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ENVIRONMENTAL PROTECTION AGENCY

BEFORE THE ADMINISTRATOR

In re	)	
	)	FIFRA Docket No. 295, et al.
2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T)	)	

DOW PREHEARING MEMORANDUM (No. 2)

This memorandum is submitted in compliance with the direction of the Chief Administrative Law Judge at the first Prehearing Conference (Tr. Nov. 12, 1973, p. 28). It will be organized as follows:

A. Dow responses to the Statement of Issues (Tr. Nov. 12, 1973, pp. 24, 27).

B. Evidentiary areas with which Dow will be concerned (id., p. 28).

C. Dow request for field hearings, reasons therefor, places proposed and number of anticipated witnesses in each place (id., p. 50).

D. Dow Repository Exhibits, indexed to applicable subject matters (id., p. 29).

E. Other matters.

F

A. DOW RESPONSES TO STATEMENT OF ISSUES.

This first Section of the Memorandum represents the Statement of Position requested of each party by the Chief Administrative Law Judge.

To avoid any misunderstanding, it should be stated at the outset that this Section has been organized by counsel to identify the contentions Dow will present during its affirmative case. Its purpose is to permit specification of issues and alignment of parties in interest. It is not a summary of the evidence to be introduced in the case. It necessarily and deliberately excludes discussion of many of the contrary positions and arguments (although not all) and is not intended to include material in response to contentions which may be asserted by other parties (to be set forth in the parties' February 22 Responses), or all the evidence which will be offered (to be set forth in the parties' March 10 Responses and at the Hearing itself). It must also be emphasized that this Statement is <u>not</u> the complete evidentiary submission of any witness or group of witnesses or of Dow.

The following are numerically keyed to the Statement of Issues:

<u>Issue I</u>: Whether 2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T) products presently registered, or other material submitted in support of these registrations, complies with the provisions of the Federal Insecticide, Fungicide and Rodenticide Act, as amended.

Response

The 2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T) products presently registered by Dow comply with the provisions of the Federal Insecticide, Fungicide and Rodenticide Act, as amended.

Issue II: Whether 2,4,5-T will perform its intended function without unreasonable adverse effects on the environment.

Response

2,4,5-T will perform its intended function without unreasonable adverse effects on the environment.

Issue III: Whether, when used in accordance with widespread and commonly recognized practice, 2,4,5-T generally causes unreasonable adverse effects on the environment, as defined by the Federal Insecticide, Fungicide and Rodenticide Act, as amended.

Response

When used in accordance with widespread and commonly recognized practice, 2,4,5-T does not generally cause unreasonable adverse effects on the environment, as defined by the Federal Insecticide, Fungicide and Rodenticide Act, as amended.

Issue IV: Whether the registrations of 2,4,5-T should be cancelled or its classification changed.

Response

The Dow registrations of 2,4,5-T should not be cancelled or any classification changed.

Issue V: The ten issues delineated in the 2,4,5-T Orders of the Administrator of November 4, 1971 and April 13, 1972 (I.F. & R. Docket Nos. 42 and 44), as follows:*

NOTE: Dow's Responses in Sections V., V.A. and V. B. hereof are in compliance with the Chief Administrative Law Judge's direction that scientific issues and positions be fully identified and explicated. This discussion, therefore, necessarily includes reference to some research as to which expertise, methodology and observation are questionable and, indeed, which may even have been biased towards a finding of hazard. Dow discusses such work as reported, but does not vouch for the integrity of all the effort considered therein. Where appropriate it intends on cross-examination and otherwise to point out the deficiences. It is pertinent, however, to note that even such work does not refute the overall conclusion of no significant hazard.

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* These and the following Responses go to substantive issues only and do not address questions of burden of proceeding or persuasion or other similar legal issues. However, it is of course Dow's position that those seeking to question an existing registration have the burden of initially presenting sufficient evidence of concern to justify the inquiry or other action taken, irrespective of where the final burden of proof on any issue may lie.

1. A contaminant of 2,4,5-T--tetrachlorodibenzo-p-dioxin (TCDD or dioxin) -- is one of the most teratogenic chemicals known. The registrants have not established that 1 part per million of this contaminant--or even 0.1 ppm--in 2,4,5-T does not pose a danger to the public health and safety.

Response

As stated in V.A. 1 below, TCDD probably is a teratogen. The question posed, however, confuses quantitative with qualitative considerations. Quantitatively the amount of TCDD required to cause a teratogenic effect of some kind is far lower than with many other compounds, and in this sense TCDD is indeed one of the most potent compounds that has been studied. Qualitatively, however, the nature of this effect is such that TCDD is far less teratogenic than many other compounds.

The one teratogenic response commonly associated with TCDD is cleft palate. Many other chemicals cause malformations more serious than cleft palate, such as defects of the heart, brain, limbs, etc. TCDD tends to cause death of the embryo or fetus rather than a wide range of abnormalities. In sum, the malformations caused by TCDD are not as significant as those caused by compounds as common as aspirin and Vitamin A, but the dose levels of TCDD required to cause malformations are much lower than with many other compounds.

With respect to the second part of this issue, several reports have been published which indicate that a TCDD level in 2,4,5-T of one ppm or less does not enhance or potentiate the toxic effect of 2,4,5-T. In one Dow teratology study (Dow Repository Exhibit DD-25*) the effect of 2,4,5-T alone was compared to the effect of 2,4,5-T in combination with TCDD. Purified 2,4,5-T acid was administered to Sprague-Dawley rats on days 6-15 of gestation at one dose level, 50 mg/kg/day. In addition, these rats were treated with 0.01, 0.03, 0.06, 0.125, 0.5 or 1 µg** of TCDD/kg/day. Both materials were administered orally. Hemorrhage in the wall of the intestine was observed at dose levels of 0.06 µg/kg/day TCDD and higher. Cleft palates were observed at 0.5 and 1 µg/kg/day TCDD given in combination with 50 mg/kg/day of 2,4,5-T. Therefore, at a dose level of 50 mg of 2,4,5-T/kg/day, 2,4,5-T would have to contain more than 1 ppm TCDD to cause intestinal hemorrhage and would require more than 10 ppm to cause a teratogenic effect, i.e., cleft palate.

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* All Dow Repository Exhibit references are listed in Exhibit A hereto in consecutive order, with Exhibit numbers 1-100 reserved for Issue V.A. references, 101-300 reserved for V.B. references and 301 et seq. reserved for V.C. references. The documents themselves are being submitted to the Hearing Clerk's Document Repository simultaneously with filing and service of this Memorandum. Exhibit references in the text are abbreviated, e.g., D[ow] D[ocument] 25.

** µg = micrograms.
mg = milligrams.

Courtney and Moore (DD-3) conducted a study in which mice were treated with 100 mg/kg/day of analytical grade 2,4,5-T plus one µg/kg/day of TCDD. While cleft palate and kidney anomalies were observed among mice receiving 2,4,5-T alone, the additional treatment with TCDD did not potentiate the effect of 2,4,5-T given alone. Thus, a dose equivalent to 2,4,5-T containing 10 ppm TCDD was no more toxic to the developing embryo and fetus than using 2,4,5-T with less than 0.05 ppm of TCDD.

Collins and Williams (DD-14) studied the effect of 2,4,5-T containing various levels of TCDD in hamsters. No fetal abnormalities were observed at dose levels of 2,4,5-T at or below 80 mg/kg/day. Among groups of hamsters treated with 2,4,5-T containing 0.1, 0.5, 2.9 and 45 ppm of TCDD, only the highest TCDD level (45 ppm) clearly increased the toxicity of 2,4,5-T to hamster embryos and fetuses.

Finally, in another teratology study reported by Neubert and Dillman (DD-6) teratogenic effects were observed in mice treated with either 2,4,5-T or TCDD alone. A potentiation of the teratogenic effects of 2,4,5-T and TCDD (i.e., incidence of cleft palate) was observed when teratogenic doses of one substance were combined with a threshold dose of the other. However, for such potentiation to occur, more

than 1.5 ppm TCDD was required. The authors concluded that a TCDD content of less than 1 ppm did not cause such effect.

These studies indicate that a TCDD content of 1 ppm or less in 2,4,5-T does not contribute to the toxicity of 2,4,5-T. Such results, extrapolated to humans, indicate that 1 ppm or less of TCDD in 2,4,5-T does not pose a danger to the public health and safety.

2. There is a substantial possibility that even "pure" 2,4,5-T is itself a hazard to man and the environment.

Response

The evidence from many studies, supported by approximately 25 years of safe usage, is that there is no hazard to man and the environment from 2,4,5-T. A more complete discussion of animal and human exposure is found, e.g., in Responses to Issues V.A. 5 and V. B. 3 and 4.

At the outset it should be noted that all compounds are hazardous to man to some degree, depending on their inherent toxicity which can be measured in laboratory animal studies. Acute or chronic toxicity hazards are tempered by the likelihood of exposure to the compound under normal and exaggerated conditions. According to the Handbook of Analytical Toxicology, 2,4,5-T is among the least dangerous pesticides in relation to acute toxic hazard to pesticide appliers.* Based on an acute oral LD_{50} of about 500 mg/kg in rats (DD-41), 2,4,5-T is classified as moderately toxic. To achieve this dose, a human would have to swallow about 1 oz. of pure 2,4,5-T and proportionally more of commercial formulations containing 5 to 65% 2,4,5-T. The hazard, if any, from exposure to dilute sprays of the herbicide is more likely due to the oil diluent or other adjuvants than to the 2,4,5-T itself. In one reported episode

* Ed. I. Sunshine, Chemical Rubber Co., Cleveland, 1969 pp. 563-565.

of 2,4,5-T "poisoning," (DD-29, p. 79-81), the physicians did not agree on whether the rashes observed in two little girls were due to contact with 2,4,5-T from the heavily sprayed area in which they were playing, or to dermatitis from the poison oak for which the spray had been applied.

Subacute (90 day) toxicity studies with 2,4,5-T and its propylene glycol butyl ether esters have demonstrated a no-effect level of at least 10 mg/kg/day in rats and dogs (DD-43, 44 and 42). This dosage rate would be achieved in humans only if the entire daily diet contained 500 ppm 2,4,5-T.* Since rare residues of 2,4,5-T have been detected in market basket surveys analyzed by methods sensitive to 0.1 ppm, a safety factor of at least 5000-fold exists between the daily dose required to cause effects in animals and the amount that could theoretically (but not practically) be ingested by humans as residue in food.

Further evidence for lack of hazard from 2,4,5-T is provided by data from several recent studies to elucidate its fate in various animals and man. The data obtained in studies by Dow indicate that a single oral dose of 5 mg/kg is rapidly excreted unchanged in the urine of rats and man, but is retained longer and is partially metabolized in dogs (DD-155, DD-159). Thus,

* Assuming a 75 kg (165 lb) human eats 1.5 kg of food each day, a dose of 10 mg/kg of body weight per day would be 750 mg in 1.5 kg, or 500 ppm.

the toxicity of 2,4,5-T in humans should be better predicted by rats than dogs.

The distribution, metabolism and excretion of 2,4,5-T in rats are much the same following doses of 5 or 50 mg/kg but are markedly altered following doses of 100 or 200 mg/kg (DD-155). Thus, detoxification of doses shown to induce toxicity are quantitatively and qualitatively different than detoxification of low non-toxic doses. This factor is of extreme importance in extrapolating effects produced at high doses as a measure of hazard from exposure to the herbicide as trace residues in food or as low levels in the environment.

Several studies have demonstrated the lack of hazard to animals grazing in areas treated with 2,4,5-T. In field studies under representative and exaggerated conditions (DD-30), no ill effects were noted in cattle maintained in a pasture sprayed once with a mixture of 2,4-D and 2,4,5-T at the recommended rate, again at twice this level, and then again at four times this level, nor from direct spraying of calves. Similarly no harmful effects were noted from <u>daily</u> spraying of their feed and water for 41 days.

Several studies have been conducted with 2,4,5-T in birds which demonstrated no effect in turkeys confined in treated areas or given treated alfalfa (DD-35), in breeding bird populations in heavily treated areas (DD-39), or in hatchability and chick viability from eggs sprayed at normal and exaggerated rates (DD-40).

In work by the USDA, no ill effect was noted in cattle, sheep or chickens from repeated oral doses of several 2,4,5-T derivatives at 50 mg/kg/day, whereas weight loss occurred at 100 mg/kg/day (DD-46, DD-47). Similarly, no effect was noted in lambs of sheep given 2,4,5-T at 100 or 113 mg/kg/day on days 14 through 27 to 36 of pregnancy (DD-17).

Controlled feeding studies have been conducted by Dow and USDA with 2,4,5-T in cattle and sheep at levels of 100 to 2000 ppm in the total diet for 28 days (DD-108). No ill effects were noted in 12 of the 15 calves nor in all six sheep receiving doses ranging from 3.4 to 63.2 mg/kg of body weight per day for 4 weeks. The only effect noted was reduced feed intake in three calves, one given 300 ppm (6.1 mg/kg) and two given 1800 ppm (33.9 mg/kg) 2,4,5-T in the total diet for 4 weeks. Increased consumption of untreated feed was noted in one of these calves during a 7-day withdrawal period from feed containing 1800 ppm 2,4,5-T, suggesting decreased palatability of feed contaminated with high levels of the herbicide.

Recent claims of hazard from 2,4,5-T have stemmed from reports of teratogenic effects produced in laboratory animals. The first such study was conducted by Bionetics in 1966, chiefly in mice by subcutaneous injection of high doses of 2,4,5-T dissolved in the penetrating solvent dimethylsulfoxide (DD-1). The inferences drawn from this study were that 2,4,5-T appeared to provoke a higher than expected level of fetal death and fetal abnormality in rats and mice at the dosages used, and there appeared to be a suggestion of a dose-response relationship over the range of doses used. However, the sample of 2,4,5-T used contained

27 ± 8 ppm 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a known highly toxic impurity kept to less than 1 ppm by most manufacturers of 2,4,5-T at that time. Other deficiencies in the study are discussed in a 1971 report of the Panel on Herbicides of the President's Science Advisory Committee (DD-163, p. 45-47). A number of additional teratologic studies have been conducted since the original Bionetics study. These studies demonstrated that no teratogenic or embryotoxic effects were associated with repeated daily doses of 2,4,5-T at levels of about 20 mg/kg/day in mice and 40 to 50 mg/kg/day in rats. Higher doses in rats were associated with symptoms of embryotoxicity rather than true teratogenic responses. Detailed discussions of each study are presented in the Response to Section V.A., infra.

Studies in pregnant animals have demonstrated that 2,4,5-T is transferred across the placenta in both directions, both into and out of the fetuses (DD-27). Placental and fetal levels were proportional to maternal serum levels and the rate of clearance of 2,4,5-T from the fetus or newborn pup was slower than from the dam. In another study (DD-155) with non-pregnant rats, peak plasma levels were reached within about 4 hours after single oral doses up to 50 mg/kg with a half-life of about 4 hours, whereas plateau values were obtained about 12 hours after doses of 100 or 200 mg/kg with an increase in half-life to 19 and 25 hours, respectively. Thus repeated high doses of 2,4,5-T could accumulate in the mother and more so in the fetuses during the treatment

period, accounting for the embryotoxicity noted in some studies at levels which are far in excess of what would be encountered in the environment.

In conclusion, many studies demonstrate the lack of hazard to man and animals from the use of 2,4,5-T as manufactured over the years, and certainly of current 2,4,5-T produced under carefully controlled conditions to reduce formation of TCDD. The materials used in most studies contained levels of TCDD in excess of the current limit of 0.1 ppm in technical 2,4,5-T and proportionally lower in its formulated products.

Review of Data

Acute Studies

Rowe and Hymas (DD-41) summarized a series of studies conducted by The Dow Chemical Company on the acute oral toxicity of 2,4-D, 2,4,5-T and various derivatives and formulations thereof. The following tables indicate that the acute LD_{50} ranged from 300 to 1000 mg/kg (except for dogs) depending chiefly on the percent phenoxy acid equivalent of the materials tested. There was some variation among species. Dogs appeared to be more sensitive in the one study conducted with this species (Drill and Hiratzka, 1953, DD-42).

TABLE I.—Acute oral toxicities of various phenoxy acetate herbicidal chemicals. Rowe and Hymas

Material	Species	Sex	Vehicle	$L.d._{50}$ (19/20 confidence limits) (mg./kg.)	Phenoxy Acid Equivalent (%)
2,4,5-T (2,4,5-Trichlorophenoxyacetic acid)	Rats	M	Olive oil	500 (391-640)	≈100
	Mice	M	Olive oil	389 (245-619)	
	Guinea pigs	M and F	Olive oil	381 (307-472)	
	Chicks	M and F	Olive oil	310 (211-456)	
	Dogs (4)		Capsule	Range 100 (50-250)	
2,4,5-T, isopropyl ester	Rats	M and F	Olive oil	495 (420-584)	86
	Guinea pigs	F	Olive oil	449 (362-557)	
	Mice	F	Olive oil	551 (350-799)	
2,4,5-T, mixed butyl esters	Rat	F	Corn oil	481 (313-739)	82
	Rabbit	M	Corn oil	Range 712 (500-1,000)	
	Mice	F	Corn oil	940 (674-1,312)	
	Guinea pigs	F	Corn oil	Range 750 (500-1,000)	
2,4,5-T, mixed amyl esters	Rats	F	Olive oil	Range 750 (500-1,000)	78
MCP (4-chloro-o-toloxyacetic acid or 2-Methyl-4-chlorophenoxyacetic acid).	Rat	M	Corn oil	Range 700 (500-1,000)	≈100
MCP, amine salt	Rat	M	Water	Range 1,200 (1,000-2,000)	62
	Guinea pigs	M	Water	Range 1,200 (630-2,000)	≈100
silvex, (2[2,4,5-trichlorophenoxy] propionic acid).	Rat	M and F	Corn oil	Range 650 (560-760)	
silvex, mixed butyl esters	Rat	F	Corn oil	Range 600 (250-1,000)	83
	Rabbits	F	Undiluted	Range 750 (500-1,000)	
	Chicks	M and F	Corn oil	1,190 (707-2,000)	
silvex, mono-, di-, tripropylene glycol butyl ether esters.	Rat	F	Corn oil	621 (473-814)	66
	Guinea pigs	M	Corn oil	Range 1,250 (500-2,000)	
	Mice	F	Corn oil	Range 1,410 (1,000-2,000)	
	Chicks	M and F	Corn oil	1,190 (847-1,670)	
	Rabbits	F	Undiluted	819 (610-1,070)	

TABLE 2.—*Summary of oral toxicities of a variety of phenoxy acetate herbicidal formulations. Rowe and Hymas*

Material	Species	Sex	Vehicle	l.d. to (19/20 confidence limits) (mg./kg.)	Phenoxy Acid Equivalent (%)
2,4-Dow weed killer	Guinea pigs	F	Water	2,000 (1,000-3,000) Range	40
2,4-Dow weed killer (formula 40)	Rats	F	Water	850 (700-1,000) Range	40
Esteron 44	Rats	M	Olive oil	650 (300-1,000) Range	37
Esteron 245 (old)	Rats	F	Emulsion in water	1,000 (300-2,000) Range	38
Esteron 245 (new)	Rats	M	Olive oil	800 (600-1,000)	45
Esteron ten-ten	Rats	F	Olive oil	760 (660-860)	45
Brush killer 50-50	Rats	F	Emulsion in water	1,070 (700-1,650)	45
	Guinea pigs	F	Emulsion in water	1,160 (820-1,630)	
	Mice	F	Corn oil	800 (624-1,070) Range	
	Rabbits	F	Undiluted	1,420 (500-2,000)	
	Chicks	M and F	Undiluted	4,000 (2,700-5,900)	
Brush killer T	Rat	F	Emulsion in water	1,200 (783-1,850)	43
	Guinea pigs	F	Emulsion in water	1,410 (875-2,290)	
	Mice	F	Olive oil	1,230 (938-1,620)	
	Rabbits	M	Undiluted	840 (604-1,190)	
	Chicks	M and F	Undiluted	2,000 (1,350-2,960) Range	
Brush killer 76	Rats	F	Corn oil	760 (500-1,000) Range	63
Brush killer 76E	Rats	F	Corn oil	300 (250-1,000) Range	63
Esteron brush killer (old)	Rats	M	Emulsion in water	1,000 (300-3,000)	45
Esteron brush killer (new)	Rats	M and F	Corn oil	860 (800-930)	45
	Guinea pigs	M	Corn oil	1,220 (1,040-1,430)	
	Guinea pigs	F	Corn oil	1,600 (1,390-1,840)	
	Rabbits	M and F	Corn oil	960 (790-1,160) Range	
	Chicks	M and F	Corn oil	2,000 (1,000-3,000)	
	Steers		Undiluted	Greater than 1,000	

TABLE 3.—Herbicidal formulations studied by Rowe and Hymas

Trade name	Active ingredients (percent)	Phenoxy Acid Equivalent (%)
2,4-Dow weed killer (formula 40)	65.0 Alkanolamine salts of 2,4-D	40
Esteron 44	44.0 Isopropyl ester of 2,4-D	37
Esteron 245 (old formulation)	33.3 Isopropyl ester of 2,4,5-T; 12.1 Mixed amyl esters of 2,4,5-T	38
Esteron 245 (present formulation)	65.3 Mono-, di-, tripropylene glycol butyl ether esters of 2,4,5-T	45
Esteron ten-ten	70.5 Mono-, di-, tripropylene glycol butyl ether esters of 2,4-D	45
Brush killer 50-50	27.2 Butyl esters of 2,4-D; 26.5 Butyl esters of 2,4,5-T	45
Brush killer T	52.2 Butyl esters of 2,4,5-T	43
Esteron 76 (used in oil solution only)	37.1 Isopropyl esters of 2,4-D; 39.0 n-Butyl ester of 2,4-D	63
Esteron 76E (used in either oil solution or water emulsion)	36.8 Isopropyl esters of 2,4-D; 38.8 Butyl esters of 2,4-D	45
Esteron brush killer (old formulaton)	25.6 Isopropyl esters of 2,4-D; 24.4 Isopropyl esters of 2,4,5-T	45
Esteron brush killer (present formulation	34.8 Mono-, di-, tripropylene glycol butyl ether esters of 2,4-D; 33.0 Mono-, di-, tripropylene glycol butyl ether esters of 2,4,5-T	45
Kuron (was called H-1078)	64.5 Mono-, di-, tripropylene glycol butyl ether esters of silvex	46
Dow MCP amine weed killer*	69.1 Alkanolamine salts of MCP	40

*2-methyl-4-chlorophenoxyacetic acid.

Subacute Studies in Laboratory Animals

(a) 2,4,5-T in Rats

McCollister, Kociba and Gehring (DD-43) recently reported the results of subacute feeding studies with 2,4,5-T in rats,which confirmed the findings in earlier studies with 2,4,5-T as propylene glycol butyl ether esters in this species (Dow Chemical Co., 1961, DD-44). Male and female rats in groups of 10/sex/dose were maintained for 90 days on diets containing various levels of 2,4,5-T with a known content of 0.5 ppm TCDD. The dietary levels were adjusted during the study to provide doses of 0, 3, 10, 30 or 100 mg/kg/day throughout the entire 90-day period.

No evidence of untoward effects was observed in rats fed dose levels of 3 or 10 mg/kg/day based on a number of clinical parameters. Evidence of treatment related effects was minimal even at the two highest dose levels. At 30 mg/kg/day, there were slight increases in liver and kidney weights in males but these were considered to be of minimal toxicological significance. Changes found in both sexes given 100 mg/kg/day included depression of body weight gain, slight decrease in food intake and elevated serum alkaline phosphatase activity. Gross necropsy examination revealed a slight paleness and accentuated pattern of the livers of some rats of both sexes at this dose, with inconsistent minimal amounts of hepatocellular swelling observed upon histopathological examination. Male rats at this dose level also had slightly increased serum glutamic pyruvic transaminase activity and very slightly decreased red blood cell counts and hemoglobin levels.

(b) 2,4,5-T Propylene Glycol Butyl Ether Ester in Rats

Comparable results were obtained in another study

conducted in the same Dow laboratory in 1960 on a mixture of mono- and poly-propylene glycol butyl ether esters of 2,4,5-T (DD-44). The acid equivalent of this DOWANOL® 97B ester was 62.5% 2,4,5-T, and the TCDD content was probably not greater than 1 ppm based on the rabbit-ear bioassay test for chloracnegenic activity. Rats were fed diets containing 0.00, 0.01, 0.03 and 0.10 or 0.30% 2,4,5-T ester for 90 days.

No adverse effects were observed in animals fed the 0.03% diets, equivalent to a dose of 15-30 mg/kg/day as the ester or to 10-20 mg/kg/day 2,4,5-T acid equivalent. This is comparable to the no-effect level of 10 mg/kg/day found in the 1970 study with 2,4,5-T indicating that the ester is no more toxic than the acid form of the herbicide.

As in the study with 2,4,5-T acid, effects were minimal at higher dose levels of the ester in the diet for 90 days. At 0.1% ester (30-60 mg of acid/kg/day) the only differences from controls were slight cloudy swelling of the parenchymal cells of the liver in both sexes with central lobular necrosis in two of the animals examined. Minor kidney changes were also noted in both sexes. At 0.3% ester in the diet (100-200 mg of acid/kg/day) significant retardation of growth was evident in males but not in females, and final average weight ratios of the liver and kidney were increased in males only. The effects in liver and kidney were more marked at 0.3% than at 0.1% ester in the diet, particularly in females.

The effects noted at the higher dose levels are not surprising in view of the altered metabolism of 2,4,5-T in rats following single oral doses of 100 or 200 mg/kg compared to 5 or 50 mg/kg (DD-155). The lower doses were rapidly absorbed and excreted unchanged via the urine, whereas the higher doses were cleared at a slower rate with formation of a small amount of unidentified urinary metabolites not detected at lower doses.

(c) 2,4,5-T in Dogs

Drill and Hiratzka (DD-42) conducted studies in mongrel dogs in 1950 using technical 2,4,5-T reported to be 98% pure but of indeterminate TCDD content. The material was administered 5 days per week for 13 weeks as a single oral dose in a capsule imbedded in a piece of commercial dog food. The dogs survived doses of 2,5, or 10 mg/kg/day without any symptoms or changes in body weight, organ weights or hematologic (blood) measurements. However, oral administration of 20 mg/kg/day caused death in all four dogs between the 11th and 75th day of the study. Deaths during chronic oral administration of the 2,4,5-T were not correlated with significant lesions in the liver, kidney, or other organs examined.

The no-effect level of 10 mg/kg/day in this study in dogs agrees with the dose levels of 2,4,5-T and 2,4,5-T ester which caused no effect in rats. The greater toxicity of higher doses in dogs may be due to the slower rate of elimination of 2,4,5-T in dogs than in rats. (DD-155).

Fate of 2,4,5-T in Animals and Man

A number of studies have been conducted recently to elucidate the fate of 2,4,5-T in rats, dogs and humans. The following table compares findings in three studies by Dow in rats and dogs (DD-155), in man (DD-159) and in pregnant rats (DD-27).

The data obtained indicate that a single oral dose of 5 mg/kg is rapidly excreted unchanged in the urine of rats and man, but is retained longer and is partially metabolized in dogs. The distribution, metabolism and excretion of 2,4,5-T in rats are much the same following doses of 5 or 50 mg/kg but are markedly altered following doses of 100 or 200 mg/kg. Thus, detoxification processes may be quite different at high doses such as those which caused effects in teratology studies with 2,4,5-T. Evidence was also obtained that 2,4,5-T is rapidly transferred across the placenta in both directions, both into and out of the fetuses.

These findings are corroborated by data from studies in other laboratories. Peak plasma levels were reached within 4 hr and the plasma half life was about 4 hr after single oral doses of 2,4,5-T ranging from 0.17 to 50 mg/kg in rats (DD-155; DD-156 and DD-34). A plateau in the serum level was obtained at 12 hr after 100 mg/kg and the half life was increased to 19 and 25 hr after doses of 100 or 200 mg/kg, respectively (DD-155 and DD-34).

SUMMARY OF DOW STUDIES ON FATE OF 2,4,5-T IN ANIMALS

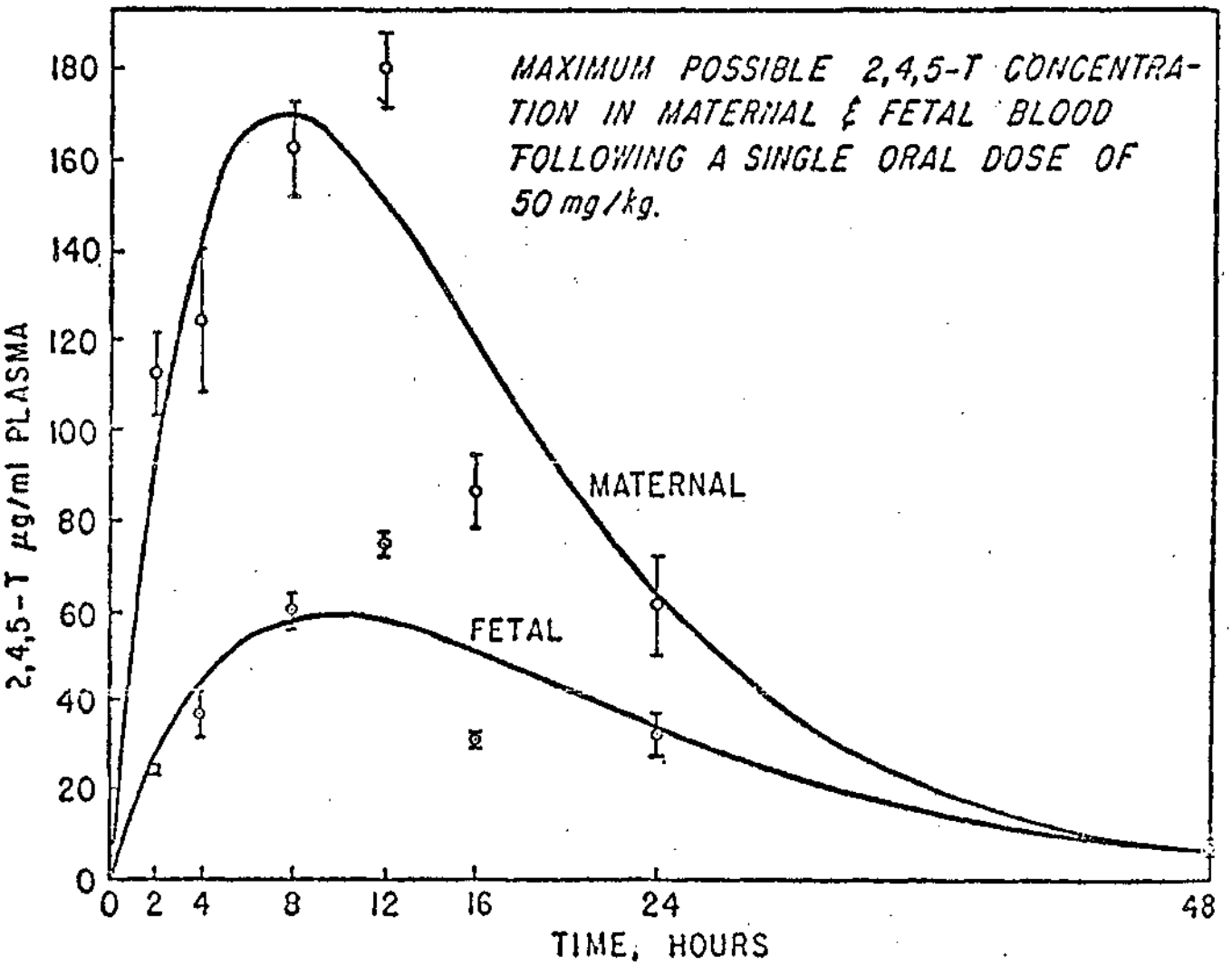
Species Differences - 5 mg/kg

	RAT	MAN	DOG
Plasma half-life (hr)	5	23	77
Body half-life (hr)	14	23	87
Volume of distribution (%)	14	8	22
Urinary metabolites	None	None	Yes
% Excreted in urine	83 (6 days)	88 (4 days)	42 (9 days)
% Excreted in feces	3 (6 days)	<1 (2 days)	20 (9 days)

Effect of Dose Level - Rats

	mg/kg			
	5	50	100	200
Plasma half-life (hr)	5	4	19	25
Body half-life (hr)	14	13	19	29
Volume of Distribution (%)	14	19	39	43
Urinary Metabolites	None	None	Trace	Trace
% Excreted in urine (6 days)	83	93	78	68
% Excreted in feces (6 days)	3	6	9	14

Placental Transfer - Rats (DD-27).



