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DOW

SPECIMEN LABEL
REDUCED TO 75%

DOW 668857

ESTERON® 245
HERBICIDE

FOR THE CONTROL OF TREES, BRUSH AND BROADLEAF WEEDS

Low-Volatile Brush and Weed Herbicide for Industrial Vegetation Control, Fencerows, and Rangeland

ACTIVE INGREDIENT	
2,4,5-Trichlorophenoxyacetic Acid Propylene Glycol Butyl Ether Esters	69.2%
INERT INGREDIENTS	30.8%
2,4,5-Trichlorophenoxyacetic Acid Equivalent — 45.0% 4 Pounds per Gallon	

EPA Registration No. 464-205 EPA Est. 464-MI-1

PRECAUCION AL USUARIO Si usted no lee ingles no use este producto hasta que la etiqueta le haya sido explicada ampliamente
TRANSLATION (TO THE USER If you cannot read English do not use this product until the label has been fully explained to you.)

KEEP OUT OF THE REACH OF CHILDREN

CAUTION

HARMFUL IF SWALLOWED • MAY CAUSE IRRITATION
Avoid Contact with Eyes, Skin and Clothing
Do Not Cut or Weld Container

In case of an emergency endangering life or property involving this product call collect
517-636-4400

AGRICULTURAL CHEMICAL
Do Not Ship or Store with Food, Feeds, Drugs or Clothing

18.93 L / 5 gal

86-1064 PRINTED IN U.S.A. IN JANUARY, 1980.
PLACES SPECIMEN LABEL 86-1064 PRINTED IN SEPTEMBER, 1979.
DISCARD PREVIOUS SPECIMEN LABELS.

SPECIMEN LABEL
(BACK)
REDUCED TO 75%

8063

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DOW ESTERON 245 HERBICIDE

Contains Propylene Glycol Butyl Ether Esters of 2,4,5-T • Acid Equivalent: 4 Pounds per Gallon

Insert 1

DIRECTIONS FOR USE

ESTERON 245 herbicide is recommended for industrial vegetation control, fencerows, and rangeland. Do not use in forest lands, rights-of-way, or pastures.

The herbicide controls herbaceous and woody plants including such 2,4-D resistant species as ash, black gum, brambles, groundcherry, hawthorn, horsenettle, maple, mesquite, oak, osageorange, palmetto, poison ivy, prickly pear cactus, redbay, salmonberry, sweetgum, wild blackberry, wild rose, and certain species of Ribes. Do not apply ESTERON 245 where spray drift may contact nearby 2,4,5-T susceptible crops or other desirable plants or may contaminate water intended for irrigation or domestic purposes. Read and follow all Use Precautions given on this label.

PREPARING THE SPRAY

Use only diesel oil, No. 1 or No. 2 fuel oil or kerosene where oil is recommended in the spray mixture.

Oil sprays: Add ESTERON 245 to the required amount of oil in the spray tank or mixing tank and mix thoroughly. This mixture can be made at any time before actual use and no separation will occur. Do not let any water, or oil-water mixture sprays get into the ESTERON 245 or into the finished mixture, as it may form a gel.

Water Sprays: Fill the spray tank about half full with clean water, add the required amount of ESTERON 245 and complete filling the tank. Mix thoroughly and continue agitation while spraying. Caution: See NOTE in paragraph on Oil-Water Mixture Sprays.

Oil-Water Mixture Sprays: When vigorous agitation is used, 1 gallon of ESTERON 245 will emulsify up to 10 gallons of oil in 100 gallons of spray mixture. First, premix the ESTERON 245 and oil in a separate container. Do not allow any water or mixtures containing water to get into the ESTERON 245 or the premix. Fill the spray tank about half full with water, then slowly add the premix with continuous agitation and complete filling the tank with water. If the premix is put in the tank without any water, the first water added may form a thick "invert" (water in oil) emulsion which will be hard to break. As an alternate procedure, the oil may be added after the ESTERON 245 is mixed in the water; but highly vigorous mechanical agitation is required and a poor emulsion may be formed. The premix method is preferred.

NOTE: ESTERON 245 in water or oil-water sprays forms an emulsion, not a solution, and separation may take place unless sprays are agitated continously. Mechanical agitation is recommended.

Insert 2

HIGH VOLUME SPRAYS

Basal Bark Treatment: Brush and small trees can be controlled by spraying the basal parts of brush stems and tree trunks to a height of 12 to 15 inches from the ground line. Use a solution of 3 gallons of ESTERON 245 in 100 gallons (1 part in 4 gallons) of oil. With certain resistant species, 4 gallons of ESTERON 245 in 100 gallons (1 part in 3 gallons) of oil, is effective. As only the basal portions of the brush are treated on a spot basis, the total amount sprayed per acre would not be expected to exceed 100 gallons. Knapsack or power equipment may be used, but complete wetting of the indicated area is necessary, particularly at the ground line. The mixture sprayed until run-down or run-off to the ground line is noticeable. Old or rough bark requires more spray than young or smooth bark. Low pressures are desirable. Apply at any time, including the winter months, except when snow, ice or water prevent spraying to the ground line. Other labeled response and killing can be expected.

Dormant Brush: Treat any time after brush is dormant and most of the foliage has dropped. Spray should be concentrated at the base of stems and in addition, the upper parts of the stems should be broadcast sprayed enough to wet them. Under root-suckering species such as sumac, persimmon, sassafras and locust, also spray the ground area to control small root suckers that may not be readily visible. Mix 1 1/2 gallons of ESTERON 245 in 100 gallons of oil. Brush of average density and 4 to 6 feet high may take up to 150 gallons of spray mixture per acre.

Stump Treatment: Where growth is more than 6 to 8 feet tall, cut it close to the ground and spray the freshly cut stumps and stubs with 3 gallons of ESTERON 245 in 100 gallons (1 part in 4 gallons) of oil, mixed thoroughly. For more resistant species, use 4 gallons of ESTERON 245 in 100 gallons (1 part in 3 gallons) of oil. Wet thoroughly all exposed bark, as well as cut surfaces. This means spraying until run down or run off to the ground line is noticeable. Old or rough bark requires more spray volume than young or smooth bark. Apply at any time, including winter months, except when ice, snow or water prevent spraying to the ground line. Best results are obtained on freshly cut stumps two inches across or larger. Adequate coverage normally requires from 10 to 100 gallons per acre depending on density of stumps and stubs.

"Frill" Treatment: For large trees, make a singlehack girdle or "frill" of overlapping axe cuts completely around the tree as close to the ground as feasible. Spray the frill thoroughly using a mixture of 2 gallons of ESTERON 245 in 100 gallons (1/2 part in 3 gallons) of oil.

Spot Foliage Treatment: Use 1/4 pint of ESTERON 245 in 3 gallons of water and spray to wet all foliage, shoots, stems and bark without runoff.

LOW VOLUME SPRAYS

Apply low volume sprays containing ESTERON 245 when foliage is well developed and plants are actively growing. For best results on woody species, soil moisture should be sufficient to promote foliar growth. Spraying during prolonged hot, dry weather or after leaves have lost their normal green color and vigor may not give satisfactory control. Apply low volume sprays by air or ground equipment only when spray drift will not be a problem - note use precautions.

Basal Treatment Using Powered Knapsack Sprayer - Mix 1 1/2 to 2 gallons of ESTERON 245 with fuel oil or kerosene to make 20 gallons of total spray solution. Apply with a portable knapsack mistblower to all sides of lower brush stems including the root collar. Good coverage of the root collar is essential for best results. Run mistblower at 1/4 to 1/3 throttle for best spray delivery and coverage. For maximum drift control use a basal nozzle attachment and do not raise nozzle above the horizontal position.

Insert 3

AIR APPLICATION FOR BRUSH CONTROL

Consult the Agricultural Experiment Station, your local Extension Service Weed or Range specialists for best time to treat and need for re-treatment in your area. Do not use from early boot to milk stage where grass seed production is desired.

Mesquite: Use 1 pint ESTERON 245 plus 1/2 to 1 gallon of oil in enough water to make 4 gallons of total spray per acre. Apply 40 to 80 days after first leaves appear.

Sand Shinnery Oak: Use 1/2 to 1 quart of ESTERON 245 plus 1 gallon of oil in enough water to make 4 gallons of total spray per acre.

Post and Blackjack Oaks: Use 2 quarts of ESTERON 245 plus 1 gallon of oil in enough water to make 4 to 6 gallons of total spray per acre.

USE PRECAUTIONS

Note: Do not graze dairy animals on treated areas within 6 weeks after application. Do not graze meat animals on treated areas within 2 weeks of slaughter.

- AVOID CONTACT WITH 2,4,5-T SUSCEPTIBLE CROPS AND OTHER DESIRABLE BROADLEAF PLANTS - ESTERON 245 Herbicide is injurious to susceptible plants. Therefore do not apply directly to or otherwise permit to drift in minute amounts to cotton, grapes, tobacco, fruit trees, vegetables, flowers, ornamentals or other desirable plants susceptible to 2,4,5-T. Do not use in or near a greenhouse.
- DO NOT APPLY IN THE VICINITY OF COTTON, GRAPES, TOBACCO, TOMATOES OR OTHER DESIRABLE 2,4,5-T SUSCEPTIBLE CROPS OR ORNAMENTAL PLANTS.
- DO NOT SPRAY WHEN WIND IS BLOWING TOWARDS SUSCEPTIBLE CROPS OR ORNAMENTAL PLANTS.

AVOID SPRAY DRIFT – Applications should be made only when there is no hazard from spray drift since very small quantities of spray, which may not be visible, may severely injure susceptible crops during both growing and dormant periods. Use coarse sprays to minimize drift since, under adverse weather conditions, fine spray droplets may drift a mile or more. The spray thickening agent, NALCO TROL[1], may be used with this product to aid in reducing spray drift. If used follow all use recommendations and precautions on the product label.

[1]NALCO TROL Trademark of NALCO Chemical Company

GROUND EQUIPMENT – With ground equipment, spray drift can be lessened by keeping the spray boom as low as possible; by applying 20 gallons or more of spray per acre, by using no more than 20 pounds spraying pressure with large droplet producing nozzle tips; by spraying when wind velocity is 8 miles per hour or less. Do not apply with hollow cone-type insecticide or other nozzles that produce a fine droplet spray.

AERIAL APPLICATION – With aircraft, drift can be lessened by applying a coarse spray; by using no more than 20 pounds spray pressure at the nozzles; by using straight stream nozzles directed straight back, by using a spray boom no longer than 3/4 the wing span of the aircraft, and by spraying only when wind velocity is less than 6 mph.

DO NOT APPLY BY AIRCRAFT WHEN AN AIR TEMPERATURE INVERSION EXISTS. Such a condition is characterized by little or no wind and with air temperature lower near the ground than at higher levels. The use of a continuous smoke column at or near site of application is suggested to indicate direction and velocity of air movement, and to indicate a temperature inversion by layering of the smoke.

At high temperatures (above 85°F) vapors from the product may injure susceptible plants growing nearby. Do not use in or near a greenhouse. Excessive amounts of this herbicide in the soil may temporarily inhibit seed germination or plant growth.

Do not use around the home, recreation areas or similar sites.

This product is toxic to fish. Keep out of lakes, streams, and ponds. Do not contaminate water by cleaning of equipment or disposal of wastes.

Do not contaminate irrigation ditches or water used for irrigation or domestic purposes. The product can be stored in an unheated building but if exposed to sub freezing temperatures, should be warmed to at least 40°F and mixed thoroughly before using. Do not store near fertilizers, seeds, insecticides or fungicides. Do not reuse containers. To avoid injury to desirable plants, do not store, handle or apply other agricultural chemicals with the same containers or equipment used with ESTERON 245 except as specified on the label.

Rinse equipment and containers and dispose of waste by burying in non crop lands away from water supplies. Containers should be disposed by punching holes in them and burying with waste or follow official local recommendations for container disposal.

Local conditions may affect the use of herbicides. Consult your State Agricultural Experiment Station or Extension Service weed specialist for advice in selecting treatments from this label to best fit local conditions. Be sure that use of this product conforms to all applicable regulations. Apply this product only as specified on this label.

NOTICE: Seller warrants that the product conforms to its chemical description and is reasonably fit for the purposes stated on the label when used in accordance with the directions under normal conditions of use. But neither this warranty nor any other warranty of MER-CHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, express or implied, extends to the use of the product contrary to label instructions, or under abnormal conditions, or under conditions not reasonably foreseeable to seller, and buyer assumes the risk of any such use.

