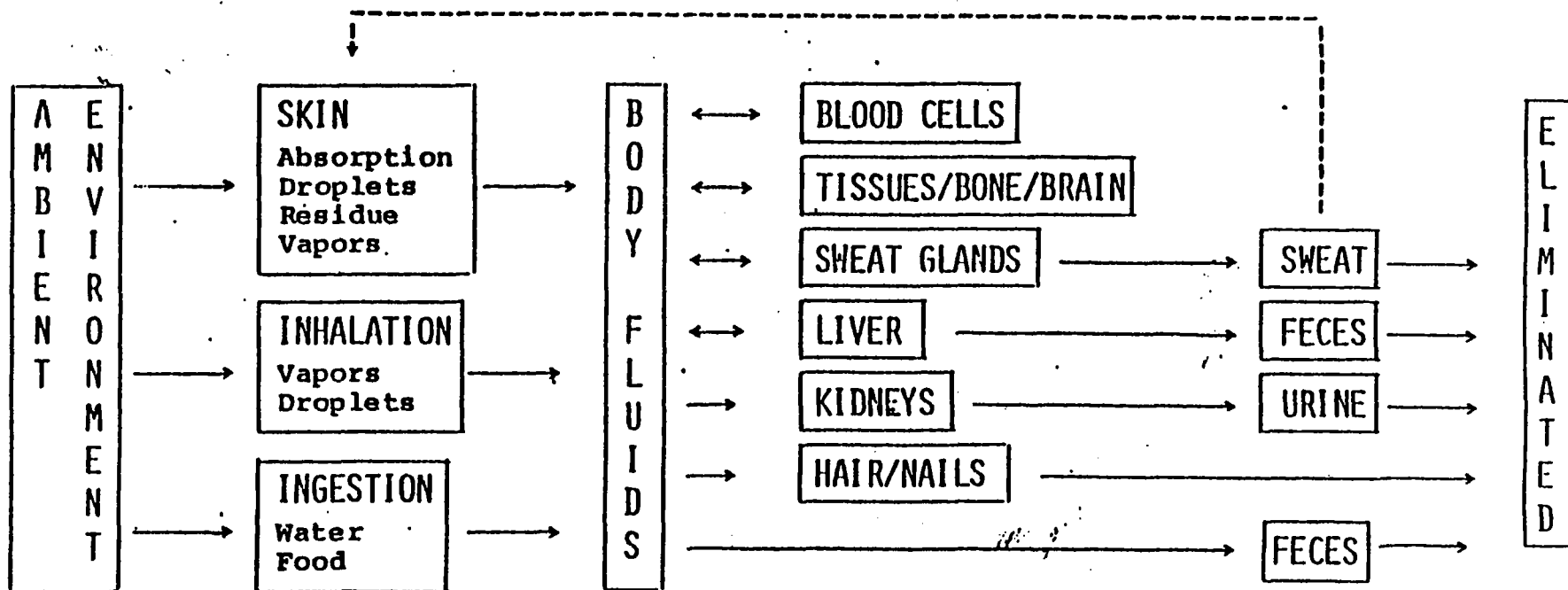
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NUMBERS OF ANIMALS SURVIVING AFTER VARIOUS TREATMENTSWITH OCDD AND DCDD (DIOXINS)^{1/}

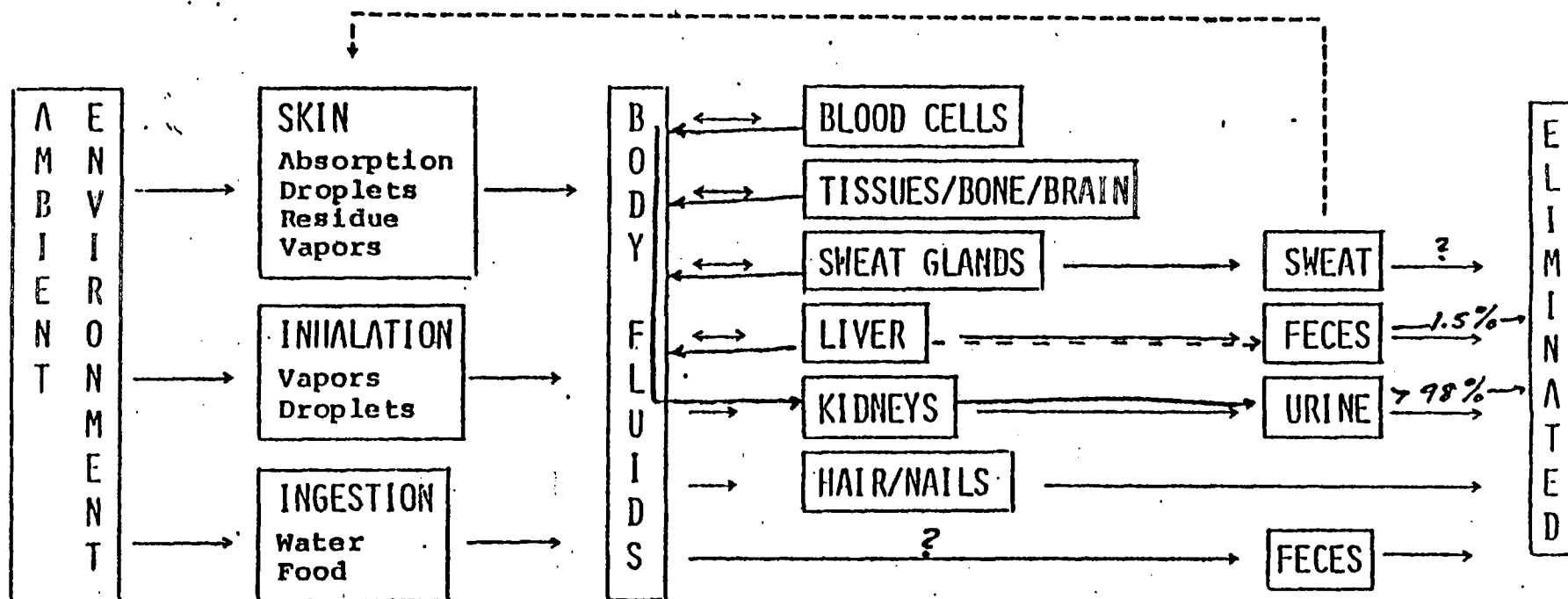
<u>Compound</u>	<u>Sex</u>	<u>Mice (50/group)</u>		<u>Rats (35/group)</u>	
		<u>Week of Test</u>	<u>No. of Survivors</u>	<u>Week of Test</u>	<u>No. of Survivors</u>
Controls	M	31	50	34	35
	F	31	50	34	35
1% DCDD	M	17	49	17	35
	F	17	48	17	35
0.5% DCDD	M	17	50	17	35
	F	17	49	17	35
1% OCDD	M	10	0	32	0
	F	37	5	22	0
0.5% OCDD	M	8	0	37	0
	F	37	45	25	0
0.25% OCDD	M	17	1	17	28
	F	15	0	17	15

^{1/} King, M.E., A.M. Skefner, R.R. Bates. 1973. Carcinogenesis bioassay of chlorinated dibenzodioxins and related chemicals. Environmental Health Perspectives 5:163-170.

HUMAN EXPOSURE PATHWAYS^{1/}



^{1/} Adapted from U.S. E.P.A. (Behar, J.V., E.A. Schuck, R.E. Stanley, G.B. Morgan. 1979. Integrated exposure assessment monitoring. Environ. Sci. and Tech. 13 (1):34-39).