Conclusion: 2,4,5-T is rapidly transferred across the placenta in both directions - into and out of the fetuses.

Toxicity Studies in Livestock and Birds

(a) Field studies

Goldstein and Long (DD-30) reported no ill effect in two calves maintained in a pasture sprayed repeatedly at recommended and exaggerated rates with a 2,4-D/2,4,5-T spray mixture. The spray contained 2 lb. 2,4-D + 2 lb. 2,4,5-T per 100 gallons and was applied to the entire pasture once at the recommended rate, then again at twice this rate and again at four times this rate. The cattle appeared to consume the vegetation at a normal rate and showed no ill effects when observed for an extended period.

In companion studies, no detectable harmful effects were noted from direct spraying of cattle, sheep and swine, nor from daily spraying of drinking water and feed. Chronic exposure was simulated by adding 1/4 pint of prepared spray to every 5 gallons of drinking water and by spraying the hay ration with 50 ml. of prepared spray twice each day for 41 days.

No preference or aversion for grazing sprayed areas was noted when only half of a pasture was sprayed with a 3 lb/100 gal 2,4,5-T solution and later with four times this concentration. The authors also mentioned that literally dozens of carefully conducted feeding experiments, both with 2,4-D and 2,4,5-T directly and with vegetation sprayed with them, have uniformly and without exception failed to show any poisonous

effects on any kind of livestock.

Roberts and Rogers (DD-35) reported two comparable studies with a low volatile ester formulation of 2,4,5-T in turkeys. No harmful effect or aversion to forage was noted in a group of toms transferred to an area immediately after spraying with 2,4,5-T at 1.6 lb/A and to another treated area after the vegetation had wilted. Similarly, addition of 0.25% 2,4,5-T or 10% sprayed alfalfa to the mash fed to the birds had no appreciable effect on the rate of growth or amount of feed consumed.

Martin (DD-39) reported no marked adverse effect upon any nesting species of wild birds from treatment with 2,4,5-T to control woody brush. The treatment actually improved the habitat for a few species. In a Canadian study (DD-40), the hatchability of chicken and pheasant eggs was not adversely affected by spraying the eggs with a 1:1 mixture of 2,4-D and 2,4,5-T esters at 1, 2.5 or 10 lb/A, and the hatched chicks exhibited no morphological abnormalities.

(b) Repeated oral doses in cattle, sheep and chickens

Early work at Dow indicated that the LD_{50} for undiluted ESTERON® Brush Killer* was greater than 1000 mg/kg in steers and 2000 mg/kg in chicks. Rowe and Hymas (DD-41) summarized their studies with ESTERON® Brush Killer as follows:

*This formulation contains 22.2% 2,4-D plus 22.2% 2,4,5-T acid equivalent as propylene glycol butyl ether esters.

ORAL ADMINISTRATION TO STEERS

Purpose.—Since essentially all of the toxicological information on 2,4-D and 2,4,5-T-type herbicides was obtained using small animals and since the practical application of these materials involves exposure also to large animals, experiments were undertaken to ascertain if extrapolation of the data obtained on the laboratory animals to large animals was justified.

Esteron Brush Killer.—Since esteron brush killer (formulation of esters of 2,4-D and 2,4,5-T) is perhaps the widest used of the products discussed herein, it was chosen for study.

In the experiments outlined in the following paragraphs, administrations were all by intubation. Treated animals were constantly under observation and the ordinary clinical observations were routinely made. In general, only positive observations are reported.

Experiment 1.—A steer weighing 291 kg. was given a single dose of 1,000 mg./kg. No perceptible symptoms of toxicity were observed.

Experiment 2.—A steer weighing 295 kg. was given 1,000 mg./kg. of esteron brush killer on each of three successive days. General depression, decreased food and water intake, and decreased rumen motility were observed following the third dose. These symptoms became increasingly severe until the steer died on the third day following the last dose. Death was undramatic; no convulsions, struggling, or signs of pain were observed at any time. Necropsy revealed the following: Rumen contents were dry and smelled strongly of the esteron; the abomasum was impacted and the contents of the intestines were entirely fluid; the mesenteric vessels were congested and the spleen was dark and shrunken.

Experiment 3.—A steer weighing 295 kg. was given 500 mg./kg. on each of two consecutive days. On the third day, the animal was off feed and rumen motility had essentially ceased. On the fourth day, the steer appeared perfectly normal and there were no discernible after-effects.

Experiment 4.—Another steer weighing 336 kg. was given 500 mg./kg. on each of three successive days. No toxic symptoms were observerd and the animal remained on full feed.

Experiment 5.—A steer weighing 250 kg. was given 100 mg./kg. of esteron brush killer on each of fifteen consecutive days without any outward appearance of adverse effects. The animal was killed for study forty-eight hours following the last dose. Gross examination of the internal organs revealed only slight petechial hemorrhage in the duodenum and a mild diffuse irritation in the abomasum. Histological examination of tissues from the lung, heart, spleen, adrenals, pancreas, thyroid, thymus, bladder, and lymph nodes revealed no abnormalities. Sections from the liver revealed small areas of focal hemorrhagic necrosis surrounded by areas of fatty degeneration. In the kidneys, very slight interstitial edema and congestion in the medulla and cortical medullary region were observed. Although gross examination of the gastrointestinal tract revealed mild irritation in the duodenum and abomasum, sections of these organs failed to indicate any changes of significance.

Extensive toxicological studies have been conducted by USDA with a number of herbicides in cattle, sheep and chickens (DD-46, DD-47). In studies with 2,4,5-T derivatives and formulations, no ill effect was noted in cattle or sheep given repeated daily doses of 50 mg/kg or sometimes 100 mg/kg/day in a capsule or drench, whereas death occurred after several doses at 250 mg/kg/day. Symptoms of poisoning included anorexia, depression and muscular weakness. At necropsy, liver, kidney, and lung inflammations were observed, along with signs of lack of proper digestive processes throughout the gastrointestinal tract. Chickens also tolerated repeated doses of 50 mg/kg/day but 100 mg/kg/day caused depressed weight gain and death of some birds.

In another USDA study (DD-17), no congenital deformities were produced in lambs from one group of eleven ewes given 2,4,5-T or another group given 2,4,5-T propylene glycol butyl ether esters, both at 100 mg/kg/day. The chemicals were mixed in 0.5 lb of ground alfalfa meal and force-fed via stomach tube daily from the 14th to 36th day of gestation. Another group of five ewes was given 2,4,5-T at 113 mg/kg/day on days 14-19, 14-27 or 14-29 of gestation; all gave birth to full-term, normal, live lambs. The 2,4,5-T used was reported to contain <1 ppm 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) so the ewes

received approximately 0.5 to 2.3 μg/kg TCDD along with 565 to 2300 mg/kg 2,4,5-T during the treatment period.

(c) Dietary feeding studies in livestock and birds

Controlled feeding studies were conducted by Dow and USDA during 1969 and 1970 with several phenoxy herbicides at levels from 10 to 2000 ppm in the total diet of dairy cows, beef calves, or sheep for intervals of 2 to 4 weeks at each level tested (DD-108). In studies with 2,4,5-T, no ill effect was noted in animals receiving dose levels ranging from 0.3 to 63.2 mg/kg/day for up to 4 weeks. In dairy cows, milk production was unaffected by incorporation of 2,4,5-T at 10, 30, 100, 300, and 1000 ppm in the diet for 2 or 3 weeks successively at each level. No apparent effect was noted in 12 of 15 calves given 300, 900 or 1800 ppm nor in 6 sheep given 2000 ppm 2,4,5-T in the total diet for 4 weeks.

Reduced feed intake was noted in three calves, one at 300 ppm and two at 1800 ppm. However, increased feed consumption occurred when one of the calves was given untreated feed during a 7-day withdrawal period from 1800 ppm in the diet suggesting decreased palatability of feed containing high levels of the herbicide.

3. The dose-response curves for 2,4,5-T and dioxin have not been determined, and the possibility of no effect levels for these chemicals is only a matter of conjecture at this time.

Response

While some 2,4,5-T and TCDD studies have used such excessive dose levels as to make it difficult to establish dose-response relationships, many studies have used dose levels which permit clear dose-response curves to be drawn. A detailed discussion of this work, including literature references and tables, is found in V.A. 1-6, infra.

Evaluation of a dose-response relationship is difficult when levels studied are in the toxic range, particularly when they approach the lethal level. As shown in one work on the effects of 2,4,5-T in rats and dogs (DD-155), distribution, metabolism and excretion were much the same following single oral doses of 5 and 50 mg/kg but were markedly altered following doses of 100 or 200 mg/kg. Thus, detoxification processes may be quite different for high doses than for low doses which cause no effects.

However, as discussed in response to question 2, supra, a no-effect level of 10 mg/kg/day has been found for 2,4,5-T in sub-acute 90-day feeding studies in rats and dogs. As noted in V.A. 1, infra, no-teratogenic-

effect levels for 2,4,5-T have been reported, at 20 mg/kg/day in mice and 40-50 mg/kg/day in rats, rabbits and hamsters (DD-14, DD-2, DD-13, DD-4, DD-6, DD-5 and DD-20). In two teratology studies in rats (DD-28, DD-24) no effect levels of 0.03-0.125 µg TCDD/kg/day have been reported.

It is concluded, therefore, that no-effect and dose-response relationships <u>have</u> been determined for both 2,4,5-T and TCDD.

4. As with another well-known teratogen, thalidomide, the possibility exists that dioxin may be many times more potent in humans than in test animals (thalidomide was 60 times more dangerous to humans than to mice, and 700 times more dangerous than to hamsters; the usual margin of safety for humans is set at one-tenth the teratogenic level in test animals).

Response

As with any substance, the remote possibility exists that TCDD may be more potent in humans than in laboratory animals. However, there is no reason to suspect a greater likelihood of such effect with TCDD than with any other chemical, drug or environmental substance.

While thalidomide caused malformations in humans at a lower absolute dose level than in laboratory animals, thalidomide was not more potent in humans than in animals on the basis of the teratogenic dose level relative to the dose level which causes maternal toxicity. The ratio between the teratogenic dose and the maternally toxic dose is the same in laboratory animals as it is in man. If such ratios had been considered and all of the available data utilized, the dose level at which thalidomide caused teratogenic effects in humans could have been predicted.*

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* Palmer, A.K., 1969, "The Relationship Between Screening Tests for Drug Safety and Other Teratological Investigations." Teratology, Proceedings of a symposium organized by the Italian Society of Experimental Teratology. Edited by A. Bertelli and L. Donati, pp. 55-72. (Excerpta Medica Foundation, Amsterdam).

Moreover, the teratogenic effect of thalidomide is dependent upon its concentration in the blood. It appears that oral dosing of small animals results in much lower blood levels of thalidomide than similar dose levels in man. When the drug is injected intravenously into small animals (to give blood levels equal to those in man) teratogenic effects are observed.* This further supports the view that thalidomide is not a more potent teratogen in humans than in laboratory animals.

Finally, a potent teratogen is a compound which causes teratogenic responses over a wide dose range without causing death of the embryo or fetus. In the TCDD teratogenicity study reported by Sparschu, et al (DD-24) the lowest dose level which caused embryotoxic effects was 0.125 µg/kg/day. At 2 µg/kg/day, 95% of the implanted embryos were killed and resorbed. Embryo and fetotoxicity were observed over this entire dose range, but teratogenic effects were not observed at any dose level. In another study (DD-25), cleft palate was observed at a dose level of 0.5 and 1 µg TCDD/kg/day given in combination with 50 mg of 2,4,5-T/kg/day. In both of these studies, embryotoxic or teratogenic effects were observed only at dose levels which also caused a high incidence of fetal deaths. TCDD, therefore, is not a "potent teratogen" in terms of ratios between teratogenic and lethal doses.

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* Brodie, B. B., 1968, The Mechanism of Adverse Reactions in Drugs, pp. 23-47, Pergamon Press, New York, 1968.

5. The registrants have not established that the dioxin and 2,4,5-T do not accumulate in body tissues. If one or both does accumulate, even small doses could build up to dangerous levels within man and animals, and possibly in the food chain as well.

Response

Accumulation of an agent in the body or the tissues of the body is a function of its rates of entry and exit. Any chemical, including components of food and water, will "accumulate" to varying degrees as the relationships between the rates of entry and exit are varied. Subject to this qualification, studies show that neither 2,4,5-T or TCDD accumulate in body tissue.

Studies which permit assessment of the degree of accumulation of 2,4,5-T in animals include those in rats, dogs, pigs, chickens and calves (DD-155, 156, 157 and 158). Dow has also conducted a study in man (Gehring et al., 1973, DD-159). In all of these studies, single doses of 2,4,5-T were administered and elimination rates from the body determined. The results of the animal studies demonstrate the following:

(a) 2,4,5-T is readily absorbed following a single oral dose.

(b) Upon absorption, the predominant portion of 2,4,5-T in the body is in plasma. The compound is concentrated to some degree by the kidney.

(c) 2,4,5-T is readily and rapidly eliminated by adult rats, pigs, calves and chickens. The times required for elimination of one-half of the ingested dose in the respective species are 3 to 14 hours for rats, about 8 hours for calves and chickens and 12 hours for pigs. The major route of excretion is via the urine. Most of the 2,4,5-T is excreted as 2,4,5-T *per se*.

(d) The rate of 2,4,5-T elimination in newborn rats is slower than for adult rats -- *i.e.*, 48 hours to eliminate one-half of the dose.

(e) The rate of elimination from dogs is slower than for other animal species, with an elimination time for one-half the dose of 87 hours. This finding coincides with the observation that dogs are more susceptible to intoxication.

(f) Elimination of 2,4,5-T from all tissues coincides with elimination from the body. Thus, 2,4,5-T is not concentrated and sequestered by any specific tissue. Greater concentrations in the kidney are due to an active transport process which serves to transfer the compound from plasma to urine for subsequent excretion.

(g) Capability to eliminate 2,4,5-T can be overwhelmed by administration of extremely large doses and excessive levels of the compound may be attained in the body, which are not proportional to those following low doses. In rats, the profiles for elimination of 5 and 50 mg/kg are superimposable. Elimination rates following doses of 100 or 200 mg/kg are much slower than when 5 or 50 mg/kg are administered. When the two larger doses are administered, excretion in the urine is swamped and more of the compound is eliminated via the feces.

The results of another collaborative study (DD-178) elucidate further the renal excretory mechanism for

2,4,5-T. 2,4,5-T was shown to be actively transported by the kidney. This active transport, which is responsible for elimination of the compound in the urine, is similar to that utilized by the kidney for the elimination of other organic acids from the body and can be overwhelmed by large concentrations of 2,4,5-T. The kidney of dogs and newborn rats had a lower capacity for the transport of 2,4,5-T, which explains why dogs and newborn rats eliminate the compound from the body more slowly than other experimental animals.

These results, together with those summarized above in (g), further support the conclusion that toxicity incurred with large doses cannot be used as a reliable prediction of results from the administration of small doses.

From the study of the fate of 2,4,5-T in man (following ingestion of 5 mg/kg), the following conclusions can be drawn:

(a) 2,4,5-T is readily and almost totally absorbed.

(b) After absorption, 2,4,5-T is readily excreted via the urine. The time required for elimination of one-half the dose is 23 hours. Doses lower than 5 mg/kg may be eliminated from the body even more rapidly.

(c) Excretion via the kidney exceeds that which can be attributed to glomerular filtration. Therefore, as in animals, excretion in urine occurs via active transport.

(d) Repetitive dosing (exposure) would result in attainment of a steady-state level in the body within a few days. Subsequent exposure would not increase the body burden.

The results of studies in experimental animals and man provide sufficient bases for concluding that exposure to levels of 2,4,5-T encountered in its present manufacture and use will not result in persistent (and eventually excessive) accumulation of the compound in the body or any of its tissues. Further discussion of this issue is found in response to question 2, supra, and in response to Issue V.B.4.

As to TCDD, there is only one study reported (DD-176) which assesses the fate of TCDD following ingestion. In this study a lethal or near lethal dose of TCDD (some of which was radioactively labeled with carbon-14) was administered orally to male rats. Subsequently, radioactivity was measured in tissues and excreta as a function of time. The results provide a basis for the following statements:

(a) Most of the orally administered TCDD is absorbed from the gut.

(b) In the body, TCDD and/or metabolite(s) of TCDD are localized in liver and fat.

(c) Absorbed TCDD and/or metabolite(s) of TCDD are eliminated predominantly via the feces. Small amounts are eliminated in the urine. It appears that an even smaller fraction is totally metabolized by the body to CO_2.

(d) The time required for elimination of one-half of the TCDD absorbed is approximately 17 days.

(e) With repetitive administration (exposure) it is projected that a steady-state amount of TCDD would be attained in the body and its tissues within 90 days. Specifically, the days of exposure required to attain the specified percent of steady-state are: 30%, 9 days; 60%, 23 days; 80%, 40 days; 90%, 58 days; 98%, 97 days.

From this study, it may be concluded that the capacity of the body to eliminate TCDD is significantly less than 2,4,5-T. Therefore, if tolerable, an equivalent exposure to TCDD and 2,4,5-T would result in the attainment of a significantly higher steady-state level of the former in the body and its tissues. Nonetheless, upon repeated exposure to small levels of TCDD, an amount in the body and concentrations in the tissues will be attained beyond which further accumulation will not occur, i.e., with subsequent exposure. This steady-state level will be attained within a definable period of time, approximately 90 days.

In studies of the repeated ingestion toxicity of 2,4,5-T in animals, toxicity associated with repeated exposure to and hence accumulation of a TCDD contaminant of 2,4,5-T should be discernible within 90 days. Additional exposure will not lead to attainment of higher

levels of TCDD (or of discernible signs of toxicity). Although the data are not yet available, additional studies of the fate of TCDD in the body are underway.

6. The question of whether there are other sources of dioxin in the environment has not been fully explored. Such other sources, when added to the amount of dioxin from 2,4,5-T, could result in a substantial total body burden for certain segments of the population.

Response

Although there are other possible sources of dioxin (i.e., those materials which require 2,4,5-trichlorophenol as a raw material) the uses of these products are so divorced from 2,4,5-T, that concern that these materials will add to the dioxin level from 2,4,5-T is unwarranted. For more detailed discussion of this point, see Response to Statement of Issues V. B. 6, infra.

7. The registrants have not established that there is no danger from dioxins other than TCDD, such as the hexa- and hepta-dioxin isomers, which also can be present in 2,4,5-T, and which are known to be teratogenic.

Response

There is no danger from dioxins other than TCDD. With the exception of hexachlorodioxin (HCDD), the other dioxins are several orders of magnitude less toxic than TCDD. For more detailed discussion, see Response to Statement of Issues V.B. 5, infra.

8. There is evidence that the polychlorophenols in 2,4,5-T may decompose into dioxin when exposed to high temperatures, such as might occur with incineration or even in the cooking of food.

Response

There is no substantial evidence that "polychlorophenols" in 2,4,5-T may form dioxin (specifically 2,3,7,8-tetrachlorodibenzo-p-dioxin) on incineration or cooking, as discussed more fully in response to V.B.1, infra.

Although trace amounts of TCDD can be observed on combustion of 2,4,5-trichlorophenoxy-containing compounds, the amounts formed are less than 0.0001% of any 2,4,5-T products burned. With respect to dioxin formation from conditions similar to cooking, Dow studies (DD-188) show that no detectable amounts of 2,3,7,8-tetrachlorodibenzo-p-dioxin were formed when sodium 2,4,5-trichlorophenate, 2,4,5-trichlorophenol, or sodium 2,4,5-trichlorophenoxyacetate were heated in fat at deep-fat frying temperatures (190°C) for up to 15 hours. The detection limit for 2,3,7,8-TCDD was 0.05 ppm. Equivalent results were obtained in an EPA laboratory study (DD-189). A similar examination of the formation of chlorinated dibenzo-p-dioxins from various chlorinated phenols boiled

in an aromatic solvent for 4 hours at 213°C (Langer, DD-101) detected no chlorinated dioxin. Rather, high molecular weight polymeric phenols appeared to be the major products.

It is concluded, therefore, that no significant amounts of chlorinated dioxins can be formed from polychlorinated phenols when subjected to environmental or food-processing thermal conditions.

9. Studies of medical records in Vietnam hospitals and clinics below the district capital level suggest a correlation between the spraying of 2,4,5-T defoliant and the incidence of birth defects.

Response

Based on the findings and conclusions of one survey team, and the conclusions reached by both the Advisory Committee on 2,4,5-T and the President's Science Advisory Committee, there is no evidence to correlate an increase in birth defects with the use of 2,4,5-T in Vietnam.

Cutting et al. (DD-162) conducted a study in Vietnam for the period 1960-1969, to determine if there was any correlation between the incidence of birth defects and the use of defoliants containing 2,4,5-T. The data are sorted into two time periods, pre - or light spraying years (1960-1965) and heavy spraying years (1966-1969).

The results of this study were published in December, 1970. In summary, it determined that:

> "(a) In four geographical regions -- capital, coastal, interior, and delta -- the rates per 1000 livebirths of stillbirth and congenital malformation were 32.5 and 5.8, respectively, in the capital area, and 36.7 and 2.9 in the three remaining areas. The differences in these rates may be attributable to better maternal and neonatal care, or to more competent or thorough examination for congenital malformations in the capital area.

"(b) The rates for stillbirths declined and for congenital malformations remained unchanged during this 10-year period.

"(c) The only differences in these rates between the years 1960-1965 and 1966-69, periods of relatively light and heavy defoliant spraying, respectively, was downward trend (from 36.1 to 32.0 for stillbirths, and from 5.5 to 4.5 for congenital malformations).

"(d) There were no consistent differences between heavily and lightly defoliant-sprayed areas."

The 2,4,5-T Advisory Committee offered an explanation for the apparent difference in stillbirth and malformation rates in the more remote areas where exposure to spraying could have been more intense, as follows:

"[I]n recent years, as a larger and larger proportion of births was registered (e.g., number recorded in noncapital areas in 1960-65 was 37,951; in 1966-69, 113,358) a larger proportion of stillbirths was ascertained and a more complete examination for and/or recording of congenital malformations was made."*

Finally, the President's Science Advisory Committee (DD-163) evaluated all available data on the use of herbicides in Vietnam and stated their conclusions, as follows:

"The Panel was aware of press reports of increased birth defects in Vietnam attributed to the use of defoliants. The lack of accurate epidemiological data on the incidence and kinds of birth defects in the Vietnamese population before or since

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* Administrative Law Judge Exh. 1, p. 55.

the military use of defoliants precludes any estimate as to whether an increase in birth defects has occurred. Calculations of potential human exposures from sources such as drinking water or direct fallout make this appear unlikely (though theoretically possible)."

10. The registrants have not established the need for 2,4,5-T in light of the above-mentioned risks. Benefits from 2,4,5-T should be determined at a public hearing, but tentative studies by this agency have shown little necessity for those uses of 2,4,5-T which are now at issue.

Response

The need for and benefits of 2,4,5-T in rice cultivation are discussed in response to Issue V.C., infra.* After approximately 25 years of use, there is no substantial evidence to indicate that when 2,4,5-T is used according to label directions, there is any unreasonable risk to humans, livestock, wildlife or the environment. 2,4,5-T, accordingly, should continue to be available to rice growers in areas where it performs an essential function, as follows:

(a) The rice-growing areas of Mississippi are ideally suited for production of high quality rice for feed grain and seed. The problem weeds are most effectively controlled by 2,4,5-T, which is also the safest of available herbicides to use near cotton, which is grown in close proximity to rice.

(b) In several of the Arkansas rice-growing areas, curly indigo and coffeeweed (sesbania) are serious weed problems. Cotton is also grown in these areas and 2,4,5-T, therefore, has been the preferred herbicide for the past 20 years. Use of 2,4-D has resulted in damage claims from spray drift to nearby cotton.

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* As noted below, it is anticipated that other parties will respond to this question and to Issue V.C. as to the benefits of 2,4,5-T for uses other than rice.

(c) Second crop rice is grown in parts of Texas. 2,4,5-T applied to the first and second crop does not significantly reduce yields or cause injury to either crop, whereas 2,4-D or MCPA applied to both crops may cause serious rice injury.

(d) Louisiana weed research experts believe it important to maintain 2,4,5-T in the available arsenal of herbicides, because of shifting weed populations depending on other cultural practices.

Issue V.A.: The health hazards to man and to other animals which may be caused by 2,4,5-T and/or its extremely toxic contaminant 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD), with emphasis on the following:

1. Is 2,4,5-T or TCDD a teratogen?

Response

A categorical "yes" or "no" answer to this question might be misleading because the results of tests on these two compounds have not been consistent and there have even been some differences of opinion as to what constitutes evidence of teratogenicity. It is clear that neither compound has any teratogenic effect at presently registered environmental use levels. There is conflicting evidence with respect to high dosages in laboratory animals. Subject to these caveats, however, 2,4,5-T may be and TCDD is a teratogen.

In view of the above, the specific questions raised under this issue must be posed within the framework of "hazard" The evaluation of whether a pesticide chemical is a hazard to man and other animals is based upon its toxicological properties and the amounts to which man and other animals are exposed. Thus, the question becomes: "Is 2,4,5-T and/or TCDD a teratogenic hazard to man or other animals?"

(a) Summary as to 2,4,5-T.

2,4,5-T has been studied extensively in various mammalian species for its effect on the development of the embryo and fetus. The first experiments to cast suspicion that 2,4,5-T could harm embryos and fetuses were conducted at the Bionetics Laboratory under a National Cancer Institute Contract. The initial study was done with a sample of 2,4,5-T which contained

27 ± 8 ppm of TCDD (DD-1). This and subsequent studies* showed that 2,4,5-T containing from 0.02 to 30 ppm TCDD could affect prenatal development in mice, specifically causing cleft palate and, in some cases, an effect on the kidney of uncertain consequences. The incidence of cleft palates in mice was low until high dose levels were reached. In some experiments these high dose levels caused the death of many fetuses and dams (e.g., DD-5).

As determined by various investigators, the no effect level in several strains of mice ranged from 20 to 50 milligrams of 2,4,5-T per kilogram of body weight per day.**

The apparent teratogenicity of 2,4,5-T towards mice at high dose levels is not surprising, since mice are quite sensitive and adverse effects on embryo and fetal development are produced under various circumstances, including fasting (DD-9), stress (DD-10), transportation by air (DD-11) and administration of large doses of common table salt (DD-8).

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* References DD-2,3,4,5,6 and 7.

**Doses were generally administered to pregnant mice on days 6-15 of gestation, the period when the tissues are differentiated into organs.

Moreover, the effects of 2,4,5-T at high doses (such as death and resorption of embryos and fetuses, and lowered body weight) are not subtle or unexpected. 2,4,5-T, like many chemicals of synthetic or natural origin, is toxic to animals at high dose levels and has no apparent toxic effect at lower levels. This is a common occurrence with drugs where doses which exceed those which produce the desired effect provoke different and possibly undesirable responses.* It has also been shown (DD-12 and 27) that 2,4,5-T will pass into the fetuses of mice and rats.

2,4,5-T has also been tested for teratogenic potential in the rat, hamster, rabbit, monkey, sheep and reindeer (DD-13,14,15,16,17,18,19,20). In most of these studies no skeletal deformities were noted. In two instances -- one a rat study (DD-19) and the other a hamster study (DD-14)-- the investigators observed delayed ossification of bones among litters delivered by Caesarean section. However, when the litters (rat) were delivered normally, the offspring were not impaired in their development.

The following table summarizes the dose levels in the various 2,4,5-T teratology experiments which gave no effect:

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* Drill's Pharmacology in Medicine, Ed. by J.R.D. Palma, McGraw-Hill Book Co., New York. Fourth Ed., 1971, p. 12.

No-Effect Dose Levels of 2,4,5-T*

AUTHOR	SPECIES	NO EMBRYOTOXIC EFFECT
Courtney, *et al.*, 1970**(DD-1)	Mice	21.5 mg/kg
Courtney & Moore, 1971, (DD-3)	Mice	50
Roll, 1971 (DD-5)	Mice	20
Neubert & Dillman, 1972 (DD-6)	Mice	30
Courtney, *et al.*, 1970**(DD-1)	Rats	4.6
Emerson, *et al.*, 1971 (DD-13)	Rats	>24****
Courtney & Moore, 1971 (DD-3)	Rats	46.4
Khera & McKinley, 1972 (DD-19)	Rats	50
Wilson, 1971 (DD-15)	Monkey	40***
Dougherty, 1972 (DD-16)	Monkey	10
Emerson *et al.*, 1971 (DD-13)	Rabbit	40
Collins & Williams, 1971 (DD-14)	Hamster	80
Binns & Balls, 1971 (DD-17)	Sheep	113****
Erne, 1972 (DD-18)	Reindeer	1****

* Studies in which 2,4,5-T was administered throughout the period of organ development.

** 2,4,5-T sample contained 27±8ppm TCDD.

*** Decreased wt. at 10-40 mg, but not thought to be significant by Wilson.

**** Highest dose given.

(b) Summary as to TCDD.

TCDD is well known as a highly toxic chemical to various species of laboratory mammals and man. 2,4,5-T now manufactured contains less than 0.1 ppm TCDD. Samples used in the tests discussed below contained up to 27 ± 8 ppm of TCDD.