[illegible] 1 [illegible]

THE DOW CHEMICAL COMPANY
AND SUBSIDIARIES
MIDLAND, MICHIGAN 48640, U.S.A. HORGEN, SWITZERLAND HONG KONG
CORAL GABLES, FLORIDA 33134, U.S.A. SARNIA, ONTARIO, CANADA

ESTERON 245 Herbicide
Proposed Label Amendments
June 2, 1980

Insert 1

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

ESTERON 245 herbicide is recommended for use to control vegetation growing on industrial sites, fencerows, and rangeland. Do not use in forest lands, rights-of-way, or pastures.

ESTERON 245 controls numerous herbaceous and woody plants, including 2,4-D resistant species, such as--ash, black gum, brambles, groundcherry, hawthorn, horsenettle, maple, mesquite, oak, osageorange, palmetto, poison ivy, pricklypear cactus, redbay, salmonberry, sweetgum, wild blackberry, wild rose, and certain species of *Ribes*.

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Insert 2

Foliage Treatment: For control of woody vegetation up to 8 feet tall, apply when foliage is well developed and plants are actively growing. Spraying during prolonged hot, dry weather or after leaves have lost their normal green color and vigor may not give satisfactory control. Use 3 to 4 quarts of ESTERON 245 in 100 gallons of water and apply as a full-coverage spray. Usually 100 to 200 gallons per acre will be required, although dense stands of brush may require up to 400 gallons per acre. Completely wet all plant parts including leaves, stems and bark. Poison ivy, some brambles and many broadleaf weeds may be controlled using 2 quarts of ESTERON 245 in 100 gallons of water.

Insert 3

AIR APPLICATION FOR RANGELAND BRUSH CONTROL

Consult your State Agricultural Experiment Station or local Extension Service weed or range specialists for best time to treat and need for retreatment in your area.

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Original Articles

Journal of Occupational Medicine
January 1980 Vol. 22 No. 1

The Mortality Experience of Workers Exposed to Tetrachlorodibenzodioxin in a Trichlorophenol Process Accident

Judith A. Zack, M.P.H., and Raymond R. Suskind, M.D.

A standardized mortality analysis was conducted on workers exposed to tetrachlorodibenzodioxin in a trichlorophenol process accident at the Monsanto Company plant in Nitro, West Virginia. One hundred and twenty-one workers who developed chloracne resulting from this accident on March 8, 1949, were selected for study. Follow-up of this group was 100% complete. The standardized mortality ratio for all causes of death was shown to be 0.69, with 32 deaths observed and 46.41 expected. For the categories of malignant neoplasms and circulatory diseases, the standardized mortality ratios were 1.00 and 0.68, respectively. Because of the small size of the cohort and the relatively small number of deaths observed, the results of this study cannot be considered conclusive. However, it is important that no apparent excess in total mortality or in deaths from malignant neoplasms or diseases of the circulatory system was observed in a group of workers with a high peak exposure to tetrachlorodibenzodioxin who were followed over a period of nearly 30 years. The results of this study will be incorporated with those of a larger study which will include plant workers exposed in the course of 2,4,5-trichlorophenoxyacetic acid production during the period 1948 to 1969.

A wide variety of acute and sub-acute health effects has been reported in workers involved in the manufacture of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) from 2,4,5-trichlorophenol (TCP). The most consistent clinical finding is chloracne, a skin disease characterized by comedones, cysts, pustules, and abscesses. Hepatic dysfunction, peripheral neuritis, disorders of fat metabolism, and porphyria cutanea tarda are other frequently reported findings in these workers.[1] Chloracne has been shown to be essentially due to 2,3,7,8-tetrachlorodibenzodioxin (TCDD),[2] a byproduct in the synthesis of 2,4,5-T. The subject of this paper is the chronic health effects of exposure to TCDD, as reflected in the mortality experience of a cohort of Monsanto Company workers who developed symptoms of chloracne following a trichlorophenol process accident at the Nitro, West Virginia, plant in 1949.

Production of trichlorophenol began in the fall of 1948 at the Nitro plant. In this process, the reactants 1,2,4,5-tetrachlorobenzene, sodium hydroxide, and methanol were all added to the autoclave. Heat was applied and, when the pressure reached the desired point, the autoclave was vented. On March 8, 1949, about six months after production start-up, a violent reaction and decomposition occurred when temperature and pressure within the autoclave became excessive. The relief valve opened and the fumes and tarry residues from the decomposed contents of the autoclave were discharged into the atmosphere and into the interior of the building.

Employees who worked in the area of TCP production or were involved in the clean-up began to develop symptoms immediately following exposure to the material which was discharged from the autoclave. Symptoms included eye and respiratory tract irritation, headache, dizziness and nausea, and a severe irritant reaction of the exposed skin. After these initial symptoms subsided, the chloracne and other symptoms became evident. Ashe and Suskind[3-5] examined a total of 12 more severely affected workers on three occasions during the period of 1949 to 1953. Another 26 persons with chloracne, apparently not related to the accident, were also examined in 1953. The

From the Department of Medicine and Environmental Health, Monsanto Company, 800 N. Lindbergh Blvd., St. Louis, MO 63166 (Ms. Zack, Epidemiologist), and the Institute of Environmental Health, Kettering Laboratory, the University of Cincinnati Medical Center, Cincinnati, OH 45267 (Dr. Suskind, Director).

Table 1. — Observed and Expected Deaths Among 121 Males Exposed to Tetrachlorodibenzodioxin in a Trichlorophenol Process Accident.

Cause	ICD No. (Eighth Revision)	Observed	Expected	SMR
All causes of death		32	46.41	0.69*
All malignant neoplasms	140-209	9	9.04	1.00
Buccal cavity and pharynx	140-149	0	0.30	†
Digestive organs and peritoneum	150-159	0	2.59	†
Stomach	151	0	0.50	†
Liver	155-156	0	0.18	†
All other digestive organs	—	0	1.91	†
Respiratory system	160-163	5	3.02	1.66
Lung	162.163	5	2.85	1.75
All other respiratory organs	—	0	0.17	†
Skin	172.173	1	0.15	†
Genitourinary organs	185-189	0	1.16	†
Lymphatic and hematopoietic tissue	200-209	3	0.88	†
Other sites	—	0	0.94	†
Diseases of the nervous system and sense organs	320-389	0	0.36	†
Diseases of the circulatory system	390-458	17	25.01	0.68
Arteriosclerotic heart disease, including coronary heart disease	410-413	13	17.74	0.73
All other disease of the circulatory system	—	4	7.27	†
Diseases of the respiratory system	460-519	1	2.78	†
Diseases of the digestive system	520-577	0	2.26	†
All other diseases	—	2	3.18	†
External causes of death	800-998	3	3.78	†

*$p < 0.05$
†Less than 5 observed deaths

tained. The underlying cause of death was coded to the 8th Revision of the International Classification of Diseases, Adapted[15] by an experienced nosologist.

Results

All of the 121 members of the study cohort were traced. Eighty-nine were verified living and 32 were verified deceased by death certificate.

The results of the standardized mortality analysis of the 121-member study cohort are shown in Table 1. The standardized mortality ratio for all deaths is shown to be 0.69, with 32 observed deaths and 46.41 expected. This is the only statistically significant difference shown in this table. There were nine deaths from malignant neoplasms with 9.04 expected. There were no deaths from stomach or liver cancer. There were five lung cancer deaths versus 3.02 expected and one skin cancer death with 0.15 expected. The malignant tumor was a fibrous histiocytoma presumably of dermal origin, which is rare. There were three deaths from neoplasms of lymphatic and hematopoietic tissue with 0.88 expected.

There were 17 observed deaths from circulatory diseases with 25.01 expected. The standardized mortality ratio for circulatory diseases was low at 0.68.

Case summaries for the cancer deaths are given in Table 2.

Discussion

Because the study cohort was small and only 32 deaths were observed, the results cannot be considered conclusive. Nevertheless, the analysis of the mortality experience of these workers indicated no apparent excess of total mortality or of deaths due to malignant neoplasms or circulatory diseases.

The TCDD-exposed workers in the present study represent the largest group ever investigated after long-term follow-up. The criteria for inclusion (presence of the workers at the 1949 accident and the subsequent occurrence of chloracne) limit the group to those with a significant exposure at that time. The latency period of 29 years

Table 2. — Cancer Deaths Among a Cohort of 121 Males Exposed to Tetrachlorodibenzodioxin in a Trichlorophenol Process Accident.

Year of Birth	Year of Hire	Year of Death	Death Certificate Statement of Cause of Death	Smoking History*
1909	1943	1962	Lung cancer (162.1)	Cigarettes
1910	1927	1970	Pulmonary carcinoma (162.1)	Cigarettes
1911	1939	1964	Bronchiogenic carcinoma (162.1)	Cigarettes
1922	1945	1973	Bronchiogenic carcinoma (162.1)	Nonsmoker
1915	1939	1970	Lung cancer (162.1)	Cigarettes
1920	1946	1978	Malignant fibrous histiocytoma of soft tissue origin (173.9)	Cigarettes
1919	1943	1973	Hodgkin's disease (201.0)	Cigarettes
1907	1943	1971	Lymphatic leukemia (204.9)	Pipe
1910	1939	1978	Acute myelogenous leukemia (205.0)	Cigarettes

*Smoking history was obtained by interviews with former co-workers of the decedents

is longer than that of any previous study, and the follow-up is complete. Therefore, although the cohort is small, it represents the best opportunity so far to study the long-term effects of TCDD on mortality. By augmenting these data with the results of comparable mortality studies, the long-term effects of TCDD may be more definitely evaluated.

The authors wish to thank Mrs. Janet Yung, Mr. Randy Piccini, and Mrs. Phyllis Korte for their assistance with the data collection.

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Future Risk

In the industrial countries we have grown rich during the age of hierarchical business corporations, in which each executive arranges what the man below him will do with his hands, all the way down to the man turning a screw on the assembly line. Now, two rather fundamental things have happened. First, we have begun to realize that workers in rich countries don't like working in such places. Secondly, the rich countries are moving out of the postmanufacturing age, but they still have great hierarchical corporations in which executives sit behind their desks trying to arrange what the man below will do with his imagination. This no longer works. New forms of business organization will have to be found, probably changing big corporations into confederations of entrepreneurs. The firms and countries that will go bust in these circumstances are those that try to replace hierarchical corporations by even more ossified forms of hierarchy — say, by deciding that you mustn't have a boss trying to arrange what free men do with their imaginations, but can have a trade union committee doing so instead.

— From "United States Can Keep Growing — And Lead — If It Wishes" by Norman Macrae, in Smithsonian, July 1978.

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Literature Reviews of Four Selected Herbicides: 2,4-D, Dichlobenil, Diquat & Endothall

Public Health Effects by Dr. Ruth Shearer
Effects on the Aquatic Environment by Mark Halter

January, 1980

Municipality of Metropolitan Seattle

PREFACE

This report is the product of a comprehensive search of the world-wide literature relating to possible effects on the public health of using the herbicides 2,4-D, dichlobenil, endothall, and diquat in the human environment. Sources included the following:

Computer searches: Medline, Cancerline, Toxline
Northwest Regional Health Sciences Library
University of Washington libraries: Fisheries, Biochemistry, Science Reading Room, and Government Documents at Suzzallo Library
National Library of Medicine
Municipality of Metropolitan Seattle Library
Friends of the Earth
Pennwalt Corporation
Thompson-Hayward Chemical Company
Chevron Chemical Company
Inter-library Loan Service of Health Sciences Library

Since most readers are not toxicologists, this report begins with a brief explanation of the vocabulary and usual testing procedures of environmental toxicology. Following this introductory chapter, there are four chapters devoted to a review and analysis of research to date on each herbicide in question. A final chapter offers general conclusions about the relative risks to human health from these substances. A brief summary and chart are included at the beginning of the report.

Studies reporting animal assays for the detection of developmental toxicity, interference with reproduction and fertility, and carcinogenesis are described in detail in a Technical Appendix to allow the more knowledgeable reader the opportunity to evaluate their validity. This author's evaluation is presented after each experiment, followed by the conclusions this author considers justified, based on the results reported and the adequacy of the methods used. Studies funded by chemical manufacturers who profit from sale of the chemicals are so identified to allow the reader to determine the possibility of bias.

Studies reported here do not involve mixtures of chemicals unless this is specifically stated and the controls used are defined.

SUMMARY OF FINDINGS

The findings and conclusions of this report are briefly summarized in answer to the questions listed below. The chart on the following page graphically illustrates the results of research to date on the four herbicides being considered for use in Lake Washington.