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ATTENTION

AVOID WATER USE BETWEEN
SIGNS UNTIL FURTHER
NOTICE DUE TO HERBICIDE
TREATMENT

FOR MORE INFORMATION CALL VERN
MINISTER OF ENVIRONMENT PROTECTION

THE OTHER FACE OF 2,4D

A Citizens' Report



SOUTH OKANAGAN
ENVIRONMENTAL COALITION

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ACUTE TOXICITY RATING OF
SOME COMMON SUBSTANCES

	<u>Rating</u>	<u>Oral LD₅₀</u> <u>(Mg/Kg for Rats)</u>
Amphetamine	2	5
Aspirin	4	750-1750
Borax	5	5560
Caffeine	3	200
Ethyl Alcohol	4-5	450-13700
Gasoline	3	150
Gravol	4	500
Salt	4	3300
2,4-D	3	300-1000
Warfarin (rat poison)	1	1

CANCER TERMINOLOGY

<u>CANCER</u>	An abnormal and unrestrained growth in cells and tissues that produces deteriorious and often fatal effects.
<u>CARCINOGEN</u> (broad sense)	An agent capable of producing either benign or malignant tumors in a variety of tissues.
<u>CARCINOGEN</u> (strict sense)	An agent capable of producing a malignant tumor.
<u>MALIGNANT</u>	An inherent tendency of cells to invade the body widely and relentlessly, to become disseminated by subtle means, and eventually to kill the host unless all malignant cells are eliminated.
<u>BENIGN</u>	An inherent tendency of the cells to remain in contact with each other in one solid mass centered on the site of origin; a benign tumor can cause death purely by virtue of location.
<u>TUMORIGEN</u>	An agent capable of producing a tumor.
<u>ONCOGEN</u>	An agent capable of producing a tumor.

KNOWN CARCINOGENS

Carcinogen is used here in the broad sense.

Alkaloids (Tansey tea)	Liver tumors
Arsenic	Respiratory tract
Asbestos	Lung
Benzene	Leukemia
Chromium trioxide	Nasal and sinus cavities; larynx and lung
Ergot	Nerve tumors
Estrogen	Uterus; fibrous tumors
Sodium nitrite	Gastrointestinal
Tobacco	Lung; mouth and throat

	1250 ^{c/}		625		125		25		5		Control	
	M	F	M	F	M	F	M	F	M	F	M	F
Total number of rats	25	25	25	25	25	25	25	25	25	25	25	25
Rats with tumors	7	15	6	17	6	14	5	13	5	9	3	12
Rats with amlignant tumors	6	8	5	3	2	5	4	3	2	6	1	5
Pituitary adenoma	0	6	0	6	2	2	0	4	1	1	0	2
Pituitary adenocarcinoma	0	0	0	0	0	2	0	0	0	0	0	0
Mammary fibroadenoma ^{a/}	0	7	0	12	0	8	0	8	0	3	0	7
Mammary adenoma	0	1	0	0	0	0	0	0	0	0	0	0
Mammary adenocarcinoma ^{a/}	0	7	0	2	0	2	1	3	0	4	0	3
Fibroma	1	0	0	0	0	0	0	0	0	0	0	0
Fibrosarcoma ^{b/}	2	0	2	0	1	0	0	0	1	2	1	0
Lymphosarcoma	2	0	3	0	1	0	3	0	1	1	0	0
Endometrial sarcoma	0	1	0	0	0	0	0	1	0	0	0	1
Interstitial cell tumor	0	0	2	0	1	0	1	0	1	0	2	0
Hemangiosarcoma (ovary)	0	1	0	0	0	0	0	0	0	0	0	1
Granulosa cell carcinoma (ovary)	0	1	0	1	0	0	0	0	0	0	0	0
Aednocarcinoma (pancreas)	0	0	0	0	1	0	0	0	0	0	0	0
Adenocarcinoma (lung)	1	0	0	0	0	1	0	0	0	0	0	0
Adenoma of liver	0	0	1	0	0	0	0	0	0	0	0	0
Adenocarcinoma of thyroid	1	0	0	0	0	0	0	0	0	0	0	0
Adenoma of adrenal	0	0	0	1	0	0	0	2	1	3	0	0
Adenoma of lung	0	0	0	1	0	0	0	0	0	0	0	0
Hemangioma of ovaries	0	0	0	0	0	0	0	1	0	0	0	0

^{a/} Only one rat mammary tumor counted when multiple.

^{b/} Only one fibrosarcoma counted when multiple.

^{1/} Hansen et al. 1971.

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KNOWN HUMAN CELL CLASTOGENS

<u>AGENT</u>	<u>SOURCE</u>
Aflatoxin	Peanut butter
Benzopyrene	Burnt toast
Caffein	Coffee, tea, cola drinks
Cyclamate	Artificial sweetener
Methanol ?	Food seasoning
Monosodium glutamate ?	Herbicide
2,4-D	Cigarettes, Cigars
Tobacco Smoke ?	

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2,4-D in Diet (ppm)	Number of Females Mated	Fertility ^{a/} %	Number of Pups Born	Litter Size ^{b/}	Pups Weaned		Number of Pups Lost or Dead	Weaning Weight(g)	
					Number	%		Female	Male
F _{1a} Generation									
0	19	100		9.6	177	97	5	33.8	32.5
100	19	95		11.4	159	78	46	30.1	28.9
500	20	95		10.5	119	60	80	32.8	30.5
1500	18	100		8.1	73	50	72	24.5	21.7
F _{1b} Generation									
0	20	100		9.3	130	70	55	36.6	35.7
100	19	100		11.2	160	75	53	41.6	38.2
500	19	95		9.9	127	71	51	35.6	33.4
1500	17	100		8.4	28	20	114	26.0	24.7
F _{2a} Generation									
0	19	100		8.4	147	92	12	38.5	38.1
100	20	100		9.5	142	75	47	40.8	37.8
500	20	100		10.4	193	93	14	37.3	34.3
1500	2	100		8.0	10	38	6	31.1	31.1
F _{2b} Generation									
0	18	100		8.5	120	78	33	41.3	39.7
100	20	100		9.8	168	86	28	38.5	37.2
500	20	100		10.6	163	77	49	33.7	32.1
1500	3	67		11.0	14	36	8	31.1	35.0
F _{3a} Generation									
0	20	90		9.9	169	95	9	37.6	36.1
100	20	85		11.2	170	89	21	38.4	35.4
500	20	100		10.6	173	82	39	38.5	38.4
1500	4	100		11.5	33	62	13	30.7	28.3
F _{3b} Generation									
0	20	95		11.6	188	85	32	52.0	49.1
100	20	70		12.4	133	76	41	49.3	46.9
500	20	100		10.9	182	84	35	45.3	42.0
1500	4	100		11.3	28	62	17	32.4	35.1

^{a/} Number of litters/numbers of females mated x 100.

^{b/} Mean values.

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KARNOFSKI'S LAW

ANY DRUG ADMINISTERED

AT THE PROPER DOSAGE,

AT THE PROPER STAGE OF DEVELOPMENT

TO THE EMBRYOS OF THE PROPER SPECIES,

WILL BE EFFECTIVE IN CAUSING DISTURBANCES

IN EMBRYONIC DEVELOPMENT.

SOURCE: WILSON 1972.