TCDD has been studied for its effects on embryo and fetal development in the mouse (DD-2,-3,-6) and the rat (DD-24). It has a propensity to cause cleft palates in mice, with some strains more susceptible than others. The incidence was highest at doses which also drastically increased fetal mortality (DD-6). While TCDD was toxic to dams and fetuses in rats, a no-effect level was established (DD-24).

The following table summarizes the dose levels in the various experiments which gave no-effect and those which gave an effect:

Summary of Teratologic Studies with TCDD
No Effect Dose/Effect Dose
(µg/kg of body wt./day)

		Mouse		Rat		
		DD-2,3	DD-6	DD-24 (Sprague Dawley)	DD-2 (Sprague Dawley)	DD-28 (Wistar)
Fetotoxicity	Charles Rvr.	-/3	--			
	DBA	-/3	--	0.03*/0.125**	-/2	.125-.25
	C57Bl/6	-/3	--			
	NMRI	---	3/4.5			
Embryotoxicity	Charles Rvr.	-/1	--			
	DBA	-/1	--	0.03/0.125	-/2	
	C57Bl/6	-/3	--			
	NMRI	---	0.3/3			

* No dose given between 0.03 and o.125 µg/kg/day.
** These include gastrointestinal hemorrhage and edema.
--- No data.

(c) Combinations of 2,4,5-T and TCDD

Two studies have been conducted with TCDD administered in combination with purified 2,4,5-T (containing $<$0.05 ppm TCDD) to pregnant rodents. The data are summarized in the tables at pp. 91-2, *infra*.

Finally, TCDD alone or in combination with 2,4,5-T, is more fetotoxic in laboratory animals than it is teratogenic. The no effect levels of TCDD for embryotoxic effects are:

Mouse = 0.3 μg/kg/day
Rat = 0.03 μg/kg/day

Although TCDD has embryotoxic tendencies at small dosages, there is no indication that it causes terata such as short limbs, absence of toes, small head, absence of lower jaw, etc., all of which have been observed from treatment of pregnant animals with vitamin A, thalidomide, and other known potent teratogens.

Evaluation and Conclusions.

From the data reviewed in (a), (b) and (c), it is concluded that both 2,4,5-T and TCDD show a graded dose-response relationship.

The animals most likely to be exposed to 2,4,5-T are those which graze on treated grass, such as sheep, cattle, deer, and possibly rabbits. Tests in sheep indicate they tolerate 113 mg 2,4,5-T/kg/day without fetotoxic or teratogenic effect. These animals eat about 3% of their body weight/day in food or about 30 grams of food/kg/day. 113 mg of 2,4,5-T/30 grams of food is equivalent to about 4000 ppm. This far exceeds residues in grass resulting from spraying 2,4,5-T according to registered uses. Thus, one can reasonably conclude that 2,4,5-T presents no teratogenic or fetotoxic hazard to these animals. The 40 mg/kg/day no effect level in rabbits also provides an adequate margin of safety for this species eating sprayed grass.

Possible human exposure to 2,4,5-T and TCDD from ingestion of foodstuffs (and otherwise) is discussed in detail in response to Issues V.A. 5 and V.B. 4, <u>infra</u>. It is concluded that 2,4,5-T as now manufactured ($<$0.1 ppm TCDD) does not present a teratogenic hazard to women when used in accordance with presently registered uses.

(d) Detailed Review of Data -- 2,4,5-T.*

(1) Mouse.

(i) Courtney et al. (1970) (DD-1)** concluded that 2,4,5-T is teratogenic and fetocidal in two strains of mice when administered daily throughout the period of organogenesis either subcutaneously in dimethylsulfoxide or orally in honey.

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* To facilitate review, various terms and standard abbreviations will be defined at the outset:

- Teratogenic: causing a toxic effect on the embryo which seriously interferes with normal development or survival of the offspring.
- Fetocidal: causing the death of the fetus (the unborn young of an animal that bears its young alive) after it has taken form in the uterus.
- Organogenesis: the formation of the organs during the development of the embryo.
- Subcutaneous: beneath the skin.
- Dimethylsulfoxide (DMSO): An organic solvent soluble in water, alcohol, benzene.
- Mg/kg/day: Milligrams of chemical administered per kilogram of body weight per day.
- Cleft palate: a fissure in the roof of the mouth.
- Scapula: shoulder blade.
- Humerus: bone of upper arm.
- Radius, ulna: bones of the forearm.
- Amniotic sac: the membrane enveloping the embryo within the womb.

** This is the publication containing the data generated at the Bionetics Laboratories under NIH contract. It was originally disclosed in October 1969, in the press and by Dr. Dubridge of the Office of Science and Technology.

When injected into mice there was no effect on the fetuses at a dose of 21.5 mg/kg/day for 6-15 days of gestation. A significant increase in percent of abnormal (cleft palate and cystic kidney)* litters of mice was observed at doses of 46.4 and 113 mg/kg/day administered to the pregnant animals on days 6 through 14 or on days 9 through 17 of gestation. There was also a significant increase in percent of fetal mortality per litter of mice at the 113 mg/kg/day dose given orally.

The sample of 2,4,5-T used in this study contained approximately 30 ppm 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).**

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* Cystic kidney: This term was not defined or described by Courtney and may be wrongly applied.

** Using this value, 30 ppm TCDD, the amount of TCDD administered along with the 2,4,5-T was:

mg 2,4,5-T/kg/day	µg TCDD/kg/day
21.5	0.6
46.4	1.4
113	3.4
(mg = milligram)	(µg = microgram)

(ii) During the Senate hearings on 2,4,5-T, on April 15, 1970, Dr. Courtney reported (DD-2) on additional teratology studies with three strains of mice and one strain of rats.* The following samples were used in mice:

[a] purified 2,4,5-T which contained less than 0.05 ppm TCDD,

[b] commercially produced 2,4,5-T containing approximately 0.5 ppm TCDD,

[c] 2,4,5-T from Eastman Organic Chemicals, and

[d] TCDD.**

The compounds were administered to pregnant mice by subcutaneous injection in dimethysulfoxide on days 6 through 15 of gestation (10 doses). The doses of 2,4,5-T used were 50, 100, 113 or 115 mg/kg/day.

The purified sample, [a], was tested in one strain (Charles River mice) at one dose level only (100 mg/kg/day). It resulted in a significantly increased incidence, over controls, of cleft palate and kidney involvement (not otherwise described). In the same strain of mice, the sample of commercial 2,4,5-T, [b], gave no adverse effects at doses of 50 or 100 mg/kg/day.

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* The results of the tests on rats are presented in this discussion under (2) Rats (ii), *infra*.

** The results of the tests on TCDD are given in this discussion under V.A.1, TCDD, *infra*.

At 150 mg/kg/day this sample, [b], resulted in a significant number of cleft palate and increased fetal mortality, but resulted in no kidney involvement. In DBA mice, the commercial samples of 2,4,5-T, [b] and [c] were judged to have caused an increase in cleft palate at doses of 100 mg and 113 mg/kg/day, respectively. There was no increased kidney involvement or fetal mortality from either sample.

In C57Bl/6 mice, 100 mg/kg/day of 2,4,5-T commercial production, [b], caused no significant increase in cleft palate or kidney involvement, but there was an increase in fetal mortality.

(iii) In 1971 Courtney and Moore (DD-3) published results of a study in mice using the same 2,4,5-T samples as were reported on at the April 1970 Senate hearings, see (ii), supra. The "technical" sample of 2,4,5-T used contained 0.5 ppm TCDD and the "analytical" sample contained $<$ 0.05 ppm TCDD.* Doses of 50, 100, 125 and 150 mg/kg/day were given but all doses were not given to all strains.

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* Described in (ii), supra as samples [a] and [b].

The 2,4,5-T was dissolved in dimethylsulfoxide and administered by subcutaneous injection to three strains of mice (CD-1 Charles River Laboratories; DBA/2J and C57Bl/6J, Jackson Laboratories) on days 6 through 15 of gestation. Both samples of 2,4,5-T produced cleft palate in all three strains at doses of 100 mg/kg/day and higher.

The technical sample was administered at a dose of 50 mg/kg/day to only the CD-1 mice, and did not result in teratological or embryotoxic effects.

Fetal deaths were observed only in the CD-1 strain at the 150 mg/kg/day dose. Kidney anomalies were seen in some experiments but were absent in others even when the same or higher dose was administered, which creates some doubt about the significance of this observation.

(iv) Hart and Valerio (DD-4) studied two samples of 2,4,5-T for teratological effects on CD-1 (Charles River) mice. One sample was from a commercial lot made by Hercules. The other was a highly purified sample prepared by Dow. According to the authors both contained "on the order of 0.05 ppm TCDD."* The 2,4,5-T was administered in either

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* Analyses of these samples in Dow laboratories showed the Dow sample to contain 0.4% total impurities with $<$0.05 ppm TCDD. The Hercules sample contained 10.3% total impurities with 0.18 ppm TCDD. In effect, this meant that the dose of 2,4,5-T from 100 mg of the Hercules sample was really 90 mg/kg/day.

dimethysulfoxide (DMSO) or propylene glycol (PG) by subcutaneous injection to pregnant females on days 6 through 15 of gestation. At a dose of 10 mg of 2,4,5-T/kg/day there was no teratological effect from either sample. The results at a dose of 100 mg/kg/day were as follows:

Sample of 2,4,5-T	Solvent	No. of litters with cleft palate/ No. of litters examined	Total number of fetuses with cleft palate/ No. of fetuses examined
Control (none)	DMSO	0/11	0/77
Control (none)	PG	2/11	2/83
Hercules	DMSO	1/10	1/69
Dow	DMSO	4/10	7/82
Hercules	PG	1/10	2/79
Dow	PG	2/10	10/83

(v) Roll (DD-5) investigated the teratogenic potential of a sample of 2,4,5-T in the NMRI strain of mice. The 2,4,5-T contained $<$0.1 ppm TCDD and the degree of purity was 99.6%. The 2,4,5-T was dissolved in peanut oil and administered orally from the 6th to the 15th day of pregnancy. The doses used were 0, 20, 35, 60, 90 and 130 mg/kg/day. There was a rather strong embryotoxic effect at the 130 mg/kg/day dosage as indicated by late fetal resorptions and dead fetuses. Cleft palates were noted as follows:

Dose 2,4,5-T mg/kg/day	% of fetuses with cleft palates
0	1
20	1
35	6
60	9
90*	15
130*	48

*maternal toxicity

The investigator considered 20 mg/kg/day as the "teratogener no effect level."

(vi) Neubert and Dillman (DD-6) studied the teratogenic effects of several samples of 2,4,5-T and one sample of the butyl ester of 2,4,5-T in NMRI mice. The compounds were dissolved in rape seed oil and given orally by stomach tube at doses from 8 to 120 mg/kg/day.

The purest sample of 2,4,5-T available produced a cleft palate frequency exceeding that of controls at dose levels of 45 mg/kg/day and higher in the NMRI mice when given on days 6 through 15 of gestation. Reductions in fetal weight were observed with doses as low as 10-15 mg/kg. No clear-cut increase in embryolethality over that of controls was seen with these doses.

Preliminary studies with 2,4,5-T-butyl ester showed this compound to have embryotoxic effects on mice comparable to those seen after administration of 2,4,5-T when given during days 6-15 of gestation. Using high doses (150-300 mg/kg), cleft palates were produced with a single oral dose of 2,4,5-T. A maximal teratogenic effect was seen when the compound was administered on day 12 or 13 of gestation.

The investigators also observed that some of the 2,4,5-T preparations available* must contain other contaminants which exaggerate the teratogenic effect to some extent. The more pronounced teratogenic effect was not considered to be due to 2,4,5-trichlorophenol.

(vii) Bage et al. (DD-7) tested commercially available formulations containing 2,4,5-T and 2,4-D + 2,4,5-T for teratogenic effects on NMRI mice. The 2,4,5-T formulation contained the butoxyethyl ester of 2,4,5-T. The paper states that 2,4,5-trichlorophenoxyacetic acid and 2,4-dichlorophenoxyacetic acid were contained in the combination formulations. The TCDD content of all samples was given as <1 ppm.

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* The "purest" sample of 2,4,5-T was considered TCDD free (<0.02 ppm). The other two 2,4,5-T samples used were evidently from commercial production; the TCDD content of one of these was given as 0.05 ± 0.02 ppm. No TCDD content was given for the other commercial sample or for the butyl ester of 2,4,5-T.

The formulations were dissolved in dimethylsulfoxide and administered by subcutaneous injection on days 6 through 14 of gestation. The most striking result was an increased frequency of cleft palate:

Dose in mg/kg/day 2,4,5-T		2,4-D	% of fetuses with cleft palate
110		0	73
50		0	20
37	+	73	68
17	+	33	10
0		0	5

Fetal mortality was increased at both dose levels of 2,4,5-T when given alone and at the high dose level of the 2,4-D and 2,4,5-T mixture. No kidney malformations were observed in this study.

The authors concluded that "the results of the present and other studies do not substantiate any special risk to the human embryo from the regular use of phenoxy herbicides."

TABLE OF TERATOLOGIC STUDIES WITH 2,4,5-T IN MICE

Strain	Route of Admin.	Carrier Solvent	No Effect Level/Effect Level (mg/kg/day) Cleft Palate	Soft Tissue Anomalies	Fetal Mortality	PPM TCDD in 2,4,5-T Used	Reference
AKR	SC	DMSO	--/113	113°/--	113°/--	ca. 30	DD 1
AKR	Oral	Honey	--/113	113/--	--/113		
C57BL/6	SC	DMSO	21.5/113	21.5/113	21.5/113		
do.	Oral	Honey	46.4/113	--/46.4*	46.4/113		
CD-1	SC	DMSO	50/100	50/100	100/150	0.05-<1	DD 2
DBA/2	SC	DMSO	--/100*	113^{h}/--	113^{h}/--		
C57BL/6	SC	DMSO	100°/--	100°/--	--/100°		
CD-1	SC	DMSO	50/100	100^{h}/--	100/150	0.05-0.5	DD 3
DBA/2	SC	DMSO	--/100^{o}(?)	100°/--	100°/--		
C57BL/6	SC	DMSO	--/100°	100°/--	100°/--		
CD-1	SC	DMSO	10*/100	100^{h}/--	100^{h}/--	0.05-0.18	DD 4
CD-1	SC	PG	10*/100	100^{h}/--	100^{h}/--		
NMRI	Oral	peanut oil	20/35	--	90/135	<0.1	DD 5
NMRI	Oral	rape seed oil	30/45	--	45/60	<0.02-0.05	DD 6
NMRI	SC	DMSO	<50/50	--	--/50*	<1^{x}	DD 7

SC = subcutaneous injection

* = lowest dose given

o = only dose given

h = highest dose given

x = 2,4,5-T was in a commercial herbicide formulation

-- = no data.

(2) Rat.

(i) Courtney et al. (DD-1)* evaluated the teratogenicity in rats of a 2,4,5-T sample containing about 30 ppm TCDD.** The 2,4,5-T was suspended in honey and administered orally. The doses of 2,4,5-T were 4.6, 10 and 46.4 mg/kg/day from day 10 through day 15 of gestation. Fetal mortality was increased at the doses of 10 and 46.4 mg/kg/day. Cystic kidney (not otherwise described) was found at all doses and considered a fetal abnormality. No cleft palate or other skeletal abnormalities were noted. Gastrointestinal hemorrhage was noted in fetuses from all dose levels.*** Absence of references to maternal toxicity or of additional signs of embryo or fetal toxicity make this study difficult to put into perspective relative to other studies.

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* This is the publication containing the data generated at the Bionetics Laboratory under a NIH contract. It was originally disclosed October 1969 in the press and by Dr. Dubridge of the Office of Science and Technology.

** Using this value, 30 ppm TCDD, the amount of TCDD administered along with the 2,4,5-T was:

mg 2,4,5-T/kg/day	µg TCDD/kg/day
4.6	0.14
10	0.3
46.4	1.4

*** This response was observed in later tests in fetuses where the pregnant dam was treated with TCDD. Cf. part V.A.1, TCDD, infra.

(ii) During the Senate hearings on 2,4,5-T, Courtney reported on additional teratological studies in CD-1 rats (Charles River) (DD-2). The 2,4,5-T was administered to the rats orally as a sugar suspension. Three samples of 2,4,5-T were used at doses which varied between samples. The time of administration also varied with one sample. The following is a summary of the data:

2,4,5-T Sample Used *	Dose mg/kg/day	Days of Gestation when Given	Terata (cleft palate etc.)	Increased Fetal Mortality	"Kidney Involvement"
"pure"	150	13-14	None	Yes	None
tech	21.5	6-15	None	No	None
tech	21.5	6-15	None	No	None
tech	80. (LD_{40}) **	6-15	None	Yes	None
Bionetics	10	6-15	None	No	Yes
Bionetics	21.5	6-15	None	No	None

* The amount of TCDD in these samples, as determined later by Dow using refined analytic methods, were:

- "pure" = 0.05 ppm
- "tech" commercial production = 0.5 ppm
- Bionetics = 27±8 ppm

The "tech" sample was used in several subsequent tests e.g., by Khera and McKinley in rats (DD-19), by Emerson in rats and rabbits (DD-13), by Binns in sheep (DD-17) and by Collins and Williams in hamsters (DD-14).

**LD_{40} = the dose which kills 40% of the animals, in this case, the dams.

(iii) In 1971 Courtney and Moore (DD-3) published the rat teratology data on the "tech" samples of 2,4,5-T as presented at the April 1970 Senate hearings. These data are reviewed at (ii), supra (see also DD-2). However, in the publication under review here they assigned some significance to "kidney anomalies" by stating "[i]n the rat, 2,4,5-T/tech produced a minimal response in kidney malformations. . ." The doses given of this sample were from 10 to 80 mg/kg/day. Additional data were also presented on an analytical grade 2,4,5-T which contained $<$0.05 ppm TCDD.

In addition to the previously cited data they also reported on a postnatal study using a purified 2,4,5-T containing $<$0.05 ppm TCDD. In this study 50 mg 2,4,5-T/kg/day was administered orally in sugar to the pregnant rats on days 6 through 15 of gestation. The rats were allowed to litter and the newborn were examined through 21 days, at which time they were sacrificed.

From both experiments the authors concluded that "[i]n the CD rat, 2,4,5-T was neither teratogenic nor fetotoxic," and "[p]renatal administration of 2,4,5-T did not affect the postnatal growth and development of the CD rat."

(iv) Khera and McKinley (DD-19) conducted teratological studies on Wistar rats with several samples of 2,4,5-T (acid) and one sample of the butyl ester of 2,4,5-T. All were analyzed and found to contain no TCDD using a method having a detection limit of 0.5 ppm. The 2,4,5-T and its butyl ester were suspended in either aqueous gelatin or corn oil and administered orally days 6 through 15 of gestation. Doses were 25, 50, 100 and 150 mg/kg/day. Not all doses were used for every sample.

The fetuses from the control animals had spontaneous malformations of the bones of the thorax, such as wavy ribs and fused sterna. The incidence of these spontaneous skeletal anomalies ranged from 6 to 26 percent malformed fetuses per litter. These skeletal anomalies increased at some of the higher dosages of some of the samples tested. The following table shows results of malformed fetuses and malformations of the forelimbs. The malformations include not only the thorax bones but also the forelimbs.

Sample	Dose mg/kg/day	Average % malformed fetuses/litter	Malformed forelimbs/ No. of fetuses
	0	4 - 19	0
2,4,5-T	50	24	0
"	100*	29	0
2,4,5-T_2	25	15	0
"	50	9	0
"	100*	32	3/77
2,4,5-T_2	25	10	0
	50	28	0
	100*	36	0
	150*	56	0
2,4,5-T_3	25	11	0
	50	56	0
	100*	37	7/151
	150*	91	4/11
2,4,5-T_4	50	14	0
2,4,5-T-Bu**	50	3	0
"	150*	11	0

* Dose levels considered by authors as inducing increased skeletal anomalies.

** 2,4,5-T-Bu: 2,4,5-T butyl ester.

In a postnatal study, groups of pregnant rats were treated with 2,4,5-T acid or the butyl ester of 2,4,5-T on days 6-15 of gestation and were allowed to deliver their offspring normally. The offspring were observed for 12 weeks. The survival and growth of offspring from treated dams were not different from the control offspring. Thus, the skeletal abnormalities noted in the teratology study were not incompatible with normal growth and development. No changes in behavior or subsequent reproductive performance were observed among the offspring.

The authors also state that malformative doses also caused a "low incidence of abnormalities (skeletal) not observed in the controls." These were fused ribs, small-sized distorted scapula, distorted humerus shaft, and bent radius or ulna. These latter defects resulted in a shortening of the forearm (see table, supra). The incidence of these abnormalities, not seen in the controls, appeared erratically among fetuses from the higher doses (100-150 mg/kg/day) and not in every experiment, and not in replicated tests. There was an increase in fetal deaths at doses of 100 mg/kg/day of 2,4,5-T acid.

(v) Emerson et al. (DD-13) conducted a teratology study with Sprague-Dawley rats using 2,4,5-T from a routine production lot made by The Dow Chemical Company, which

contained 0.5 ppm TCDD. The 2,4,5-T was suspended in a water solution of a soluble cellulose derivative suspending agent and given orally during days 6 through 15 of gestation. The doses were 0, 1, 3, 6, 12 and 24 mg/kg/day. No clinical or gross pathological sign of adverse effect was observed in dams during, or after the period of treatment or gestation. Detailed observations and examinations of the fetuses did not reveal any teratogenic or embryotoxic effects from any dose administered.

(vi) Sparschu et al. (DD-20) conducted a study similar to that by Emerson et al. (DD-13) to determine if higher doses of 2,4,5-T would adversely affect development of the embryo and fetus.

A commercial product lot of 2,4,5-T containing 0.5 ppm TCDD did not produce a teratogenic response when administered orally to rats on days 6-15 at a dose of 50 mg/kg/day. In the fetuses, minimal effects in the form of a slightly higher incidence of delayed ossification of the skull bones were observed. The authors state that in other experiments where delayed ossification of the normally developed bones of the skull has been observed in fetuses delivered by Caesarian section no differences could be detected from the controls in the ossification of skeletons of the 3-week old neonates from litters which were delivered normally and reared by the mothers.

A dose of 100 mg of 2,4,5-T/kg/day was so toxic to the dams that it was only given on days 6-10 of gestation. Of the 4 dams surviving out of 25 treated, three had complete early resorptions and one had a litter of 13 viable fetuses which showed toxic effects but no terata.

(vii) King et al. (DD-26) administered "purified" and "technical" grade 2,4,5-T by application to Millipore filters that were then placed on the amniotic sac* of the rat embryo (Sprague Dawley) on any one day of gestation from day 12 to 16. The results were as follows:

2,4,5-T Used	Dose: µg/embryo	No. of embryos Treated	No. of cleft palates
"purified"	50-125	93	0
"technical"	50-125	118	2 (on day 15)
controls	--		0

These investigations also administered 2,4,5-T and/or combined with 2,4-D orally to Sprague Dawley rats at critical stages of organogenesis at a total dosage range of 60 to 120 mg/kg. These rats yielded 2231 fetuses, 9 of which had cleft palates. Dr. King evidently assumed these results to be negative (See letter attached to DD-26).

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* anmiotic sac: The membrane enveloping the embryo within the womb.

(viii) C.H. Boehringer Sohn (DD-22) tested 2,4,5-T (<0.02 ppm TCDD) for its embryotoxic and teratogenic effects in a prenatal toxicological trial using FW-49 rats. The investigations were carried out in compliance with the F.D.A. guidelines issued in 1966 (Phase II) and took place in Ingelheim in September/October 1970.

Dose levels of 25, 50, 100 and 150 mg of 2,4,5-T/kg/day were employed. Each group, including the controls, consisted of 23 animals. The substance was made up as a suspension in peanut oil and administered orally by gavage (0.5 ml/100 g/day) from day 6 to day 15 of gestation. The fetuses were delivered by Caesarean section on the 21st day of gestation. All the fetuses were examined for external malformations. Two thirds of each litter were examined for skeletal and one third for soft tissue malformations (histological investigation of the kidneys).

The examination of the fetuses revealed no signs of a teratogenic effect of the compound. Even at the high dosages (100 and 150 mg/kg) which probably cause toxic effects in the dams, no malformations were observed in the surviving fetuses which could be associated with the substance. On the other hand, beginning from 50 mg/kg there was a dose-dependent increase in the resorption rate and in 100 and 150 mg there was a reduction in the mean fetal weight.

(ix) Hall (DD-23) studied the effects of 2,4,5-T on pregnant rats receiving an adequate or low protein diet. The diets contained 250 and 1000 ppm. At their rate of food consumption, these rats were receiving approximately 20 and 80 mg of 2,4,5-T/kg/day. The effect of 2,4,5-T was studied in conjunction with the effect of low and normal protein diets. With a normal level of protein in the diet, rats that were fed the high level of 2,4,5-T showed a decrease in food consumption and weight gain. There was no effect on the incidence of fetal deaths, but the offspring of rats treated with the high level of 2,4,5-T had a lower body weight than control offspring. In animals receiving 2,4,5-T in a diet that was low in protein the adverse effects associated with 2,4,5-T were enhanced, but there was no teratogenic effect.

(x) Sjoden et al. (DD-21) conducted a study with rats to determine if 2,4,5-T given to pregnant rats affected the behavior of their offspring. All of the rats were allowed to deliver their offspring, which were subsequently subjected to open-field behavior tests for two consecutive days at 90 days of age. Dose levels of 2,4,5-T ranged from 4 to 100 mg/kg. Maternal toxicity was not observed at any dose level. There were no fetal abnormalities observed among any of the offspring at birth. The incidence of fetal death was greater than control values at dose levels of 40 mg/kg

and higher. Regarding the behavioral observations, it was found that male offspring of treated mothers were significantly more explorative than male offspring of control mothers. No effect of treatment on emotional reactivity was observed in male offspring. The open-field behavior of female offspring was not affected by treatment with 2,4,5-T. There was no clue as to the possible mechanism for this open-field effect and it was not possible to determine if this effect was mediated before birth or after birth.

SUMMARY TABLE OF TERATOGENIC STUDIES WITH 2,4,5-T IN RATS

Strain	Route of Admin.	Carrier-Solvent	cleft palate	no effect level/effect level (mg/kg/day) soft tissue anomalies	fetal mortality	ppm TCDD in 2,4,5-T	Reference
--	oral	honey	0/46.4[h]	--/4.6	4.6/10	ca. 30	DD 1
CD 1	oral	sugar	0/150[h]	150[o]/--	48.4/80	<0.05	DD 2
CD 1	oral	sugar	0/150[h]	150[o]/--	--/150[o]	<0.05	DD 3
CD 1	oral	sugar	0/80[h]	80[h]/--	46.4 /80[b]	0.5	DD 3
Wistar	oral	gelatin soln. or corn oil	0/150[h]	150[h]/--	50/100	≦0.5	DD 19
Sprague-Dawley	oral	cellulose derivative	0/24	24[h]/--	24[h]/--	0.5	DD 13
Sprague-Dawley	oral	cellulose derivative	0/100	100[h]/--	50 /100	0.5	DD 20
Sprague-Dawley	intra-uterine	[re] millipore filter	0/93 fetuses, tech 2,4,5-T } 50-125 µg/embryo			---	DD 26
	intra-uterine		2/118 fetuses, "pure" 2,4,5-T } 50-125 µg/embryo				
	oral		9/2231 fetuses 2,4,5-T, 2,4,5-T + 2,4-D, 2,4-D } at 60-120 mg/kg				
FW-49	oral	peanut oil	0/150[h]	150[h]/--	150[h]/--	<0.02	DD 22
?	oral	Diet	80[h]/--	80[h]	80[h]/--		DD 23
?	oral	?	100[h]/--	100[h]	16/40		DD 21

b = maternal LD_{40}; m = skeletal anomalies other than cleft palate; o = only dose given; h = highest dose given

(3) Hamsters.

(i) Collins and Williams (DD-14) studied the teratogenic effects of 2,4,5-T (acid) in the hamster. The 2,4,5-T was administered orally on days 6 through 10 of gestation at dose levels of 20, 40, 80 and 100 mg/kg/day. Seven 2,4,5-T samples containing from non-detectable amounts to 45 ppm TCDD were used. Not all dose levels were used for all samples. The experimental information and results were as follows:

2,4,5-T Sample/ ppm TCDD	2,4,5-T Dose mg/kg/ day	% Total Mortality of Fetuses	% Abnor- malities*/ Live Litter	% Hemor- rhages/ Total live Fetuses
Control	--	3	4	0.3
A/45	100	100	--	--
	80	94	100	43
	40	74	33	76
	20	32	25	28
B/3	100	11	50	13
	80	10	13	2
	40	7	0	0
C/0.5	100	57	40	8
	80	44	40	13
	40	4	11	3
	20	9	0	9
D/0.1	100	47	0	6
	80	33	0	2
	40	2	0	0
E/ND**	100	56	36	0
	80	30	0	4
	40	11	0	2
F/ND	100	31	40	7
G/ND	100	30	0	17

* = bulging eyes (absence of eyelid) and delayed ossification of skull bones accounted for the majority of effects.

** ND = Non-detectable

Note the increased incidence of adverse effects from higher amounts of TCDD in the 2,4,5-T.

(4) Rabbit.

(i) Emerson (DD-13) studied the teratogenicity of 2,4,5-T in tne white New Zealand rabbit using oral doses of 10, 20 or 40 mg/kg/day on days 6-18 of gestation. This regimen caused no maternal toxicity, fetal toxicity or fetal deaths and no soft tissue or skeletal malformations.

(5) Monkeys.

(i) Wilson (DD-15)* treated 17 pregnant rhesus monkeys orally with 2,4,5-T at dose levels of 5, 10, 20 and 40 mg/kg for three times per week between days 20 and 48 of gestation. No malformations were found, but 1 of 5 animals at 40 mg/kg aborted* and some fetuses from females dosed at the 10, 20 and 40 mg/kg levels were moderately smaller in size The results are given in the following table:

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* In the same paper (DD-15) the author indicates that in his laboratory 26% of 220 pregnancies used for teratological testing aborted before day 100 of gestation.

Results of treating pregnant rhesus monkeys orally with 2,4,5-T acid, 3 times per week for 4 weeks* (foetuses removed by hysterotomy on day 100 of gestation).

Dose mg/kg	Period of treatment (days of gestation)	Condition of 100-day foetus			
		wt. (g)	external	autopsy	skeleton
5	22-48	149	normal	normal	normal
	21-48	175	normal	normal	normal
	20-45	150	normal	normal	normal
	20-46	137	normal	normal	normal
	mean body weight	154			
10	22-47	126	normal	normal	pubis small
	22-46	127	normal	normal	pubis not ossified
	22-48	128	normal	normal	normal
	22-48	151	normal	normal	pubis small
	mean body weight	133			
20	20-45	128	normal	normal	talus and pubis not ossified
	20-45	139	normal	normal	pubis not ossified one sternebra
	22-48	153	normal	normal	normal
	22-46	123	normal	normal	normal
	mean body weight	136			
40	20-46	139	normal	normal	normal
	22-48	126	normal	normal	talus and pubis not ossified
	22-48	aborted day 61			
	22-48	125	normal	normal	talus not ossified, pubis small
	22-48	135	normal	normal	pubis small
	mean body weight	131			
7 untrtd. controls		140±5**	normal	normal	2 pubis small or not ossified 1 talus not ossified

* These data are reproduced with the consent of the Swedish National Poisons and Pesticides Board, which supported this study.