1. What are the potential risks to human health from aquatic use of these herbicides?

Potential risks include both acute and long-term toxic effects. Acute effects are those likely to be experienced by people applying the chemical without adequate precautions, for example by inhaling it or spilling it on skin or eyes. Long-term effects, which are the main subject of this report, may result from repeated exposure to small amounts of the substances, for example by swimming in treated water, ingesting contaminated food or water, or walking in sprayed areas. These include developmental effects on fetuses and growing children (malformations, malfunctions, growth retardation or death); reproductive effects on the rate of pregnancy and the number of embryos; genetic effects (mutations, damage to DNA molecules or the process of cell division); and carcinogenic effects.

It is important to note that in the United States, people are widely exposed to a variety of untested, potentially cancer-causing substances along with a lesser number of proven carcinogens, which lead to an accumulation of pre-cancerous cells in the body. Americans now face a 25% chance of developing cancer at some time during their lives. Under such conditions, the presence in the environment of additional chemicals which can stimulate these pre-cancerous cells to grow into tumors must be considered a significant hazard.

2. Which of these risks is associated with each of the herbicides under consideration?

The risks for each herbicide are displayed in Columns 5 and 6 of the accompanying chart, and summarized below:

For 2,4-D, laboratory tests have shown developmental toxicity of all four varieties listed above, and have been positive for genetic and carcinogenic effects; there is no indication of effect on reproduction. Acute effects of 2,4-D observed in humans include headaches, dizziness, impaired senses of taste and smell, nausea, sore throat, muscular spasms and nerve damage.

Toxicological testing of dichlobenil has been extremely limited. Carcinogenic tests have been inadequate and there has been no testing of developmental or genetic effects in animals. One study indicates that dichlobenil inhibits the growth of young rats and decreases fertility. Some of its breakdown products are known to be highly toxic

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	1	2	3	4	5 Non-acute Toxic Effects in Animals											6		7	
					Developmental				Repro-ductive	Genetic				Carcinogenic		Toxic Effects in Humans		Risk of adverse health effects in humans after aquatic use based on existing information:	
	Location of Breakdown	Rate of Absorption	Acute Lethal Dose (LD_{50}) in rats	Maximum Tolerated Dose (MTD) in rats	malformation	malformation	growth retardation	lethality		Alteration in genetic material	Alteration in somatic cell cells	DNA damage	Effect on cell division	Complete Carcinogen	promoter	Lowest Reported Lethal Dose (LDLo)	Acute Effects	Medium dose acute exposure	Low dose repeated exposure
2,4-D	Environment	Rapid	375 mg/kg	≥1500 ppm	±,±,+	±	++	+++	-	-	++	(+)-	+(+)-	±±	+	<486 mg/kg	Headache, weakness, dizziness Impaired senses of taste & smell Nausea, vomiting, epigastric pain Sore throat, irritation in nose Hypotonia Peripheral neuropathy with demyelination	high	high
Impurities																			
Breakdown products		Rapid	500 mg/kg		-	+	-	+						+	+				
Dichlobenil	Body	Rapid	4500 mg/kg	≥5000 ppm					+	--				?			Chloracne	high	high
Impurities (none)									+					?					
Breakdown products		Rapid																	
Endothall	Environment	Slow	51 mg/kg not toxic	2400 ppm	-	-	-	-	-	-	+-		-	-Inc		5 mg/kg	Local irritation	medium	low
Impurities																			
Breakdown products																			
Diquat	Intestinal Tract	Slow	231 mg/kg	500 ppm	-	+			-+	±?	-?	(±)		??		50 mg/kg	Bleeding nose Myalgia, stiff neck Periorbital headache Pneumonitis, fever, cough with bloody sputum	medium	medium
Impurities																			
Breakdown products		Slow																	

Code:

Blank space means no information

+,- = positive, negative results in adequate test

? = negative results in inadequate test

Inc = adequate test, has not been completed

++ = positive results in two species

± = positive & negative results in two tests, one species

± = positive results in two tests, one species

(±) = positive results in human cells

Medium dose, acute exposure would be typical for unprotected herbicide applicators and protectors

Low dose, repeated exposure would be typical for swimmers and people irrigating with the herbicide

range from the nearly meaningless dichlobenil cancer tests to the nearly adequate diquat cancer tests. Where conflicting results were obtained in two or more technically adequate studies, additional tests should be conducted by another laboratory to clarify the conclusions reached.

It should be noted that all the tests for developmental toxicity, reproduction/fertility and carcinogenesis reviewed in this paper were done with mammals. Mutagenic tests reported here include those done with cultured cells or lower organisms as well as with mammals.

6. Based on existing information, what conclusions can be drawn about the possible toxic effects on humans of the aquatic use of these herbicides, their chemical impurities and breakdown products?

Column 7 of the chart indicates the relative risk to human health of both acute and chronic exposure to the four aquatic herbicides. Toxic effects are summarized briefly below, in order of increasing risk to human health:

Endothall is poorly absorbed through the skin, lungs or gastrointestinal tract, unless the membrane is first damaged. It is not metabolized in the body, and is excreted without chemical change. At low doses, little of the chemical is absorbed into the body and the only acute effects are local irritation to skin, lungs and eyes. Research to date has given negative indications of developmental toxicity, effects on reproduction and fertility, and mutagenic effects in rats. One impartial test indicates a mutagenic effect in fruit flies. One test for carcinogenic effect has been negative, but another is still incomplete; results of this study are essential before a conclusion can be made about this product.

Diquat is also poorly absorbed into the body unless the membrane is first damaged. It is metabolized by intestinal bacteria to unknown products of unknown toxicity which are partially absorbed. The substance does not accumulate in the body; however, it can alter metabolism in many organs. A number of acute effects have been observed in humans. Inadequate tests in mammals suggest possible developmental toxicity; one study in amphibians shows developmental toxicity at concentrations lower than proposed for Lake Washington. At low doses, chronic exposure to diquat has caused cataracts in rats and dogs. Cancer experiments on diquat have been less than adequate, but one screening test for possible carcinogens with cell cultures was positive.

2,4-D is rapidly absorbed through the skin, lungs and gastrointestinal tract and rapidly distributed to all tissues. It is not metabolized in the body, but is excreted more slowly than endothall and diquat. This herbicide causes a number of acute effects in humans. It has been found to cause all four types of developmental toxicity in a number of tests in several animal species. Tests of 2,4-D for carcinogenicity have been inadequate but have still demon-

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CHAPTER 2:

HEALTH EFFECTS OF 2,4-D (2,4-dichlorophenoxyacetic acid) AND ITS DERIVATIVES

A. Introduction

The herbicide 2,4-D was prepared in 1941 by the interaction of 2,4-dichlorophenol, monochloroacetic acid and sodium hydroxide, and a similar process is used in its commercial production. 2,4-D is a systemic herbicide widely used for site preparation and conifer release in forestry, for control of broadleaf weeds in cereal crops and sugar cane, and on turf, pastures and non-cropland. It is also used to control the ripening of bananas and citrus fruits, to delay preharvest dropping of some fruits, and in some countries as a fungicide for the control of Alternaria rots when lemons are to be held for storage. As a component of "Agent Orange," 2,4-D was used to defoliate jungle areas in South Vietnam (IARC, 1977). The EPA has approved the use of 2,4-D, marketed as "Aqua-Kleen" by Amchem Products, Inc., for control of several aquatic plants including water milfoil. Label requirements include a "caution" against accessibility of the product to children; applying to water used for irrigation, sprays, dairy animals or domestic use; or contact with skin, eyes, and clothing.

B. Metabolism of 2,4-D

A total of nine human male "volunteers" in two different studies have been fed a single dose of 5 mg/kg of 2,4-D (Kohli et al., 1974; Sauerhoff et al, 1977) to determine its metabolism. Essentially all of the 2,4-D was absorbed from the gastrointestinal tract. It was distributed widely through the body and excreted in the urine unchanged. No metabolites were detected. No symptoms of illness or abnormal blood chemistry were detected. 95% of the dose was recovered from urine in six days.

The metabolism of isotope-labeled 2,4-D in rats has been determined and is in agreement with the human studies above (Khanna and Fang, 1966). Radioactivity was found in all organs and tissues examined, with 9% to 32% in the nuclear fraction. All was unchanged 2,4-D, suggesting that the chemical in the cytosol was not peptide-bound as found in plant tissues.

2,4-D is lipid-soluble and therefore rapidly absorbed from the lung (Burton et al., 1974), when assayed in rats.

2,4-D amine salt administered orally was readily absorbed by rats, pigs, calves, and chickens, but 2,4-D butyl ester was much more slowly absorbed and the circulating chemical was all in acid form, indicating that the ester was hydrolyzed during absorption (Erne, 1966). Absorbed 2,4-D was distributed rapidly through the body with

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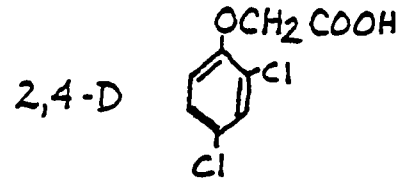
pg. 17 first para., line 3: 4,6'-tetrachloro-;
line 4: diphenoxymethane

diagram should be:



pg. 18 corrected diagram below:

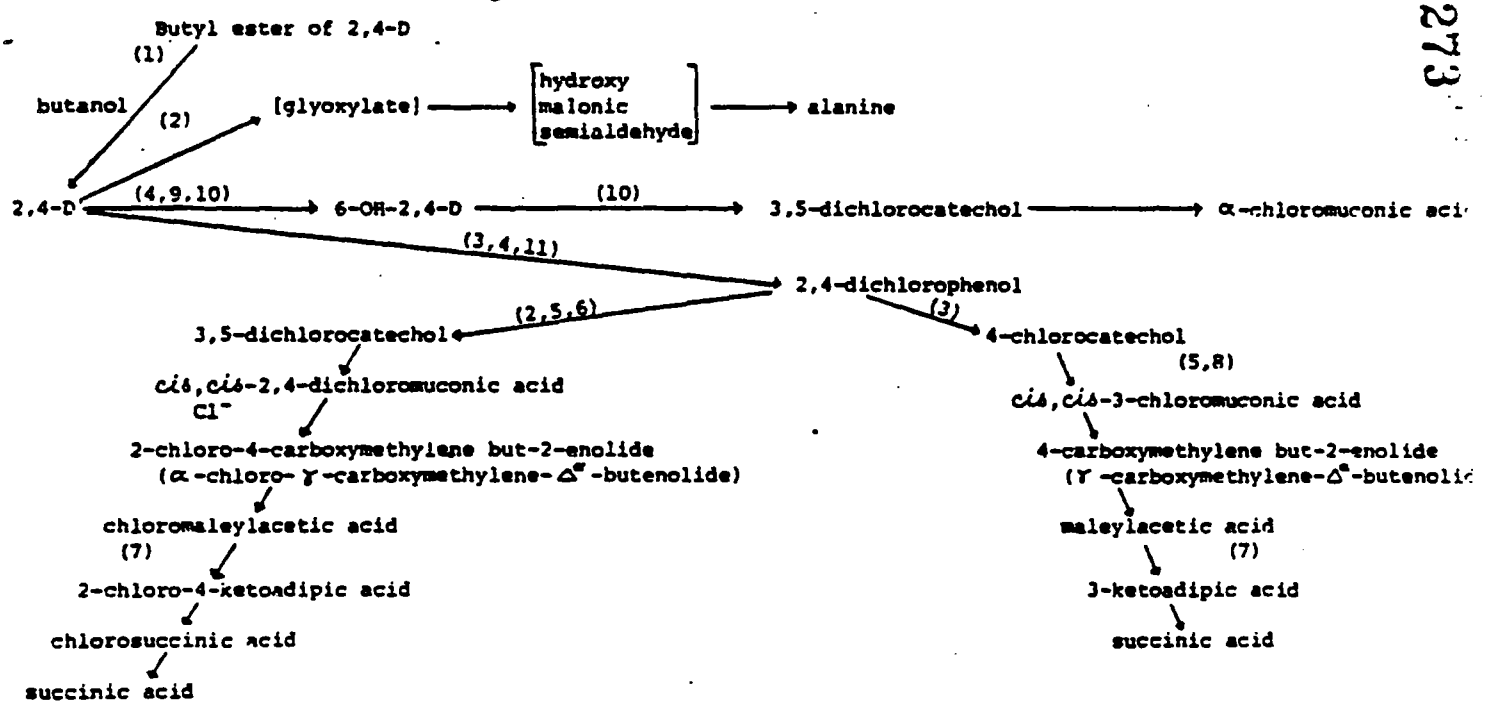


Fig. 1. Pathways of microbial degradation of butyl ester of 2,4-D. Numbers are references: (1) Aly and Faust 19 (2) Tiedje and Alexander 1969, (3) Steenson and Walker 1957, (4) Bell 1957, (5) Bollag et al. 1968, (6) Loos et al. 1967, (7) Duxbury et al. 1970, (8) Tiedje et al. 1969, (9) Audus 1960, (10) Fernley and Evans 1959, and (11) Evans and Smith 1954.