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DRUGS AND CHEMICALS
THAT CAUSE BIRTH DEFECTS
IN AT LEAST ONE SPECIES OF
LABORATORY MAMMAL^{1/}

SALICYLATES (Aspirin, oil of wintergreen)
 CERTAIN ALKALOIDS (Caffeine, Nicotine)
 TRANQUILIZERS (Meprobamate, Chlorpromazine)
 ANTIHISTAMINES (Buclizine, Meclizine, Cyclizine)
 ANTIBIOTICS (Chloramphenacol, Streptonigrin, Penicillin)
 ANESTHETICS (Nitrous Oxide, Pentobarbital)
 SOLVENTS (Benzene, Dimethylsulfoxide/DMSO, Propylene Glycol)

^{1/} Wilson, James G. 1972. Address presented to 25th Annual Meeting Southern Weed Science Society. 4 p. (Dr. Wilson is with Children's Hospital Research Foundation and Departments of Pediatrics and Anatomy, University of Cincinnati, College of Medicine)

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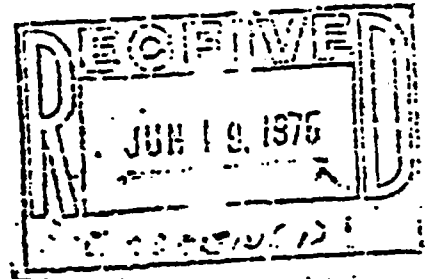
RATS & MICE RELATIVELY AN INSENSITIVE
ANIMAL TO TERATOGENS. WIDELY WRITTEN
UP IN MEDICAL & SCIENTIFIC LITERATURE.

DRAFT MANUSCRIPT

FOR OFFICIAL USE ONLY

PRENATAL EFFECTS OF HERBICIDES: EVALUATION BY THE PRENATAL DEVELOPMENT INDEX

→ K. Diane Courtney²



CLEFT PALATES
FROM 2,4-D

¹ Presented in part at the 15th Annual Meeting of the Teratology Society,
May 11-14, 1975, Pennsylvania.

² Pesticides and Toxic Substances Effects Laboratory
Environmental Protection Agency
Research Triangle Park, North Carolina 27711

RUNNING TITLE: Herbicides: Prenatal Development Index

TABLES: 9

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KEY WORDS: Teratology, Herbicides, 2,4,5-T, 2,4-D, Silvex, Agent Orange,
Phenoxyacetic Acid Esters, Fetal Toxicity, Prenatal Development,
Prenatal Development Index.

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DRAFT MANUSCRIPT (CD-1 MICE)

NOTE: PREGNANT MICE FED { 2,4,5-T }
NOT EARLIER THAN DAY 10 { 2,4-D }
OF GESTATION PERIOD. SILVEX
TOO LATE TO PRODUCE BIRTH DEFORMITIES
OF LIMBS WHICH WOULD HAVE BEEN OBSERVED

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DOW

AGENTS DEMONSTRATED TO CAUSE BIRTH DEFECTS

IN LABORATORY MICE

<u>Agent</u>	<u>Defect</u>	<u>Source</u>
Airplane ride	Cleft palate	Brown, et al. 1970
24-hour fast		Kalter and Warkany 1959
Movement limitation	Cleft palate	Rosenzweig & Blaustein 1970
Subcutaneous sodium chloride		Nishimura & Miyamoto 1969
5°C temperature change		Davis 1979
2,4-D	Cleft palate	Courtney 1977
Water deprivation	Cleft palate	Schwetz, et al. 1977
Raisin diet 1 day	Cleft palate	Peters & Strassburg 1969
Loud noises		Davis 1979

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Ban spraying after Madison child affected

MADISON, Wis. (AP) — The weed killer 2,4-D was temporarily banned by city officials Wednesday after a child, whose father had been exposed to Agent Orange in Vietnam, had what his parents called a seizure while a Parks Department crew sprayed the herbicide.

The moratorium was issued by parks superintendent Daniel R. Stapay after officials were notified that Zachary Wachtendonk, 21 months, became ill when the herbicide was sprayed in a park near his home.

The child was treated and discharged from University

Hospitals.

James Wachtendonk said his son suffered the seizure just after his wife Mary detected a chemical smell in their home.

"I've never seen Zachary in that shape in my life," Wachtendonk said.

"I can handle what happens to me because I'm an adult, but I can't stand it when it happens to them. It's chemical genocide," he said.

Wachtendonk said his son is seizure-prone as the result of birth defects, and that he had an ear infection Wednesday which may have lowered his resistance.

Nevertheless, he said he feels the chemicals triggered the seizure.

Wachtendonk said he was "frantic" after the herbicide was sprayed near his home and said he may sell his home.

"I don't know if a safe place exists," he said.

Wachtendonk, 30, said he was sprayed with Agent Orange on

at least three occasions while serving as a scout in Vietnam.

Agent Orange, used to defoliate jungle growth that concealed enemy soldiers, contains chemicals which are blamed by many Vietnam War veterans for causing ill health and affecting their offspring.

Wachtendonk said he and his wife believe the chemical was responsible for his nervous system problems and the congenital problems of Zachary and their daughter, Reeanne, 3.

Countywide ban on 2,4-D to be sought in Madison

Milwaukee Journal 10/10/80

Special to The Journal

MADISON, Wis. — Lynn Haanen, a member of the Dane County Board, said Thursday that she would introduce resolutions in the County Board and the Madison City Council calling for a moratorium on the use of the herbicide 2,4-D.

Haanen's request for the moratorium was issued Thursday after Zachary Wachtendonk, 21 months old, had a seizure Wednesday while a city park attendant was spraying the weed killer in Warner Park, near the child's home.

The boy's father, James, was exposed to Agent Orange, another herbicide, in Vietnam. He believes it is responsible for his nervous sys-

tem problems and for congenital problems of Zachary and a daughter, Reeanne, 3.

The Environmental Protection Agency has issued a report saying that there is a "significant gap" in the information on the effects of the 2,4-D on human beings.

Haanen's resolution calls for discontinuance of the use of the chemical in Madison and Dane County until the EPA issues "conclusive evidence as to its safety."

Madison Mayor Joel Skornicka had already ordered a moratorium on the chemical's use, at least until the Madison Health Department issues a report on the herbicide's safety. Susan

Springman, an aide to the mayor, said Skornicka might keep the ban in effect even after the Health Department report was issued. He would then await EPA findings.

According to Haanen, the chemical has been used in all Madison parks, although Springman said Skornicka had been unaware of that until Wednesday.

Dennis Kroll, of the Vietnam Veterans Against the War, criticized the chemical's use in parks.

"I think it is insane to spray parks with a chemical that causes nerve damage, cancer and

birth defects, especially in a place where people send their kids to play," he said.

Haanen said she is optimistic about the passage of the measure in both the County Board and the City Council.

The Wachtendonk child was treated and discharged from University Hospital Wednesday.

Wachtendonk said his son suffered the seizure just after his wife Mary detected a chemical smell in their home.

"I've never seen Zachary in that shape in my life," Wachtendonk said.

"I can handle what happens to me because

Turn to Herbicide, Page 5

Herbicide

2,4-D ban asked

From Page 1

I'm an adult, but I can't stand it when it happens to them. It's chemical genocide," he said.

Seizure-prone

Wachtendonk said his son was seizure-prone as the result of birth defects, and that he had an ear infection Wednesday which might have lowered his resistance.

Nevertheless, he said, he feels the chemicals triggered the seizure.

May sell home

Wachtendonk said he was frantic after the herbicide was sprayed near his home and said he might sell his home.

"I don't know if a safe place exists," he said. Wachtendonk, 30, said he was sprayed with Agent Orange on at least three occasions while serving as a scout in Vietnam.

Agent Orange contains chemicals which are blamed by many Vietnam War veterans for causing ill health and affecting their offspring.

Mrs. Wachtendonk said her son had had problems at other times in the past when people in their neighborhood had lawns sprayed for weed control.