** Standard error, range 119-154 g.

(ii) Dougherty *et al*. (DD-16) administered a technical grade of 2,4,5-T (<0.05 ppm TCDD) orally to pregnant rhesus monkeys on days 22-28 of gestation. Doses of 0.05, 1 and 10 mg/kg/day were given. No maternal toxicity or fetal abnormalities were observed at any dose level of 2,4,5-T. The authors concluded that "under the conditions of this experiment there is no evidence that 2,4,5-T is teratogenic in the rhesus monkey nor that it interferes in any way with normal development of the young."

(6) Sheep.

(i) Binns and Balls (DD-17) mixed 2,4,5-T and its PGBE esters with ground alfalfa meal and fed them via stomach tube to pregnant sheep. The dosages given and the results are as follows:

Compound	Dose mg/kg/day	Days of Gestation Dose Given	Total Days Dosed	No. of Ewes	Congenital** Deformities
2,4,5-T Acid	100	14-36	23	11	0
2,4,5-T PGBE esters*	100	14-36	23	11	0
2,4,5-T Acid	113	14-19	6	1	0
2,4,5-T Acid	113	14-27	14	2	0
2,4,5-T Acid	113	14-29	16	2	0

* The 2,4,5-T propylene glycol butyl ether esters were from a commercial production lot of Dow Chemical U.S.A. and contained ca. 0.5 ppm TCDD.

** Alkaloids from Hellebore species (a member of the lily family) given orally to pregnant sheep during the periods of gestation (i.e., at the time of organogenesis in the embryo) used in this study causes very serious deformities in the offspring.

(7) Reindeer.

(i) Erne (DD-18) conducted a study in which a commercial preparation consisting of 2,4,-D and 2,4,5-T in a ratio of 2:1 was sprayed on birch leaves which were then fed to reindeer during the last 1 to 1-1/2 months of gestation. The sprayed leaves contained about 45 ppm total phenoxy acid and the reindeer consumed about 1 mg/kg/day of phenoxy acid. No maternal toxicity was observed and all embryos were alive and normally developed at delivery. The authors also determined that both 2,4,-D and 2,4,5-T crossed the placenta and neither one accumulated in the fetus.

TABLE OF TERATOGENIC STUDIES WITH 2,4,5-T IN MISCELLANEOUS SPECIES

Species	Strain	Route of Admin.	Carrier - Solvent	No-effect level/effect level (mg/kg/day) Skeletal Malformalies	Fetal mortality	ppm TCDD in 2,4,5-T Used	Reference
Hamster	Golden Syrian	Oral	acetone: corn oil: CMC	--/20*	--/20*	45	DD 14
				80/100	40/100	3	
				40/80	40/80	0.5	
				--/100^{h}	40/80	0.1	
				80/100	--/40*	ND	
				--/100°	--/100°	ND	
				100°/--	--/100°	ND	
Rabbit	New Zeal. White	Oral	cellulose derivative	40^{h}/--	40^{h}/--	0.5	DD 13
Monkey	rhesus	Oral	?	40^{h}/--	40**/---	0.5	DD 15
Monkey	rhesus	Oral	?	10^{h}/--	10^{h}/--	?	DD 16
Sheep	?	Oral	alfalfa meal	113^{h}/--	113^{h}/--	0.5	DD 17
Reindeer	?	Oral	Sprayed on Birch Leaves	1^{h}/--	1^{h}/--	?	DD 18

* = lowest dose level given

^{o} = only dose level given

^{h} = highest dose level given

ND = none detected

** = one out of five pregnant females aborted on day 61 at 40 mg dose.

--- = no data.

(e) Detailed Review of Data -- TCDD.

(1) Mouse.

(i) During the Senate hearings on 2,4,5-T on April 15, 1970, Courtney et al. (DD-2) reported on studies with TCDD in three strains of mice. The TCDD was dissolved in DMSO and injected subcutaneously into pregnant mice on days 6-15 of gestation: The results were as follows:

Strain of Mouse	Dose Micrograms of TCDD/kg/day	PERCENT* Cleft Palates	Kidney Involvement	Fetal Mortality
Charles River	0	0	1	8
	1	3	25	14
	3	5	62	12
DBA	0	0	3	26
	3	3	34	11
C57Bl/6	0	0	2	11
	3	23	97	5

*The manner of calculating "percent" was not described.

(ii) Courtney and Moore (DD-3) published the results of the tests on mice presented orally at the 1970 hearings -- see DD-2 and (i), supra). The results on incidence of cleft palates in the published paper were presented differently and reflected the low incidence of this anomaly:

Strain of Mouse	Dose in Micrograms of TCDD/kg/day	No. of Live Litters	CLEFT PALATES No. of Litters Affected	CLEFT PALATES Av. No. Cleft Palates in Affected Litters
Charles River	0	9	0	0
	1	9	1	2
	3	10	3	1
DBA	0	23	0	0
	3	9	2	1
C57Bl/6	0	23	0	0
	3	7	5	3

(Gastrointestinal hemorrhage observed in 6 of the approximately 300 fetuses from the treated litters.)

(iii) Neubert and Dillman (DD-6) studied the teratogenic effect of TCDD in NMRI mice. The TCDD was dissolved in rapeseed oil and given orally at doses of 0.3, 3.0, 4.5 and 9.0 µg/kg/day on days 6-15 of gestation or in single oral doses of 23 or 45 µg/kg on one of the days 6-15 of gestation. The significant teratological observations were as follows:

Dose µg TCDD/ kg/day	Days	Fetuses With Cleft Palate Per No. of Fetuses		Litters With Cleft Palate	
		Total	%	No.	%
Oil only	6-15	5/669	<1	4	6
0.3	6-15	0/138	0	0	-
3	6-15	9/271	3	7	29
4.5*	6-15	16/124	1	6	50
9.0*	6-15	22/27	82	3	100
9.0)*	9-13	38/64	59	5	83
23	9-12**	-	<5-30	1-4	13-50
45	60-15**	-	10-50	0-10	0-71

*Embryomortality drastically increased at these dosages.

**Dose given on only one day between days indicated.

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(2) Rat.

(i) During the 1970 Senate hearings, Courtney et al. (DD-2) reported on studies with TCDD in Charles River (CD-1) rats. The TCDD was dissolved in DMSO and administered by subcutaneous injection to pregnant rats at varying periods of organogensis. The results were as follows:

Dose in Micrograms of TCDD/kg/day	Days of Gestation Administered	Percent*		Fetal Mortality
		Cleft Palate	Kidney Involvement	
(DMSO only)	6-15	0	0	0-3
0.5	6-15	0	13	3
2	9-10	0	11	7
2	13-14	0	34	1

(ii) Courtney and Moore subsequently published (in part) the results of this TCDD rat study. The publication (DD-3) contained information on only one dose level, 0.5 µg/kg/day, on days 6-15 of gestation as follows:

Dose in Micrograms of TCDD/ kg/day	No. Live Litters	Cleft Palates	Kidney Anomalies		Av. % Fetal Mortality/ Litter
			No. of Litters Affected	Av. No. of Affected Fetuses in Affected Litters	
0	9	0	0	0	0
0.5	6	0	4	2	3

* The manner of calculating "percent" was not described.

(iii) Sparschu *et al*. (DD-24) conducted a study in rats to determine the fetotoxicity and teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The TCDD was administered orally in 9:1 corn-oil acetone solution in doses of 0 (control), 0.03, 0.125, 0.5, 2.0 and 8.0 micrograms per kilogram body weight per day to groups of 24 (control) and 12(treatment) rats on days 6 through 15 to gestation. The fetuses were taken by Caesarean section on day 20 of gestation. The number of viable and dead fetuses and early and late resorptions was recorded. Each fetus was examined for any gross abnormalities. Two-thirds of each litter were fixed in Bouin's solution, Wilson sections were examined under the dissection microscope, and tissues were studies for histopathology. One-third of each litter were fixed in alcohol and examined for skeletal abnormalities by alizarin red-S staining. The principal observations are summarized in the following table:

Dose: Micrograms of TCDD/ kg/day	Viable Fetuses, Mean Per Litter	Total Dead Fetuses	Gastro-intestinal Hemorrhage	Subcutaneous Edema	Skeletal Deformities (**)	Total No. of Fetuses Examined in Each Case
0	10 ± 4	0	0	0	0	246
0.03	12 ± 4	0	0	0	0	115
0.125	12 ± 3	3	18	0	1	127
0.5	8 ± 4	6	36	0	0	99
2	*	0	4	3	1	7
8***	0	0	-	-	-	0

*Seven viable fetuses in four litters.
**Misshapen limbs, rudimentary tail, kinked tail, no cleft palates.
***Severe maternal toxicity, all resorptions of fetuses were early.

Table of Teratogenic Studies with TCDD.

SPECIES	STRAIN	ROUTE OF ADMINISTRATION	CARRIER/ SOLVENT	NO EFFECT LEVEL/EFFECT LEVEL (Micrograms/kg/day) CLEFT PALATE	FETAL MORTALITY	KIDNEY ABNORMALITIES	GI HEMHORRAGE	REFERENCE
Mouse	CD-1	S.C.	DMSO	--/1[1]	--/3[h]	--/1[1]	N.M.	
	DBA	S.C.	DMSO	--/3[o]	--/3[o]	--/3[o]	N.M.	DD2
	C57BL/6	S.C.	DMSO	--/3[o]	--/3[o]	--/3[o]	N.M.	
Mouse	CD-1							
	DBA	(Publication of data from same experiment as above (DD2)					Some*	DD3
	C57BL/6							
Mouse	NMRI			0.3/3	3/4.5	N.M.	N.M.	DD6
Rat	Sprague-Dawley	oral	Corn oil acetone	Misc.Skeletal Anomalies 0.03/0.125(?)	0.03/0.125	N.M.	0.03/0.125	DD22
Rat	CD-1	SC	DMSO	2/---	2/---	--/0.5	N.M.	DD2

S.C. = Subcutaneous Injection
DMSO = Dimethylsulfoxide
1 = Lowest dose used
h = Highest dose used
o = Only dose used
N.M. = Not mentioned
* = 6 of 300 fetuses showed some G.I. hemorrhage but not described as to dosage or strain.
-- = No data

COMBINATIONS OF 2,4,5-T + TCDD

(i) Sparschu *et al.* (DD-25) studied the effects of fetal development in the rat, by administering orally various amounts of TCDD in conjunction with 50 mg of purified* 2,4,5-T/kg/day during days 6-15 of gestation.

The doses of TCDD given were 0.01, 0.03, 0.06, 0.125, 0.5 or 1 microgram/kg/day.

The principal observations are summarized in the following table.

DOSE		Equivalent ppm TCDD on basis of 2,4,5-T used	Viable fetuses, mean per litter	Total dead fetuses	Gastro-intestinal hemorrhage	Subcutaneous edema	SKELETAL DEFORMITIES		Total no. of fetuses examined in each case
mg 2,4,5-T /kg/day	µg TCDD/ kg/day						Rudimentary or kinked tail, shortened limb	Cleft palate	
0	0		11	0	0	0	0	0	194
50	0		9	0	0	0	0	0	172
50	0.01	0.2	11	0	0	0	0	0	150
50	0.03	0.6	12	0	0	0	0	0	173
50	0.06	1.2	10	3	12	0	1	1	155
50	0.125	2.5	10	1	25	3	0	0	134
50	0.5	10	6	3	44	20	0	5	76
50	1.0	20	8	3	22	30	1	17	46

* Contains <0.05 ppm TCDD, same sample as "pure" 2,4,5-T.

(ii) Neubert and Dillman (DD-6), along with their teratological studies on 2,4,5-T, carried out a study in which they combined varying amounts of TCDD with an oral dose of 30 or 60 mg of 2,4,5-T/kg/day from days 6-15 of gestation in NMRI mice. The 2,4,5-T used contained $<$0.02 ppm TCDD. The doses of TCDD used in combination with the 2,4,5-T and the principal observations are summarized in the following table:

DOSE		equivalent ppm TCDD	Viable	No. of cleft	
mg 2,4,5-T /kg/day	µg TCDD /kg/day	on basis of 2,4,5-T used	fetuses mean/litter	palate/no. of fetuses	%
0	0	0	11	5/669	1
0	0.3	NA	11	0/138	0
0	3.0	NA	11	9/271	3
30	0	0	11	1/93	1
30	0.3	10	10	1/118	1
30	3	100	11	18/100	18
60	0	0	10	16/319	5
60	0.1	1.7	10	9/194	5
60	0.3	5	9	18/130	14
60	3	50	12	65/333	20

NA = not applicable

2. Does 2,4,5-T or TCDD induce other adverse reproductive effects?

Response

2,4,5-T and TCDD at 0.1 ppm in 2,4,5-T as presently manufactured, do not induce other adverse reproductive effects.

As previously concluded in V.A. 1., supra, both 2,4,5-T and TCDD have embryotoxic and fetotoxic effects when administered in sufficiently high doses to certain species of test animals. In both cases dose levels have been established at which no such effect is produced in experimental animals.

With respect to 2,4,5-T, the discussion and evaluations of embryotoxic and fetotoxic effects (and no effect levels) in test animals are given in V.A. 1., supra.

Data that bear on other reproductive effects are summarized below.

Lack of adverse effects on survival and fertility in progeny from 2,4,5-T treated dams has been demonstrated in two studies. In a postnatal study, Khera and McKinley (DD-19) treated groups of pregnant rats orally with 2,4,5-T and/or the butyl ester of 2,4,5-T at doses up to 150 mg/kg/day on days 6-15 of gestation. The rats were allowed to deliver their offspring normally. The offspring were observed for 12 weeks. The survival and growth of the offspring were not different from that of the controls. The fertility of the

female progeny of the dams given 100 mg 2,4,5-T/kg/day (the highest dose given) was not impaired. Emerson et al. (DD-13) in a study with 2,4,5-T in rabbits, incubated the 29 day old fetuses (removed by Caesarean section) for 24 hours to determine survival rate. Some mortality occurred in both the controls and fetuses from the treated group given the highest dose of 2,4,5-T/day (40 mg/kg), with no significant differences between the two groups.

Sparschu et al. (DD-20) showed that oral doses of 100 mg/kg/day to pregnant rats caused severe maternal toxicity. Wilson (DD-15) found that one of five pregnant female monkeys aborted on day 61 when dosed with 40 mg of 2,4,5-T/kg/day during days 22-48 of gestation. Although none of the five untreated monkeys aborted in the experiment, the author states that in his laboratory, 26% of 220 pregnancies used for teratological studies aborted before day 100 of gestation. There were no abortions at doses of 20, 10 or 5 mg/kg/day. Dougherty et al. (DD-16), in conducting a teratology study with monkeys, noted no abortions at the 0.05 mg/kg/day dose, 1 abortion at the 1 mg/kg/day dose and two abortions at the 10 mg/kg/day dose. The colony had a spontaneous abortion rate of 12%.

As to TCDD, Khera and Ruddick (DD-28) treated pregnant rats orally with TCDD on days 6-15 of gestation. The dams were allowed to deliver their offspring normally. Postnatally, the survival, body weight gain and reproductive ability of the progeny were adversely affected from dose levels of 0.5 and 1 µg/kg/day to the pregnant dams. There were no such effects in the 0.25 µg/kg progeny. Similarly, the progeny (mated within the experimental group) had a decreased number of pregnancies and reduced litter size at the 0.5 µg/kg/day dose with no effect on fertility noted in the 0.25 µg/kg progeny. It may be concluded, therefore, that a no effect level of 0.25 µg/kg was established for TCDD as to these incidents of reproduction.

3. Is 2,4,5-T or TCDD a mutagen?*

Response

There is no substantial evidence to indicate that either 2,4,5-T or TCDD is mutagenic.

Tests conducted with mammals, and particularly dominant lethal studies, are the most reliable basis for evaluating mutagenic potential of agents (DD-33, p. 602).

Buselmaier, et al. (DD-32) conducted host-mediated mutagenic tests in NMRI mice using mutants of the bacteria Salmonella typhimurium and Serratia marcescens introduced into the mice by intraperitoneal injection. No mutagenesis was found at 2,4,5-T doses of 500 mg/kg and doses of the n-butyl ester of 2,4,5-T of 1000 mg/kg. These investigators also reported on a dominant lethal test with 2,4,5-T in NMRI mice at doses of 1000 mg/kg administered by intraperitoneal injection, with no indication of a dominant lethal effect.

This conclusion is further supported by the fact that chlorophenoxyacetic acids such as 2,4,5-T do not have the type of chemical structure which would react with DNA, causing damage to the genetic material in cells (DD-33, p. 606).

* A mutagen is any agent which causes a change in the character of a gene which is perpetuated in subsequent divisions of the cell. Sometimes such change has an adverse effect on the progeny.

As to TCDD. Khera and Ruddick (DD-28) conducted dominant lethal tests in Wistar rats where groups of male rats were closed orally with 4 or 8 µg TCDD/kg/day for seven consecutive days, after which seven sequential mating trials (with virgin females) were conducted with the surviving males. Reproductive values (pregnancies, viable embryos and resorption sites) indicated no dominant lethal mutations during 35 days post-treatment at both doses. In sum, toxic level doses failed to produce any mutations.

4. Is 2,4,5-T or TCDD a carcinogen?

Response

There is no substantial evidence to indicate that either 2,4,5-T or TCDD is carcinogenic.

The experimental study of most value in this area was done by Innes et al. (DD-36) with the same 2,4,5-T samples containing 27 ± 8 ppm TCDD used in the early Bionetics Laboratory (Courtney et al.) teratological tests. The Innes study involved continuous oral administration to two strains of mice, at doses of 21.5 mg/kg/day, for a period of 18 months. This was the maximum tolerated dose. There was no significant increase in tumors in the treated mice.

Since the 2,4,5-T used in the Innes carcinogenicity screening study contained approximately 27 ppm TCDD, the test animals were exposed to about 0.60 μg TCDD/kg/day for 18 months without any increased number of tumors found.

Walker et al. (DD-37) found that 2,4,5-T shows appreciable inhibitory effects on the in vivo development of the Ehrlich ascites* tumor in mice. They also state results

* Ascites is an accumulation of fluid in the abdominal cavity.

from a USPHS chemotherapy screening program indicating that 2,4,5-T caused inhibition of sarcoma in mice.

Furthermore, 2,4,5-T does not have the type of structure or properties (such as an alkylating agent) which would arouse suspicions of carcinogenicity. Hansen, Quaife, Haberman and Fitzhugh (DD-38) did not find 2,4-D (analogous in this respect to 2,4,5-T) to have carcinogenic properties in a life-time dietary feeding study in rats.

5. Can exposure to 2,4,5-T or TCDD induce sublethal chronic health effects?

Response

Exposure to 2,4,5-T as presently used, and to TCDD resulting from its presence in 2,4,5-T at $<$0.1 ppm as now produced, causes no chronic sublethal health effects in man or other animals.

This response will consider (a) man primarily, with additional discussion of (b) tests in various animal species and (c) results of TCDD feeding studies.

(a) Man. The Dow Medical Department (DD-50) has analyzed laboratory findings and health history responses among men exposed to 2,4,5-T in the manufacture of this herbicide between 1950 and 1970.* A total of 126 employees, whose exposure ranged from about 60 days to more than 960 days, were studied. Exposure was by inhalation, at an estimated rate of 1.6 mg to 8.1 mg of 2,4,5-T/day, which is equivalent to approximately 0.02-0.1 mg/kg/day. These men were given extensive physical examinations, including a battery of at least 20 laboratory (clinical chemistry and hematological) tests. No differences were found between the exposed individuals and a control group of 4600 men. In addition, karyotyping was carried out on 52 exposed men. There was no indication that

* The 2,4,5-T was known to contain $<$1 ppm TCDD from 1965-1970 and believed to have had $<$1 ppm in the period prior to that. As noted elsewhere, after 1971 Dow 2,4,5-T contained $<$0.1 ppm.

2,4,5-T exposure had affected the structural integrity or rearranged the genetic material of the lymphocyte chromosomes.

The EPA Advisory Committee on 2,4,5-T concluded that the study indicated that no illness was associated with such intensive 2,4,5-T intake, and that "[s]pecifically, there was no increase in skin ailments or of alkaline phosphatase or SGPT [serum glutamic pyruvic transaminase] levels as compared with controls having no exposure to 2,4,5-T."*

Most of the literature and early Dow experience indicates that identified cases of chloracne, an acute skin disorder caused by exposure to certain chlorinated hydrocarbon chemicals,** result from industrial exposure of workmen in 2,4,5-trichlorophenol plants, where the likelihood of exposure to significant quantities of TCDD is much greater than in 2,4,5-T plants, or in plants manufacturing

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* Report of the Advisory Committee on 2,4,5-T to the Administrator of the EPA, May 7, 1971, Adm. Law Judge Exh. 1, p. 31.

** Such chemicals include chlorinated diphenyls, chlorinated napthalenes and crude chlorinated phenols. Various chlorinated dibenzo-p-dioxins found in such products, including TCDD, are the active chloracnegenic agents (DD-52). Chloracne, so named because of its similarity in appearance to severe acne suffered by teenagers, is not a chronic condition. The disorder slowly disappears when the affected individual is removed from exposure to the chloracnegen.

both 2,4,5-trichlorophenol and 2,4,5-T.*

As for other possible human exposure, under presently registered uses foodstuffs for human consumption may not contain more than negligible residue levels (0.1 ppm or less) of 2,4,5-T. The following table sets forth the maximum amounts of 2,4,5-T which might be consumed per human per day as a result of such uses of 2,4,5-T.

Foods with Possible 2,4,5-T Residues**	USDA 9th Decile kg of Food Eaten Daily***	Ppm 2,4,5-T Negligible Residue Level	Possible mg of 2,4,5-T/ 60 kg Human/ Day
Meat	0.4	0.1	0.004
Dairy Products	1.1	0.05	0.05
Rice	0.006	0.1	0.0006
		Total	0.0546

$$\frac{0.0546 \text{ mg/day}}{60 \text{ kg}} = 0.0009 \text{ mg/kg/day}$$

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* In reviewing the literature, one must be careful to recognize that some investigators have described 2,4,5-trichlorophenol as "2,4,5-T," whereas "2,4,5-T" is now used to describe only 2,4,5-trichlorophenoxyacetic acid. TCDD, as noted below (Issue V.B.8), is a reaction by-product in manufacture of 2,4,5-trichlorophenol which, in turn, is an intermediate in the manufacture of 2,4,5-T.

** See response to Issues V.B.3 and 4, *infra*.

*** The ninth decile is the value that divides the highest 10% of consumers from the other 90% (DD-51).

Human consumption of as much as 0.0009 mg of 2,4,5-T/kg/day, every day, which is highly unlikely, is still only a small fraction of the no ill-effects dose level of 10 mg/kg/day determined in laboratory animals. The 10 mg/kg/day no ill-effect level is 11,000 times the 0.0009 mg/kg possible consumption figure, which is far greater than the 2000-fold factor accepted by EPA in calculating safe negligible residue levels of pesticides in foods, pursuant to 40 CFR 180.1(l). In terms of health effects, such exposure should also be compared to the Dow workmen exposed for as long as 960 days to estimated intakes of 0.02 to 0.1 mg/kg/day, with no chronic or other health effects (DD-50, supra).

In the absence of probative data on TCDD residues in human foods, it is difficult if not impossible at this time to evaluate possible chronic effects of this substance in conventional terms. However, in view of the infrequent application of 2,4,5-T (once a year or less), the minute amounts of TCDD at current $<$ 0.1 ppm levels actually distributed per acre, the low solubility of TCDD in fat and water, its miniscule uptake by plants and its degradability (although slow), one can reasonably expect no TCDD residues in foods, or residues of such ultra low level as to provide an adequate margin of safety.

(b) Other Animals. Various dietary feeding studies and other long-term treatment with 2,4,5-T in animal species have determined levels at which no adverse effects (clinical biochemical or pathological changes) are detected.* Based on this work it is possible to conclude that there are no chronic sub-lethal effects from exposure to 2,4,5-T. Such studies may be summarized as follows:

(i) Rats. In one study by McCollister, Kociba and Gehring (DD-43) groups of 10 male and 10 female rats per group were maintained for 90 days on diets containing 2,4,5-T at dosage levels of 0, 100, 30, 10 or 3 mg/kg body weight/day.

The 2,4,5-T used was from commercial production and contained 0.5 ppm TCDD. Concentrations of test material in the diet were adjusted weekly to maintain appropriate doses. Observations and tests conducted were appearance and behavior, growth, food intake, hematologic studies and

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* Other studies have determined acute lethal oral toxicity of 2,4,5-T, in terms of LD_{50} (lethal dose in 50% of the animals) in various species, as follows:

Animal	mg/kg LD_{50}	References
Mouse	389	DD-41
Rat	500	DD-41
Guinea pig	381	DD-41
Dog	<100	DD-42

urinalyses during week 12; and terminal clinical chemistry determination of blood urea nitrogen (BUN), serum alkaline phosphatase (AP) and serum glutamic pyruvic transaminase (SGPT) activities, organ weights, gross examination at necropsy, and histopathologic evaluation of the tissues.

Visual observation revealed no changes in appearance or behavior in any of the rats. There was 100% survival in all groups. Evidence of compound-related effects was minimal and was limited to rats at the two highest dose levels. Changes found in both sexes at the 100 mg/kg/day dose included depression in body weight gain, slight decrease in food intake, elevated AP activities, and minor gross and histopathological changes in the liver of some rats. Male rats at this dose also had slightly increased SGPT activity and slight decreases in red cell counts and hemoglobin levels. There were detectable changes at 30 mg/kg/day (increased liver and kidney weights in males, slight elevations in AP and SGPT activities in females); however, the authors concluded these changes were of questionable toxicological significance. At doses of 10 mg/kg/day there were no changes observed which were considered related to the inclusion of 2,4,5-T in the diet. The no-effect level, accordingly, was 10 mg/kg/day.

In another study, groups of male and female rats (10 of each sex per group) were maintained for 90 days on diets containing 0, 100, 300, 1000 and 3000 ppm of a mixture of the mono-, di-, and tripropylene glycol butyl ether esters of 2,4,5-T (DD-44).* No adverse manifestations attributable to 2,4,5-T were observed at dietary levels of the ester of 300 ppm (10-20 mg 2,4,5-T/kg/day) or 100 ppm (3-6 mg 2,4,5-T/kg/day). The no-effect level in both male and female rats, accordingly, was 300 ppm ester or 10-20 mg 2,4,5-T/kg/day.

(ii) Mice. The principal experimental work in mice involving long-term dietary feeding is that by Innes et al. (DD-36), in which 2,4,5-T** was administered orally to two strains of mice for a period of 18 months. The maximum tolerated dose (zero mortality) was determined with single doses, 6 daily doses, and finally 19 daily doses. Administration was by stomach tube at 21.5 mg/kg/day from

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* The ester mixture had an average molecular weight of 409.5 with an acid equivalent of 62.5% 2,4,5-T. Therefore, 3000 ppm ester in the diet was equivalent to 2000 ppm 2,4,5-T, amounting to a dosage rate of 100-200 mg 2,4,5-T/kg/day in maturing rats.

** As noted above (V.A.4), this was the same 2,4,5-T sample used in the Bionetics Laboratory teratology tests which contained 27 ± 8 ppm TCDD.

the end of the first through the fourth week; thereafter the test material was mixed in the diet at a level of 60 ppm (approximately equivalent to 21.5 mg/kg/day) and continued until 18 months of age. There was no significant increase in tumors in the treated mice over those observed in the controls. The authors state that "the postmortem procedure included an external examination and a thorough examination of thoracic and abdominal cavities, with histologic examination of major organs and of all grossly visible lesions."

(iii) Dogs. In one study with dogs, 2,4,5-T was administered orally in capsules to adult mongrel dogs five days a week over a 13 week period, at doses of 2, 5, 10 and 20 mg/kg/day (DD-42).

All dogs receiving 2, 5 or 10 mg/kg/day survived the 90-day test period with no evidence of adverse effects as judged by general appearance, body weights, hematological examination, gross observations of the organs and organ weights obtained at necropsy, and microscopic examination of the tissues. Although all dogs in the highest dosage group died between the 11th and 75th day of the study, their deaths were not correlated with significant lesions in the liver, kidney or other organs examined.

(iv) Monkeys. Preliminary tests were carried out in non-pregnant, female rhesus monkeys. One was given

a single dose of 50 mg/kg and another 10 daily doses of 10 mg/kg. Neither animal showed overt signs of toxicity (DD-45).

(v) Cattle and Sheep. The results of Palmer and Radeleff's work with 2,4,5-T esters in cattle (DD-46) and Palmer's multiple oral dosing studies in cattle (DD-47) are set forth below:

Summary of Toxicity Trials With 2,4,5-T Esters in Cattle (DD-46)

Compound*	No. of animals	Dose (mg/kg on basis of active ingredient)	No. of doses	Results
2,4,5-trichloro-phenoxyacetic acid propylene glycol butyl ether esters	1	250	7	Lethal (sick after 4 doses)
2-(2,4,5-trichloro-phenoxy)-propionic acid, butyl ether esters	1	25	73	Unaffected
	1	50	73	Unaffected
	1	100	29	Lethal
	1	250	5	Lethal

* In all cases commercially available formulations of the various compounds were utilized and were administered as fluid dilutions thereof or put into gelatin capsules for oral administration.

Results of Multiple Oral Dosing of 2,4,5-T (ester and salt) by capsule in Cattle (DD-47)

Compound	Dosage (mg/kg)	No. of doses	Results and Remarks
2,4,5-T, 2-ethyl hexyl ester	50	10	NIE*
	50	10	NIE
	100	10	NIE
	100	10	8-percent weight loss
	250	7	Overt toxicity and death
2,4,5-T, triethylamine salt	50	10	NIE
	50	10	NIE
	100	10	NIE
	100	10	17-percent weight loss
	175	4	Overt toxicity after 1 dose and survival
	250	4	Overt toxicity after 3 doses and death 2 days after last dose

In another study, for 28 days beef cattle (calves) were fed a complete basal ration to which various amounts of 2,4,5-T were added (DD-48). Treatment groups of 3 calves each were fed 0, 100, 300, and 900 ppm 2,4,5-T in the diet (equivalent to 0,

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* NIE indicates no ill effects apparent.