SOURCE: Doris F. Paris and David L. Lewis, "Chemical and Microbial Degradation of Ten Selected Pesticides in Aquatic Systems," Residue Reviews, Volume 45, 1973, p.107

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in initiated controls). After a longer period of application to the skin, it was able to induce tumors without prior application of the initiator (75% with papillomas and 6% with carcinomas after 24 weeks). After 39 weeks of treatment with 2,4-dichlorophenol, 62% of the mice had carcinomas. The test substance was dissolved in benzene in these experiments, and control animals were treated with benzene alone (Boutwell and Bosch, 1959). This indicates that 2,4-dichlorophenol is a skin carcinogen in mice, or at least a cocarcinogen with benzene which is not carcinogenic by itself in this system.

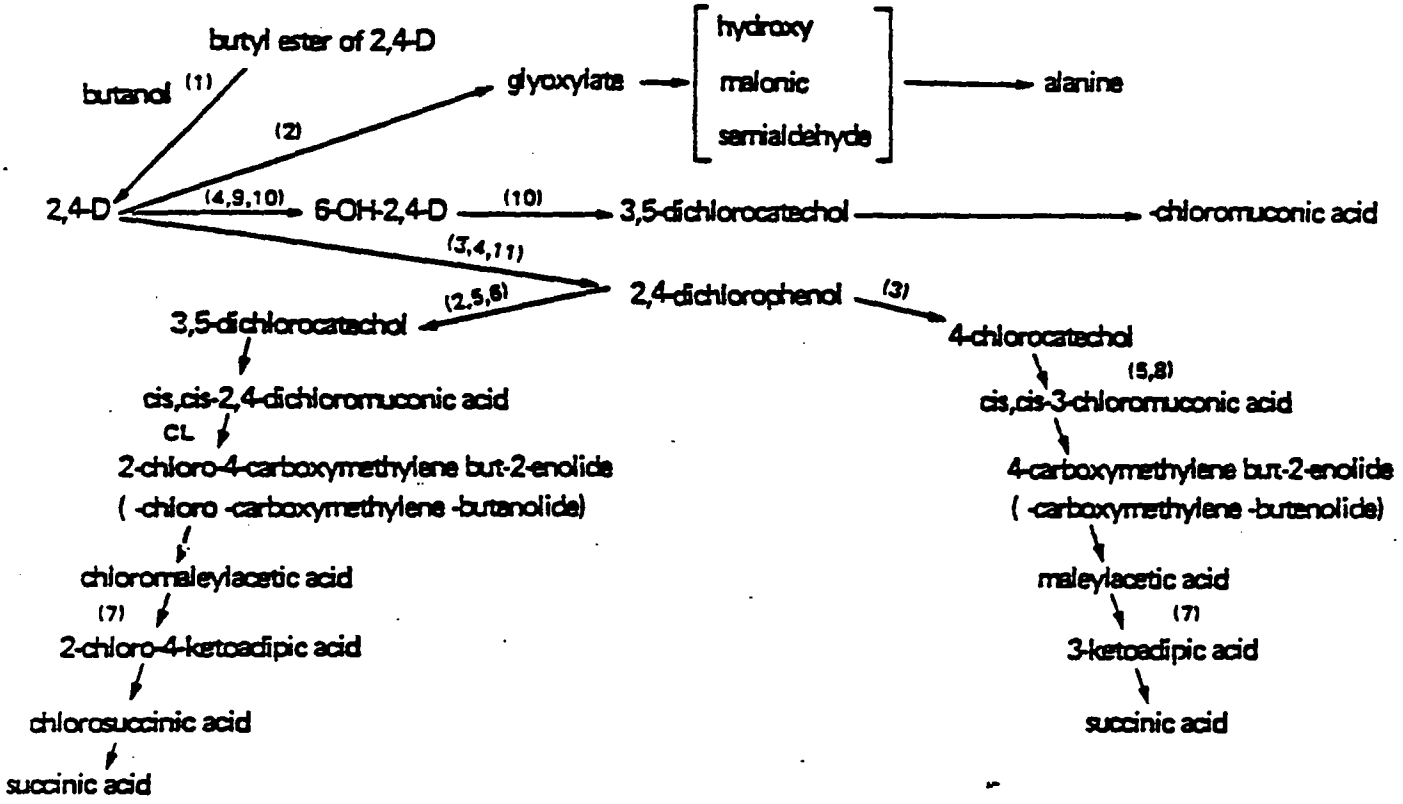

Fig. 1 Pathways of microbial degradation of butyl ester of 2,4-D. Numbers are references: *(1) Aly and Faust 1964; (2) Tiedje and Alexander 1969; (3) Steenson and Walker 1957; (4) Bell 1957; (5) Bollag et al., 1968; (6) Loos et al., 1967; (7) Duxbury et al., 1970; (8) Tiedje et al., 1969; (9) Audus 1960; (10) Fernley and Evans 1959; and (11) Evans and Smith 1954.*

SOURCE: Doris F. Paris and David L. Lewis, "Chemical and Microbial Degradation of Ten Selected Pesticides in Aquatic Systems," Residue Reviews, Volume 45, 1973, p. 107.

2,4-dichlorophenol, like other polychlorinated phenols, can form chlorodibenzo-dioxins when heated (Epstein, 1970), but not the infamous TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) found in 2,4,5-T (Gribble, 1974). The most likely dioxin produced by heating 2,4-dichlorophenol would be 2,7-dichlorodibenzo-p-dioxin, which is reported to be minimally toxic (Schwetz et al, 1973, Dow Chemical Co.). No deaths occurred in four male mice given 2000 mg/kg or in two female rats given 1000 mg/kg. No signs of toxicity were observed in these

throat, irritation of the nasal mucosa, substernal pain, and loss of consciousness. Recovery took four to nine days.

Workers engaged in the spraying of 2,4-D and its derivatives from aircraft for three to five years and longer complained of rapid fatigue which usually cleared overnight. They periodically had headaches, pain in the liver and epigastric regions, and poor appetite. They had impaired taste sensitivity to salty, sour, bitter, and sweet test solutions. There was a deterioration in sensitivity to odors also. No changes in blood chemistry were found (Fetisov, 1966).

In addition to the symptoms above, peripheral neuropathy has been reported in humans hours or days after exposure to 2,4-D on the skin and probably simultaneously by inhalation (Goldstein et al., 1959; Berkley and Magee, 1963). The symptoms progressed through several weeks until pain, paresthesias, and paralysis were severe. Disability was protracted, and recovery was incomplete even after the lapse of years. Numbness and aching had extended proximally from the fingers and toes, and the patients became unable to walk because of pain and weakness. They also suffered moderately severe sensory deficits on tests of touch, pain, and temperature.

Autopsy of a human fatality due to ingestion of 2,4-D revealed widespread plaques of acute demyelination in all parts of the brain, with central petechiae (Dudley and Thapar, 1972). Multiple petechiae were seen throughout the white matter of the brain, and the kidneys were hyperemic.

The nervous system of rats, cats, and dogs was studied after 2,4-D administration parenterally (Desi et al., 1962). A reversible inhibition of cerebral electrical activity was observed in the acute experiments, and in chronic experiments the same was present to a gradually increasing degree. According to conditioned-reflex experiments, the higher nervous activity suffered severe damage. The point of attack seemed to be the reticular formation. Lesions in this region paralyze the function of the cerebral cortex.

Pretreatment of rats with 250 mg/kg 2,4-D three hours prior to administration of 9 mg/kg ^{14}C-2,2-D greatly increased the level of ^{14}C in rat brain and spinal fluid as compared to plasma level (Elo and Ylitalo, 1977). The increase was much more striking in the brain (11-fold) and spinal fluid (39-fold) than in the liver (4.5-fold). The likeliest explanation of this is that 2,4-D impaired function of the blood-brain barrier by causing capillary injuries.

Cattle and sheep which died after 5 to 34 daily oral doses of 2,4-D alkanolamine salt were necropsied (Palmer and Radeleff, 1964). Lesions included liver and kidney degeneration, the heart usually contained hemorrhages, and there was usually an excessive quantity of pericaridal fluid.

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hemorrhaging into the abdominal cavity at the higher dose and vascular distention at both doses. The other experiment tested single doses of 1/2 LD_{50} given intraperitoneally on various days of gestation, and found increased resorption of fetuses with reduced litter size, growth reduction with increased size of brain ventricles, and hemorrhaging into the abdominal cavity.

A test for developmental toxicity in hamsters was done by Collins and Williams of the U.S. Food and Drug Administration. They used oral doses of 20 to 100 mg/kg/day during organogenesis and found a dose-dependent increase in fused ribs at 60 mg/kg/day and above which was significant only if repeats were pooled.

Two studies of the teratogenicity of 2,4-D in mice have been done. A large series of tests using different strains of mice, different doses, and different esters of 2,4-D was completed in 1968 by Bionetics Research Laboratories, and has now been published. Oral administration of 100 mg/kg/day of 2,4-D acid during organogenesis caused a significant increase in fetal mortality and percent of abnormal fetuses, with most of these being eye and jaw malformations.

2,4-D acid produced a significant increase in fetal abnormalities in four of six adequately-sized groups of three strains, when given subcutaneously at 100 mg/kg/day. Subcutaneous administration resulted in a significant increase in abnormal fetuses in one strain after 48, 94, 100, or 130 mg/kg/day of the isooctyl, isopropyl, butyl, and isooctyl esters respectively. This was a repeat of a previously negative study. The anomalies were mainly of the eye and jaw. All of these subcutaneous administrations were dissolved in dimethylsulfoxide, which is a teratogen for the nervous system of the hamster (Ferm, 1966). However, the DMSO controls in this mouse study showed no significant increase in developmental toxicity over untreated controls.

The other mouse study was done by Courtney of the U.S. Environmental Protection Agency. She used oral doses of 150 or 250 mg/kg/day of 2,4-D and four of its esters during organogenesis and found growth retardation at both doses and cleft palate at the higher dose. Other malformations were not assayed.

Two developmental studies on pigs have been done by Bjorklund and Erne of the Swedish Royal Veterinary College and National Veterinary Institute. A pig was fed 500 ppm of 2,4-D amine while pregnant plus six weeks after. The fifteen piglets born were underdeveloped, apathetic, and did not want to suck, and ten died the first day. No malformations were observed. In the second study, eight-week-old pigs were fed 500 ppm of 2,4-D amine for 12 months. After one month, 2 out of 5 in the experimental group developed malformations in the hooves on the forelegs, making walking difficult.

F. Tests for Effects on Reproduction and Fertility

1. Summary of Research

A study by Schwetz et al., of Dow Chemical Company, claims to show that 2,4-D has no effect on fertility, but it actually contains no such experiment.

The only study of the effect of 2,4-D on reproduction and fertility was done by Hansen et al., of the U.S. Food and Drug Administration. They used rats for a three-generation study and found no effect on fertility.

2. Conclusions

On the basis of a single study in a single species, there is no indication that 2,4-D might interfere with reproduction and fertility in mammals.

G. Tests for Mutagenic Effects and Other Short-Term Tests for Cancer

1. Summary of Research

Assays of 2,4-D for both forward and reverse mutation in bacteria and bacterial virus are consistently negative (Fahrig, 1974; Shirasu et al., 1976; Simmon et al., 1977: Andersen et al., 1972). These included tests run in the presence of an activation system prepared from the livers of rats or mice. This is to be expected since 2,4-D is a chlorinated hydrocarbon and these as a class are negative in the Ames test.

2,4-D caused a significant increase in recessive lethal mutations in Drosophila melanogaster when it was fed to male flies at 1000 ppm for two weeks (Magnusson et al., 1977), but was negative when the flies were treated with a 9mM solution for 3 days (Vogel and Chandler, 1974) and after unspecified treatment (Fahrig, 1974).

0.001 mM to 1.0 mM 2,4-D with or without rat liver activation induced unscheduled DNA synthesis in SV-40 transformed human fibroblast cells in culture (Ahmed at al., 1977a).

0.01 mM 2,4-D in the medium of primary human fibroblast cultures caused DNA damage leading to increased removal and reinsertion of bases. The type of repair was that seen following ionizing radiation (Hart et al., 1977).

0.01 mM 2,4-D in the culture medium caused a significant increase in forward mutation to ouabain resistance in the Chinese hamster V79 aneuploid lung cell line (Ahmed et al., 1977b).