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Public intervenor urges dialogue between farmers, environmentalists

Environmentalists should "open the door of dialogue" with farmers, according to Wisconsin's public intervenor, because many farmers are equally concerned with the adverse effects of pesticide use.

Thomas Dawson spoke to about 15 people Sunday night during a meeting of the Central Wisconsin Citizens Pesticide Control Committee at the Sentry Auditorium.

"Farmers are not your adversaries on this issue," Dawson said. "Farmers are concerned about their land, about surface water from which their cattle drink and they irrigate, they are concerned about the ground water from which their families drink and they irrigate, about their children, about rising costs of pesticides and about pests that are building immunities to pesticides."

Environmentalists should realize that "there is pressure on farmers not to speak out," Dawson said, adding that farmers are beginning to contact the public intervenor's office for help.

"We must reach out to them too," he said.

But Dawson said a distinction must be made between farmers

and "agri-industrialists."

"A lot of family farmers are concerned. There are more lawsuits filed by farmer against farmer (for pesticide misuse) than any other group," he said.

One farmer, a member of the state Department of Agriculture, Trade and Consumer Protection Board, suggested instituting buffer zones, a concept that is advocated by environmentalists, Dawson said.

He said Integrated Pest Management, another concept strongly espoused by environmentalists, is the salvation of family farms.

"Otherwise they will be doomed to the huge agri-industrialist complexes," Dawson said. "We need, not to preach to farmers, but to open dialogue. We have to keep that door open, especially with farmers that are on the fence."

Despite advances being made through the proposed revisions to the state's pesticide rules, major issues still remain, Dawson said, and the issues must be addressed during the agriculture department's public hearings this fall.

(Hearings will be held at Stevens Point Area Senior High School Nov. 12 and 13).

An overall issue, Dawson said, is whether the state's proposed rules will protect the health and environment in the state.

"The rules are an attempt to throw a bone to environmentalists and the farming communities. We don't know the full impacts of pesticide use, yet we are expected to constantly show harm and this, as a matter of public policy, is wrong," Dawson said.

He said the burden of proving safety should be on the industry, rather than putting the burden of proving harm on the victim.

Another issue is the extent of public participation in policymaking, Dawson said. The two ways to be heard, he said, are through testimony at the public hearings or through direct contact with the Agriculture Board. But people who wish to address the board must give notification at the hearings.

"Even then, the board may choose to hear you only in writing," Dawson said. "We need constant pressure on the agriculture department to open up the process."

The public has a right to basic data on pesticide use in the

state, Dawson said, and the record keeping provisions in the proposed rules need to be strengthened.

"We don't know what is being used, how much, where, who is using it or how it's applied," he said. "The Wisconsin public will not demand action be taken until they know these facts."

He said the agriculture department is resisting strict record keeping provisions because it says it would be a "bureaucratic hassle" and there is insufficient staff time.

The department is contemplating taking a survey of pesticide use, Dawson said, and the public must demand that enough expertise be included to assure accuracy.

"We also need to know the human health effects, the environmental effects, the effect on streams, ground water, air quality and wildlife. We need to know the effects on agriculture. We need to know about long and short term effects on crops. We are hearing about pests becoming super bugs that are resisting pesticides. We are hearing of effects on livestock," Dawson said.

An alternative to current (See pesticides page 2)

pesticides

(Continued from page 1)

pesticide use is Integrated Pest Management, he said, and that concept should be included in the pesticide rules.

Although the agriculture department seems to be learning toward advance notification of adjacent landowners of pesticide application, it has refused to discuss buffer zones and wind speed standards, Dawson said. It also has neglected to provide alternative proposals.

Liability for violations should be the same for drift and overspray, he said, and the rules should include mandatory sanctions and adequate enforcement standards, including license and registration suspension and revocation.

In other action, the pesticide control committee re-elected the following officers: Mary Ann Krueger, chairman; Ken Gray, vice chairman; Maureen Fazen, secretary and Arvella Joost, treasurer.

The committee also went on record expressing concern over the quality of the research being conducted on aldicarb in the ground water of the Central Sands area, and it went on record supporting Dawson's proposal for including Integrated Pest Management in the administrative rules.

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M. C. FOONG HNGKM
CC: S. ANDREWS MARCM 2030
E. TANG HNGKM
Y. KUFCTA HNGKM
J. DRENCKPOHL BICPM 9008

BCC: R. F. KINCAID CORPM
2030

2,4,5-T / ESTERON TRADEMARK

I HAVE HAD SEPARATE DISCUSSIONS WITH STEPHEN ANDREWS, JOHN
DRENCKPOHL AND BOB KINCAID ON THE ABOVE SUBJECT.

CPS'S VIEW IS THAT THE ESTERON TRADEMARK IS TO BE USED ON 2,4,5-T
PRODUCTS ONLY. WE CANNOT SUPPORT THIS TRADEMARK BEING USED FOR MCPA.

YOUR USE OF ESTERON TRADEMARK FOR 2,4,5-T PRODUCTS SUCH AS ESTERON
HI ESTER T, ESTERON 2,4,5-T BUTYL ESTER AND ESTERON BRUSHKILLER 404
ARE VERY CLOSE AGREEMENT. STEPHEN WILL ANSWER SEPARATELY. TO SHOW
HOW CLOSE YOU ARE, HE IS GOING TO SUGGEST ESTERON 404 BRUSHKILLER,
IF PRACTICABLE.

KNOWING THAT YOU HAD PREVIOUSLY SOLD ESTERON BRUSHKILLER AND THAT
BECAUSE YOU NOW HAVE TO RE-SOURCE CN IWD FOR A DIFFERENT FORMULATION,
YOU HAVE ALSO GOOD REASONS TO USE ESTERON BRUSHKILLER 404. THIS
WILL TELL USERS THIS IS ESTERON BRUSHKILLER BUT WITH A SMALL DIFFERENCE.

I HAD THE OPPORTUNITY OF GIVING STEPHEN MORE BUSINESS BACKGROUND. HE
WILL RESPOND TO YOU MORE FULLY AND NO DOUBT SOME PRACTICAL SOLUTIONS
WILL BE OFFERED.

IF I CAN BE OF FURTHER HELP, PLEASE DO NOT HESITATE TO CONTACT ME.

BEST REGARDS.

ANTHONY LEE CPD 2030
1-31-80 IK CORPM

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THE FERTILIZER COMPANY OF AMERICA, INC. 28749
FERTILIZER DIVISION

PAGE: 1

PRODUCT CODE: 28749 GAC: 28749 PESTICIDE: 28749 SUBSEQUENCES: 4 JUN 79

NAME: ESTERON (H) 245 HERBICIDE

DESC: ESTERON, GAC, FERTILIZER DIVISION

APPL: 28749 SUBS: 28749 PESTICIDE: 28749

ESTERON, GAC, FERTILIZER DIVISION

ESTERON, GAC, FERTILIZER DIVISION

FRUIT: 28749 U.S. 28749

WEIGHT: 31

TEST: 28749 : UNIT : LBS/GAL : TEST METHODS

2,4,5-TRICHLOROETHYLENE

ACETIC (2,4,5-TRICHLORO)

PROPYLENE GLYCOL ETHYLENE

ETHER SULFONATES, 28749

2,4,5-TRICHLOROETHYLENE

2,4,5-TRICHLOROETHYLENE

2,4,5-TRICHLOROETHYLENE

INERT INGREDIENTS

2,3,7,8-TRICHLORODIBENZO-

P-DIOXIN

2,4,5-TRICHLOROETHYLENE

*EMULSION CREAM RATE @ 1

HR.