3, 9, 29 mg 2,4,5-T/kg/day, respectively). Two groups of 3 calves were fed 1800 ppm in the diet (equivalent to 44 mg 2,4,5-T/kg/day). One group was slaughtered on the 29th day, and the second group was held for a 7-day withdrawal period. All animals with the exception of the withdrawal group and the control group were slaughtered on the day following the end of the feeding period. The latter group was slaughtered on the 8th day after completion of dosing. No symptoms of toxicity were observed in any of the animals.

The Palmer and Radeleff results with sheep are also summarized below:

Summary of Toxicity Trials with 2,4,5-T Esters and Salt in Sheep (DD-46)

Compound	No. of sheep treated	Dosage mg/kg	No. of doses	Results
2,4,5-trichlorophenoxyacetic acid, propylene glycol butyl ether esters	1	100	369	Lethal
	1	250	7	Lethal (sick after 3 doses)
2,4,5-trichlorophenoxyacetic acid, triethylamine salt	1	100	481	Unaffected
2-(2,4,5-trichlorophenoxy)-propionic acid, butyl ether esters	1	100	11	Lethal

Finally, a feeding trial was conducted in which sheep were fed a complete ground ration to which 2000 ppm 2,4,5-T was added (equivalent to 56 mg 2,4,5-T/kg/day) (DD-49). Groups of 3 sheep were fed, one at 2000 ppm 2,4,5-T in the total diet for 28 days, another at 2000 ppm 2,4,5-T for 28 days followed by six days of untreated feed, and a control group fed untreated feed. Observations by a veterinarian were made at frequent intervals to note any differences in the sheep due to the various treatments. The sheep fed 2000 ppm 2,4,5-T in the diet ate almost as much feed as sheep fed unfortified ration, and had about the same weight gain as the control group. No symptoms of toxicity were reported.

(c) TCDD feeding studies. As to TCDD it has been concluded that the teratogenic and/or fetotoxic no-effect dose level of TCDD is 0.3 ug/kg/day in mice and at least 0.03 µg in rats (see Issue V.A.1, supra).

In the McCollister, Kociba and Gehring 90-day studies with rats described above (DD-43), the 2,4,5-T samples contained 0.5 ppm TCDD. The no-effect level for 2,4,5-T was 10 mg/kg/day. The corresponding no-effect level for TCDD was 0.005 µg/kg/day.*

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* The next highest dose of 2,4,5-T given was 30 mg/kg/day which caused slight changes which were considered of questionable significance by the authors. 30 mg of the 2,4,5-T/kg/day delivered .015 µg of TCDD/kg/day.

At the present time the only available results from repeated feeding of TCDD alone in laboratory animals is with rats for 31 consecutive days (DD-53-55). The no ill-effect level observed was 0.1 μg/kg/day.

In studies carried out at the National Institute of Environmental Health Sciences, National Institute of Health (DD-53-55), groups of female rats received 0, 0.1, 1 and 10 μg TCDD/kg/day for 31 consecutive days. The TCDD was administered in an acetone-corn oil solution by gastric intubation. The daily dose of 0.1 μg TCDD/kg/day for 31 days was shown to be the no-effect dose level as judged by the following parameters: body weights (DD-53); SGPT activity, SGOT activity, blood glucose concentration, serum protein concentration, serum bilirubin, hematologic values (erythrocyte counts, hemoglobin concentrations, hematocrits, leucocyte counts and differentials) (DD-54); gross and microscopic examination of the tissues (DD-55). Examination of the organ weight data (DD-53) shows that the mean liver weights were slightly greater at the 0.1 μg TCDD/kg/day level than those for the controls; however, the authors state that "the statistical significance of these increases was inconsistent." Similarly, the mean thymus weights were slightly lower at the 0.1 μg/kg/day level than those from the controls. Again, the statistical significance of these decreases was inconsistent. The authors state "[t]hymus weights at the

0.1 μg/kg dose were significantly reduced when evaluated for an overall dose response effect." Since "[s]ignificant microscopic changes were not observed in [the] different organs of rats given TCDD at levels of 0.1 μg/kg [multiple daily doses] . . ." (DD-55), these minor organ weight fluctuations are of unknown importance.

A study is currently underway at Dow in which groups of rats (12 of each sex per group) received TCDD by daily oral intubation 5 days per week, for a 90-day period at dose levels of 0, 0.001, 0.01, 0.1 and 1.0 μg TCDD/kg/day. Records were kept of general demeanor and appearance, body weights and food consumption. Hematological examinations and urinalyses were made during the course of the study. At the end of the 90-day period 5 rats from each group were killed for gross and microscopic examination. The remaining animals were placed on the control diet and are being followed closely during recovery. These animals will be killed at an appropriate interval following the oral administration of TCDD and subjected to careful gross and microscopic examination.

6. Can chronic low-level exposure to 2,4,5-T and/or TCDD cause delayed lethality?

Response

Present uses of 2,4,5-T as currently manufactured will not cause delayed lethality in man or other animals because exposure to both 2,4,5-T or TCDD is many times less than that which could cause such an effect.

This is a similar inquiry to that in Issue V.A. 5, *supra*. It follows that if there is no expected morbidity from levels of 2,4,5-T and TCDD encountered by man and animals as was shown in V.A. 5, there would also be no delayed lethality.

This inquiry is believed to have been prompted by delayed deaths observed among some test animals in TCDD acute toxicity studies by Schwetz *et al*. (DD-52). While time of death (days post-administration) varied widely even within the same species,* some of the moribund animals in the TCDD studies lingered up to 43 days after administration of the lethal dose. Data from such acute toxicity studies using massive doses of TCDD has no bearing on the extremely low human or animal exposure likely from current uses of 2,4,5-T with<0.1 ppm TCDD content.

* E.g., male guinea pigs given the same doses lingered 5-34 days, while female rats given the same doses lingered 13-43 days (DD-52, Table II).

Issue V. B.: The extent of the health risk for man and other animals posed by 2,4,5-T and TCDD, with emphasis on the following conditions:

1. Can additional TCDD be generated in the environment by the thermal stress of 2,4,5-T or its metabolites?

Response

Dow has subjected a wide variety of chlorinated phenolic material to various forms of thermal stress, including burning. 2,4,5-T acid did not produce detectable amounts of TCDD by heating. Only under conditions where 2,4,5-T is first hydrolyzed to phenol, then exposed to base to produce the alkali salt of phenol, and subsequently heated to 400°C could 0.1% TCDD be observed. In contrast, under conditions of natural combustion, less than 0.0001% of various trichlorinated phenoxy-containing chemicals* are converted to 2,3,7,8-tetrachlorodibenzo-p-dioxin. As a result of these data, it is clear that no significant amounts of TCDD can be generated in the environment by thermal stress to 2,4,5-T or any of its metabolites.

H. G. Langer, et al. (DD-101) presented the results of the pyrolysis of a variety of chlorinated phenols. From an examination of the various products formed and a consideration of the organic chemistry involved in phenolic condensation reactions, the authors show that the position of chlorine atoms is critical in determining the amounts

*Including sodium 2,4,5-trichlorophenoxyacetate, sodium 2,4,5-trichlorophenate, butyl 2,4,5-trichlorophenoxyacetate, 2,4,6-T acid and 2,4,5-trichlorophenol.

of condensation products. Indeed, while 2,4,6-trichlorophenate (sodium salt) produced up to 15% conversion to the 1,3,6,8-tetrachlorodibenzo-p-dioxin (as well as large amounts of polymeric condensation products) less than 1% 2,3,7,8-dioxin was formed from 2,4,5-trichlorophenate (sodium salt). In an effort to exaggerate the pyrolysis conditions which might occur in nature, a sample of 2,4,5-trichlorophenoxyacetic acid was refluxed at 100°C with water and potassium carbonate for 3 hours (corresponding to spraying an old fire-pit with extremely high rates of 2,4,5-T, followed by rainfall, followed by moderate heat to hydrolyze the 2,4,5-T acid), and then the mixture heated at 200°C for 15 hours and then raised to 400°C for 43 more hours (corresponding to two prolonged fires on top of the sprayed fire-pit). 2,3,7,8-dioxin condensation products were detected to the extent of about 0.1%. The low yield of the expected tetrachlorodibenzo-p-dioxin indicates that dioxin formation even under these severe conditions is not the predominant fate of any 2,4,5-trichlorophenoxy-containing material which might be subjected to thermal stress in the environment.

R. H. Stehl, et al. (DD-102) describe the results of combustion of a variety of trichlorinated phenoxy-containing chemicals to determine the extent of 2,3,7,8-tetrachlorodioxin formation. Particular attention has been paid to several items which are critical:

(a) The use of conditions similar to those expected in the environment.

(b) The use of well-defined analytical methods to assure that any dioxin formed could be detected.

(c) The use of chemicals whose 2,3,7,8-dioxin content was known to be low to assure that any dioxin detected was the result of formation during combustion and not present initially.

The result of the combustion of the materials is shown in Table 1. As can be seen, when equi-molar amounts of 2,4,5-trichlorophenoxy compounds are burned, less than 0.0001% of the compound is converted to 2,3,7,8-tetrachlorodibenzo-p-dioxin.

TABLE I

COMBUSTION OF 2,4,5-TRICHLOROPHENOXY-CONTAINING MATERIAL

Trichlorophenolic Material	Burning Surface application Rate *- Acid Equiv.	TCDD Conversion**
2,4,5-Trichlorophenol	25 lbs/acre	0.00005%
Sodium 2,4,5-trichlorophenate	25 lbs/acre	0.00007
2,4,5-Trichlorophenoxy-acetic acid	25 lbs/acre	0.00002
Sodium 2,4,5-Trichloro-phenoxyacetate	25 lbs/acre	0.00001
Butyl 2,4,5-trichlorophenoxy-acetate	25 lbs/acre	0.00004

* This is the rate of application of the compounds listed to the surface to be burned, expressed as the equivalent amount of 2,4,5-T acid.

** Under these conditions, the limit of detection was 0.000005%.

2. Can 2,4,5-T or TCDD persist and bioaccumulate in the environment?

Response

2,4,5-T does not persist in the environment and is decomposed readily by a number of routes -- microbially and photolytically in water or soil, and metabolically in animals and plants. Esters of 2,4,5-T are readily deesterified to 2,4,5-T acid by the same routes. 2,4,5-T is not bioaccumulated significantly in animal organisms and does not concentrate preferentially in fatty tissues.

TCDD does not appear to be widely distributed in nature at detectable levels. Distribution of low levels of TCDD in the environment may be prevented where degradative forces are sufficient to reduce residues at the same rate or faster than they are distributed. Under laboratory conditions TCDD appears persistent in soil and water at residue levels far exceeding those detected or possible from 2,4,5-T applications in nature. TCDD is capable of being degraded photolytically, microbially, and metabolically in animals at rates which will reduce TCDD to levels of toxicological insignificance. Evaluation of all available data suggests there is no significant risk of bioaccumulation.

In order to persist and bioaccumulate in the environment a compound must be stable under most environmental conditions and must partition selectively from the treated environment to certain surfaces or tissues of organisms which come in contact with or consume the compound. Compounds such

as DDT, and its metabolites DDD and DDE, have certain physical and chemical properties which favor such environmental persistence and bioaccumulation. Among these indicator properties are (a) very low water solubility, (b) high organic solvent solubility, (c) high partitioning coefficient of fat solvents (octanol) over water, (d) partitioning selectively into fat tissues in animal organisms, (g) stability in soil, and (h) low volatility. For purposes of comparison, solubilities for DDT, 2,4,5-T, and TCDD are given in Table 1, *infra*.

Summary as to 2,4,5-T*

The physical and chemical properties of 2,4,5-T are such that they would not be expected to be partitioned to fatty substances preferentially over water (Tables 1 and 2, *infra*.) The very low *n*-octanol over water partitioning coefficient (Table 3, *infra*) is indicative of this property, which means animals would not be likely to store much 2,4,5-T in fatty tissues. Examples of this are shown in tissue studies in calves and in milk (Jensen *et al*., 1971, 1972 (DD-48); and Bjerke *et al*., 1972 (DD-160)).

2,4,5-T is absorbed, translocated, and metabolized by plants. Although the half-life varies, it is concluded

*Studies referred to in this summary are discussed in greater detail in the Review of Data, *infra*, pp. 132 *et seq*.

that 2,4,5-T residues in plants do not last from year to year.* In an aquatic ecosystem study, no increase in 2,4,5-T residues was seen in organisms in the feeding chain of algae, daphnids and fish. In fact there was a decrease in residues going up the chain, especially in fish (Isensee, 1974 (DD-105)). This indicates much of the residue was probably due to surface adsorption.

2,4,5-T does not affect growth of populations of fungi, yeast, bacteria, actinomycetes, and green algae at concentrations occurring in field tests (Shennan and Fletcher, 1965 (DD-106)).

With regard to 2,4,5-T degradation, microorganisms are believed to be the principal cause of decomposition in the soil (Norris et al., 1972 (DD-107)). Dosages of 4-16 lb/A 2,4,5-T (acid equivalent) as the sodium salt, amine salt, or propylene glycol butyl ether (PGBE) ester are usually biologically inactivated in 4-8 weeks after application to sand, silt, loam and muck (Warren, 1954 (DD-103)). Other tests using very large dosages of 57 to 947 lb. 2,4,5-T/A showed 2,4,5-T to be biologically inactivated, or with very low residue values within one growing season (Woolson et al., 1972 (DD-109);

*Report of the EPA Advisory Committee, Administrative Law Judge Exh. 1.

Young et al., 1972 (DD-110)). The conclusion is that 2,4,5-T does not remain in soil more than one growing season, even with enormous dosage applications.

2,4,5-T undergoes photolytic decomposition in water, principally to the corresponding phenol. Photolysis rates depend on access to sunlight and possibly the presence of trace quantities of organic materials in natural water to energize the reaction, which under certain circumstances can be quite rapid (Crosby and Wong, 1973 (DD-119)). A review of the available data by EPA's Science Advisory Committee* shows that the amount of 2,4,5-T entering water is small and does not persist. This is further demonstrated by data from extensive monitoring in 11 streams in the western United States, discussed in V.B.3, infra.

Whether 2,4,5-T is applied as the acid or the salt, the aqueous form at normal pHs of 6-8 is usually ionic. However, as an ester it may act entirely differently until it is de-esterified, hydrolytically or otherwise. Whether esters of 2,4,5-T are significantly different in their activity depends on how long they remain stable as the ester molecule. This is significant when it is observed that the partition coefficient of n-octanol to water is

*Administrative Law Judge Exh. 1.

greatly increased with 2,4,5-T present as an ester rather than as the acid. See, e.g., Table 3, infra (Skelly and Lamparski, 1974 (DD-116)).

2,4,5-T does not remain in the ester form very long in most environments. Esters of 2,4,5-T and 2,4-D are hydrolyzed in plants in hours or days (Morton et al., 1967 (DD-120)). Animal tissues hydrolyze the PBGE ester in a few hours (Clark, 1969 (DD-121)). Teasley (1974) (DD-122) found that the 2-ethylhexyl ester of 2,4,5-T was rapidly hydrolyzed at 20°C in water receiving ultraviolet light and containing water soluble soil organic matter and microbes. In such water, after 16 hours exposure, deesterification was 78% completed at pH 6.5, and 88% completed at pH 5.3.

Thus, while esters of 2,4,5-T may effect the initial adsorption of 2,4,5-T to and volatility from various organisms and surfaces, 2,4,5-T esters are rather quickly returned to the ionic form of 2,4,5-T in nature and behave as such thereafter.

Summary as to TCDD

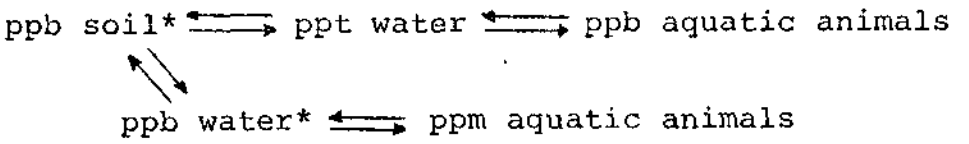
The physical and chemical properties of TCDD indicate very low solubility in nearly all solvents, including water. A relatively low partitioning coefficient (Crummett *et al*. (1973) (DD-112)) between *n*-octanol and water indicates some potential for bioaccumulation in animal tissues if concentrations of TCDD are high enough in the environment to exceed its rate of degradation. TCDD becomes widely distributed in tissues of orally treated rats and has a 50% clearance rate from tissues of about 17.4 days. However, the greatest residues are in liver and fat tissues (Piper *et al*., 1973 (DD-123)).

Residues of DDT, DDE, PCB and mercury are found to be distributed widely, as determined through monitoring of human food samples, animal tissues and water by chemical analysis. These compounds are found in such tissues and other material because they are relatively stable in the environment, used in substantial volume over large areas, get into water and bioaccumulate, especially in aquatic animal organisms.

Monitoring for TCDD in tissues of herring gull, sea lions, eagles, cormorants, butterfish, eel, chain pickerel from large bodies of fresh water and salt water, and in groundfish herringmeal in the United States, however, have *not* revealed the presence of TCDD (Bowes *et al*., 1973 (DD-124); Woolson *et al*., 1973 (DD-125); Zitko, 1972 (DD-126)).

Based on low residues or lack of residues, accumulation of TCDD by plants from soil or foliar translocation was considered unlikely (Isensee and Jones, 1971 (DD-127)). Residues on plant surfaces are subject to volatility, washing and degradation.

Aquatic ecosystem laboratory tests by Isensee and Jones (1973) (DD-128), and Matsumura (1973) (DD-129) show that TCDD can bioaccumulate in algae, snails, ostracods, and fish at levels where TCDD is applied to soil and then put in water for equalibration before introducing organisms. The distribution pattern and ratio of TCDD in such tests is:



DDT has a 1-2 order of magnitude bioaccumulation factor higher than TCDD as expected from the solubility ratio of organic solvents and water, and by the n-octanol-water partitioning coefficient shown in Tables 2 and 3. In Isensee's tests, even though TCDD was present at ppm levels

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* The ratio of TCDD in soil over water is easily varied when the solubility in water is exceeded. With DDT the distribution ratio would be something like:

ppb soil ⇄ ppt water ⇄ ppm aquatic animals

in organisms, they lived and reproduced. TCDD has a clearance half-life from snails of about 10 days in clean water.

Despite the fact that these tests show such bioaccumulation can occur with TCDD, the following facts must be considered in evaluating the test results:

> (a) TCDD is present as an impurity in 2,4,5-T in quantities which, when applied as a herbicide, total at most about 10-100 pounds TCDD over the last 25 years in the United States and about 1 pound per year recently. This is in great contrast to DDT which may have been used at a rate which totaled 100 million pounds in the United States during the same period of time. DDT was frequently applied at 0.25-2 lb/A, while TCDD in 2,4,5-T is applied at the estimated average rate of 0.0000001 lb/A/year.
>
> (b) TCDD appears to bioaccumulate less than DDT by 1-2 orders of magnitude in laboratory studies.
>
> (c) Dosages of 0.0000001 lb/A are so low that environmental degradation factors -- e.g., microbial degradation, volatility from water, metabolic degradation in animal organisms -- are significant.

Moreover, the Isensee and Jones and Matsumura tests do not take into account additional degradative and dilution factors, such as:

> (a) Photodegradation in water (this can be rapid under conditions where organic compounds are present in water solution).
>
> (b) High temperatures which may accelerate degradation.
>
> (c) Dilution of any soil particles containing TCDD in rivers, lakes and oceans in unmeasurable amounts.

(d) Wind which increases evaporation of water and codistillation of TCDD from water. (Wind and water currents also cause water turnover, which brings TCDD into contact with sunlight).

(e) Photodegradation on organic soil, leaves, etc. in the presence of an organic solvent and water, which is not the same as photodegradation on sandy soil.

(f) Not all soil particles which are eroded by water from 2,4,5-T treated ecosystems contain 2,4,5-T or TCDD.

(g) Rarely, if ever, is the land in a water drainage system all treated with 2,4,5-T.

(h) Rarely, if ever, does a rain storm occur in a drainage system which washes all of the top soil surface of a treated land all at once into a pond or stream.

(i) High concentrations are used in the laboratory tests, often exceeding the water solubility of TCDD.

In laboratory tests TCDD was applied at 1,000,000 times the concentrations likely to occur from field use of 2,4,5-T containing TCDD at 1 ppm (present specifications are 0.1 ppm or less). Under these exaggerated conditions residues of TCDD were persistent, having a half-life of about one year (Helling *et al*. DD-130). Despite apparent persistence in such laboratory tests, no TCDD was found in soil where as much as 947 lb/A of 2,4,5-T had been dumped over a period of several years (Woolson *et al*., 1972 (DD-109); Helling *et al*., 1973 (DD-130)).

TCDD dosages in water below the water solubility saturation level decrease rapidly soon after application. This is probably due to adsorption and loss by codistillation (Miller et al., 1973, DD-131). TCDD is capable of rapid decomposition by ultraviolet light in organic solvents (Crosby et al., (1971) (DD-132); Stehl et al., (1973) (DD-133)). Decomposition in distilled water was negligible. However, natural waters draining from land contain traces of many organic solvents and compounds.

Table 1. Some Physical and Chemical Properties of DDT, 2,4,5-T, and TCDD.

Property	DDT[a]	2,4,5-T	TCDD[b]
Molecular weight	354.5	255.5	322
Vapor pressure	1.5×10^{-7} (20°C)	7.46×10^{-5}[c]	
Water solubility (ppm)	0.0012 (22°C)	[d] 280[e] 198[g]	0.0002
Solubility in organic solvent g/100 g (PC)			
A. benzene rings			
benzene	77-83	0.33[g]	0.057
xylene	56-62	0.61	--
B. aliphatic alcohols			
methyl alcohol	--	46.6[h]	0.001
ethyl alcohol (95%)	1-5	54.8[e]	
n-octanol	--	0.03[f]	0.0048
C. aliphatic hydrocarbons			
n-hexane	3.9	0.002[f]	--
D. ketone			
acetone	50.55	33(19°C)[g]	0.011
E. chlorinated methanes			
chloroform	--	1.7[g]	0.037
methylene chloride	84-91	--	--

a/ Kenaga, 1972 (DD-111)
b/ Crummett and Stehl, 1973 (DD-112)
c/ n-propyl ester (Hamaker and Kerlinger, 1969 (DD-113)).
d/ Solubility in water of salts of 2,4,5-T in g/100 g water at 20°C are: sodium 3.5, diethanolamine > 50, triethylamine 400 (Melnikov, 1971 (DD-114)).
e/ Streeter, 1954(DD-115)(25°C).
f/ Skelly and Lamparski, 1974 (DD-116).
g/ Furches, 1970 (DD-117)(25°)
h/ Marquardt 1971 (DD-118)(25°)

Table 2. Approximate Ratio of Solubility in Organic Solvent to Solubility in Water.

Solvent	DDT (water sol = 1 at 0.001 ppm)	2,4,5-T (water sol = 1 at 280 ppm)a/	TCDD (water sol = 1 at 0.0002 ppm)	DDT Ratio ÷ TCDD ratio
acetone	550,000,000	1,180	550,000	1000
aliphatic alcohols	30,000,000	1770-1960	150,000	200
hexane	39,000,000	0.07	--	
benzenes	800,000,000	12-22	2,850,000	280
chlorinated aliphatics	840,000,000	61	1,850,000	454

Calculated from Table 1.

a/ The ionic or salt forms of 2,4,5-T are much more soluble in water and so the ratios would be much lower than those given for the acid. The esters are probably less soluble in water.

Table 3. Partitioning Coefficients of DDT, 2,4,5-T, and TCDD in n-Octanol and Water (Skelly and Lamparski, 1974 (DD-116)).

Toxicant	Partitioning coefficient of toxicant in n-octanol water layers
DDT	370,000[a/]
2,4,5-T acid	
pH5	7.08[b/]
pH7	0.533[b/]
pH9	0.165[b/]
2,4,5-T butyl ester	64,000
TCDD	3,300[c/]

a/ Average of data from several concentrations.

b/ Buffered solutions

c/ The partition coefficient was calculated because of analytical difficulties in working with the extreme low water solubility of TCDD in mixtures with other solvents. The partition coefficient was based on the solubility of TCDD in water (0.2 ppb) and in octanol (48 ppm) layers, and 300 ppm octanol saturated with TCDD in the water layer.

REVIEW OF DATA

2,4,5-T Residues in Animal Tissues

Leng *et al*. (1972) (DD-108) reported on analyses of residues in tissues of beef calves fed rations containing 100-1800 ppm of 2,4,5-T for 4 weeks. Of the 4 tissues studied (muscle, kidney, liver and fat), kidney had the highest residue of 2,4,5-T (4.5-26 ppm) which decreased to 0.07-.09 ppm one week after removal from feed containing 2,4,5-T. Low levels of 2,4,5-trichlorophenol were also found, primarily in kidney and liver tissue. These studies show the lack of significant residue accumulation in fat or other tissues of 2,4,5-T and 2,4,5-trichlorophenol even at high feeding levels, as well as rapid clearance from tissue after feeding has ceased.

Bjerke *et al*. (1972) (DD-160) analyzed pesticide residues in milk and cream from cows fed rations containing 10-1000 ppm 2,4,5-T for 2 or 3 weeks at each level. Average residues found in milk at the highest feeding level was 0.42 ppm 2,4,5-T and 0.23 ppm 2,4,5-trichlorophenol. Residues of the chemical decreased rapidly upon removal of the 2,4,5-T from the feed. No significant partitioning of 2,4,5-T into fatty substances was shown as judged by the lack of difference between residues in milk and cream.

2,4,5-T Residues in Plant Tissues

Morton et al. (1967) (DD-120) found that concentrations of 100 ppm of 2,4,5-T in grasses were decreased to 2 ppm after 16 weeks. They concluded that the half-life of 2,4,5-T esters in green grass tissues ranged from 1.6-2.9 weeks.

2,4,5-T Distribution in Ecosystems

Isensee (1974) (DD-105) studied the distribution of ^{14}C labeled 2,4,5-T in a semi-aquatic ecosystem and in aquatic organisms using a modified Metcalf ecosystem.

2,4,5-T was allowed to come to equilibrium with water, soil, daphnids, algae, snails and Gambusia fish over a 31-day period. 2,4,5-T in water at 31 days time was 0.12 ppm while the bioaccumulation ratios were as follows: daphnids, 180; algae, 267; snails, 71; and fish, 25. No differentiation was made between residues adsorbed (on outside surface of organism) and residues absorbed (inside organism). Much of the residue pickup could be ascribed to adsorption. Residues were measured as ^{14}C and so are not necessarily 2,4,5-T. In similar studies with other herbicides such bioaccumulation numbers were between 20-2000. Many insecticides would be much higher. However, it is not felt that the bioaccumulation residues for 2,4,5-T in this test method represents a significant accumulative residue problem for

chain of life organisms since no increase in residue was noticed for algae ⟶ daphnids ⟶ fish.

2,4,5-T Persistence in Soil

Warren (1954) (DD-103) studied the leaching and herbicidal persistence of the sodium salt, amine salt, and propylene glycol butyl ether ester (PGBE) of 2,4,5-T in fine sand, silt loam, "old" muck, and "new" muck by use of crabgrass seed as a bioassay tool. Results were as follows in Table 5.

Table 5. Herbicidal Bioassay of 2,4,5-T Derivatives for Leaching and Persistence in Soil.

Form of 2,4,5-T	Dosage 2,4,5-T a.e./A	Soil type			
		sand	silt loam	old muck	new muck
sodium salt	8	(8)M	(>8)R	R	R
	16	--	--	(4)	(8)
amine salt	4	(8)M	(4)R	R	R
	8	--	--	(2)	(4)
PGBE ester	4	(>8)R	(4)R	R	R
	8	--	--	(2)	(4)

M = Compound moves readily in soil with 2 inches of water for leaching.

R = Compound is resistant to leaching with 2 inches of water.

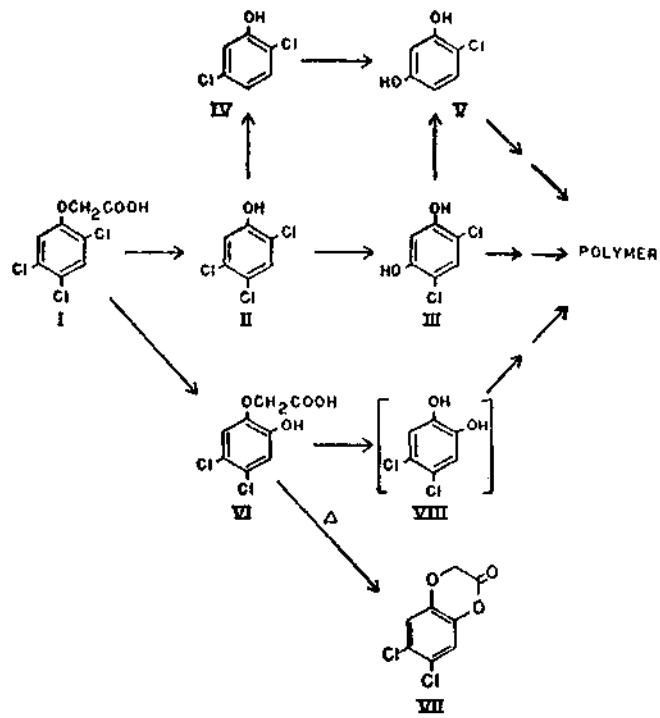
(8)= Number of weeks before herbicidal activity is gone in persistence tests.

Shennan and Fletcher (1965) (DD-106) tested 2,4,5-T *in vitro* on 34 species of fungi, yeasts, bacteria, actinomycetes, and green algae. The minimum concentrations of 2,4,5-T causing growth inhibition were 1250 ppm. With most organisms, concentrations of 10,000 ppm or more were needed. These results show that at concentrations approximating field rates of application, 2,4,5-T is harmless to microorganisms. The microorganisms are thus not inhibited from decomposing 2,4,5-T at such rates.

Woolson *et al.* (1972) (DD-109) and Young *et al.* (1972) (DD-110) reported on the measurement of residues of 2,4-D and 2,4,5-T applied to soil at the Eglin Air Force Base between 1962 and 1970. Approximately 947 lb 2,4,5-T/A was applied between 1962 and 1969. In May 1970 plant bioassays indicated that the maximum concentration of 2,4-D and/or 2,4,5-T in the soil was 5 ppm. If all of the 2,4-D and 2,4,5-T from these herbicide applications had remained in the top six inches of soil and had not decomposed during the eight-year period, then the approximate concentration of 2,4-D and 2,4,5-T combined would have been 1,550 ppm. In December 1970 the maximum detectable level in the soil was 0.1 ppm. These data indicate that under such conditions, 2,4,5-T (and 2,4-D) readily disappear from soil even under dosage conditions representing a cumulative dosage of hundreds of pounds per acre.