0.01 mM or 0.1 mM 2,4-D in the culture medium of bovine fetal muscle cells caused the mitotic cells to exhibit unipolar and tripolar

A mouse carcinogenesis study was sponsored by the National Cancer Institute, also in the 1960's, and the data published years later. It consisted of both oral feeding studies and single dose subcutaneous injection studies. Two strains and both sexes were studied, but only 18 mice were included in each group and all were killed by 18 months. In the original study, strains and sexes were pooled to give a large enough sample size for statistical analysis by the chi-square method, and a significant increase in total tumors and in reticulum cell sarcoma was found after subcutaneous administration of 2,4-D isooctyl ester. No other tests were postitive using this approach, which hides strain and sex differences in sensitivity. Analysis of the data by strain and sex, using the chi-square method, indicates a carcinogenic effect of feeding the isooctyl and butyl esters of 2,4-D to females of one strain, with the reservation that the method is not totally reliable with such small samples. Analysis of the data by strain, sex, and organ system using more elegant statistical methods indicated that the induction of reticulum cell sarcoma by injection of the isooctyl ester is most significant in females of the other strain. However, the importance of this observation to human health is limited by the injection route of administration and the knowledge that 2,4-D esters taken orally are probably split into the acid form before absorption (Erne, 1966) so that circulation of the ester might not happen after contamination of humans. This study is described, analyzed, and discussed in Bionetics, 1968, Innes et al., 1969, Reuber, 1979, Mrak report, 1969, and Jurek, 1974. Its primary defect is its short duration, but the small group size and less-than-optimal oral dose given the adult animals could also contribute to false negative results. This study also had a rather high background level of tumors in the control animals.

A study at the Institute of Nutrition of the USSR Academy of Medical Sciences included three experiments. The first experiment used adequate numbers of rats and duration of feeding 2,4-D amine, but the dose was not over 1/2 MTD. The background was very low and the tumor increase insignificant. However, the publication (Arkhipov and Kozlova, 1974) does not state whether the rats were autopsied and whether histopathology was done, so small tumors might not have been found. A similar experiment with mice (100/group) was also negative, with no tumors in either the control or treated animals. The third experiment involved application of the herbicide to the skin of mice (100/group), with or without prior application of a low dose of an initiator of skin carcinogenesis. Animals treated with either the herbicide alone or the initiator alone did not develop any tumors, but 17.7% of those given the sequential treatment developed skin papillomas, the premalignant lesion of skin carcinomas, indicating strong tumor-promoting activity of 2,4-D. Again, there is no report of histopathology, so it would be impossible to distinguish conclusively between papillomas and carcinomas.

The conditions of the American experiments approximate the conditions of American people: wide exposure to a variety of cancer initiators and a 25% spontaneous cancer rate in lifetime studies. Over such a background, the presence of additional nonphysiologic chemicals which can stimulate the rate of development of cancers from premalignant cells must be considered a significant hazard.

I. Conclusions About Health Effects of 2,4-D

2,4-D is lipid soluble and is rapidly and completely absorbed through all normal routes of exposure. Its butyl ester, and therefore probably all of its esters, is hydrolyzed before absorption from the gastrointestinal tract. It is not metabolized in animals, but rapidly penetrates the placenta.

2,4-D as normally manufactured does not contain chlorodibenzodioxins because the reaction is not heated sufficiently to form them. However, 2,7-DCDD (also known as 3,8-DCDD) could be formed if the reaction mix was overheated or if partially degraded 2,4-D were heated during storage or disposal. This dioxin is far less toxic than the TCDD found in 2,4,5-T, but has been shown to be fetotoxic to the heart muscle in rats.

Many cases have been reported of human poisoning by inhalation or absorption through the skin. Damage is primarily to the nervous system, and some such symptoms are not readily repaired. Gastrointestinal symptoms and irritation of mucous membranes are also seen.

Laboratory tests have shown developmental toxicity of 2,4-D in four species of animals. These include all four classes of developmental toxicity (malformation, malfunction, growth retardation, and lethality) but not all four in any one experiment. They include tests of the esters and amine of 2,4-D as well as the parent compound, and both pre- and postnatal adverse effects. A synergistic toxicity of 2,4-D and its primary microbial breakdown product, 2,4-dichlorophenol, on the fetal circulatory system was demonstrated in rats. The abstract of a Russian study, which is not available in the United States, reports a survey of workers in the production of herbicides of the 2,4-D family and finds that "substantial impairment of menstrual and child-bearing functions arise manifested as higher rate of miscarriages, premature births, toxicosis of second half of pregnancy, and the menace of miscarriages during the whole pregnancy period" (Elina, 1974).

An adequately designed study indicated that 2,4-D does not interfere with fertility in rats, although other studies have shown that it causes point mutations in animal cells, damages DNA in a manner similar to ionizing radiation, and stimulates cell division.

Carcinogenicity testing of 2,4-D has been limited to three studies, none of which meets today's minimum standards. In spite of the inadequate experimental design or assay, two of these studies

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DOW 49230

0004195 8087

DOW230201
075346 D.L. Barsten

January 3, 1980

TO: ALL DOW 2,4,5-T AND SILVEX DISTRIBUTORS

RE: ESTERON* BRUSH KILLER, ESTERON* 2,4,5 AND KURON*

The E.P.A. emergency suspension of 2,4,5-T and Silvex has caused problems in disposing of stocks of the above items. There is confusion in people's minds as to what are the non-suspended uses of these products. This confusion is compounded by the fact that both E.P.A. and state officials have changed their minds on this point.

The attached sheet is the latest E.P.A. official policy on the legal and non-legal uses of 2,4,5-T and Silvex. There are still plenty of areas and uses for which these products are legally valid.

Confusion continues as to what is rangeland and what is pasture. The official E.P.A. definition of these two words follows:

> "Rangeland is defined as land producing forage for animal consumption, harvested by grazing, which is not cultivated, seeded, fertilized, irrigated or treated with pesticides or other such similar practices on an annual basis. Fence rows enclosing such areas are included as part of the range."
>
> "Pasture is defined as land producing forage for animal consumption, harvested by grazing, which has annual or more frequent cultivation, seeding, fertilization, irrigation, pesticide application and other similar practices applied to it. Fence rows enclosing pastures are included as part of the pasture."

Two points in these definitions are particularly important. First - the long list of things needed to be done that can make grasslands a pasture (i.e. cultivated, seeded, fertilized, irrigated, etc.) This may be interpreted as meaning that all of these practices need to be done or it is rangeland. Another interpretation would be that if any one of these practices (i.e.

irrigation, seeding, etc.) are followed it would make the grassland a pasture. Regardless of which interpretation is used, the use of the word annual is important. Thus, if these things (seeding, fertilization, irrigation, etc.) are not done on an annual basis, it is not a pasture. This definition would mean there is practically no pasture in this country. It is all rangeland. Nevertheless, publicity should be avoided even though the uses are legally correct.

You should understand that these products are safe to humans, wildlife and the environment when used according to labeled instructions. Two outside groups of scientists have confirmed Dow's stand on this safety question.

The best of luck and good selling. There is a real opportunity for you and your customers.

Yours very truly,

W. J. McCoy
District Sales Manager
Agricultural Department

enc.

jmz

* Trademark of The Dow Chemical Company

it feeds and then is transferred through pupa to adult (*11*). Similarly, senecio alkaloids are incorporated by moths from food plants of the genus *Senecio* (*12*), and cardenolides are accumulated in grasshoppers and butterflies from milkweed plants (*13*). In *Romalea*, sequestration may account for more than just the 2,5-dichlorophenol in the froth. The other components all occur as such or in similar form in many species of plants (*14*), and the grasshopper may simply incorporate them with slight or no change from the diet. But 2,5-dichlorophenol would still be unique because of its apparent ultimate derivation from an exogenous source recently unleashed upon the ecosystem by man himself.

THOMAS EISNER
Division of Biological Sciences, Cornell University, Ithaca, New York 14850
L. B. HENDRY*
Department of Chemistry, Cornell University, Ithaca
D. B. PEAKALL
Division of Biological Sciences, Cornell University
J. MEINWALD
Department of Chemistry, Cornell University

References and Notes

1. Pieces of fresh integument (25 mm²) of *Romalea*, treated with droplets (1 to 2 μl) of froth, were ignored by ants (*Paratrechina longicornis*) when placed in their foraging trail. Untreated controls were carried away. Tethered *Romalea* exposed on soil to foraging ants (*Pogonomyrmex badius*) discharged froth (and regurgitated crop fluid) when attacked, thereby repelling their assailants. After depletion of froth (and crop fluid) the grasshoppers were vulnerable.
2. J. Meinwald, K. Erickson, M. Hartshorn, Y. C. Meinwald, T. Eisner, *Tetrahedron Lett.* 1968, 2959 (1968); ———, L. Hendry, *ibid.* 1969, 1657 (1969).
3. Over 30 additional components of the froth remain unidentified.
4. T. Eisner and J. Meinwald, *Science* 153, 1341 (1966); ———, in *Chemical Ecology*, E. Sondheimer and J. B. Simeone, Eds. (Academic Press, New York, 1970), pp. 157–217.
5. J. Weatherston and J. E. Percy, in *Chemicals Controlling Insect Behavior*, M. Beroza, Ed. (Academic Press, New York, 1970), pp. 95–144.
6. J. Roche, M. Fontaine, J. Lepoup, in *Comparative Biochemistry*, M. Florkin and H. S. Mason, Eds. (Academic Press, New York, 1963), vol. 5, pp. 493–547. Alkaloids with chlorinated aliphatic side chains have been reported from some higher plants but are suspected of being artifacts rather than natural products [J. W. Hylin, R. E. Spenger, F. A. Gunther, *Residue Rev.* 26, 127 (1969)].
7. D. Townsend and R. Burgess (county agents, Collier and Hendry counties, Florida), personal communication.
8. The rearrangement of chlorine from a 2,4 to a 2,5 substitution pattern presupposed by this assumption seems plausible in view of the demonstrated occurrence of such rearrangement in the degradation of 2,4-D by fungi and higher plants. [J. K. Faulkner and D. Woodcock, *Nature* 203, 865 (1964); E. W. Thomas, B. C. Loughman, R. G. Powell, *ibid.* 204, 765 (1964)].
9. Archbold Biological Station, Lake Placid, Highland County, Florida.
10. Lethal range: 0.5 to 2.8 g/kg (V. K. Rowe, Dow Chemical Co., personal communication).
11. J. von Euw, T. Reichstein, M. Rothschild, *Israel J. Chem.* 6, 659 (1969).
12. R. T. Aplin, M. H. Benn, M. Rothschild, *Nature* 219, 747 (1968).
13. L. P. Brower, J. van Zandt Brower, J. M. Corvino, *Proc. Nat. Acad. Sci. U.S.* 57, 893 (1967); T. Reichstein, *Naturwiss. Rundschau* 20, 499 (1967); ———, J. von Euw, J. A. Parsons, M. Rothschild, *Science* 161, 861 (1968).
14. W. Karrer, *Konstitution und Vorkommen der organischen Pflanzenstoffe (exclusive Alkaloide)* (Birkhäuser, Basel, 1958).

15. Supported by NIH grants AI-02908 and RR-00355. We thank Dr. J. Hribar for his help with the chromatographic and spectroscopic studies, Dr. R. D. Liske for reading the manuscript, and Mr. R. Archbold, Director, Archbold Biological Station, for help and hospitality during our stay at the Station. Report No. 30 of our series "Defense Mechanisms of Arthropods."
* Present address: Department of Chemistry, Pennsylvania State University, University Park 16802.

12 February 1971

Aplysia californica: Analysis of Nuclear DNA in Individual Nuclei of Giant Neurons

Abstract. *The nuclei of the giant neurons of the marine mollusk* Aplysia californica *can contain more than 0.2 microgram of DNA. This is more than 200,000 times as much DNA as the haploid amount found in* Aplysia *sperm. On the basis of nuclear DNA content, the giant neurons R-2, P-1, and L-6 of adult animals can each be divided into at least two populations. The mean DNA content of these two populations (0.067 and 0.131 microgram of DNA) are approximately related by a factor of 2. This suggests that much and perhaps all of the genome replicates repeatedly (up to 16 times) during the growth and development of these neurons and that each replication is synchronous. The enormous amount of DNA in these cells opens up the possibility of characterizing the DNA and other constituents of chromatin from individual but phenotypically different neurons.*

The giant neurons of *Aplysia* represent one of the largest somatic cell types in the animal kingdom. These neurons, which range in size up to 1 mm in diameter, each contain a single nucleus which comprises approximately 30 percent of the volume of the cell body. The large size of the nucleus and the staining characteristics of the nucleoplasm with the Feulgen stain led Coggeshall (*1*) to suggest that the giant cell nuclei contain considerably more DNA than the diploid amount for *Aplysia*. This possibility was supported by an unpublished observation of Strumwasser (*2*) that the largest neurons contain 50,000 times as much DNA as mammalian cells. We have quantified the nuclear DNA from individual giant neurons and have found that the amount of DNA in *Aplysia* giant neurons is many thousands of times greater than the haploid value for these animals.