* 100 PPM HARD WATER

* 500 PPM HARD WATER

ML

ML

0.3 MAX.

0.2

AG 15E-2

DOW0730290

THE IGA CHEMICAL COMPANY QUALITY ASSURANCE
PRODUCTION SPECIFICATION

28749
PAGE: 2

PRODUCT CODE: 28749 (CONTINUED)
NAME: HYPER-101 2-5 CHEMICAL

TEST ITEM	UNIT	LIMITS	TEST METHODS
---PAC MATERIALS--- (CONTINUED) ---PAC SPEC CASE---			

*POLYMER-COL 59-13			024938-91-R
*EACOL (CONTINUED) 31-2			IND
*KEROSENE			008008-20-6
*2,4,5-T ACID, FREE ESTER			027613-72-5

PI: 1773311 FISC. SAMPLE
PI: 1772514 1 x 1 GAL CAN
PI: 1175514 5 GAL PAIL
PI: 1175514 40 GAL DRUM
PI: 1175515 55 GAL DRUM
PI: 2137225 5 GAL PAIL (SPANISH LABEL)
PI: 1775517 55 GAL DRUM (SPANISH LABEL)

PRODUCT CODE:
(1) REVISION 2 SEP 80 TO CHANGE TEST METHOD NAME FOR EMULSION CREAM RATE.
(2) DELETED TO DELETE BATCH FORMULA FROM TEST ITEM SECTION.
(3) NO FURTHER PRODUCTION EXPECTED OF THIS PRODUCT. QUANTITIES ON HAND TO BE SOLD UNTIL SUPPLY DEPLETION.
(4) FORMULATION IS #3506.

PRODUCTION SPEC APPROVERS:

W.L. GOLD GAC 29 AUG 80
W.F. KRACHT METHODS 22 APR 80
S.J. ULSTAD PROD. 7 APR 80
J.R. GLENNIE ACPL 24 APR 80
J.S. JONES GAC/QAA 29 AUG 80
E.J. KING PAC 25 JUN 80(2)
C.D. JONES FSC 18 JUN 80
J.M. PRASER G.A. DEPT. 2 SEP 80

APPROVALS	DIV-DEPT	DATE	APPROVALS	DIV-DEPT	DATE

PRODUCTS NOT MEETING THIS SPECIFICATION MUST NOT BE SHIPPED
UNLESS AUTHORIZED BY SALES AND PRODUCTION MANAGEMENT
* * * * * (CONTINUED) * * * * * LAST PAGE

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COMPARATIVE TOXICOLOGY OF VARIOUS CHLORINATED DIOXINS
AS RELATED TO CHEMICAL STRUCTURE *

Marguerite L. Leng

Health and Environmental Sciences
The Dow Chemical Company
Midland, Michigan
U.S.A. 48640

SUMMARY

The generic term "dioxin" pertains to a family of compounds which are structurally similar but vastly different in toxicity. It is often used incorrectly to designate one member of the family, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). There are 75 possible polychlorinated dibenzo-p-dioxins (PCDDs) with a million-fold spread in the dosage level required to kill laboratory animals. Those with four or five chlorines located at all four lateral positions (2,3,7 and 8) are extremely toxic. The toxicity is progressively decreased by moving one or more chlorines to peri positions (1,4,6 or 9), and/or by having fewer or more positions substituted. Data are reviewed from a number of studies demonstrating this relationship. The relative hazard from potential exposure to the highly toxic 2,3,7,8-TCDD is also discussed.

FORMATION OF DIOXINS

Low levels of polychlorinated dibenzo-p-dioxins (PCDDs) can be formed as byproducts during the manufacture of chlorophenols under alkaline conditions at elevated temperatures and high pressures. The reaction is a two-step process involving bimolecular condensation of chlorophenates followed by internal ring closure. The number and position of the chlorine substituents on the dioxins depend on the chlorophenates present in the reaction mixture.

For example, trace amounts of the highly toxic 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) are formed during the manufacture of 2,4,5-trichlorophenol by alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene (Figure 1). This TCDD can be carried through into products made from 2,4,5-trichlorophenol, such as 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and hexachlorophene [2,2'-methylene bis (3,4,6-trichlorophenol)]. Similarly, condensation of 2,4,6-trichlorophenolate during its manufacture under alkaline conditions produces the expected 1,3,6,8-TCDD, as well as the isomeric 1,3,7,8-TCDD by Smiles rearrangement (Figure 2). On the other hand, the expected 2,7-dichloro isomer is not likely formed by condensation of 2,4-dichlorophenolate under the acid conditions used in its manufacture by chlorination of phenol (Figure 3).

* Presented at symposium of Collaborative International Pesticide Advisory Council (CIPAC), Baltimore, Maryland, June 7, 1979

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In all, 75 possible PCDDs could originate from condensation of chlorophenols with two to five chlorine substituents (Table 1). Of these, 22 are tetrachloro isomers. However, as shown in Figures 1, 2 and 3, only symmetrically substituted isomers with an even number of chlorines are likely to be formed from reaction mixtures containing predominantly one chlorophenol such as in manufacturing processes.

Other isomers could also result from progressive chlorination or dechlorination of lower or higher analogs (Figure 4). However, photolysis in solution appears to preferentially remove chlorines from the lateral positions (Buser and Rappe, 1978). Thus isomers substituted at the 2,3,7,8-positions are not likely to be formed from higher PCDDs by the action of light.

TOXICOLOGY OF CHLORODIOXINS

Acute Oral Toxicity

The acute oral toxicity of several PCDDs has been investigated in guinea pigs, rats and mice (Schwetz et al., 1973; McConnell et al., 1978b). Table 2 lists the amount of chemical which would be expected to cause death of 50% of the animals within 30 days after administration of various isomers as a single dose by stomach tube in each species which has been tested. (Large numbers mean low toxicity and small numbers indicate high toxicity.) In all cases, guinea pigs were more sensitive than rats, and rats were more sensitive than mice.

The degree of toxicity is highly dependent on the number and position of the chlorine atoms. The lateral positions at 2,3,7 and 8 must be chlorinated to achieve the greatest toxicity. Additional chlorine atoms at the peri positions 1,4,6 and 9 reduce toxicity but not nearly to the degree caused by deletion of one or more chlorines at the lateral positions.

The toxic symptoms produced by single doses of the various isomers are similar if not identical -- the only difference is the amount of the isomer required to produce a given effect. The effects of single lethal doses of TCDD in guinea pigs, mice and female monkeys are compared in Table 3 (McConnell et al., 1978a,b; Moore 1978). Typically there was an almost immediate dose-related effect on body weight, with loss of up to 50% in weight prior to death. Only monkeys exhibited cutaneous lesions comparable to the chloracne observed in humans, such as in some of the children accidentally exposed to TCDD following a runaway reaction in a trichlorophenol plant at Seveso in Italy in 1976 (Reggiani, 1978).

Enzyme Induction

The ability of various PCDDs to induce enzyme production is also correlated to structure in much the same way as acute toxicity. The 2,3,7,8-TCDD has been shown to be a potent inducer of δ -aminolevulinic acid

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synthetase (ALA) and aryl hydrocarbon hydroxylase (AHH). ALA is the rate limiting enzyme in the synthesis of heme and porphyrins while AHH is an enzyme which catalyzes hydroxylation of compounds such as benzo[a]pyrene, a known carcinogen in humans.

The effect of PCDDs on these enzyme systems has been investigated by injection of p-dioxane solutions of 15 congeners into chick embryos (Poland and Glover, 1973b). Data outlined in Table 4 show a well-defined structure-activity relationship, requiring halogen atoms in at least three of the four lateral positions and at least one nonhalogenated ring position to cause induction of both enzymes in chick livers. The 2,3,7,8-TCDD has been reported to be at least three orders of magnitude more potent than any other compound known to produce experimental porphyria (Poland and Glover, 1973a). However, there was no significant increase in ALA synthetase activity nor porphyrin accumulation in mice given four weekly doses of 1 or 5 µg/kg TCDD (Goldstein et al., 1973).