2,4,5-T Persistence in Water

Crosby and Wong (1973)(DD-119) found that aqueous solutions of phenoxy herbicides decompose in sunlight, undergoing a variety of photodecomposition pathways proposed, as shown below:



Although reduced products are present, oxidation represents the most important route of photodecomposition. The principal photolysis intermediates, the chlorophenols, readily undergo further photolysis replacing chlorine on the ring with H or

OH groups. The photolysis rate of 2,4,5-trichlorophenol formation from 2,4,5-T (breakage of the ether linkage) is slower than the equivalent phenol from 2,4-D and probably can be considered to be useful in long term exposures as a source of degradation. No TCDD was detected among the photodecomposition products. The rate of 2,4,5-T photolysis was somewhat more rapid at pH 8 than at pH 3.

In nature, organic solvents and other organic compounds are normally present in water. Crosby and Wong (1973) (DD-119) found that low levels of acetone and riboflavin acted as sensitizers for drastically increasing the rate of 2,4,5-T disappearance.

2,4,5-T Ester Stability

Morton et al. (1967) (DD-120) applied 2.0 and 0.5 lb/A of the butoxyethyl ester of 2,4,5-T to 3 species of range forage grasses. One hour after application both the acid and ester were found in green and litter tissues of the plants. One week after treatment 2,4,5-T and unknown metabolites were found but no ester, indicating rapid hydrolysis of the ester. The work of Morton et al. (1967)(DD-120). shows that apparent half life of 2,4,5-T in green tissues was about 2.6 weeks and in litter tissues about 2.7 weeks.

Clark (1969) (DD-121) used raw sheep muscle to check the hydrolysis rate of the propylene glycol butyl ether ester of 2,4,5-T. Over 80% of a 20 ppm spiked amount of the ester was hydrolyzed to 2,4,5-T in less than 1 hour.

Teasley (1974) (DD-122) studied the hydrolysis of the 2-ethylhexyl ester of 2,4,5-T; and the propylene glycol butyl (PGBE) ether ester, the butoxy ethanol ester, and isooctyl ester of silvex. The test water was conditioned in soil and humus and the supernatant water used for degradation. The water had a pH of 6.5, held at 20°C and was irradiated with ultraviolet light. All compounds had nearly identical rates of deesterification using concentrations of 1 ppm (acid equivalent). Under these conditions the percent of the original 2-ethylhexyl ester of 2,4,5-T present in the water at various times over a 24-hour test period was as follows: 1 hr, 91%; 4 hr, 72%; 8 hr, 54%; 16 hr, 22%; and 24 hr, 14%. Under the same conditions except for change to river water having a pH of 5.3, the remaining ester present was as follows: 4 hr, 58%; 8 hr, 33%; and 16 hr, 12%. The data shows that all of the esters of 2,4,5-T and silvex hydrolyzed faster at pH 5.3 than at pH 6.5 and both are rather rapidly hydrolyzed at a calculated linear rate under the conditions of the test which were meant to simulate natural conditions.

Since the hydrolysis data do not differ greatly between the 4 esters mentioned above, a more detailed study of the PGBE ester of silvex will represent principles of the effect of temperature, pH, and microorganisms on ester of 2,4,5-T. The relationship of deesterification to pH is inversely proportional (from pH 6.5 to 3.5) to the rate increase. The presence of microorganisms and/or soil in water increased hydrolysis. The most important factor was UV light which overlapped the absorption spectra of the esters in the region of 290-305 mμ.* A test using KURON®, a formulation containing silvex PGBE ester, in Oconee river water at 1 ppm (acid equivalent) subjected to sunlight on a clear summer day in Athens, Georgis showed no ester remaining after 4 hours, indicating rapid hydrolysis.

TCDD Residue in Animal Tissues

Piper *et al*. (1973) (DD-123) studied the tissue distribution of ^{14}C over a period of 21 days in the rat, resulting from a single 50 μg/kg acute oral dosage of ^{14}C labeled TCDD. Of the total dosage of ^{14}C activity 53.2% was excreted in the feces, 13.2% was excreted in the urine and 3.2% was excreted in the expired air. The half-life for clearance from the body was calculated to be 17.4 days, excluding the fecal excretion of the first two days which was calculated as unabsorbed. Analyses of 14

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* mμ = millimicrons

tissues indicated that the remaining 30.4% of the ^{14}C activity was widely distributed, but was located chiefly in the liver and fat. Liver and fat tissues may contain approximately 10-fold greater residue levels than that found in other tissues.

The presence of small amounts of ^{14}C activity in the expired air and urine in the first 10 days is evidence that some metabolic alteration or breakdown of TCDD occurs.

Bowes et al.(1973)(DD-124) reported on a search for TCDD, DDE, and PCB's in wildlife populations reportedly showing elevated levels of embryonic death. Herring gull eggs from the Lake Ontario region and sea lion blubber and liver samples from the California coast taken from such affected populations were analyzed, with the following results shown in Table 4:

Table 4. Residue Levels of DDE, PCB, and TCDD in Aquatic Birds and Mammals.

	ppm - Residues		
	DDE	PCB	TCDD
Herring gull eggs			
wet weight	35	300	0
lipid	440	3700	0
Sea lion liver			
wet weight	12	3	0
lipid	300	80	0
Sea lion blubber			
wet weight	512	62	0
lipid	630	76	0

Woolson et al. (1973) (DD-125) analyzed 19 eagle carcasses and found no detectable dioxins at an analytical sensitivity of 50 ppb.

Zitko (1972)(DD-126) found no detectable amount of TCDD (analytical sensitivity of 0.04 ppm) in the muscle and liver of white shark, eggs of double-crested cormorants and herring gulls, muscle of eel and chain pickerel, and in commercial samples of herring oil and groundfish-herring fishmeal. In contrast Zitko found PCB's, DDE, and DDT present in all samples, the maximum being 218, 335, and 63 ppm, respectively, in shark liver.

TCDD Residues in Plant Tissues

Isensee and Jones (1971) (DD-127) measured the adsorption and translocation of root and foliage applied ^{14}C-labeled TCDD from nutrient solution, soil and foliage. Solutions and soils were treated with 0.18 (900X water solubility) and 0.06 ppm respectively. Accumulation of TCDD by plants from soil, or translocation of foliar applied TCDD, were considered unlikely based on low residues or lack of residues. More TCDD was removed from oats and soybeans by simulated rainfall two hours after application than after seven days.

TCDD in Aquatic Ecosystems

Matsumura et al. (1973) (DD-129) introduced TCDD into water at 32.4 ppb (in excess of 0.2 ppb water solubility

of TCDD) and found a 49-fold bioconcentration in daphnia in the presence of algae and a 218 bioconcentration in ostracods after 4-7 days exposure. Using DDT under the same conditions at 35.8 ppb in water resulted in 1234-fold and 1418-fold bioconcentration in daphnia and ostracods, respectively. This test, while not typical of concentration values of TCDD which could occur naturally in water, does show the much greater affinity of DDT for daphnia and ostracods than TCDD.

In another type of test Matsumura placed 1.62 μg of TCDD on 1 gram of sand (no organic matter for adsorption) for a calculated soil concentration of 1.62 ppm (a higher concentration than that known to occur even from a dosage of 942 lb 2,4,5-T containing 2 ppm TCDD/A). This soil was added to 200 ml water. If all of the TCDD came off the sand into the water, the concentration would be over 8 ppb or 40 times the water solubility of TCDD. With these exaggerated dosages, TCDD bioconcentrated by brine shrimp and mosquito larvae were two or four times less than DDT. In conditions where TCDD may be present in concentrations above the water solubility of TCDD, excess amounts deposit or adsorb out of water and form a reservoir for replenishing TCDD lost from water due to decomposition or evaporation. Concentrations such as these seem mathematically and practically impossible from present use patterns of 2,4,5-T containing TCDD.

Isensee and Jones (1973) (DD-128) studied the movement of ^{14}C-labeled TCDD applied to soil in a laboratory aquatic ecosystem. The transfer of TCDD residues from soil to water and to aquatic organisms was measured and bioaccumulation ratios in tissues calculated on the basis of the amount in water. The tests used included a range of concentrations in soil related to TCDD concentrations which might occur from the field use of 1 lb 2,4,5-T/A containing 0.1 ppm TCDD as an impurity. In this laboratory ecosystem, soil dosages of TCDD at ppb levels resulted generally in ppt to ppb concentrations in water and in ppb to ppm concentrations in organisms such as algae, snails, daphnids, and fish, often of a 10,000-fold bioaccumulation ratio as measured by ^{14}C radioactivity. Increasing the amount of untreated soil in the treated ecosystem resulted in decreasing amounts of residues in water and organisms due to increased adsorption on soil, but did not greatly change the bioaccumulation ratio of animal tissues to water.

These ratios are generally 1 to 2 orders of magnitude less than DDT, which is in keeping with the relative solubilities of DDT and TCDD in water and organic solvents. An interesting finding in these tests is that although residues of ^{14}C-labeled TCDD (assuming no significant decomposition of TCDD) are present in organisms at the ppm level, the organisms are able to not only live but also reproduce.

Isensee and Jones (1973) also measured TCDD clearance rate in snails. After 31 days' exposure to TCDD snails accumulated 1.83 ppm. These snails, when held in clean water for 10 days, contained 0.72 ppm. This indicates a clearance half-life of about 10 days.

At the higher concentrations on soil, water concentrations of TCDD remained rather constant. Actually this constancy may have been because of the replenishment of TCDD from the soil reservoir of TCDD into water to maintain an equilibrium between soil and water. In this manner any TCDD lost from water by codistillation or other ways could be replenished.

Assumptions apparently made in setting up test methods for these bioaccumulation tests by Isensee and Jones (1973) were:

(1) TCDD is not significantly leachable and therefore TCDD reaching water would normally get there on surface soil particles by water or wind erosion from treated land.

(2) Reasonable concentrations of TCDD on soil would be those resulting from a dosage of 1 lb 2,4,5-T/A having a TCDD impurity of 0.1 ppm, taken from the top few mm of treated soil surface.

(3) Soil particles containing TCDD would come to equilibrium with water and aquatic organisms over a period of 28-31 days.

(4) TCDD is relatively stable in sandy soil and water under laboratory conditions and therefore ^{14}C radiation measurements are adequate analytical representations of concentrations of TCDD in water, soil, and aquatic animal tissues.

It is recognized that any test method run in the laboratory is only representative of the measurement of certain limited interactions of segments of the environment. It is obvious that not all conditions can be simulated.

TCDD Persistence in Soil

Helling et al. (1973) (DD-130) have summarized the persistence of TCDD in soils as follows:

"Persistence is often measured as half-life ($t_{1/2}$) since pesticide disappearance from soil typically approximates a first-order reaction. This can be a misleading concept since several mechanisms simultaneously act on a residue to alter its rate of disappearance from soil. The persistence of a pesticide that is biologically metabolized, for example, will be increased or decreased depending on whether conditions favorable (warm,moist) or unfavorable (cold, dry) to microbial growth prevail. Likewise, adsorption might be expected to be higher in soils having high rather than low organic matter and/or clay contents. Persistence may also be measured as the time required for residues to reach a non-detectable level in soil or when plants no longer accumulate detectable quantities. Such measurements would be as variable as

$t_{1/2}$, but may be better environmental barometers.

"The persistence of TCDD in two soils, Lakeland sand and Hagerstown silty clay loam, at three rates of application (1, 10, and 100 ppm) was studied for 360 days (Kearney et al., 1971). The soils represented extremes in biological activity and in physical and chemical properties. They were maintained at 28 to 30°C and with a moisture content equivalent to 70% of field capacity.

"TCDD was extracted by repeatedly shaking moist soil with acetone-hexane (1:1). After 1 year, 56 and 63% of the originally applied TCDD was recovered in the Hagerstown and Lakeland soils, respectively. The persistence of TCDD is not surprising since it is an insoluble, nonpolar, chlorinated molecule, devoid of biologically labile functional groups. As Kearney et al. (1971) pointed out, however, a concentration of 1 ppm of TCDD in soils is 10^6 times greater than the residues likely to be encountered in a 2.24 kg/ha (2 lb/acre) application of 2,4,5-T containing 1 ppm TCDD.

"Despite the persistence of TCDD [in laboratory tests], no residues were found in Lakeland sand which had received 1,060 kg/ha [947 lb/A] of 2,4,5-T during 1962-64 (Woolson et al., 1973). These unusually high doses resulted from testing of aerial application equipment at Eglin AFB, Florida."

2,4,5-T containing 2 ppm of TCDD applied at 947 lb/A is equivalent to an application of 0.0019 lb TCDD/A. Assuming the immobility of TCDD in soil shown by Helling et al (1973) the concentration of TCDD in the top 3 inches evenly distributed if none were lost would be 1.4 ppb. Six years after the first application and 2 years after the last application, when the soil was first analyzed, no TCDD (<1 ppb) was found.

Matsumura and Benezet (1973) (DD-129) carried out soil microorganism degradation studies on TCDD using about 100 microbial strains in which the ability to degrade persistent pesticides had been previously demonstrated. Five of these strains showed some ability to degrade TCDD; thus TCDD appears to be quite stable to microbial degradation at the concentrations tested.

TCDD Persistence in Water

Miller et al. (1973)(DD-131) analyzed TCDD in water from 2 sets of static water experiments. The treatments were started with 50 ppt TCDD (water solubility = 200 ppt). One set contained water and Coho salmon, while the second set was similar except no fish were present. TCDD recovery in the first set was about 48% after 24 hours and 20% after 96 hours, decreasing at a linear rate after 24 hours. TCDD recovery in the second set was only 60% in 4 hours. In spite of being well below the water solubility

limit, TCDD concentrations in water were rapidly decreased during the first 4 to 24 hours after introduction to the aquaria. The cause of loss was not specifically determined but is assumed to be similar to many other compounds of low water solubility and due to adsorption on the aquaria, fish, and evaporative loss from codistillation with water. These data indicate that most of the TCDD would be lost from the water soon after application.

Crosby et al. (1971) (DD-132) and Crosby and Wong (1973) (DD-119) studied the UV decomposition of TCDD in sunlight or fluorescent ultraviolet in methanol or ethanol, and water. TCDD was present in methanol or ethanol in a few ppm concentrations and as an insoluble suspension in water. All of these concentrations would be perhaps 1000-fold or more higher than water solubility limits in water. Photodecomposition of TCDD was negligible in distilled water under these conditions. In alcohol solution TCDD and its homologs decomposed rapidly under artificial and natural sunlight. Apparently the presence of organic hydrogen donors as might be present in waxy cuticle of leaves, surface slicks on water (which contain organic solvents) or even ingredients of the 2,4,5-T formulation may be sufficient to furnish such donors as to energize the rapid destruction of TCDD. Decomposition of TCDD in alcohol is accomplished by reductive dechlorination and appears to remove one chlorine at a time from the ring.

Stehl *et al.* (DD-133) reported that solutions of 12 ppm of TCDD in isooctane subjected to artificial sunlight were reduced to less than 1 ppm after 24 hours illumination using a General Electric R.S. sunlamp at a 0.5 and 1.0 meter distance from the solution.

3. What are the avenues of human and animal exposure to 2,4,5-T and TCDD? For example, can aerial drift or water transport of 2,4,5-T or TCDD cause movement of these compounds away from the site of application?

Response

There is little or no significant movement of 2,4,5-T and TCDD from the site of application to other areas. TCDD is nearly immobile in soil. 2,4,5-T can move in soil more readily, but under field conditions not much movement occurs. Both compounds degrade in the soil -- TCDD slowly and 2,4,5-T relatively rapidly. An extensive body of research shows that there are insignificant amounts or no 2,4,5-T in soil, water, and food for man and animals. TCDD to date has not been found in the environment in the United States. This is in accord with theoretical knowledge of the behavior of these compounds, as well as reported residue data. It is concluded, therefore, that movement of these compounds from the site of application is minimal, with no unfavorable effects upon the environment.

The simplified diagram below (Figure 1) is derived from general knowledge as to herbicide action. It shows how a herbicide such as 2,4,5-T enters the environment after application to vegetation, and the major processes involved therein.

Pesticide residues in the environment are subject to various physical, biological and chemical processes, which for convenience are summarized as follows:

(a) Physical - sorption, leaching, runoff, spray drift, and volatility.

(b) Biological - metabolism and/or degradation by higher plants and animals and soil microorganisms.

(c) Chemical - oxidation, hydrolysis and photodecomposition.

The major pathways by which a pesticide residue could enter man or a higher animal are through the air, water, soil, or by eating plant or animal food. These possible avenues of exposure will be considered below.

Air

Generally, applicators strive for a minimum coverage of 90% on the target area when a herbicide is applied by ground equipment. With 2,4,5-T, applicators strive for a minimum of 95%. Spray drift off the target area has long been recognized as an environmental problem (DD-134) and, as a result, there have been and continue to be constant efforts to minimize such drift.

Although there have been few studies measuring herbicide content of air after spraying, Bamesberger and Adams (DD-135) give some data on this subject. Monitoring at two locations over a three-month period during the

spraying season, the maximum percentage of days during which 2,4,5-T was detected was 21%. The maximum amount of 2,4,5-T found was 3.38 μg/liter. The highest average amount found was 0.045 μg/liter.

Such figures result in an exposure level to man or other animals of approximately 1.4 μg/kg body weight/day. In this instance, using the highest exposure level found, the maximum time 2,4,5-T could be detected, and acute oral LD_{50} data for rats,* a rough calculation of the inhalation toxicity of 2,4,5-T can be made. From this it is reasonable to conclude that there is no practical toxicological hazard to man or animals from drift of the material in air off the target site.

While it has been claimed that dust containing 2,4,5-T has been transported in air (DD-136) this does not appear to be a significant factor in its dissemination.

Soil

Leaching and persistence

Some of the earliest investigations on the length of time 2,4,5-T will remain herbicidally active in the soil

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* 500 mg/kg

were done by DeRose in 1946 (cited in DD-135). Warren (DD-103) showed that 2,4,5-T is resistant to leaching, and that its residual herbicidal activity in soil varied between 2 and 8 weeks depending upon soil type. More discussion of soil persistence is found in V.B.2, supra.

Runoff

O'Connor and Wierenga (DD-137), in experiments involving both leaching and degradation, state that 2,4,5-T will degrade completely in 85 days when applied to soil not previously treated, and that it will degrade in 45 days after repeated applications of 2,4,5-T. They also state that such rapid degradation protects deep ground water supplies from 2,4,5-T pollution, since the rate of movement downward is slow -- 0.5 cm/day or less. They and other investigators conclude that application of 2,4,5-T at normal rates does not constitute a hazard to moderately deep ground waters.

Trichell et al. (DD-138) reported after an application of 2 pounds of 2,4,5-T an acre, the maximum amount of 2,4,5-T found (following 1/2 inch of artificial rain applied 24 hours after application) was 3.3 ppm. There was no significant difference between losses of

2,4,5-T from a 3% slope versus an 8% slope. There was also more of the herbicide found in runoff water than on soil particles, with the latter being insignificant.

Sheets and Lutz (DD-139) applied 2,4,5-T to two watersheds in the mountains of North Carolina in 1968 and again in 1969. No 2,4,5-T was found in flume water from either watershed in 1968. In 1969, 2,4,5-T was found in flume water from one watershed, but not the other. The highest amount found, after a storm, was 48 ppb. In small plot work in 1968, the total amount of 2,4,5-T removed was 0.01% of the total applied. The same investigators later examined the runoff question (DD-140) and found little movement of 2,4,5-T, even on 27% slopes. In this case, practically no herbicide was found more than 0.3 miles downslope and none was found beyond 1.2 miles downslope.

Soil Monitoring Programs

Stevens et al. (DD-141) reported on monitoring soils for pesticides from areas of regular, limited and no pesticide use. No 2,4,5-T was found, even in areas where it was known to be applied. Wiersma et al. (DD-142), in a report on the national soils monitoring

program for six states (Georgia, Idaho, Maine, Nebraska, Virginia, and Washington) where soil samples were taken from 242 sites on cropland and 117 sites on non-cropland, did not note 2,4,5-T found anywhere. This was also true in soil samples from eight cities (DD-143).

Water

Norris (DD-107) discusses studies in the Northwest which indicate most herbicide contamination of forest streams results from drift or direct application of chemicals to water surfaces. Detectable quantities of 2,4,5-T have not been found in western streams during fall and winter months after spray applications to nearby forest lands the previous spring. Reigner et al. (DD-144) concluded 2,4,5-T could be used safely on municipal watersheds.

Lichtenberg et al. (DD-145) report on a five year (1964-1968) survey of pesticides in U.S. surface waters. 2,4,5-T is not mentioned in the report. Presumably it was not found, inasmuch as it was one of the chemicals on the list to be monitored. Manigold and Schulze (DD-146), in a report of water monitoring results from October 1966 to September 1968, found that

2,4,5-T was not present in 211 samples out of 235, or 90% of the time. The highest amount, when found, was 0.07 μg/liter, or 0.07 ppb. Schulze et al. (DD-147), in the most recent monitoring results (1968-1971), found 2,4,5-T in 109 out of 661 samples, or approximately 16.5% of the time. The highest amount found was 0.4 μg/liter. Ninety percent of the time the amount found was 0.06 μg/liter or less; ten percent of the time it ranged from 0.07 μg/liter to 0.4 μg/liter, with the high level occurring only once in four years. It is also noteworthy that the number of occurrences peaked in 1969 and have been decreasing generally since then, both in number and magnitude of 2,4,5-T found in the samples.

Food

According to the national monitoring program on pesticides in food (DD-148), the average amount of all herbicides found in our food from 1964 through 1967 was 0.00013 mg/kg body weight/day. Such small quantity (0.13 ppb) was found for all herbicides. Martin and Duggan (DD-149) reported 2,4,5-T at a level of 0.19 ppm in one sample of dairy products and a trace below the sensitivity of the analytical method in meat, fish and poultry. This was an

occurrence in two out of 360 samples or 0.5%. Lipscomb (DD-150) analyzed 684 samples of prepared baby foods, with no 2,4,5-T reported.

Corneliussen (DD-152), from June 1968 to April 1969 in the national food monitoring program, reported that although phenoxy compounds were found four times in the 360 samples, no 2,4,5-T was found.

Duggan and Corneliussen (DD-153) found no 2,4,5-T in the food samples analyzed for the period June 1968 to April 1970. In addition, they report that herbicide residues as a class were only 0.8% of the total pesticide residue intake. They summarize their findings as follows:

> Herbicides were found in 9 of the 12 food classes during the years studied. No herbicide residues were reported in legume vegetables, root vegetables and garden fruits. The average daily intake of all herbicides for the period 1965-1968 was 0.0001 mg/kg of body weight. This intake decreased to 0.00006 in 1969 and to an insignificant trace in 1970.

Summary as to TCDD

Isensee and Jones (DD-127), using radioactive ^{14}C labelled 2,7-dichloro-and 2,3,7,8-tetrachlorodibenzo-p-dioxin, found no translocation of TCDD from leaves and

concluded that accumulation of TCDD in plants from the soil is highly unlikely. This work also indicated that TCDD could be washed off leaves by simulated rainfall.

Crosby et al. (DD-154) conclude that in view of the probable photolysis of TCDD to nontoxic products, non-detection of TCDD in environmental samples is not surprising. Miller et al. (DD-131) cites a calculated maximum expected level of TCDD in forest streams of 0.01 ppt from spray operations using current 2,4,5-T with $<$ 0.1 ppm TCDD. In this regard, it should be noted that Stehl et al. (DD-133) found that TCDD is subject to rapid photolytic decomposition under artificial sunlight.

Helling et al. (DD-130) have considered the effects of dioxins in pesticides, soils, and plants. Their conclusions may be summarized as follows:

> (a) Samples of 2,4,5-T currently manufactured contain $<$ 0.1 ppm TCDD.
>
> (b) TCDD was not photodecomposed in soil, nor was it formed from 2,4,5-trichlorophenol in water.
>
> (c) No leaching of TCDD occurred. Approximately half the TCDD applied to the soil persisted at the end of one year under laboratory conditions.
>
> (d) When TCDD was incorporated in the soil, it was undetectable (less than 1 ppb) in mature plants and seeds. It did not translocate in plants, but washoff and perhaps volatilization occurred.

Woolson *et al*. (DD-125) reported analyses of Florida soil which had a total of 947 pounds of 2,4,5-T per acre applied to it between 1962 and 1969. No TCDD could be detected at depths up to 3 feet, using an analytical method with a minimum detection limit of less than 1 ppb. The soil was also analyzed for 2,4,5-T and a small amount ($<$20 ppb) was found at all depths. Eagle tissue from 19 carcasses obtained from various parts of the United States were also analyzed for TCDD and none could be found. The analytical method used had a minimum detection limit of 50 ppb.

A Simplified Diagram Showing The Environmental Fate of a Herbicide

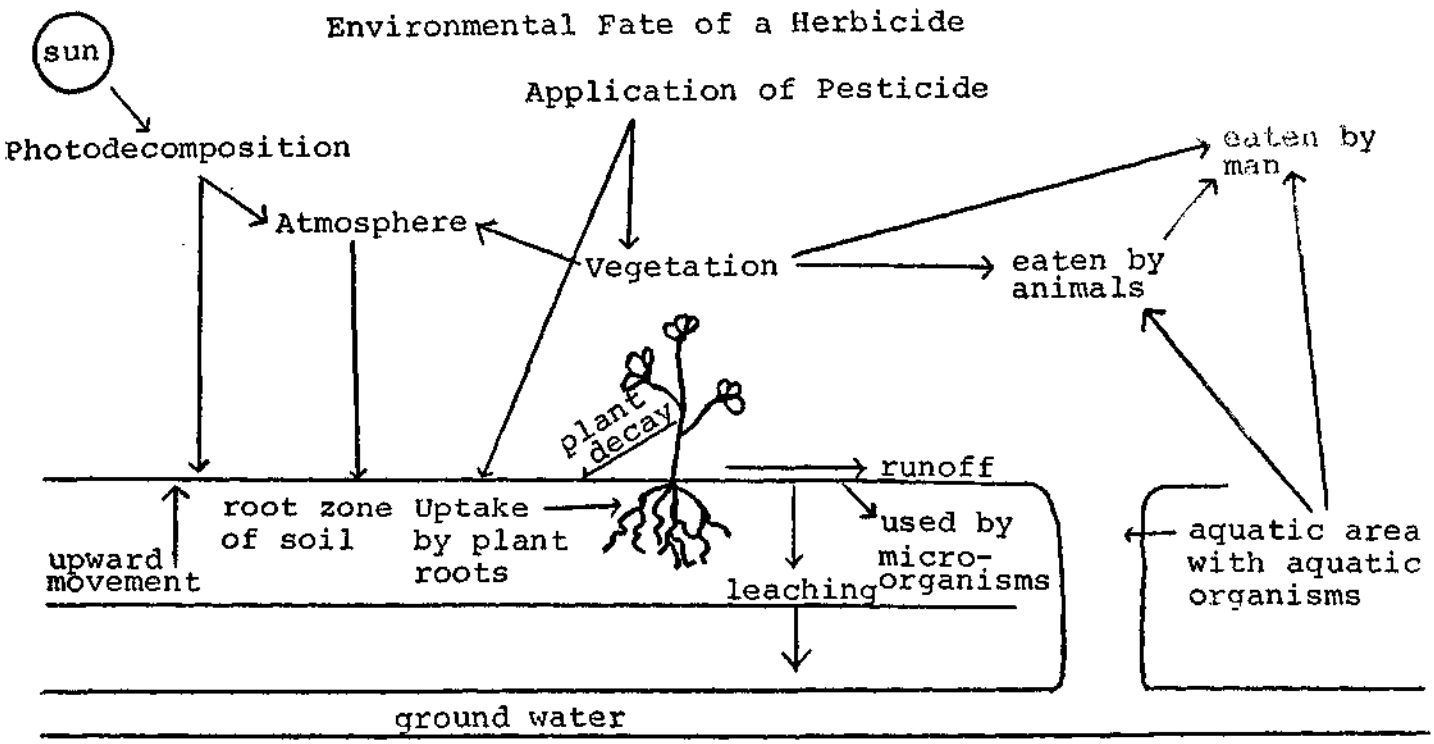

FIGURE 1

4. Are 2,4,5-T or TCDD residues being stored and accumulated in the human food supply and in human and animal tissue including humans and wildlife directly exposed to 2,4,5-T?

Response

Accumulation of an agent in the body or the tissues of the body is a function of its rates of entry and exit. Any chemical including components of food and water will "accumulate" to varying degrees as the relationships between the rates of entry and exit are varied. Food, for example, accumulates as fat. (See Admin. Pt. 5). Except to the extent accumulation takes place in this respect, the answer to this question is "no".

It is shown here and in other Responses that residues of 2,4,5-T do not accumulate in plant or animal tissue. TCDD did not accumulate in beef liver from a 2,4,5-T feeding study and has not been found in the environment of the United States; thus it does not accumulate.

Studies have been conducted which permit assessment of the degree of accumulation of 2,4,5-T, not only in animals but in humans as well. Studies in animals include those of Piper et al. in rats and dogs (1973, DD-155), as well as other work in rats, pigs, chickens and calves (DD-155-158). Dow has recently conducted a study in man (Gehring et al. 1973, DD-159). The results of these studies (as well as the Piper et al. work [DD-176] which assesses the fate of TCDD following oral ingestion in rats), and the conclusions which may be

drawn therefrom, are discussed in detail at pp. 32-37, supra and in the review of data below.

As to human food supply, it has been shown that feed ingredients for meat and milk producing animals may have residues of 2,4,5-T. Because of the practices in production of meat and milk and label statements precluding use of food materials containing high levels of residue, the consumption of 2,4,5-T by such animals is limited. Also, because of rapid and continual decline of residues in plants such as grass which may be treated with 2,4,5-T, exposed animals consume constantly decreasing quantities of the chemical. This would be reflected immediately in decreasing residue levels in milk and tissue, if they occur at all. Animals for meat are seldom, if ever, slaughtered directly out of a pasture or range, so the common practice of feeding for fattening would be expected to further eliminate trace residues from meat supplies. Rapid elimination of 2,4,5-T gives further assurance that wildlife which may forage in areas where 2,4,5-T is used will not accumulate the chemical.

Based on the data available, it is concluded that TCDD did not accumulate in the bodies of the cattle fed 2,4,5-T for 28 days. Over that period, the animals fed at the 1800 ppm level consumed an average of 1120 grams of 2,4,5-T which contained 0.5 ppm or about 0.56 mg of TCDD. The liver analyzed from one animal contained 0.00036 ppm of TCDD.*

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* Data from this study (DD-48) are presented in Table II below. To facilitate reference, Tables I, II, IV and V and Figures 1 and 2 appear at the end of this Response.
Table III is found in the text, at page 168, infra.

For purposes of estimating the total potential body burden of TCDD, it will be assumed that all tissues contained that level of residue. Assuming a 216 kg animal gives a tissue level of 0.08 mg of TCDD.* Thus 14% of the TCDD consumed is estimated to have remained at time of slaughter. These figures are high by a considerable factor, because liver is known to have greater concentrations of many exogenous chemicals than most other tissues. There was a sharp decrease in TCDD concentration in the liver of the animal held for seven days on feed without 2,4,5-T in the diet vs. the animal slaughtered while on the 2,4,5-T diet, indicating a biological half-life in the liver of less than seven days.