One of the remarkable features of the *Aplysia* nervous system is that individual neurons can be easily recognized in the abdominal ganglion; over 30 of these cells have been characterized electrophysiologically and morphologically (*3*). We chose to study cells R-2 and L-6 of the abdominal ganglion [nomenclature of Frazier *et al.* (*3*)] and the single giant cell of the left pleural ganglion, which we have abbreviated P-1. Cells R-2 and P-1 have been called the colossal cells and are the largest in the *Aplysia* nervous system; L-6 is somewhat smaller.

The giant cells are surrounded by thousands of glial satellite cells and contain a large complement of mitochondria. Therefore, in order to quantify the nuclear DNA of the giant neurons, it seemed necessary at the outset of these experiments to isolate the nuclei from the giant cells and rule out any contamination from glial or mitochondrial DNA. This precaution was justified in light of the finding that the glial cells and neuronal cytoplasm contribute 33 percent of the DNA to the intact giant cell (*4*).

An abbreviated description of the procedure for removing the giant cell nucleus from the cell body follows. A more complete description will be published separately (*4*). The abdominal and left pleural ganglia were removed from the animal and immersed in Millipore-filtered seawater (*p*H 7.4). The ganglia were incised under observation with the dissecting microscope, and selected cells were removed by severing the single axonal process. The neurons were transferred to a depression slide containing Millipore-filtered seawater. A small hole was made in the giant cell membrane, and the nucleus was extruded from the hole by gentle squeezing of the cell. The nuclei of the largest neurons are polymorphic and take on many odd shapes. However, when the nuclei are extruded into sea-

SUSPENDED USES

2,4,5-T[1]	SILVEX
[2,4,5-trichlorophenoxy acetic acid, esters, amine salts]	[2-(2,4,5-trichlorophenoxy) propionic acid, esters, amine salts]
Firetrails and lanes	Farm buildings
Forest lands, management areas, plantations, and stumplands	Forestlands and management areas
Rights-of-way: highways, pipelines, powerlines, utilities, roadsides, roadways, etc.	Golf courses
Pasture	Home use, lawns, grass, ornamental turf, patios, sidewalks, driveways, farmyards
	Ditchbanks, drainage ditchbanks, ponds, pond margins, standing water
	Lake, lake margins
	Rights-of-way, all; roadsides, roadways, etc.
	Pasture
	Ditches - water
	Parks, athletic fields
	Marshlands, canals, aquatic sites

NON-SUSPENDED USES

2,4,5-T	SILVEX
Rice	Rice
Rangeland	Rangeland
Airports	Sugarcane
Fences, hedgerows (not otherwise included in suspended uses, e.g., rights-of-way, pasture)	Preharvest fruit drop of apples, prunes and pears
Lumberyards	Fence rows, hedgerows, fences (not otherwise included in suspended uses, e.g., rights-of-way, pasture, home and garden)
Refineries	Nonfood crop areas
Nonfood crops	Noncrop areas
Storage areas	Storage areas
Noncrop areas	Waste areas
Wastelands (not otherwise included in suspended uses, e.g., forestry)	Vacant lots, parking areas, etc.
Vacant lots	Industrial sites or buildings (not otherwise included in suspended uses, e.g., rights-of-way, commercial/ornamental turf)
Industrial sites and areas (not otherwise included in suspended uses, e.g., rights-of-way)	

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[1] Certain uses of 2,4,5-T were suspended and cancelled in 1970. P. R. Notice 70-11, April 20, 1970, suspended the registrations for products containing 2,4,5-T and bearing directions for all uses in lakes, ponds and ditchbanks, and liquid formulations for use around the home, recreation areas, and similar sites. P. R. Notice 70-13, May 1, 1970, cancelled the registrations of 2,4,5-T products including all granular formulations for use around the home, recreation areas and similar sites, and all uses on food crops intended for human consumption, except for products whose labeling could be modified by deleting such claims.

CONFIDENTIAL - SUBJECT TO INJUNCTION
D.C., E.D. MI. 4-4-78; DOW/EPA AGREEMENT 9-79

DOW0052814

M A T E R I A L S A F E T Y D A T A S H E E T PAGE: 1

DOW CHEMICAL U.S.A. MIDLAND MICHIGAN 48640 EMERGENCY PHONE: 517-636-4400

EFFECTIVE DATE: 08 JAN 80 PRODUCT CODE: 28749

PRODUCT NAME: ESTERON (R) 245 BRUSH AND WEED KILLER MSD: 0303

INGREDIENTS (TYPICAL VALUES-NOT SPECIFICATIONS)	%
2,4,5-TRICHLOROPHENOXYACETIC ACID,	
PROPYLENE GLYCOL BUTYL ETHER ESTERS	69.2
EMULSIFIERS PLUS PETROLEUM SOLVENT	30.8

SECTION 1 PHYSICAL DATA

BOILING POINT: IBP > 300F (150C) : SOL. IN WATER: EMULSIFIABLE
VAP PRESS: < 6 MMHG @ 20C : SP. GRAVITY: 1.065 (68/68F)
VAP DENSITY (AIR=1): NOT APPLIC. : % VOLATILE BY VOL: NIL UNDER 150C
APPEARANCE AND ODOR: AMBER LIQUID.

SECTION 2 FIRE AND EXPLOSION HAZARD DATA

FLASH POINT: (1) 180F (2) 154F : FLAMMABLE LIMITS (STP IN AIR)
METHOD USED: (1) TOC (2) TCC : LFL: NOT DETER. UFL: NOT DETER.
EXTINGUISHING MEDIA: WATER FOG, FOAM, ALCOHOL FOAM, CO2, DRY CHEMICAL.
SPECIAL FIRE FIGHTING EQUIPMENT AND HAZARDS: USE SELF-CONTAINED AIR SUPPLY.
NOXIOUS FUMES UNDER FIRE CONDITIONS.
CONTAIN WATER FROM FIRE FIGHTING TO PREVENT ENTRY TO WATER SUPPLIES.

SECTION 3 REACTIVITY DATA

STABILITY: AVOID TEMPERATURES NEAR OR ABOVE FLASH POINT.
INCOMPATIBILITY: ACID, BASE, OXIDIZING MATERIAL. CONSULT
MANUFACTURER FOR SPECIFIC CASES.
HAZARDOUS DECOMPOSITION PRODUCTS: NOXIOUS FUMES UNDER FIRE CONDITIONS - HYD
CHLORIDE AND OTHERS.
HAZARDOUS POLYMERIZATION: WILL NOT OCCUR.

SECTION 4 SPILL, LEAK, AND DISPOSAL PROCEDURES

ACTION TO TAKE FOR SPILLS (USE APPROPRIATE SAFETY EQUIPMENT): ABSORB SPILLS
WITH INERT DRY MATERIAL SUCH AS SAND OR SAWDUST. DIKE AREA IN
IN CASE OF LARGE SPILLS. DO NOT USE WATER FOR CLEANUP.
DISPOSAL METHOD: BURY WASTE IN NON-CROP AREA AWAY FROM WATER SUPPLIES.

(CONTINUED ON PAGE 2)

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0003203

DOW CHEMICAL U.S.A. MIDLAND MICHIGAN 48640 EMERGENCY PHONE: 517-636-4400

EFFECTIVE DATE: 08 JAN 80 PRODUCT CODE: 28749
PRODUCT (CONT'D): ESTERON (R) 245 BRUSH AND WEED KILLER MSD: 0303

SECTION 5 HEALTH HAZARD DATA

INGESTION: MODERATE SINGLE DOSE ORAL TOXICITY. LD50 (RAT) IN THE RANGE OF 700 TO 1000 MG/KG.
EYE CONTACT: MAY BE A MILD IRRITANT BUT SHOULD CAUSE NO MORE THAN SLIGHT TRANSIENT CORNEAL EFFECTS.
SKIN CONTACT: MAY CAUSE MILD TO MODERATE IRRITATION ON REPEATED CONTACT.
SKIN ABSORPTION: NOT ABSORBED IN TOXIC AMOUNTS.
INHALATION: NO GUIDE FOR CONTROL OF MIXTURE ESTABLISHED. DOW IHG 10 MG/M3 KEROSENE.
EFFECTS OF OVEREXPOSURE: NAUSEA IF SWALLOWED.

SECTION 6 FIRST AID--NOTE TO PHYSICIAN

FIRST AID PROCEDURES:

EYES: IRRIGATE WITH FLOWING WATER IMMEDIATELY AND CONTINUOUSLY FOR FIFTEEN MINUTES. REFER TO MEDICAL PERSONNEL.
SKIN: CONTACT WILL PROBABLY CAUSE NO MORE THAN IRRITATION. WASH OFF IN FLOWING WATER OR SHOWER. WASH CLOTHING BEFORE REUSE.
INHALATION: REMOVE TO FRESH AIR IF EFFECTS OCCUR. CONSULT MEDICAL PERSON
INGESTION: DO NOT INDUCE VOMITING. CALL A PHYSICIAN AND/OR TRANSPORT TO EMERGENCY FACILITY.

NOTE TO PHYSICIAN: EYES - MAY CAUSE MILD IRRITATION. MAY CAUSE CORNEAL INJ OR BURN. STAIN FOR EVIDENCE OF CORNEAL INJURY. IF CORNEA IS BURNED, INSTILL ANTIBIOTIC STERIOD PREPARATION FREQUENTLY. CONSULT OPTHALMOLOGIST.
SKIN - MAY CAUSE MILD IRRITATION.
INHALATION - NO TOX DATA. NO EFFECT EXPECTED.
INGESTION - MAY CAUSE REACTION SIMILAR TO PETROLEUM OR PETROLEUM-LIKE SOLVENT. MAY CAUSE CHEMICAL PNEUMONIA IF ASPIRATED INTO LUNGS. NOT LIKELY TO BE ABSORBED IN ACUTELY TOXIC AMOUNTS. IF LAVAGE IS PERFORMED SUGGEST ENDOTRACHEAL AND/OR ESOPHAGOSCOPIC CONTROL.
SYSTEMIC - ANESTHETIC OR NARCOTIC EFFECT MAY OCCUR. MAY CAUSE LIVER DAMAGE. MAY CAUSE KIDNEY DAMAGE. NO SPECIFIC ANTIDOTE. TREATMENT BASED ON SOUND JUDGMENT OF PHYSICIAN AND THE INDIVIDUAL REACTIONS OF THE PATIENT. BASED ON MINIMAL DATA. HUMAN EFFECTS NOT ESTABLISHED.

SECTION 7 SPECIAL HANDLING INFORMATION

VENTILATION: RECOMMEND CONTROL OF KEROSENE VAPORS TO SUGGESTED GUIDE.
RESPIRATORY PROTECTION: NONE LIKELY TO BE NEEDED IN ANTICIPATED OPERATIONS.
PROTECTIVE CLOTHING: CLEAN BODY-COVERING CLOTHING.
EYE PROTECTION: SAFETY GLASSES WITHOUT SIDE SHIELDS.

(CONTINUED ON PAGE 3)

DOW CHEMICAL U.S.A. MIDLAND MICHIGAN 48640 EMERGENCY PHONE: 517-636-4400

EFFECTIVE DATE: 08 JAN 80 PRODUCT CODE: 28749
PRODUCT (CONT'D): ESTERON (R) 245 BRUSH AND WEED KILLER MSD: 0303

DOW052806

SECTION 8 SPECIAL PRECAUTIONS AND ADDITIONAL INFORMATION

PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE: SEE LABEL. KEEP OUT OF REACH OF CHILDREN. AVOID CONTACT WITH SKIN AND EYES. PROVIDE WASHING FACILITIES NEAR WORK AREA. DO NOT STORE NEAR FERTILIZER, SEEDS, INSECTICIDES, AND FUNGICIDES. KEEP AWAY FROM OPEN FLAME.
ADDITIONAL INFORMATION: REVISIONS 1/8/80 -- SECTIONS 5, 7.

LAST PAGE

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8096

DOW CHEMICAL U.S.A. MIDLAND MICHIGAN 48640 EMERGENCY PHONE: 517-636-4400

EFFECTIVE DATE: 08 JAN 80 PRODUCT CODE: 28750

PRODUCT NAME: ESTERON (R) 245 BRUSH AND WEED KILLER (PL & BULK) MSD: 0303

INGREDIENTS (TYPICAL VALUES-NOT SPECIFICATIONS)	%
2,4,5-TRICHLOROPHENOXYACETIC ACID, PROPYLENE GLYCOL BUTYL ETHER ESTERS	69.2
EMULSIFIERS PLUS PETROLEUM SOLVENT	30.8

SECTION 1 PHYSICAL DATA

BOILING POINT: IBP > 300F (150C) : SOL. IN WATER: EMULSIFIABLE
VAP PRESS: < 6 MMHG @ 20C : SP. GRAVITY: 1.065 (68/68F)
VAP DENSITY (AIR=1): NOT APPLIC. : % VOLATILE BY VOL: NIL UNDER 150C
APPEARANCE AND ODOR: AMBER LIQUID.