Induction of AHH by 23 halogenated isomers has also been studied in vitro using rat hepatoma cell cultures (Bradlaw et al., 1976). Table 5 compares the concentration in picomoles required to cause 50% of maximum induction of AHH activity in this system.

The dose-response relationship for 2,3,7,8-TCDD induction of AHH in liver of female rats has also been studied (Kitchin et al., 1978). The single oral dose ED₅₀ was 0.62 µg/kg and the lowest dose which significantly increased AHH activity was 0.002 µg/kg. Radiotracer experiments using ³H-TCDD indicated that 1.1% of this minimal dose was incorporated per gram of liver at 3 days after administration. The authors estimated that this amounted to about 65 molecules per hepatocyte. Induction of AHH activity per se may not be a toxic response, but its correlation with toxicity suggests that this response is in some way a clue to the mechanism of the toxic action of 2,3,7,8-TCDD and its congeners (Poland and Goyer, 1978).

Chick Edema Disease

An extensive outbreak of a disease in broiler chickens in 1957 led to the discovery that PCDDs in toxic fat added to feed could cause excessive fluid to collect in the heart sac (pericardium) and the abdominal cavity of chicks (Firestone, 1973). Table 6 summarizes the results of bioassays for chick edema in which the test chemicals were fed to chicks for 21 days beginning at 3 days of age (Schwetz et al., 1973). Positive effects were produced by 2,3,7,8-TCDD at 1 and 10 µg/kg per day, and by mixed hexachloro isomers at ten times these levels, with all chicks dying at the higher dose in each case. On the other hand, little effect was produced by the octachloro isomer, even at 0.5% in the diet equivalent to about 500 mg/kg/day.

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Chloracne

Classical chloracne is a hallmark of exposure to certain PCDDs in humans (IARC 1978). It is a form of acneform dermatitis which is occupationally related to the manufacture of chlorophenols, chloronaphthalenes, polychlorinated biphenyls (PCBs), and related compounds. A bioassay to evaluate the potential for a substance to cause chloracne is conducted by painting solutions of the test substance on the inner ear of rabbits and observing the degree of hyperkeratosis produced.

Table 7 summarizes the results obtained with PCDDs containing from two to eight chlorines. A solution containing 0.04 ppm 2,3,7,8-TCDD caused a positive response when 0.1 ml was applied five days per week for four weeks. However, a concentration of 5000 ppm was needed to elicit a positive response with a mixture of 1,3,6,8 and 1,3,7,9-TCDDs (Dow unpublished data). The reaction produced by a 10 ppm solution of mixed hexachloro isomers was likely due to the presence of isomers substituted at three or four key positions. The 2,7-dichloro and octachloro isomers were negative when tested as chloroform extracts from 10% suspensions indicating they have little or no acnegenic activity (Schwetz et al., 1973).

Fetotoxicity and Teratogenicity

The relative potential of several PCDDs to cause teratogenic or fetotoxic effects has also been studied. In these investigations, the chemicals were administered to pregnant animals by stomach tube daily during the critical period of development of the fetuses. In rats, this was generally on days 6 through 15 or 16 of the 21 day gestation period. Table 8 compares the findings in studies conducted in rats in Canada (Khera and Ruddick 1973) and by Dow (Schwetz et al., 1973; Sparschu et al., 1971). The absolute values for 2,3,7,8-TCDD in the two studies depend on the strains of animals used and on minor differences in experimental conditions. It is apparent that the 2,7-dichloro and the octachloro isomers are relatively innocuous. The potential for 2,3,7,8-TCDD to cause fetotoxic effects is relatively great, provided there is significant exposure to this specific isomer.

Effects in Monkeys

Studies have also been conducted in a limited number of female monkeys. The results of three studies by Allen's group in Wisconsin are summarized in Table 9 for 15 adults fed 2,3,7,8-TCDD at 500 parts per trillion (ppt) in the total diet for 9 months (Allen et al., 1977; Barsotti et al., 1979), or at 50 ppt for up to 2 years (Schantz et al., 1979); and for two juveniles fed the 1,2,3,6,7,8-hexa isomer at 5000 ppt for up to 10 months (Allen et al., 1979).

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Preliminary data have also been reported for a study in Oregon where eight pregnant monkeys were given 2,3,7,8-TCDD by intubation three times per week for three weeks with little or no food during the critical stages of gestation (McNulty, 1978). Total doses administered ranged from 0.2 to 5 ug/kg of body weight as nine relatively large doses at two to three day intervals. These were equated by the author to levels of 200 to 5000 parts per trillion in the diet (Table 10). However, the effects from individual large doses without food are likely exaggerated compared to what might occur from slow assimilation of the same total dose from the diet.

Carcinogenicity Studies

The International Agency for Research on Cancer (IARC, 1978) listed 24 ongoing long-term carcinogenicity studies on PCDDs (Table 11). To date, only two of these studies have been reported (Kociba et al., 1978; NCI, 1979).

The results of bioassays conducted with 2,7-DCDD in rats and mice were reported recently by the U.S. National Cancer Institute (Table 12). Under the conditions of the study, it was not carcinogenic at 5000 or 10,000 parts per million in the diet of rats of either sex or for female mice. The marginal increased incidence of combinations of tumors in only male mice was considered "suggestive" of a carcinogenic effect in these animals. Thus, 2,7-DCDD has an extremely weak potential for causing cancer (NCI, 1979).

Table 12 also summarizes the results of an extensive study by Dow on 2,3,7,8-TCDD in a total of 472 rats of both sexes (Kociba et al., 1978). It is interesting that continuous administration of TCDD at 0.1 ug/kg/day for 2 years caused an increased incidence of tumors in the liver, lungs, palate, nasal turbinates and tongue, and a dramatic decrease in the incidence of tumors in mammary glands, uterus, adrenals, pituitary and pancreas compared to the normal incidence for these sites in Sprague Dawley rats.

Positive findings were also reported for TCDD in rats in a study conducted by Allen's group at the University of Wisconsin (Van Miller et al., 1977). However, they used only 10 male animals per dosage level and their experimental design was deficient in many respects. Thus, their conclusions about effects produced at dosage levels below 1000 ppt TCDD in the diet are not valid (U.S. EPA, 1979).

Mutagenicity Studies

Available data on the genetic toxicology of chlorinated dibenzo-p-dioxins have been reviewed (Wassom et al., 1977/1978). No definite conclusions could be made about potential mutagenicity since only four compounds were evaluated: unsubstituted dibenzo-p-dioxin, the 2,7-dichloro isomer,

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2,3,7,8-TCDD, and the octachloro isomer. However, the positive mutagenicity and cytological effects reported seemed to depend on the position of chlorine substitution, and the most active form was 2,3,7,8-TCDD, as in other studies.

Metabolism

Primary metabolism of dibenzo-p-dioxins in rats is by hydroxylation, and appears to take place exclusively at the 2,3,7, or 8 position in the molecule (Tulp and Hutzinger, 1978). Thus, detoxification by hydroxylation would likely be delayed by substitution of chlorines at all four key positions.