The likely maximum intake of TCDD by cattle is extremely low when recommendations for use of 2,4,5-T are followed. In current production of 2,4,5-T, TCDD is limited to a maximum concentration of 0.1 ppm, or approximately 20% of the TCDD concentration in the 2,4,5-T samples fed to the cattle in the residue experiment. In calculations of potential residues in animal tissues it is important, obviously, to use the <0.1 ppm TCDD figure in current 2,4,5-T formulations.

An additional factor, which will limit TCDD residue levels still further, is the proposed label limitation against cattle consuming grass containing more than 300 ppm of 2,4,5-T.

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* 216 kg x 0.00036 mg/kg = 0.08 mg.

The reports on root uptake of TCDD and eagle-tissue analysis add further to the assurance that TCDD is not accumulating in human food.

REVIEW OF DATA

Because animals producing meat and milk for human consumption may consume feeds which contain residues of 2,4,5-T, experiments have been conducted to determine levels of residue in meat and milk when feed with known amounts of chemicals are consumed.

Milk (DD-160, 161)

Two groups of three Holstein cows were maintained on dairy feed, one group as controls and one group with a dairy ration containing 2,4,5-T. The fortified feeds were prepared by blending a 10 to 25% concentrate of 2,4,5-T on silica gel with feed, to make rations containing 10, 30, 100, 300, or 1000 ppm of 2,4,5-T in the feed. A commercial production lot of 2,4,5-T was used.

The cows were fed 14 days at each of the lower levels, followed by 21 days at 1000 ppm, and then seven days on feed containing no chemical. Milk and cream were collected during the experiment.

Animal weight and milk production records were kept. No adverse effect due to ingestion of 2,4,5-T, was noted in any of the animals.

The efficiency of the analytical method was determined by fortifying control milk with amounts of both 2,4,5-T and trichlorophenol varying from 0.01 to 1.0 ppm and applying the appropriate analytical procedure. The recoveries of 2,4,5-T and of trichlorophenol from milk were 93% and 88% respectively.

Control cream was fortified with 2,4,5-T and 2,4,5-trichlorophenol from 0.05 to 1.0 ppm and analyzed by the standard procedure. Recovery of 2,4,5-T was 90% and of 2,4,5-trichlorophenol 88%.

Heating the sample before extraction with ether was done only to facilitate phase separation upon centrifuging. The same levels of residues were found when the samples were not heated.

Multiple extractions of samples containing residues showed the extraction procedure completely removed all of the 2,4,5-T or 2,4,5-trichlorophenol from the milk or cream.

Treatment of milk with potassium hydroxide before extraction with ether did not result in higher residues being found.

No significant blanks were found in milk or cream from the control cows. No residues of 2,4,5-T greater than 0.01 ppm were found at the 10-ppm feeding level. At this level 0.01 ppm 2,4,5-trichlorophenol was found. Residue levels increased as 2,4,5-T feeding levels increased. At the highest level fed, 1000 ppm, average residues of 0.42 ppm 2,4,5-T and 0.23 ppm of 2,4,5-trichlorophenol were found in milk. At all feeding rates residues had reached a plateau by the time sampling began on the second or third day.

Withdrawal of the chemical from the diet resulted in rapid disappearance of residues from milk.

No significant difference was found between residues in milk and cream (Table I).

Beef Cattle (DD-48)

Beef cattle at Dow's Lake Jackson, Texas laboratories were fed a complete basal ration for 28 days to which various amounts of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) were added. Treatment groups of 3 calves each were fed 0, 100, 300, and 900 ppm 2,4,5-T in the diet. Two groups of 3 calves each were fed 1800 ppm in the diet, one group terminating with slaughter on the 29th day, and the second group being held for a 7-day withdrawal period without added 2,4,5-T. All animals, with the exception of the withdrawal group and the control group, were slaughtered on the day following the end of the feeding period; the latter groups were slaughtered on

the 8th day after completion of dosing.

Samples of muscle, kidney, liver and fat tissues from each calf were analyzed for residues of 2,4,5-T and of 2,4,5-trichlorophenol by a gas chromatographic method (Table II).

The 2,4,5-T fed to the cattle was from a production lot several years ago when the specification for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was 1 ppm. Subsequent analysis found 0.5 ppm TCDD in the 2,4,5-T which was fed to the cattle. A sample of liver from each of the groups was analyzed for TCDD by the gas chromatography-mass spectrometric technique (DD-177). Residues (Table II) indicate that the level is roughly proportional to the feeding rate, and that the apparent half-life is about 7 days in cattle.

In correlating these data with present production and use of 2,4,5-T, it must be borne in mind that the present specification for TCDD in 2,4,5-T is 0.1 ppm maximum or approximately 20% of the amount present in the chemical fed to these cattle.

Sheep

A feeding trial (DD-49) was conducted at the USDA station in Kerrville, Texas where sheep were fed a complete ground ration to which 2000 ppm of 2,4,5-trichlorophenoxyacetic-acid (2,4,5-T) was added. This was done to compare residues in sheep to those found in beef cattle fed 2,4,5-T. Groups of three sheep were fed; one at 2000 ppm 2,4,5-T in the total diet for 28 days, another at 2000 ppm 2,4,5-T for 28 days

followed by 6 days of untreated feed, and a control group fed untreated feed.

Samples of body tissues from each sheep were analyzed for residues of 2,4,5-T and 2,4,5-trichlorophenol by a gas chromatographic method, verified as with the cattle tissues. The results are shown in Table III, below.

Table III Average Residues of 2,4,5-T and 2,4,5-Trichlorophenol in Tissues of Sheep Consuming 2,4,5-T.

Residue Determined	Tissue	2,4,5-T Feed Rate, ppm 2000	2000 w/d
		Average Residue Found, ppm	
2,4,5-T	Muscle	0.46	<0.05
	Kidney	20	<0.05
	Liver	2.6	<0.05
	Fat	0.5	<0.05
Trichlorophenol	Muscle	<0.05	<0.05
	Kidney	0.9	0.27
	Liver	2.1	1.8
	Fat	<0.05	<0.05

Metabolism Studies

In a study it was shown that 2,4,5-T was eliminated in urine quantitatively from a dairy cow (DD-164), when given for 4 days at 5 ppm in feed. In another study (DD-165) 2,4,5-T was given as the acid and as propylene glycol butyl ether esters to cattle and sheep in single oral doses and in repeated oral doses. In all cases, elimination via urine was rapid. Massive doses, calculated to be lethal, of 250 mg/kg body weight were given to sheep daily for 4 to 6 consecutive days. Residues in the tissues of the sheep killed by this procedure were about equal in fat, muscle, and liver, about 100 ppm, and about

250-350 ppm in kidney.

Miscellaneous

In experiments with rats and pigs (DD-166) 2,4,5-T as the amine salt was given in single oral doses of 100 mg/kg. Excretion was rapid via the kidneys resulting in a plasma half life in rats of about 3 hours.

In another study (DD-167) mice were treated by subcutaneous injection of 2,4,5-T in dimethylsulfoxide while animals were analyzed at intervals after treatment. The biological half-life was observed to be about 14 to 32 hours.

Piper et al. (DD-155) gave single oral doses of 2,4,5-T to rats and dogs, as follows:

> Clearance of ^{14}C activity from the plasma and its elimination from the body of rats and dogs were determined after single oral doses of [*carboxy*-^{14}C]2,4,5-T. The half-life values for the clearance of ^{14}C activity from the plasma of rats given doses of 5, 50, 100 or 200 mg/kg were 4.7, 4.2, 19.4 and 25.2 hr, respectively; half-lives for elimination from the body were 13.6, 13.1, 19.3 and 28.9 hr, respectively. The apparent volume of distribution also increased with dose. Urinary excretion of unchanged 2,4,5-T accounted for most of the ^{14}C activity eliminated from the body of rats. A small amount of unidentified metabolite was detected in the urine when rats were given 100 or 200 mg/kg but not 5 or 50 mg/kg. These results show that the distribution, metabolism and excretion of 2,4,5-T are markedly altered when large doses are administered.
>
> In dogs given 5 mg/kg, the half-life values for clearance from plasma and elimination from the body were 77.0 and 86.6 hr, respectively, offering a plausible explanation of why 2,4,5-T is more toxic in dogs than in rats. Appreciable excretion in the feces was noted and three unidentified metabolites were detected in urine of dogs, indicating a considerable difference in metabolism of 2,4,5-T by dogs and rats given the same dose.

In a parallel study in man, Gehring *et al*. (DD-159) studied the fate of 2,4,5-T after a single oral dose.

> Five human male volunteers ingested a single dose of 5 mg/kg without incurring detectable clinical effects. Concentrations of 2,4,5-T in plasma and its excretion were measured at intervals after ingestion. The clearances of 2,4,5-T from the plasma as well as its excretion from the body occurred via apparent first-order rate processes with half-lives of 23.10 and 23.06 hr, respectively. Essentially all of the 2,4,5-T was absorbed into the body and excreted unchanged in the urine. In the body, 65% of the 2,4,5-T resided in the plasma where 98.7% was bound reversibly to protein. The volume of distribution was 0.079 liters/kg. Utilizing the kinetic constants from the single dose experiment, the expected concentrations of 2,4,5-T in the plasma of individuals receiving repeated daily doses of 2,4,5-T were calculated. From these calculations, it was determined that the plasma concentrations would essentially reach a plateau after 3 days. If the daily dose ingested in mg/kg is A_0, the concentration in the plasma after attaining plateau would range from 12.7 A_0 to 22.5 A_0 μg/ml. This range would converge to approximately 17 A_0 μg/ml as the daily dose A_0 is distributed throughout the day.

Urine from occupationally exposed people has been analyzed (DD-168). Values of from 0.05 to 3.6 ppm of 2,4,5-T were reported, indicating that urine is a route of excretion from humans as well as other animals.

Plant Tissue

Experiments have been carried out to determine the levels if any, of residues of 2,4,5-T in several crops. These will be discussed separately below.

Rice

Registered labels recommend application of 2,4,5-T at a maximum of 1.25 lb/A between tiller and boot stage before flooding (4-8 weeks after rice emerges) and/or 1.5 lb/A after flooding (7-10 weeks after emergence). Experiments designed to determine what residues of 2,4,5-T were likely to occur from such uses were carried out in Texas, Louisiana and

Arkansas (DD-169).

An amine salt formulation of 2,4,5-T was applied with ground equipment calibrated to give 15-16 gal. of spray/A. The plots were treated twice to simulate maximum use of 2,4,5-T. The first 2,4,5-T application was 0.75 lb/A, 3-5 weeks after emergence of the rice, the second was 1.5 lb/A just before panicle initiation, 7-8 weeks after emergence of the rice. Rice grain and straw were collected. Rough rice from the Stuttgart test only was milled to give rice and hull fractions for analysis.

Samples were analyzed for residues of 2,4,5-T by gas chromatography with electron capture detection after conversion to the methyl ester. Included in the validation was an alkaline hydrolysis study to determine if any residue existed in an unextractable or "bound" form. No "bound" residue was found which was not extracted by the usual aqueous caustic extraction procedure.

Results (Table IV) show that no residue was found in the rough rice, while residues in the range of 1 to 10 ppm were found in the straw.

Sugarcane

Test plots were established in Florida during the 1969 growing season (DD-170).

One aspect of the study involved determination of the rate of decline of 2,4,5-T residues in the sugarcane plant after recommended treatment with the herbicide. Another dealt

with determination of the amount of residue likely to be present in raw cane at normal harvest time and whether such residues, if present, would concentrate in any of the products obtained from processing the cane.

Sugarcane plots were sprayed with VEON 245, a triethylamine salt formulation of 2,4,5-T, at the rate of one quart in twenty gallons of water per acre, equivalent to 1 pound of 2,4,5-T per acre. The first application was on May 21, 1969, when the cane was about three feet tall, and the second was on June 9 when the cane was five to six feet tall.

Samples for determination of the rate of decline of 2,4,5-T residues in sugarcane were collected at intervals of one day, one month, two months, four months, and six months (early normal harvest) after the second application.

Two separate studies were conducted to determine the distribution of 2,4,5-T residues present in raw cane, in the various processed products which might be used as food or in feed. One study involved separation of the raw cane into juice and bagasse in a sample mill while the second involved processing juice, fortified with 2,4,5-T, in a pilot factory. These studies were designed to generate data suitable for calculating distribution factors of 2,4,5-T which would be likely to occur in bagasse, factory syrup, raw sugar, and first molasses produced from raw sugarcane containing a

known quantity of the herbicide.

The method of analysis was verified by normal recovery experiments, and by hydrolysis studies on cane containing known residue, to show that no untreated residue remained.

Analysis of the samples of sugarcane showed that on the average, residues decreased one hundred-fold, from 10 ppm to a level of about 0.1 ppm, during the 18 weeks of sugarcane growth following final application of the herbicide. At early normal harvest time, 8 weeks later, residues were well below 0.1 ppm in all samples analyzed (Figure 1).

Distribution of residue between stalks and tops

Samples of cane were collected at early normal harvest time (26 weeks after final application of VEON 245), were topped as normally done in preparation for milling, and the stalks and tops were analyzed separately. The few lower semi-dry leaves which remained on the stalk portions of the plants were included with the stalk samples.

No residues of 2,4,5-T were found in the tops from any of the treated plots. A few samples of stalks, notably those from the Ritta location, contained detectable residues, but in no sample did the residue level approach 0.1 ppm. Residues in cane from Ritta are estimated to average approximately 0.05 ppm.

Distribution of residue between bagasse and juice

Results from the sample milling experiment, designed

to establish the distribution of 2,4,5-T between bagasse (fiber) and juice when sugarcane bearing a residue is milled in a manner to simulate the commercial process.

The data concerning bagasse and juice reveal that any 2,4,5-T residue remaining in the sugarcane plant in the latter stages of growth is associated almost entirely with the fiber. Residues in bagasse ranged from 0.1 to 0.4 ppm, while only traces were noted in some of the raw juice samples. Since raw juice contains a considerable amount of small fibers (bagacillo), produced when the cane is crushed, the concentration in juice may be further reduced when this material is removed during clarification of the juice prior to processing.

The samples analyzed from the processing experiment included first molasses and raw sugar, end products of the Audubon pilot factory, as well as factory syrup, representing an intermediate stage of the process.

Concentrations of 2,4,5-T in syrup, molasses, and sugar for each mill run were related to the concentration in the fortified mixed juice from which they were derived to produce the distribution factors shown in Table V. The averaged results for syrup and molasses, indicating 5-fold and 12-fold concentrations of the herbicide, respectively, correlate closely with the degree to which water has been evaporated from the juice at these processing stages. Residual

used, ESTERON 245 and ESTERON Brush Killers, contained the

propylene glycol butyl ether esters of 2,4,5-T, the latter being an equal mixture of 2,4-D and 2,4,5-T. In another series of experiments 2,4,5-T was applied in Formulation M-3060 with picloram as the triisopropanolamine salt, at a rate of 0.5 lb 2,4,5-T acid equivalent per acre. Grass was collected within one day, and at 1, 2, 4, 8, and 16 weeks after the applications.

The grass was analyzed for residues of 2,4,5-T by well verified methods. Figure 2 shows the results from the first series of experiments. The term "specific residue" is used so that all rates of application can be viewed on the same basis. This is defined as specific residue = ppm per lb/A applied. Thus multiplying any point by a given application rate will show the residue level to be expected if that amount of 2,4,5-T had been applied. This shows that the residue level decreases rapidly with a half life of 1-2 weeks. This is in line with the study published by Morton et al. (DD-120).

Miscellaneous

Blueberries have been given a roller application of 2,4,5-T at a rate of 1 lb/A, followed by burning. Berries harvested 2 years after treatment contained no residue (DD-174).

A study was conducted by Chow et al. (DD-173) on wheat treated with 2,4,5-T, at a rate of 1 lb/A. The residue on green plants decreased from 9 ppm seven days after application to 1 ppm 28 days after application. Grain and straw, 56 days after application, contained 0.0 and 0.1 ppm respectively.

Coon (DD-175) reported on results of analysis of sweet and field corn which had been treated with 2,4,5-T at a rate of 1 lb/A late postemergence just prior to tasseling. Samples of plants from one day after application through crop maturity contained up to 4 ppm of 2,4,5-T, while mature grain contained no residue using a method sensitive to 0.1 ppm.

TCDD Studies

There is one study, Piper *et al*. (DD-176), reported which assesses the fate of TCDD following ingestion. In this study, a near lethal or lethal dose of TCDD (some of which was radioactively labeled with carbon-14) was administered orally to male rats. Subsequently, the ^{14}C activity was determined in tissues and excreta as a function of time. The results provide a basis for the following statements:

(a) Most of the orally administered TCDD is absorbed into the body.

(b) In the body, TCDD and/or metabolite(s) of TCDD are localized in liver and fat.

(c) TCDD and/or metabolite(s) of TCDD are eliminated predominantly via the feces. Small amounts are eliminated in the urine. It appears that an even smaller fraction is totally metabolized by the body to CO_2.

(d) The time required for elimination of one-half of the TCDD absorbed is approximately 17 days in the rat. The clearance of the compound from various tissues including liver and fat is comparable to its clearance from the body.

(e) With repetitive administration (exposure) a steady-state amount of TCDD would be attained in the body and its tissues within 90 days. Specifically, the days of exposure required to attain the specified percent of steady-state are: 30%, 9 days; 60%, 23 days; 80%, 40 days; 90%, 58 days; 98%, 97 days.

From the results of this study, it may be concluded that the capacity of the body to eliminate TCDD is significantly less than 2,4,5-T. Therefore, if tolerable, an equivalent exposure to TCDD and 2,4,5-T would result in the attainment of a significantly higher steady-state level of TCDD than 2,4,5-T in the body and its tissues. Nonetheless, upon repeated exposure to small levels of TCDD, an amount in the body and concentrations in the tissues will be attained beyond which further accumulation will not occur with subsequent exposure. This steady-state level will be attained within a definable period of time, approximately 90 days.

In studies of the repeated ingestion toxicity of

2,4,5-T in animals, toxicity associated with repeated exposure to and hence accumulation of a TCDD contaminant of 2,4,5-T should be discernible within 90 days. Additional exposure will not lead to attainment of higher levels of TCDD.

Although the data are yet available, additional studies of the fate of TCDD in animals are underway.

Isensee (DD-127) studied absorption and translocation of root- and foliage-applied ^{14}C-labeled TCDD. In this study it was necessary to use rates of application several orders of magnitude greater than would be applied by even heavy applications of 2,4,5-T. Isensee stated that "accumulation of TCDD by plants from soil was concluded to be highly unlikely." No translocation of foliar-applied TCDD was measured. Two hours after foliar application of TCDD, 50 to 60% was removed by rainfall, while 25% was removed 7 days after application to oats.

A report on analysis of tissues from eagles, which are representatives of the top of the food chain, indicated no residues of TCDD above the 0.05 ppm limit of detection (DD-125). This absence of residues in eagle tissues suggests that residues of TCDD from past applications of 2,4,5-T are not available to enter the food chain.

TABLE I AVERAGE RESIDUES OF 2,4,5-T AND 2,4,5-TRICHLOROPHENOL IN MILK AND CREAM

2,4,5-T In Diet (ppm)	2,4,5-T		2,4,5-Trichlorophenol	
	Milk	Cream	Milk	Cream
10	<0.01	<0.01	0.01	0.01
30	0.03	0.03	0.03	0.03
100	0.02	0.03	0.05	0.06
300	0.11	0.08	0.10	0.10
1000	0.42	0.26	0.23	0.19
Withdrawn				
1 Day	0.10	--	0.15	--
3 Days	0.02	--	0.02	--
5 Days	0.01	<0.01	0.01	<0.01
7 Days	<0.01	--	<0.01	--

Table II Average Residues of 2,4,5-T and 2,4,5-Trichlorophenol and TCDD in Tissues of Cattle Consuming 2,4,5-T for 28 Days.

Residue Determined	Tissue	2,4,5-T Feed Rate, ppm					
		0	100	300	900	1800	1800 w/d
		Residue Found, ppm					
2,4,5-T	Muscle		0.05	0.1	0.2	0.4*	<0.05
	Kidney		1.3	3.2	7.5	6.2*	0.08
	Liver		0.1	0.2	1.0	1.4*	<0.05
	Fat		0.2	0.3	0.4	0.8*	<0.05
Trichloro-phenol	Muscle		<0.05	<0.05	<0.05	0.06	<0.05
	Kidney		0.25	0.21	0.28	2.7	0.05
	Liver		0.23	0.48	1.1	3.0	1.9
	Fat		<0.05	<0.05	<0.05	0.1	<0.05
2,3,7,8 tetrachloro-dibenzo-p-dioxin	Liver	0.000000	0.000013	0.000061	0.000150	0.000360	0.000160

*excluding one animal with abscessed liver
w/d indicates withdrawal of 2,4,5-T from feed 7 days before slaughter.

TABLE IV. RESULTS OF ANALYSES FOR 2,4,5-T RESIDUES IN ROUGH RICE, HULLS, AND STRAW.

Sample	2,4,5-T Applied lb/A[1/]	Interval After Last Treatment Days	Range of Residues Found, ppm 2,4,5-T
		Beaumont, Texas	
Rough Rice	0.75+1.5	54	0[2/]
Straw	0.75+1.5	54	1.2-12.6
		Baton Rouge, Louisiana	
Rough Rice	0.75+1.5	50	0[2/]
Straw	0.75+1.5	50	3.8-10.1
		Stuttgart, Arkansas	
Rough Rice	0.75+1.5	85	0[2/]
Hulls	0.75+1.5	85	---
Straw	0.75+1.5	85	1.1-3.2

[1/] First application 24 to 30 days after emergence; second application about 50 days after emergence.

[2/] Lower limit of sensitivity of method = 0.025 ppm.

TABLE V

DISTRIBUTION OF 2,4,5-T IN SUGARCANE PLANT AND PRODUCTS

STALKS > TOPS

BAGASSE > JUICE

$$\frac{\text{SYRUP}}{\text{JUICE}} = 5$$

$$\frac{\text{MOLASSES}}{\text{JUICE}} = 12$$

$$\frac{\text{SUGAR}}{\text{JUICE}} = 0.6$$

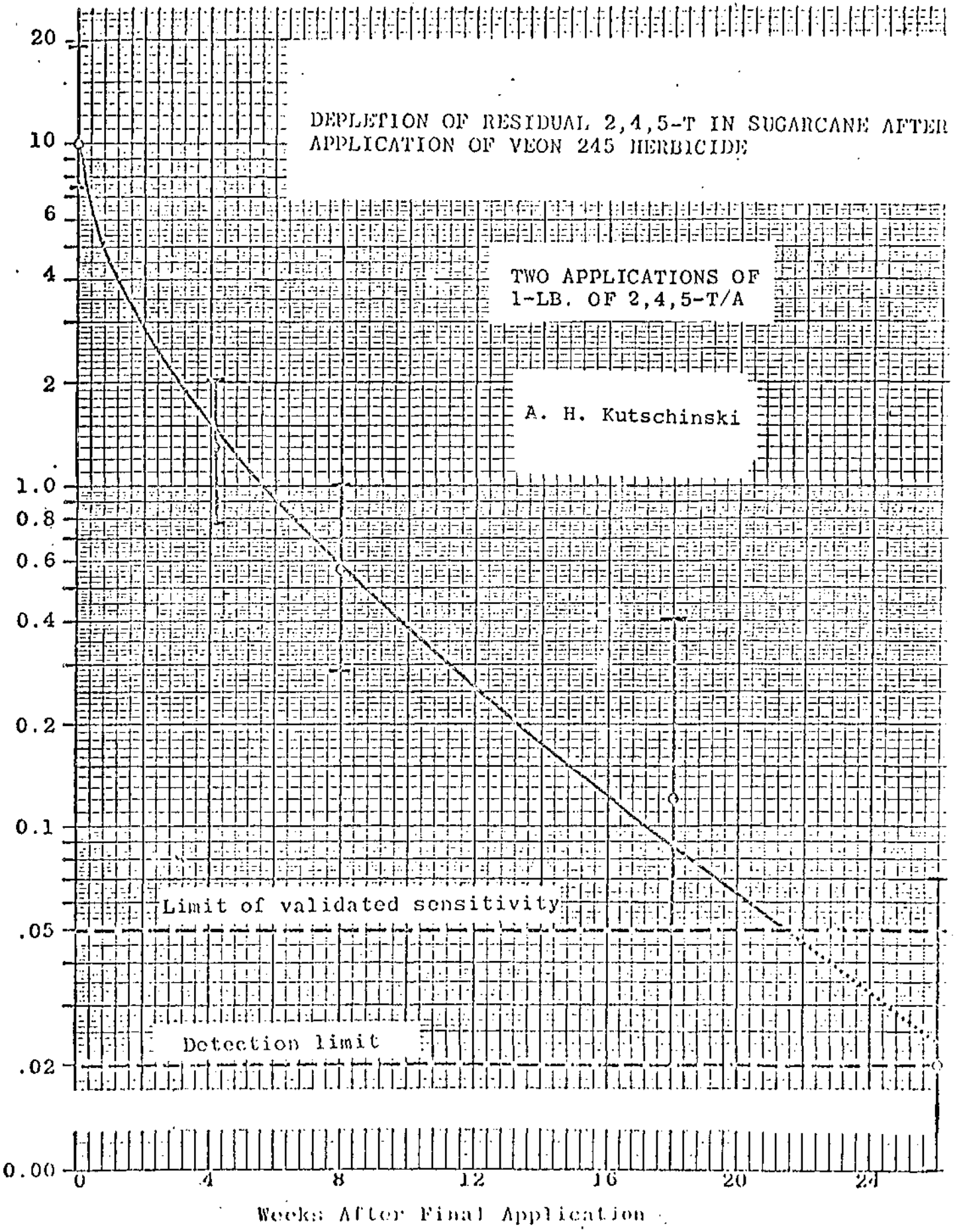
DEPLETION OF RESIDUAL 2,4,5-T IN SUGARCANE AFTER APPLICATION OF VEON 245 HERBICIDE
TWO APPLICATIONS OF 1-LB. OF 2,4,5-T/A
A. H. Kutschinski
Limit of validated sensitivity
Detection limit
ppm 2,4,5-T
20
10
6
4
2
1.0
0.8
0.6
0.4
0.2
0.1
.05
.02
0.00
0
4
8
12
16
20
24
Weeks After Final Application

FIGURE 1

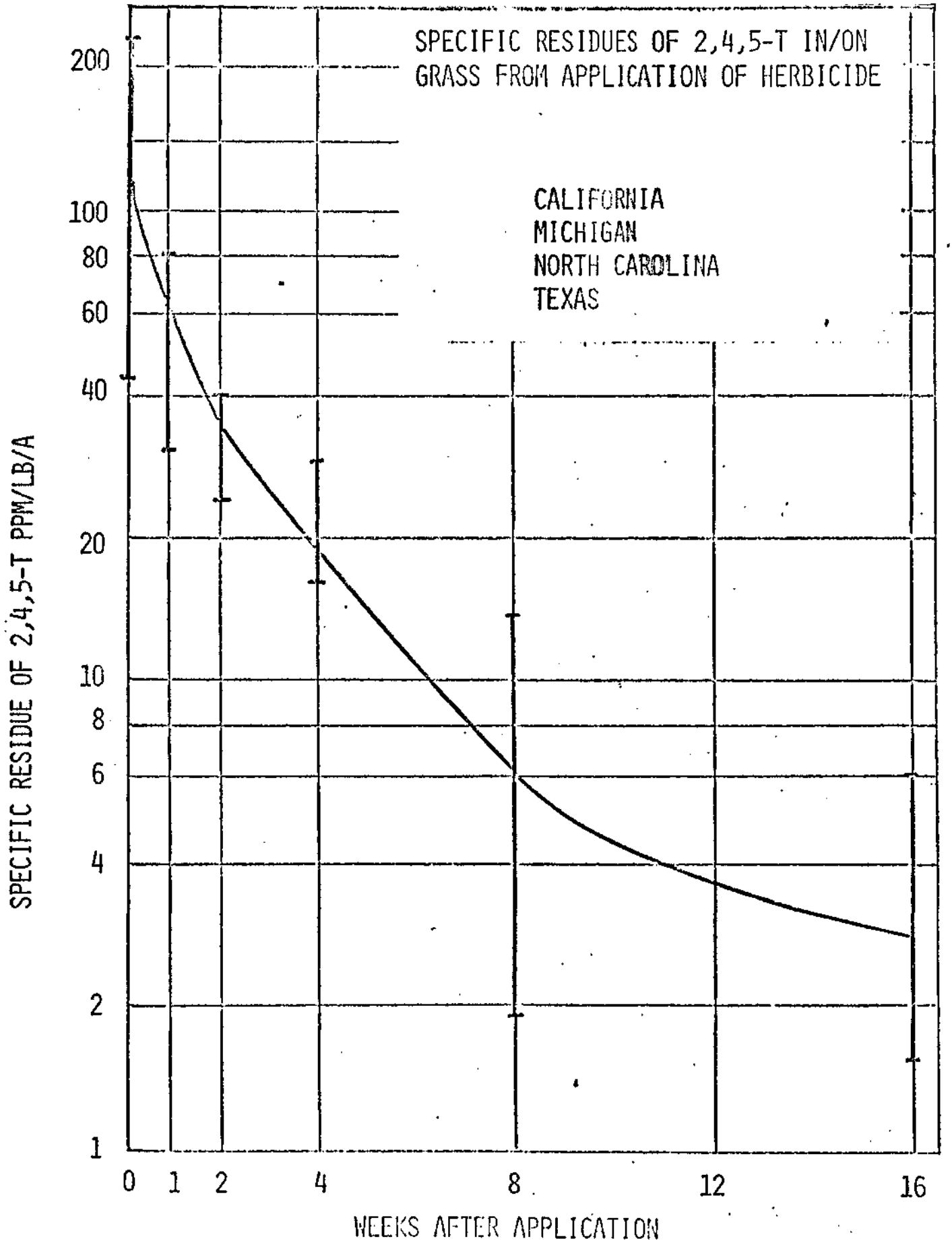
SPECIFIC RESIDUES OF 2,4,5-T IN/ON
GRASS FROM APPLICATION OF HERBICIDE
CALIFORNIA
MICHIGAN
NORTH CAROLINA
TEXAS
SPECIFIC RESIDUE OF 2,4,5-T PPM/LB/A
200
100
80
60
40
20
10
8
6
4
2
1
0
1
2
4
8
12
16
WEEKS AFTER APPLICATION

FIGURE 2

5. Are other dioxins and similar contaminants, besides TCDD, present in 2,4,5-T, if so, what risks to health do they constitute?

Response

Dioxins other than TCDD are not routinely assayed. Spot checks of current Dow 2,4,5-T production indicate the levels stated in V. B. 7, *infra*. These levels do not constitute risks to health.