SECTION 2 FIRE AND EXPLOSION HAZARD DATA

FLASH POINT: (1) 180F (2) 154F : FLAMMABLE LIMITS (STP IN AIR)
METHOD USED: (1) TOC (2) TCC : LFL: NOT DETER. UFL: NOT DETER.
EXTINGUISHING MEDIA: WATER FOG, FOAM, ALCOHOL FOAM, CO2, DRY CHEMICAL.
SPECIAL FIRE FIGHTING EQUIPMENT AND HAZARDS: USE SELF-CONTAINED AIR SUPPLY.
NOXIOUS FUMES UNDER FIRE CONDITIONS.
CONTAIN WATER FROM FIRE FIGHTING TO PREVENT ENTRY TO WATER SUPPLIES.

SECTION 3 REACTIVITY DATA

STABILITY: AVOID TEMPERATURES NEAR OR ABOVE FLASH POINT.
INCOMPATIBILITY: ACID, BASE, OXIDIZING MATERIAL. CONSULT MANUFACTURER FOR SPECIFIC CASES.
HAZARDOUS DECOMPOSITION PRODUCTS: NOXIOUS FUMES UNDER FIRE CONDITIONS - HYDROGEN CHLORIDE AND OTHERS.
HAZARDOUS POLYMERIZATION: WILL NOT OCCUR.

SECTION 4 SPILL, LEAK, AND DISPOSAL PROCEDURES

ACTION TO TAKE FOR SPILLS (USE APPROPRIATE SAFETY EQUIPMENT): ABSORB SPILLS WITH INERT DRY MATERIAL SUCH AS SAND OR SAWDUST. DIKE AREA IN IN CASE OF LARGE SPILLS. DO NOT USE WATER FOR CLEANUP.
DISPOSAL METHOD: BURY WASTE IN NON-CROP AREA AWAY FROM WATER SUPPLIES.

(CONTINUED ON PAGE 2)
(R) INDICATES A REGISTERED OR TRADEMARK NAME OF THE DOW CHEMICAL COMPANY

DOW CHEMICAL U.S.A. MIDLAND MICHIGAN 48640 EMERGENCY PHONE: 517-636-4400

EFFECTIVE DATE: 08 JAN 80 PRODUCT CODE: 28750
PRODUCT (CONT'D): ESTERON (R) 245 BRUSH AND WEED KILLER (PL & BULK) MSD: 0303
PROTECTIVE CLOTHING: CLEAN BODY-COVERING CLOTHING.
EYE PROTECTION: SAFETY GLASSES WITHOUT SIDE SHIELDS.

SECTION 8 SPECIAL PRECAUTIONS AND ADDITIONAL INFORMATION

PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE: SEE LABEL. KEEP OUT OF REACH OF CHILDREN. AVOID CONTACT WITH SKIN AND EYES. PROVIDE WASHING FACILITIES NEAR WORK AREA. DO NOT STORE NEAR FERTILIZER, SEEDS, INSECTICIDES, AND FUNGICIDES. KEEP AWAY FROM OPEN FLAME.
ADDITIONAL INFORMATION: REVISIONS 1/8/80 -- SECTIONS 5, 7.

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21 8117

The following is a report on odor and taste thresholds as requested.

Product	Batch	Date	Odor Threshold (ppm)
Dowicide 1	1179	--	0.4
Dowicide 2	10069	--	0.008
Dowicide 2S	--	6/49	0.015

Pure Compound	Odor Threshold(ppm)	Taste Threshold(ppm)
Orthophenylphenol	3.0	10.0
2-4-5 Trichlorophenol	0.5	0.5
2-4-6 Trichlorophenol	24.0	20.0
2-4 Dichlorophenol	0.2	--
2-4 Dichlorophenoxyacetic		
Untreated	50	--
Treated	50	--

Fish Toxicity:

	Lethal Concentrations (ppm)
2-4 Dichlorophenol	5 to 10
2-4-5 Trichlorophenol	1.5 to 2.0
2-4-5 Trichlorophenoxy-acetic	500

Fish Tainting:

The following is a summary of the pure compounds tested for taste in fish during the period 1949 to October 1950:

Compound	Taste Threshold (p
Phenol	1.0
Para tertiary butylphenol	0.01
2-4 Dichlorophenol	0.3
Ortho chlorophenol	0.05
Para chlorophenol	0.10
Ortho phenylphenol	0.5
Diphenyloxide	0.5

Additional information on Fish Toxicity

Esteron and Brush Killer

Emulsions of both Esteron and Brush Killer were prepared by adding 1% cc of each preparation to 99 cc of our laboratory tap water. Both mixtures were agitated for several minutes until a good emulsion was formed. These emulsions were then allowed to stand for 24 hours. After standing 24 hours, a precipitate of oil was observed in each emulsion. These emulsions were then used as stock for all tests performed.

Toxicity experiments were run on both the supernatant emulsion and the entire emulsion for Esteron. Toxicity experiments for the Brush Killer were run only on the entire emulsion.

Toxicity to Fish:

	Safe Dilution (based on original product preparation)
Esteron	
Supernatant emulsion	
Entire emulsion	
	1/16,000 chub and shiner minnows (62.5 ppm)
	1/40,000 chub minnows (25 ppm)
	1/80,000 shiner minnows (12.5 ppm)
Brush Killer	
Entire emulsion	1/120,000 chubs and shiners (8.3 ppm)

	Dilution for Lowest Detectable (based on half-hour exposure)
Esteron	(0.25 ppm)
Brush Killer	(0.2 ppm)

Conclusions:

Esteron in a dilution of 1/[illegible] would be toxic to fish.

Brush Killer in a dilution of 1/[illegible] would be toxic to fish.

Based upon toxicity experiments [illegible] the fish quickly exhibited by the Esteron and Brush Killer [illegible] can be attributed to the oily [illegible] and not to the [illegible]

The [illegible] threshold of Esteron and Brush Killer [illegible] of the milky stream and the [illegible] in the [illegible]

-4-5 Trichloromethoxybenzene

Color Threshold:

1: orm (as 2-4-5 T) in distilled water
5 p.p.m (as 2-4-5 T) in aerated tap water

Fish Toxicity:

p.p.m
2-4-5 T | Kill Time

50 | 1 hour
5 | to 5 hours
50 | 1 death after 12 hours
1 killed after 4 hours
No deaths 6 hours
No deaths 4 hours

Properties of water as influenced by 2-4-5 T

	Start	50 ppm	5 ppm
pH	7.0	7.0	7.0 (24 hours)
p.p.m NaCl	70	70	
p.p.m Alk. (as $CaCO_3$)	230	230	

Conclusions:

1. To prevent death of rainbow trout fingerlings in 24 hours, taste indicates the concentration of 2-4-5 T should be kept at 5 p.p.m or less.

2. From above data, the safe concentration of 2-4-5 T would be below 50 p.p.m. Concentrations above 50 p.p.m show marked toxicity to chub minnows.

CENTRAL RESEARCH INDEX

Chlorinated, toxic to fish, test, [illegible] 3-10

Marr, T.J. Waste Disposal Plant 12/2/50

INFORMATION ON ORGANIC COMPOUND TASTE, ODOR AND FISH TOXICITY

Fish toxicity with 2,4,5-trichlorophenoxyacetic acid
Fish toxicity with water
Fish toxicity with brush killer
Fish toxicity with chlorinated phenols
Odor and taste threshold caused by chlorinated phenols, peteron brush killer and 2,4,5-trichlorophenoxyacetic acid

3-1 BC + 3 men in Files

S. Kleaney
Midland CRI
We would like a copy of this report, please.
Dela. Chem. Co.
Pittsburg, Calif.
21 years of fruitless [illegible] waste problems. [illegible]
Bill Wachter, Wash. Utilities [illegible]
[illegible]
[illegible]

DOW

SPECIMEN LABEL
REDUCED TO 75%

ESTERON® 245
HERBICIDE

FOR THE CONTROL OF TREES, BRUSH AND BROADLEAF WEEDS

Low-Volatile Brush and Weed Herbicide for Industrial Vegetation Control, Fencerows, and Rangeland

ACTIVE INGREDIENT	
2,4,5-Trichlorophenoxyacetic Acid, Propylene Glycol Butyl Ether Esters	69.2%
INERT INGREDIENTS	30.8%
2,4,5-Trichlorophenoxyacetic Acid Equivalent = 45.0% 3 Pounds per Gallon	

EPA Registration No. 464-205 EPA Est. 464-MI-1

PRECAUCION AL USUARIO: Si usted no lee ingles, no use este producto hasta que la etiqueta le haya sido explicada ampliamente.
TRANSLATION: (TO THE USER: If you cannot read English, do not use this product until the label has been fully explained to you.)

KEEP OUT OF THE REACH OF CHILDREN

CAUTION

HARMFUL IF SWALLOWED • MAY CAUSE IRRITATION
Avoid Contact with Eyes, Skin and Clothing
Do Not Cut or Weld Container

In case of an emergency endangering life or property involving this product, call collect
517-636-4400

AGRICULTURAL CHEMICAL
Do Not Store or Ship with Food, Feeds, Drugs or Clothing

18.93 L / 5 gal

DOW 252061

8105

86-1064 PRINTED IN U.S.A. IN JANUARY, 1980.
REPLACES SPECIMEN LABEL 86-1064 PRINTED IN SEPTEMBER, 1979.
DISCARD PREVIOUS SPECIMEN LABELS.
REVISIONS INCLUDE: USES ON INDUSTRIAL SITES AND
FENCEROWS REINSTATED BY EPA.

SPECIMEN LABEL
(BACK)
REDUCED TO 75%

DOW ESTERON 245 HERBICIDE

Contains Propylene Glycol Butyl Ether Esters of 2,4,5-T • Acid Equivalent: 4 Pounds per Gallon

Insert 1

DIRECTIONS FOR USE

~~ESTERON 245 herbicide is recommended for industrial vegetation control, forestry and rangeland. Do not use in forest family, rights-of-way or pastures.~~

~~This herbicide controls herbaceous and woody plants including most 2,4,5-trioxane species as – ash, black gum, hackberry, groundsel tree, hawthorn, horsenettle, maple, mesquite, oak, sassafras, sumac, poison ivy, prickly pear cactus, ragweed, blackberry, sweetgum, wild blackberry, wild rose, and certain species listed on the label. Do not apply ESTERON 245 where spray drift may contact nearby 2,4,5-T susceptible crops or other desirable plants or may contaminate water intended for irrigation or domestic purposes. Read and follow all Use Precautions given on this label.~~

PREPARING THE SPRAY

Use only diesel oil, No. 1 or No. 2 fuel oil or kerosene where oil is recommended in the spray mixture.

Oil sprays: Add ESTERON 245 to the required amount of oil in the spray tank or mixing tank and mix thoroughly. This mixture can be made at any time before actual use and no separation will occur. Do not let any water, or oil-water mixture sprays get into the ESTERON 245 or into the finished mixture, as it may form a gel.

Water Sprays: Fill the spray tank about half full with clean water, add the required amount of ESTERON 245 and complete filling the tank. Mix thoroughly and continue agitation while spraying. Caution: See NOTE in paragraph on Oil-Water Mixture Sprays.

Oil-Water Mixture Sprays: When vigorous agitation is used, 1 gallon of ESTERON 245 will emulsify up to 10 gallons of oil in 100 gallons of spray mixture. First, premix the ESTERON 245 and oil in a separate container. Do not allow any water or mixtures containing water to get into the ESTERON 245 or the premix. Fill the spray tank about half full with water, then slowly add the premix with continuous agitation and complete filling the tank with water. If the premix is put in the tank without any water, the first water added may form a thick "invert" (water in oil) emulsion which will be hard to break. As an alternate procedure, the oil may be added after the ESTERON 245 is mixed in the water; but highly vigorous mechanical agitation is required and a poor emulsion may be formed. The premix method is preferred.

NOTE: ESTERON 245 in water or oil-water sprays forms an emulsion, not a solution, and separation may take place unless sprays are agitated continously. Mechanical agitation is recommended.