In the case of 2,3,7,8-TCDD, little or no metabolism has been noted in studies reported to date (Piper et al., 1973; Vinopal and Casida, 1973; Fries and Marrow, 1975; Rose et al., 1976; Allen et al., 1975; Van Miller et al., 1976). Unchanged compound was excreted in the feces with a whole-body half-life of about one month. Most of the total body burden was found in the liver and fat, and was unchanged TCDD. Data from a ^{14}C study in rats indicate that a steady state concentration of about 20 times the dosage level would be reached with 13 weeks of continuous administration (Rose et al., 1976).

Analyses for TCDD in tissues of rats from the Dow 2-year feeding study suggests that TCDD levels are higher in liver than in fat when dosage levels are high enough to cause toxic symptoms (Table 13). It should be noted that the amount accumulated in liver was only about 2.5% of the total amount fed to the animals over the 2-year treatment period.

PERSPECTIVE ON HAZARD FROM EXPOSURE TO DIOXINS

The relative toxicity of various dioxins has been reviewed. The hazard due to the presence of these compounds in the environment is also relative, and is a function of exposure to them as well as of their inherent toxicity.

Available data indicate that 2,3,7,8-TCDD may be the most toxic simple molecule known to man -- perhaps ten times more toxic than aflatoxin B₁ (Harris, 1978). Thus, great care should be taken to avoid human exposure, particularly during synthesis or experimental investigations involving the chemical itself. However, as reported by others in this symposium, the potential for exposure to residues of 2,3,7,8-TCDD in the environment is extremely low.

Dr. Bosshardt has discussed the work of Rappe et al., and of the need to differentiate among the various polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs) which can form during burning of chlorophenols or polychlorobiphenyls (PCBs). Dr. Harless has also discussed the need for great specificity and sensitivity of analytical methods used in analyzing for TCDD in samples collected for monitoring purposes.

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Dr. Crummett has reported negative findings in monitoring studies for TCDD in a variety of likely substrates using a GC/MS method developed by Stehl et al., with low part per trillion sensitivity. The results of these analyses have been reported for samples of beef fat (Kocher et al., 1978); cow's milk, (Mahle et al., 1977); fish, human milk, rice, water, and soil (Shadoff et al., 1977), all collected from areas where the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) had been used for up to 30 years for control of weeds and brush.

Dr. Wipf has reported the levels of TCDD in soil and crops from the Seveso area in Italy, both shortly after accidental release of a relatively large quantity of this toxic chemical during a runaway manufacturing reaction in 1976, and one and two years later. His data demonstrate that there is little potential for uptake of residues by plants from soil contaminated with TCDD.

The relative hazard from exposure to TCDD near Seveso is infinitely greater than from potential low level exposure in areas treated with 2,4,5-T. For example, the maximum residue found in Seveso was 15.8 parts per million TCDD in a sample of grass collected near the factory. In contrast, application of 2,4,5-T containing the maximum permissible level of 0.1 ppm TCDD at a rate of 1 lb/A (1.1 kg/ha) would result in a residue of only about 10 parts per trillion TCDD in/on the grass at the time of treatment, and such residues would decrease with a half life of less than one week (Getzendaner and Hummel, 1975). Numerous studies have demonstrated that TCDD undergoes photodegradation within a few hours in the presence of hydrogen donors such as the herbicide carrier (Crosby et al., 1971; Crosby, 1977; Crosby and Wong 1977; Botré, 1978; Plimmer, 1978).

Contamination of soil would also be orders of magnitude less than at Seveso. For example, the maximum amount of TCDD deposited during treatment with 2,4,5-T at 1.1 kg/ha would not exceed 0.01 microgram per square meter of horizontal surface, amounting to less than 0.1 part per trillion TCDD in the top 3 inches (7.6 cm) of soil. On the other hand, the highest level of contamination at Seveso was 5000 $\mu\text{g}/\text{m}^2$, equivalent to about 50 parts per billion TCDD in soil. Similarly, analyses of soil from a horse arena in Missouri revealed a level of 33 parts per million TCDD, as a result of spraying waste oil containing more than 300 ppm TCDD and very large quantities of 2,4,5-trichlorophenol.

Symptoms of toxicity were observed in humans exposed to these high levels of TCDD. The chief symptom at Seveso was chloracne in 22 children who were heavily exposed (Reggiani, 1978). Similarly, one child was affected in Missouri (Carter et al., 1975). In both cases a large number of animals died from exposure to the toxicant. However, it is highly unlikely that the extremely low levels which might result from use of 2,4,5-T herbicide would cause any significant effect.

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CONCLUSION

A number of studies with various PCDDs confirm that the inherent toxicity of the compounds is greatly enhanced by substitution at the four lateral positions. Since hydroxylation is generally a detoxification process, and takes place exclusively at the 2,3,7 and 8 positions in dioxins, substitution of chlorine at all four key positions in TCDD may prolong its half life sufficiently in animals so that much smaller doses are toxic. It should also be noted that, although TCDD tends to bioaccumulate in liver and fat, the amount retained by animals is only a small fraction of the total dose ingested over a long period of time. Thus the hazard from eating immeasurably small residues in food would be infinitely slight.

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Table 1. Number of Polychlorinated Dibenzo-p-dioxins (PCDDs) Possible from Condensation of Polychlorinated Phenols.

<u>Chlorophenols</u>	<u>Dioxins</u> ^a	<u>Number Possible</u>
Di + Di	Di	10
Tri + Di	Tri	14
Tri + Tri	Tetra	22
Tetra + Tri	Penta	14
Tetra + Tetra	Hexa	10
Penta + Tetra	Hepta	2
Penta + Penta	Octa	1
	TOTAL	75

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^a Total number of chlorines minus the two which are removed during bimolecular condensation of chlorophenates to predioxins and internal ring closure to form dioxins.

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Table 2. Acute Oral Toxicity of Polychlorinated Dibenzo-p-dioxins as Dose Expected to Cause Death of 50% of the Animals within 30 Days.

PCDD	Acute Oral LD50, µg/kg Body Weight		
	G. pig ^a	Rat ^b	Mouse ^a
Di <u>2,7</u> <u>2,8</u>	>300,000	>1,000,000	>2,000,000
Tri <u>2,3,7</u>	30,000		>3,000
Tetra <u>1,3,6,8</u> <u>1,3,7,9</u> } mixed <u>2,3,7,8</u>	0.6 ^b 2.1 ^b 2	>100,000 ^c 22 (M) 45 (F)	280
Penta <u>1,2,3,7,8</u> <u>1,2,4,7,8</u>	3 1,100		340 >5,000
Hexa <u>1,2,3,4,7,8</u> <u>1,2,3,6,7,8</u> <u>1,2,3,7,8,9</u> Mixed isomers	73 70-100 60-100	100,000	825 1,250 >1,440
Hepta <u>1,2,3,4,6,7,8</u>	>600		
Octa <u>1,2,3,4,6,7,8,9</u>		>1,000,000	>4,000,000

^a McConnell et al, 1978.

^b Schwetz et al., 1973.

^c Dow unpublished data.

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Table 3. Comparison of the Effects Produced by a Single Lethal Dose of 2,3,7,8-TCDD in Guinea Pigs, Mice and Female Monkeys. ^a

<u>Effect Noted</u>	<u>G. pigs</u>	<u>Mice</u>	<u>Monkeys</u>
Body weight loss	+++	++	+++
Thymus involution	+++	+++	+++
Spleen reduction	+	+	+
Bone marrow hypoplasia	++	±	+
Liver degeneration	-	+++	-
Bile duct hyperplasia	±	±	+++
Testicle degeneration	+++	++	b
Renal pelvis hyperplasia	++	-	+
Urinary bladder hyperplasia	++	-	-
Adrenal cortical atrophy	++	-	-
Intestinal hemorrhage	+	+	-
Adrenal hemorrhage	++	-	-
Peritoneal edema	-	++	+
Cutaneous lesions	-	-	+++

^a McConnell et al., 1978 a,b; Moore, 1978.