Schwetz *et al*. (DD-180) reported on the toxicity of several dioxins including 1,2,3,4-tetrachlorodioxin, hexachlorodioxin, dichlorodioxin, and octachlorodioxin. Only hexachlorodioxin (HCDD) showed any toxicity at the dose levels tested. HCDD caused chloracne when applied to rabbit ears at 10-50 µg/kg/day. HCDD also caused a significant increase in the incidence of soft-tissue at 10 µg/kg/day and skeletal anomalies at the 100 µg/kg/day dose level in rats. However, these levels are such that the HCDD contained in current 2,4,5-T Dow products does not constitute a significant risk to health.

Heptachlorodioxin was not studied directly because of the difficulty in securing pure samples. However, it cannot be highly toxic since studies on octachlorodioxin containing several percent heptachlorodioxin have tested the same as pure octachlorodioxin.

6. What are other environmental sources of dioxins, particularly TCDD, and do these sources enhance the total dioxin body burden and exacerbate the health risks raised by 2,4,5-T and related TCDD?

Response

Other environmental sources of dioxin contribute such a small amount to the environment that they do not exacerbate the health risks.

The other possible sources of TCDD are 2,4,5-trichlorophenol (and sodium salt), O,O-dimethyl-O-2,4,5-trichlorophenyl phosphorothioate (ronnel), and 2-(2,4,5-trichlorophenoxy) propionic acid (silvex). TCDD has not been detected in pentachlorophenol manufactured in the United States with a detection limit of 0.05 ppm.

2,4,5-Trichlorophenol, sodium salt of the trichlorophenol, ronnel, and silvex each have less than .1 ppm of TCDD. Dow's new technical pentachlorophenol (DOWICIDE® EC-7 Antimicrobial) contains no TCDD, $\leq$1 ppm hexachlorodibenzo-p-dioxin and $\leq$30 ppm octachlorodibenzo-p-dioxin. (DD-181) A summary of the uses and recommended concentrations of these chemicals follows:

2,4,5-Trichlorophenol (DD-182)

DOWICIDE® 2 Antimicrobial is Dow's designation for 2,4,5-trichlorophenol, technical grade (95% active).

This antimicrobial is used as a fungicide by the adhesive industry for preserving polyvinyl acetate emulsions; by the textile industry for preserving emulsions used in rayon spinning, rayon yarns, and silk yarns; and by the automotive industry for preserving rubber gaskets.

The recommended concentration of DOWICIDE® 2 for use by the adhesive industry is 0.4% by weight of total adhesive solution; by the automotive industry 0.5-1.0% mixed into molten rubber; and by the textile industry 0.1% by weight of the emulsions.

Sodium 2,4,5-trichlorophenate (DD-183)

DOWICIDE® B Antimicrobial is Dow's designation for the sodium salt of 2,4,5-trichlorophenol, technical grade (85% active). DOWICIDE B meets the requirements of FDA for use in slime control agents in paper manufacture (21 CFR 121.2001)* in slimicides (CFR 121.2505) and in defoaming agents (CFR 121.2519 and 121.2557). This product is used by adhesive manufacturers to preserve adhesives derived from casein, as well as polyvinyl acetate emulsion-type adhesives. Added to leather dressings and finishes, DOWICIDE B prevents decomposition of nitrogenous components such as casein, gelatin, and egg albumen, and, consequently, ruination of the formulations. Metalworkers

* All subsequent references in this Response are to 21 CFR.

employ DOWICIDE B to protect against breakdown and spoilage of metal-cutting fluids and foundry core washes. It is also added to the recirculating cooling water of cooling towers to control bacteria and fungi.

The recommended concentrations of DOWICIDE B are as follows:

Adhesive preservative	0.15 - 1.0% by wt. of adhesive
Cooling tower water	50-100 ppm added initially to recirculating water, then 50 ppm each 2-6 weeks thereafter.
Leather dressings and finishes	0.25-0.5% by wt. of formulation
Metal-cutting fluids	0.05-0.5% by wt. with an equal amount of DOWICIDE A (sodium salt of o-phenylphenol - not a source of dioxins)

Pentachlorophenol (DD-184)

DOWICIDE® EC-7 Antimicrobial is Dow's designation for pentachlorophenol, technical grade. DOWICIDE EC-7 meets the requirements of FDA for use in adhesives (CFR 121.2520) and in wooden articles (CFR 121.2556).

Mixtures of DOWICIDE® EC-7 and DOWICIDE® 1* Antimicrobials are utilized by paint producers for the shelf

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* (o-phenylphenol, not a source of dioxins)

preservation of protein-based latex paints. The textile industry uses DOWICIDE EC-7 Antimicrobial to preserve rope, binder twine, burlap, cable covering and rubberized canvas belting; and leather manufacturers use it to impart temporary mold resistance to leather uppers for shoes. It is also utilized by the wood construction industries to impart termite resistance to wood and to control mold growth on lumber products and building surfaces; and by the ink industry to prevent breakdown and spoilage of finished formulations.

The recommended concentration for incorporation in construction materials is 0.5-5.0%, in treating leather used for shoes 2.0-3.5% by weight of the treating formulation, and in ink formulations 500-2000 ppm.

Sodium Pentachlorophenate (DD-185)

DOWICIDE® G Antimicrobial is Dow's designation for the sodium salt of pentachlorophenol. DOWICIDE G meets the requirements of FDA in the following uses:

CFR 121.2001	Prior sanction as a slime control agent in the manufacture of paper products
CFR 121.2505	Slimicides
CFR 121.2514	Resinous and Polymeric Coatings: Par. (b) (3) (xxxi), can-end cements
CFR 121.2519	Defoaming Agents Used in the Manufacture of Paper and Paperboard
CFR 121.2520	Adhesives
CFR 121.2526	Components of Paper and Paperboard in Contact with Aqueous and Fatty Foods

CFR 121.2534	Animal Glue
CFR 121.2535	Textiles and Textile Fibers
CFR 121.2548	Zinc-Silicon Dioxide Matrix Coatings
CFR 121.2550	Closures with Sealing Gaskets for Food Containers
CFR 121.2556	Preservatives for Wood
CFR 121.2557	Defoaming Agents Used in Coatings
CFR 121.2562	Rubber Articles Intended for Repeated Use
CFR 121.2571	Components of Paper and Paperboard in Contact with Dry Food
CFR 121.2596	Sodium Pentachlorophenate. Preservative for ammonium alginate employed in the manufacture of polyvinyl chloride emulsions

Adhesive manufacturers incorporate this antimicrobial into adhesives based on starch, vegetable protein, and animal protein to protect them against attack by bacteria and mold, during manufacture and storage and throughout their service life. In the leather industry, DOWICIDE G Antimicrobial plays an important role in various pre-tanning and tanning stages of treatment, in protecting shaved and split stock during storage, and in imparting mold resistance to finished luggage leather. Stored disposable raw materials for paint are protected by the addition of DOWICIDE G or 50-50 mixture of DOWICIDE A and DOWICIDE G Antimicrobials; and shelf preservation of protein-base latex paints is accomplished by use of this same mixture. Finished paper and fiberboard products are protected against mildew, rot, and termites by

the use of DOWICIDE G, which also prevents deterioration of coatings, sizings, and printing colors. Textile sizing and finishing solutions, printing pastes, gray goods, cloth, and carpet yarn are treated with DOWICIDE G Antimicrobial to prevent microbiological attack.

In addition, DOWICIDE G Antimicrobial is used to control mold growth on construction materials and in petroleum drilling mud; to achieve optimum secondary oil recovery in flooding operations by controlling microbial growth in underground strata; to inhibit fungal growth in underground strata; to inhibit fungal growth in photographic solutions, and to treat industrial water.

The recommended concentrations of DOWICIDE G in the various applications are as follows:

Construction Materials	1.0% by wt. in water; 0.5-3.0% by wt. of product in which incorporated.
Leather	0.06-10.0% by wt. in water; 0.5-3.0% by wt. of product in which incorporated.
Paint	Minimum of 0.6% by wt. of DOWICIDE G or a 50-50 mixture of DOWICIDE A and DOWICIDE G antimicrobials.
Petroleum	0.25-0.5 lb. of antimicrobial per barrel of mud or packer fluid; 15-40 ppm in underground flooding water.
Photographic Solutions	0.05-0.2% by wt. of solution.

Pulp and Paper	0.1-1.0% by wt. of paper product, pulp, or processing material.
Textiles	0.1-0.75% by wt. of material treated.
Water Treatment	20-80 ppm

Ronnel (Dow Trademark-Korlan® Insecticide) is registered for a number of insecticide uses, including certain livestock insects, flies, cockroaches, fleas, ants, spiders and bedbugs (DD-186). Concentrations of spray range from 0.15-2.0% depending on use.

Silvex (Dow Trademark-Kuron® Low-Volatile Brush and Weed Herbicide) is registered for weed control in lawns, golf courses, rice, sugarcane, brush control and aquatic weed control (DD-187).

Silvex, ronnel and pentachlorophenol each have extremely small dioxin levels. Dow knows of no other sources of dioxins to the United States environment. Uses of the products discussed are sufficiently remote in time and space so that the cumulative impact is negligible and health risks are not significantly affected.

7. What are the current levels of dioxin in registered 2,4,5-T products and in technical material used to formulate these products?

Response

The current levels of dioxins in the technical material used to make formulations of registered Dow 2,4,5-T products are as follows:*

TCDD	<.1 ppm
Pentachlorodioxin	<.1 ppm
Hexachlorodioxin	<.1 ppm
Octachlorodioxin	<.1 ppm

Because formulations for marketing are diluted, levels in registered 2,4,5-T products are necessarily lower than the above.

* As noted in Response to V.B. 5, supra, with the exception of TCDD which is routinely assayed, spot checks have been done for other dioxins. With a .05 ppm limit of detection, dichlorodioxin has never been detected.

8. Do the current methods of manufacture of 2,4,5-T provide for consistently low levels of dioxins in the final technical product and what are the quality control measures used to minimize dioxin levels?

Response

Note: The Response in this Section refers only to the quality control procedures in effect at Dow and does not presume to address the quality control procedures of other manufacturers.

The methods of manufacture used by Dow provide for consistently low dioxin levels in 2,4,5-T products. The chemistry of dioxin formation is well known, and Dow's method of processing trichlorophenol and 2,4,5-T products limits dioxin formation to the lowest extent possible.

In the trichlorophenol and 2,4,5- T manufacturing plants, processing conditions (such as temperature, pressure, pH, and chemical composition) are continuously measured and recorded by on line process monitors. These measurements are then used to adjust the process variables within known limits, to minimize dioxin formation. In the trichlorophenol process these adjustments are done automatically by preprogrammed computer control. The 2,4,5-T ester process uses more conventional control techniques.

The process monitor and control schemes are designed to minimize dioxin formation but are not the final quality control check. The program for final quality check, shown in Figure 1, infra, is designed to assure that every lot of 2,4,5-T formulated product or technical ester is within specification, including less than 0.1 ppm 2,3,7,8-tetrachlorodibenzo-p-dioxin.

The quality check points on all products sold by Dow are also shown in Figure 1. Each quality check shown includes an assigned lot number and a complete analysis, including TCDD analysis by the GC-MS method (DD-112). The actual analytical techniques have been developed over a period of time and are now established for each individual technical material and formulation.

All trichlorophenol is shipped by tank car, either for sale or to the 2,4,5-T ester process. Each tank car is assigned a lot number and a sample is then taken from the tank car and analyzed (including 2,3,7,8-tetrachlorodibenzo-p-dioxin analysis) to insure that it meets specification.

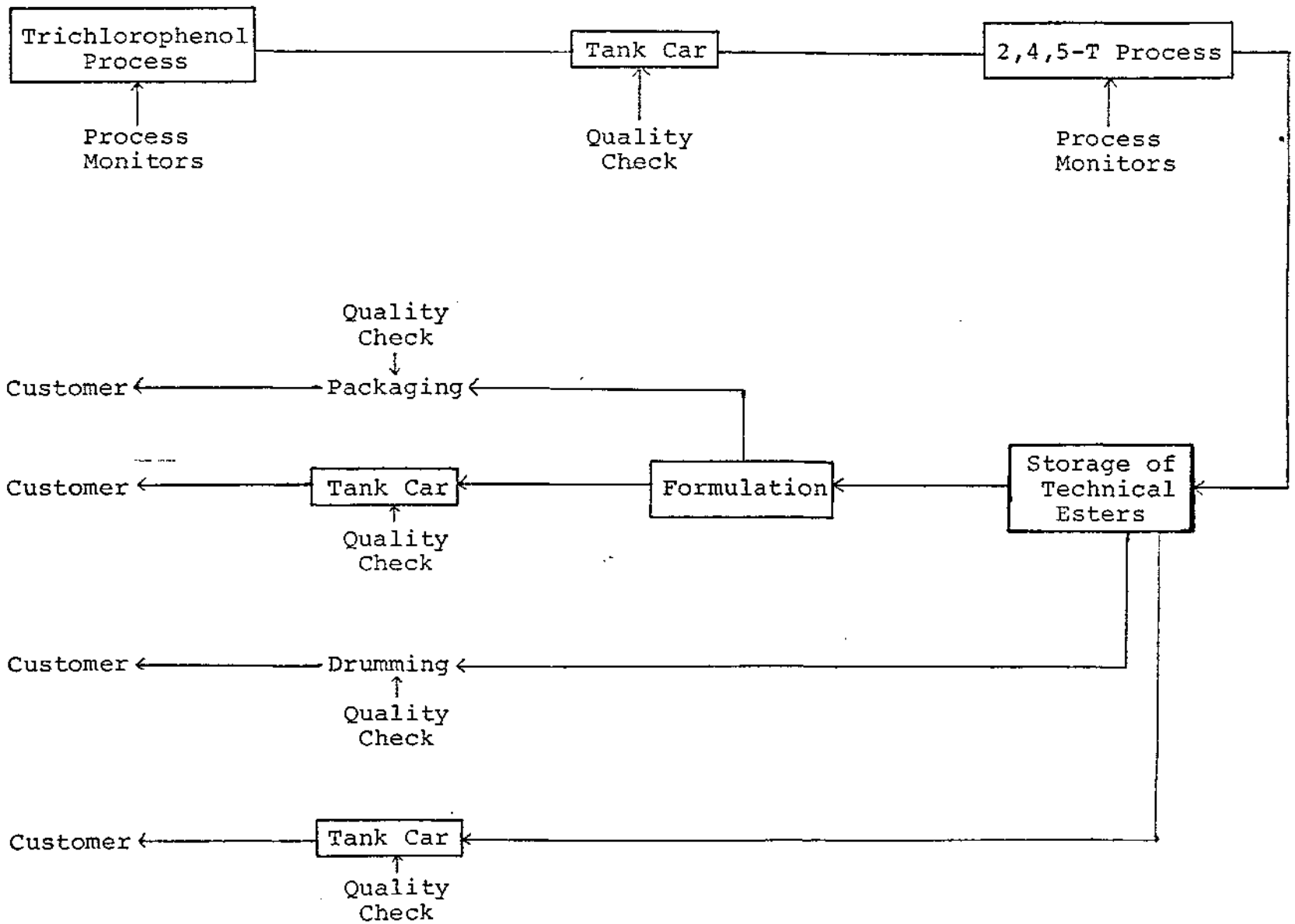
2,4,5-T technical esters and formulated products take a variety of routes from bulk storage to sale (Figure 1). Bulk technical esters shipped by tank car are handled the same way as trichlorophenol -- i.e., a

lot number is assigned to each tank car and a sample taken and analyzed to insure that specifications are met. TCDD determination is also part of this analysis. If the technical ester is sold in drums, the quality control sample is taken at the packaging line. For each product, the ester packaged in one day is assigned a lot number. For each lot number, a sample is taken at the filling spout and analyzed to see that it meets specification.

Formulated bulk esters have the same quality control procedures as bulk technical esters. The same quality control procedures are used for formulated esters packaged in drums as for technical esters packaged in drums -- i.e., each product has a lot number assigned to each day's packaging and samples of each lot are then taken at the filling head and analyzed.

This program means that each lot of 2,4,5-T product sold by Dow has been analyzed and that each package will have a lot number stamped on it. By simply knowing the lot number, Dow can furnish the analytic results for the material in the package. Such rigid quality control procedures assure that all material contains less than 0.1 ppm 2,3,7,8-tetrachlorodibenzo-p-dioxin.

FIGURE 1


Trichlorophenol Process
Process Monitors
Tank Car
Quality Check
2,4,5-T Process
Process Monitors
Quality Check
Customer
Packaging
Customer
Tank Car
Quality Check
Formulation
Storage of Technical Esters
Customer
Drumming
Quality Check
Customer
Tank Car
Quality Check

Issue V.C: The necessity for the continuation of the registered uses of 2,4,5-T, with emphasis on the following:

This Response is limited to the use of 2,4,5-T on rice. Dow is informed that other parties will respond with respect to all other existing 2,4,5-T uses (rangeland, forestry, highway, utility and rail -- see Exhibit B-1, annexed to Dow Prehearing Memorandum [No. 1], filed December 10, 1973). Dow requests leave to supplement this Response in its February 22 Prehearing Memorandum [No. 3] if any of these use areas is not adequately covered in the submissions of other parties.

Following preparation of this section, on January 14, 1974 Dow received the American Farm Bureau Federation's ("AFBF") Prehearing Brief. AFBF was not admitted as a party until November 12, 1973 and had not previously undertaken to address the rice issue. It did not attend the preparation meeting on that date or earlier meetings at which initial allocations of responsibility for preparation of subject areas were considered.

AFBF represents farm user groups, including rice users. It is well qualified to present evidence in the rice use area, in the same fashion that Government and user representative groups will present evidence of use by the persons and organizations for whom they speak. Dow intends to make available to AFBF its hearing preparation

as referred to in this Section, and to defer to AFBF in this use area. It will offer evidence supporting the assertions in this Section only to the extent not adduced by other parties.

1. What are the pests which each registered use is intended to control and the degree of control achieved by each use?*

Response

2,4,5-T is used to control broadleaf and aquatic weeds which infest rice plantings in Arkansas, Mississippi and portions of Louisiana and Texas. The more important of such weed species, which vary from area to area, are alligatorweed, arrowhead, cocklebur, coffeebean (hemp sesbania), curly indigo (northern jointvetch), dayflower, ducksalad, gooseweed, morning glory, redstem, spikerush, smartweed, umbrellasedge,

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* Because weed and grass problems are largely the results of soil productivity, climatic conditions and cultural practices in specific areas, this and the following Responses to Issue V.C could specify contentions varying from state to state, farm to farm and even from weed to weed. Dow is hopeful that such detailed consideration will not be required and that the proper conclusions can be drawn from the evidence of relatively few witnesses testifying generally to the issues. However, it requests leave to supplement this Response on February 22 if it appears from the January 18 submission of other parties that greater specification will be required.

waterhyacinth and waterhyssop. 2,4,5-T, used as part of a coordinated program of preventative, cultural, mechanical and chemical methods, provides excellent control (up to 95%) of cocklebur, coffeebean and curly indigo, with control of other species ranging from excellent to fair.

2. What is the cost, timing, and rate of application of 2,4,5-T for each use?

Response

2,4,5-T is a post-emergence or mid-season herbicide applied five to nine weeks after rice emergence, as the amine salt formulation at rates of one-half to one and a half pounds per acre acid equivalent. While costs vary depending on rates of application and other factors, average cost for once a season application is estimated at $3.00 to $4.00 per acre.

3. What alternative controls exist for each registered use and what is the cost and effectiveness of each alternative?

Response

Hand labor for weeding is unavailable and/or prohibitive in cost and effective biological controls have not yet been developed. Principal alternatives for broadleaf weed control are the other phenoxy herbicides -- 2,4-D, Silvex and MCPA -- and propanil.

Application costs for Silvex and MCPA are roughly the same as for 2,4,5-T, while 2,4-D at average application rates costs approximately $1.50 per acre. Propanil, when used as recommended for post-emergence control of grassy and very young broadleaf weeds, costs $7.00 to $9.00/acre. When used as an alternative to 2,4,5-T or other phenoxies for control of larger weeds, two or more applications per season are required.

2,4-D is excellent for certain weeds such as morning glory and ducksalad but is less effective for the major problem species, is injurious to young rice and highly toxic to cotton which is grown in close proximity to rice, particularly in Mississippi and some areas of Arkansas. Silvex is less effective than 2,4,5-T for some of the more important broadleaf weeds and is damaging to soybeans, which is the principal adjacent crop in Arkansas. MCPA is effective against certain weed species in Texas but is injurious to rice plants and lowers yield when used in the local second or stubble-crop practice. Propanil has a very short residual effect and is not the herbicide of choice for mid-season control. When used as a phenoxy substitute, multiple applications are required, which may not comply with label directions or state weed

control recommendations and may result in residues which exceed approved tolerances. In addition, propanil is injurious to soybeans and cannot be used safely within 15 days before or after application of certain rice insecticides or any time after application of carbofuran insecticide.

4. Do alternative pesticide products cause adverse environmental effects:

Response

See answer to 3, above.

5. What are the economic implications of these alternatives, including that of no control?

Response

Recent studies indicate that without 2,4,5-T, weed infestation would increase rapidly to a point where yields would be reduced 10 percent or more within two or three years. Presence of weed seeds also reduces rice quality for use as food and for seed, and creates other risks of uncertain character. Resulting income losses to area rice farmers, based on yield and quality decline, are estimated at approximately $4,461,620. These figures are based on total rice acreage currently treated with 2,4,5-T.

Documentary references for the foregoing Responses are contained in Dow Repository Exhibits (DD-301-309).

B. DOW EVIDENTIARY AREAS

Dow expects to be concerned primarily with the scientific issues covered in V, V.A and V.B, above. It expects to deal with other issues, including use of 2,4,5-T on rice, V.C. supra, only to the extent they are not adequately covered by other parties who have indicated an intention to assume responsibility for the preparation of such issues.

C. NEED FOR FIELD HEARINGS

Subject to discussion with AFBF Dow requests that field hearings be held in Stuttgart, Arkansas and Cleveland, Mississippi, with respect to the issue of use of 2,4,5-T on rice. The reason is to convenience witnesses, many of whom are self-employed rice farmers and certified seed growers and others whose time available for travel is limited. Dow expects that there will be approximately thirty such witnesses in the two locations, including growers, aerial applicators, county agents, and state extension service and USDA personnel from the four rice-growing states.

D. DOW REPOSITORY EXHIBITS

Exhibit "A" annexed is a list of the documents now being submitted to the Hearing Clerk's Document Repository. Dow anticipates offering most of these documents into evidence during its affirmative case. Some, however, are included because they are necessarily discussed and referred to in Dow's Responses to the Statement of Issues (see note p.4, supra). Dow does not question the authenticity of any exhibit included herein, but only intends to rely upon and offer in evidence those for which it can vouch as to methodology and integrity as well as authenticity.

Documents are identified as "Dow Repository Exhibits," followed by a numerical designation -- e.g., Dow Repository Exh. DD-12.* Exhibit numbers 1-100 have been reserved for documents relating to Issue V.A.; Exhibit numbers 101-300 are reserved for documents relating to Issue V.B.; and Exhibit numbers 301 et seq. are reserved for Issue V.C. references.

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* As noted above, references in the text of Dow's Responses to the Statement of Issues have been abbreviated -- e.g., DD-12.

E. OTHER MATTERS

1. Society of American Foresters. We are hopeful that the Society of American Foresters has been able to work out an acceptable arrangement for the introduction of its evidence into the record, as suggested in the Chief Administrative Law Judge's December 17, 1973 Order. If not, however, we urge that the Society be accorded a status which will permit it to offer whatever evidence it chooses to adduce, subject, of course, to appropriate objections and rulings in the course of the Hearing.

Since all parties are committed to the development of a complete, thorough and unbiased Hearing record, it would be unfortunate if the evidence of this group were excluded for technical reasons only.

2. Dow 2,4,5-T Registrations. In accordance with the direction of the Chief Administrative Law Judge (Tr., Nov. 12, 1973, p. 24), Exhibit "B" attached contains Dow's corrections and supplements to the EPA analysis of existing Dow registrations, served December 12, 1973. Dow has checked the details of its own registrations only, on the assumption that other registrants will deal with their own.

3. State Restrictions on 2,4,5-T. In response to the Order of the Chief Administrative Law Judge at the November 12, 1973 Prehearing Conference (Tr., p. 34), EPA

on December 12 furnished a partial description of some state restrictions on 2,4,5-T.

Exhibit "C" hereto supplements such information with a detailed summary of statutory and administrative provisions in Arkansas, Louisiana, Mississippi and Texas, the four rice-growing states in which 2,4,5-T is used in significant quantities. In addition, copies of the applicable statutes, regulations and state Plant Board or Department of Agriculture forms will be placed in the Document Repository, with identifying exhibit numbers as set forth in Exhibits A and C.

Dow has not made a similar analysis of the EPA summary for other jurisdictions but requests leave to supplement this submission on February 22 if information as to restrictions in other states has not been provided by other parties to the proceeding.

4. November 12, 1973 Transcript. Exhibit "D" hereto contains Dow's proposed additional corrections to the transcript of the Prehearing Conference held November 12, 1973.

5. Additional Witness Letter. Subsequent to service of Dow's Prehearing Memorandum (No. 1), a copy of Harold J. Hardcastle's November 27 request for leave to testify was received from the Hearing Clerk. Dow sent a witness information letter to Mr. Hardcastle on December 11, in

form similar to that earlier sent to witnesses, as described at page 2 of Exhibit B-1 to the original Memorandum. By letter dated December 20, Mr. Hardcastle advised that he would participate in the proceedings and offer his evidence through USDA.

Dated: New York, New York
January 18, 1974

Respectfully submitted,

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Dow Repository Exhibits

No.	
DD-1	Courtney, K. D., D. W. Gaylor, M. D. Hogan, H. L. Falk, R. W. Bates, and I. Mitchell. Teratogenic Evaluation of 2,4,5-T. Science, 168, 864-866 (1970).
DD-2	Courtney et al. Summary Teratogen Study. Typescript draft of record of 15 April 1970 Hearing on 2,4,5-T before the Subcommittee on Energy, National Resources and the Environment of the U. S. Senate Committee on Commerce, pp. 225-232. (Does not appear in final, printed report of Senate Committee).
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DD-312 Arkansas State Plant Board Form 1007, "Record of Custom-Application With 2,4-D, 2,4,5-T, or Other Hormone-Type Herbicide."

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DD-316 Mississippi Economic Poisons Act and Act Regulating the Application of Hormone-Type Herbicides by Aircraft, Miss. Code Ann. §§ 69-21-101 et seq.

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Corrections to EPA December 12, 1973
Analysis of Existing Dow 2,4,5-T
Registrations

Registration No.	Change
464-204	Delete "O.S." in name of product
464-205	Delete "O.S." in name of product
464-272	"6T" in name of product should be "T6". The form should be "Propylene glycol butyl ether ester" rather than "Butoxyethyl".
464-364	The form should be a "low" volatile ester.
464-365	This product is no longer manufactured and sold.
464-289	"CD" in name of product should be "CE." The form should also be changed, as in 464-272 above.

EXHIBIT B

Supplement to Description of State Restrictions on 2,4,5-T Submitted by EPA - December 12, 1973

1. ARKANSAS: The Arkansas Economic Poisons Act, 6C Ark. Stat. Ann. §§ 77-201 *et seq*. imposes registration and labeling requirements similar in broad outline to those imposed by FIFRA, as amended. "Regulations on 2,4-D, 2,4,5-T and Other Hormone-Type Herbicides" promulgated by the Arkansas State Plant Board impose various requirements as to shipping, marking, storage and recording of sales information with respect to such products. To minimize drift problems, sale and use of any but low-volatile esters is prohibited, except with written permission of the State Plant Board Director. Sale of dust in packages of more than one pound is also prohibited.

The Regulations also establish stringent financial responsibility and technical requirements for custom applicators of these herbicides, set standards for aircraft and application equipment, and specify permissible wind velocity, height, pressure, distance from susceptible crops and other conditions of application. In addition, detailed records of each custom application must be filed with the State Plant Board.

Copies of the Arkansas statute, regulations and "Record of Custom-Application With 2,4,-D, 2,4,5-T or Other Hormone-Type Herbicide" forms are part of Dow's documentary

EXHIBIT C

submissions and are identified as Dow Repository Exhibits (DD-310-312).

2. LOUISIANA: The Louisiana pesticide statute, La. R.S. 3: 1622 et seq. provides, inter alia, for licensing of aerial and ground applicators upon showing of financial responsibility and technical qualifications. Regulations applicable to hormone-type herbicides require registration of such products with the Louisiana Department of Agriculture, restrict sale and use of certain dust and ester formulations and fix standards as to spray distances under various wind conditions, as well as seasonal restrictions to protect sensitive crops. Detailed forms for all aerial applications must also be filed with the state Department of Agriculture.

Copies of the Louisiana statute, regulations and application forms are identified as Dow Repository Exhibits (DD-313-315).

3. MISSISSIPPI: The Mississippi Economic Poisons Law, Miss. Code Ann. §§ 69-23-1 et seq. also imposes registration and labeling requirements similar in broad outline to the Federal statute. Other statutory provisions (§§ 69-21-101 et seq.) regulate the application of hormone-type herbicides by aircraft, including detailed financial responsibility and technical standards for applicators and aircraft.

Regulations promulgated by the state Department of Agriculture and Commerce contain license requirements (including examination of applicators for skills in specific categories such as "Weed Control in Rice," "Weed and Brush Control on Rights-of-Way," etc.), specify application conditions and reporting requirements.

Copies of the Mississippi statutes, regulations and applicators' report forms are identified as Dow Repository Exhibits (DD-316-318).

4. TEXAS: The Texas Herbicide Law, Vernon's Ann. Civ. Stat., Art. 135b-4, regulates the sale and use of 2,4,5-T and other hormone-type herbicides, imposes financial responsibility, reporting and technical requirements on applicators and sets standards for equipment and issuance of spraying permits.

Because of widely varying wind, weather and crop conditions, Texas Herbicide Regulation No. 1-G limits the statute's applicability to certain counties and imposes additional restrictions for other counties (e.g. high volatile esters are prohibited in some areas, use of 2,4-D is banned during the cotton-growing season in other areas, etc.). Specific rules govern type and concentration of herbicide, height, pressure, distance and other application

conditions. In addition, dealers and applicators must file reports with the state Department of Agriculture.

Copies of the Texas statute, regulations and forms are identified as Dow Repository Exhibits (DD-319-321).

Proposed Additional Corrections
to Transcript of Prehearing
Conference - November 12, 1973

Page 4	Line 15	"Saunders" should be "Sanders"
Page 26	Line 14	"Wessell" should be "Wessel"
	Line 18	"facor" should be "favor"
Page 36	Line 16	"Bitman" should be "Ditman"
Page 45	Line 3	"testigying" should be "testifying"
	Line 24	"E" should be "(e)"

EXHIBIT D