^b Not applicable for female monkeys.

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Table 4: Induction of δ -Aminolevulinic Acid Synthetase (ALA) and Aryl Hydrocarbon Hydroxylase (AHH) in Liver of Chick Embryos by Injection of Chlorodioxins into Eggs. ^a

<u>Chlorodioxin</u>	<u>ALA</u>	<u>AHH</u>
Unsubstituted	-	-
Mono 1	-	-
Di <u>2,3</u>	-	-
<u>2,7</u>	-	-
<u>2,8</u>	-	-
Tri 1, <u>2</u> ,4	-	-
<u>2,3,7</u>	++	++
Tetra 1, <u>2,3</u> ,4	-	-
<u>1,3,6,8</u>	-	-
<u>2,3,7,8</u>	++++	++++
Penta 1, <u>2,3</u> ,4, <u>7</u>	++	++
Hexa 1, <u>2,3</u> ,4, <u>7,8</u>	++	++++
<u>1,2,4,6,7,9</u> (90%)	±	+
Octa 1, <u>2,3</u> ,4,6, <u>7,8</u> ,9	-	-

^a Poland and Glover, 1973b.

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Table 5. In Vitro Induction of AHH in Rat Hepatoma Cell Cultures by PCDDs, as Picomoles Required to Cause 50% of Maximum Response. ^a

<u>Chlorodioxin</u>	<u>ED50 (p mol)</u>
Unsubstituted	Negligible at 5,000
Di 1,3 or 1,6	Negligible at 5,000
2,3 or 2,8	Negligible at 5,000
2,7	Detectable at 500
Tri 2,3,7	4,600
Tetra 1,2,3,4	Negligible at 5,000
1,3,6,8	Negligible at 5,000
1,2,3,8	3,300
1,3,7,8	114
2,3,7,8 chloro	1.08
2,3,7,8 bromo	3.64
Penta 1,2,4,7,8	Detectable at 500
1,2,3,4,7	121
1,2,3,7,8	20.5
Tri 4,5,6] Predioxin	Negligible at 50,000
Di 2,4	
Hexa 1,2,4,6,7,9	Negligible at 5,000
1,2,3,6,7,9	Detectable at 500
1,2,3,6,7,8	701
1,2,3,7,8,9	84.5
1,2,3,4,7,8	49.9
Hepta 1,2,3,4,6,7,9	3,790
1,2,3,4,6,7,8	129
Octa 1,2,3,4,6,7,8,9	3,400

^a Bradlaw et al., 1976.

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Table 6. Production of Chick Edema Disease by
Feeding PCDDs to Chicks for 21 Days. ^a

<u>Chlorodioxin</u>	<u>µg/kg/day</u> <u>21 Days</u>
Tetra <u>2,3,7,8</u>	positive at 1 or 10
Hexa (2 isomers)	positive at 10 or 100
Octa 1, <u>2,3</u> ,4,6, <u>7,8</u> ,9	negative at 0.1 or 0.5 x 10 ⁶ (0.1 or 0.5% in diet)

^aSchwetz et al., 1973.

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Table 7. Chloracnegenic Potential of PCDDs as Measured
by Concentration Required to Cause Rabbit Ear
Hyperkeratosis. ^a

<u>Chlorodioxin</u>	<u>Response</u>	<u>ppm</u>
Di 2,7	-	>100,000
Tetra 1,2,3,4	-	50
1,3,6,8 } mixed ^b	-	50
1,3,7,9 }	+	5000
2,3,7,8	-	0.004
	+	0.04
Hexa (2 or 3 isomers)	+	10
Octa 1,2,3,4,6,7,8,9	-	>100,000

^a Schwetz et al., 1973.

^b Unpublished data for mixture of
1,3,6,8 and 1,3,7,9-TCDD isomers.

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Table 8. Comparison of Effects Produced by PCDDs in Two Teratologic Studies in Rats (in Canada ^a and by Dow ^b).

<u>Chlorodioxin</u>	<u>µg/kg/day</u>	<u>Effect</u>
Mono <u>2</u>	2,000	Slight
Di <u>2,7</u>	2,000	Slight
<u>2,3</u>	2,000	None
Tetra <u>1,2,3,4</u>	800	None
<u>2,3,7,8</u>	0.125	None
	>0.25	Edema, hemorrhage
	>1	Fetotoxic
		Toxic to dams
	4	Embryolethal
Di <u>2,7</u>	100,000	None
Tetra <u>2,3,7,8</u>	0.03	None
	>0.125	Loss in weight
		Edema, hemorrhage
Hexa (2 isomers)	>10	Fetotoxic
Octa <u>1,2,3,4,6,7,8,9</u>	100,000	None

^a Khera and Ruddick, 1973.

^b Sparschü et al., 1971; Schwetz et al., 1973.

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Table 9. Observations in Female Monkeys Fed 2,3,7,8-TCDD or 1,2,3,6,7,8-HCDD in Diet for up to 2 Years.

<u>ppt in</u> <u>Diet</u>	<u>Months</u> <u>Fed</u>	<u>Total</u> <u>ug/kg</u>	<u>Effects Noted</u>
Tetra <u>2,3,7,8</u>			
50 a	24	1	2/8 showed slight effect around eyes; 6/8 conceived; only 2 bore normal young
500 b	9	3	5/7 died; 2 aborted; 3 failed to conceive; 1 unaffected, bore normal infant; 1 recovered and later bore normal infant
Hexa <u>1,2,3,6,7,8</u>			
5000 c	7-10	80-85	2/2 died. Symptoms similar to 500 ppt 2,3,7,8-TCDD but less severe. Animals were juveniles so not bred.

a Schantz et al., 1979.

b Allen et al., 1977; Barsotti et al., 1979.

c Allen et al., 1979.

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Table 10. Effects of 2,3,7,8-TCDD in Pregnant Monkeys Given Three Doses per Week for Three Weeks by Intubation. ^a

<u>Dosage Rate (μg/kg/dose)</u>	<u>Total Dose in 3 weeks μg/kg)</u>	<u>Dietary Equivalent (ppt)</u>	<u>No. of Abortions vs. total</u>	<u>Maternal Effects</u>
0	0	0	0/4	None
0.022	0.2	200	1/4	None
0.11	1.0	1000	3/4	None in 3. One had slight chloracne months later.
0.55	5.0	5000	2/2	Both well at end of 3-week treatment period. One died 7 weeks later and one died 14 weeks later. Both had chloracne and other signs of toxicity due to TCDD exposure.

^a McNulty; 1978.

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Table 11. Long-Term Carcinogenicity Studies on PCDDs
Currently Underway or Recently Reported. ^a

<u>Chlorodioxin</u>	<u>Diet</u>	<u>Gavage</u>	<u>Skin</u>
Unsubstituted	Mouse Rat		Mouse +DMBA ^d
Di <u>2,7</u>	Mouse ^b Rat ^b		Mouse +DMBA
Tri <u>2,3,7</u>		Mouse Rat	Mouse
Tetra <u>2,3,7,8</u>	Rat ^c	Mouse Mouse Rat	Mouse
Hexa <u>1,2,3,6,7,8</u>		Mouse Rat	Mouse
<u>1,2,3,7,8,9</u>		Mouse	Mouse
Octa <u>1,2,3,4,6,7,8,9</u>	Mouse Rat		Mouse

^a IARC, 1978.

^b U.S. National Cancer Institute, 1979.

^c Kociba et al., 1978; Van Miller et al., 1977.

^d Dimethylbenzanthracene.

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