Insert 2

HIGH VOLUME SPRAYS

Basal Bark Treatment: Brush and small trees can be controlled by spraying the basal parts of brush stems and tree trunks to a height of 12 to 15 inches from the ground line. Use a solution of 3 gallons of ESTERON 245 in 100 gallons (1 pint in 4 gallons) of oil. With certain resistant species, 4 gallons of ESTERON 245 in 100 gallons (1 pint in 3 gallons) of oil, is effective. As only the basal portions of the brush are treated on a spot basis, the total amount sprayed per acre would not be expected to exceed 100 gallons. Knapsack or power equipment may be used, but complete wetting of the indicated area is necessary, particularly at the ground line. This means spraying until run-down or run-off to the ground line is noticeable. Old or rough bark requires more spray than young or smooth bark. Low pressures are desirable. Apply at any time, including the winter months, except when snow, ice or water prevent spraying to the ground line. Often delayed response and killing can be expected.

Dormant Brush: Treat any time after brush is dormant and most of the foliage has dropped. Spray should be concentrated at the base of stems and in addition, the upper parts of the stems should be broadcast sprayed enough to wet them. Under reclouducing species such as sumac, persimmon, sassafras and locust, also spray the ground area to control small root suckers that may not be readily visible. Mix 1 1/2 gallons of ESTERON 245 in 100 gallons of oil. Brush of average density and 4 to 6 feet high may take up to 100 gallons of spray mixture per acre.

Stump Treatment: Where growth is more than 6 to 8 feet tall, cut it close to the ground and spray the freshly cut stumps and stubs with 3 gallons of ESTERON 245 in 100 gallons (1 pint in 4 gallons) of oil, mixed thoroughly. For more resistant species, use 4 gallons of ESTERON 245 in 100 gallons (1 pint in 3 gallons) of oil. Wet thoroughly all exposed bark, as well as cut surfaces. This means spraying until run down or run off to the ground line is noticeable. Old or rough bark requires more spray volume than young or smooth bark. Apply at any time, including winter months, except when ice, snow or water prevent spraying to the ground line. Best results are obtained on freshly cut stumps two inches across or larger. Adequate coverage normally requires from 10 to 100 gallons per acre depending on density of stumps and stubs.

"Frill" Treatment: For large trees, make a single-hack girdle or "frill" of overlapping axe cuts completely around the tree as close to the ground as feasible. Spray the frill thoroughly using a mixture of 2 gallons of ESTERON 245 in 100 gallons (1/2 pint in 3 gallons) of oil

Spot Foliage Treatment: Use 1/4 pint of ESTERON 245 in 3 gallons of water and spray to wet all foliage, shoots, stems and bark without runoff.

LOW VOLUME SPRAYS

Apply low volume sprays containing ESTERON 245 when foliage is well developed and plants are actively growing. For best results on woody species, soil moisture should be sufficient to promote foliar growth. Spraying during prolonged hot, dry weather or after leaves have lost their normal green color and vigor may not give satisfactory control. Apply low volume sprays by air or ground equipment only when spray drift will not be a problem – note use precautions.

Basal Treatment Using Powered Knapsack Sprayer – Mix 1 1/2 to 2 gallons of ESTERON 245 with fuel oil or kerosene to make 20 gallons of total spray solution. Apply with a portable knapsack mistblower to all sides of lower brush stems including the root collar. Good coverage of the root collar is essential for best results. Run mistblower at 1/4 to 1/3 throttle for best spray delivery and coverage. For maximum drift control use a basal nozzle attachment and do not raise nozzle above the horizontal position.

Insert 3

~~AIR APPLICATION FOR BRUSH CONTROL~~

~~Consult the Agricultural Experiment Station, your local Extension Service Weed or Range specialist for best time to treat and read for re-treatment in your area.~~

Do not use from early boot to milk stage where grass seed production is desired.

Mesquite: Use 1 pint ESTERON 245 plus 1/2 to 1 gallon of oil in enough water to make 4 gallons of total spray per acre. Apply 45 to 90 days after first leaves appear.

Sand Shinnery Oak: Use 1/2 to 1 quart of ESTERON 245 plus 1 gallon of oil in enough water to make 4 gallons of total spray per acre.

Post and Blackjack Oaks: Use 2 quarts of ESTERON 245 plus 1 gallon of oil in enough water to make 4 to 6 gallons of total spray per acre.

USE PRECAUTIONS

Note: Do not graze dairy animals on treated areas within 6 weeks after application. Do not graze meat animals on treated areas within 2 weeks of slaughter.

AVOID CONTACT WITH 2,4,5-T SUSCEPTIBLE CROPS AND OTHER DESIRABLE BROADLEAF PLANTS – ESTERON 245 Herbicide is injurious to most broadleaf plants. Therefore, do not apply directly to or otherwise permit even minute amounts to contact cotton, grapes, tobacco, fruit trees, vegetables, flowers, ornamentals or other desirable plants susceptible to 2,4,5-T. Do not use in or near a greenhouse.

DO NOT APPLY IN THE VICINITY OF COTTON, GRAPES, TOBACCO, TOMATOES OR OTHER DESIRABLE 2,4,5-T SUSCEPTIBLE CROPS OR ORNAMENTAL PLANTS.

DO NOT SPRAY WHEN WIND IS BLOWING TOWARDS SUSCEPTIBLE CROPS OR ORNAMENTAL PLANTS.

AVOID SPRAY DRIFT – Applications should be made only when there is no hazard from spray drift since very small quantities of spray, which may not be visible, may severely injure susceptible crops during both growing and dormant periods. Use coarse sprays to minimize drift since, under adverse weather conditions, fine spray droplets may drift a mile or more. The spray thickening agent, NALCO TROL[1], may be used with this product to aid in reducing spray drift. If used follow all use recommendations and precautions on the product label.

[1]NALCO-TROL – Trademark of NALCO Chemical Company

GROUND EQUIPMENT – With ground equipment, spray drift can be lessened by keeping the spray boom as low as possible, by applying 20 gallons or more of spray per acre; by using no more than 20 pounds spraying pressure with large droplet producing nozzle tips; by spraying when wind velocity is 8 miles per hour or less. Do not apply with hollow cone-type insecticide or other nozzles that produce a fine-droplet spray.

AERIAL APPLICATION – With aircraft, drift can be lessened by applying a coarse spray, by using no more than 20 pounds spray pressure at the nozzles; by using straight stream nozzles directed straight back; by using a spray boom no longer than 3/4 the wing span of the aircraft; and by spraying only when wind velocity is less than 6 mph.

DO NOT APPLY BY AIRCRAFT WHEN AN AIR TEMPERATURE INVERSION EXISTS. Such a condition is characterized by little or no wind and with air temperature lower near the ground than at higher levels. The use of a continuous smoke column at or near site of application is suggested to indicate direction and velocity of air movement, and to indicate a temperature inversion by layering of the smoke.

At high temperatures (above 85°F) vapors from this product may injure susceptible plants growing nearby. Do not use in or near a greenhouse. Excessive amounts of this herbicide in the soil may temporarily inhibit seed germination or plant growth.

Do not use around the home, recreation areas or similar sites.

This product is toxic to fish. Keep out of lakes, streams, and ponds. Do not contaminate water by cleaning of equipment or disposal of wastes.

Do not contaminate irrigation ditches or water used for irrigation or domestic purposes. This product can be stored in an unheated building but if exposed to subfreezing temperatures, should be warmed to at least 40°F and mixed thoroughly before using. Do not store near fertilizers, seeds, insecticides or fungicides. Do not reuse containers. To avoid injury to desirable plants, do not store, handle or apply other agricultural chemicals with the same containers or equipment used with ESTERON 245 except as specified on this label.

Rinse equipment and containers and dispose of waste by burying in non-crop lands away from water supplies. Containers should be disposed by punching holes in them and burying with waste or follow official local recommendations for container disposal.

Local conditions may affect the use of herbicides. Consult your State Agricultural Experiment Station or Extension Service weed specialist for advice in selecting treatments from this label to best fit local conditions. Be sure that use of this product conforms to all applicable regulations. Apply this product only as specified on this label.

NOTICE: Seller warrants that the product conforms to its chemical description and is reasonably fit for the purposes stated on the label when used in accordance with directions under normal conditions of use, but neither this warranty nor any other warranty of MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, express or implied, extends to the use of this product contrary to label instructions, or under abnormal conditions, or under conditions not reasonably foreseeable to seller, and buyer assumes the risk of any such use.

62-0000-0000-0 T100

THE DOW CHEMICAL COMPANY
AND SUBSIDIARIES
MIDLAND, MICHIGAN 48640, USA HORGEN, SWITZERLAND HONG KONG
CORAL GABLES, FLORIDA 33134, USA SARNIA, ONTARIO, CANADA

®Trademark of THE DOW CHEMICAL COMPANY

DOW 252062

000133 8106

DOW CHEMICAL U.S.A.

MIDLAND, MICHIGAN 48640

February 4, 1980

To: R. R. Cook, M.D.

Re: A CRITICAL REVIEW OF: "CASE-CONTROL STUDY OF MALIGNANT MESENCHYMAL SOFT-TISSUE TUMORS AND EXPOSURE TO CHEMICAL SUBSTANCES."

SUMMARY

This report presents a critique of the study by Hardell and Axelson which according to the authors "indicates that exposure to phenoxy acids must constitute a risk factor with regard to the origin of malignant mesenchymal soft-tissue tumors, and that the risk relates not only to those phenoxy acids that like certain chlorophenols, may contain polychlorinated dibenzo-dioxins and dibenzofurans but also to other phenoxy acids."

It is not clear whether the cases selected for study are representative of all cases in the area. The individual diagnoses of soft-tissue sarcoma include a rather diverse listing of tumor types. Several subtle sources of bias may have been introduced in the selection of the controls, which may have influenced the percentage reporting employment in the occupations of interest, agriculture and forestry. Information concerning exposure was obtained via telephone interview and a mailed questionnaire; there was no documented evidence of exposure presented. Media attention to previous studies by Hardell may have sensitized the cases to recalling exposures better than controls. Questionnaire information was, in some cases, supplemented by a telephone interview and this further increased the possibility for the introduction of bias. The individual relative risks for exposure to a number of specific chemical pesticides were significantly greater than one. It can be argued that the study did not test the risk of exposure to specific chemical agents but instead assessed the risk associated with employment in agriculture and forestry.

In view of the lack of reliable exposure information, in consideration of the several sources of bias introduced by the methodology employed, and despite the consistency of the findings between this and another identical study done by Hardell in the north of Sweden, one must regard the suggested association as suspect.

INTRODUCTION

In a recent case-control epidemiologic study[1] an association between soft-tissue sarcomas and prior occupational exposure to phenoxyacetic acids or chlorophenols was suggested. One hundred and ten (110) male patients, aged 25-75 years, with malignant mesenchymal soft-tissue tumors verified at histopathological review, were individually matched with two controls each on the basis of sex, age, place of residence, vital status, and year of death for those deceased. Living patients and controls were contacted by telephone and mailed a questionnaire concerning past occupations, types of occupational exposure (especially chemical), smoking habits, etc. The next of kin of deceased patients and controls was contacted and mailed a similar questionnaire. The answers were studied for possible exposure to phenoxyacetic acids or chlorophenols and it was noted that exposure had occurred to 22.7% of the patients and to 5.9% of the controls, thus generating a relative risk of 5.1.

This study is remarkably similar in design to an earlier study done by Hardell et al[2], which demonstrated a very similar relative risk (5.7) for soft-tissue sarcoma associated with exposure to phenoxyacetic acids or chlorophenols in a geographically distinct area from the area surveyed in the present study. These two studies by Hardell are, to the best of my knowledge, the only ones to suggest an association between soft-tissue sarcoma and exposure to phenoxyacetic acids or chlorophenols. Other reports[3] suggesting an association with cancer have been confined to case-reports and geographically limited studies; the lack of a sentinel tumor has somewhat weakened the putative association. Available data concerning human exposure to the phenoxy herbicides, 2,4-dichlorophenoxyacetic acid (2,4-D) and 4-chloro-2-methyl-phenoxy-acetic acid (MCPA), which do not contain the contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin, indicate no associative relationship with the development of neoplasia.[3] Carcinogenic or tumorigenic responses have not been produced in mice fed 46.6-100mg/kg, 2,4-D of diet nor in rats fed 1,250 mg/kg, 2,4-D of diet for 18 to 24 months. Single subcutaneous injections of 21.5-215 mg/kg, 2,4-D did not produce carcinogenic or tumorigenic responses in mice.

CRITIQUE

Background

The authors present background information on the tonnage of phenoxy acid used in Sweden in 1977. Figures regarding phenoxy acid use 10 years ago and before would have more relevance to the cancer cases diagnosed from 1974 to 1978. It is mentioned that as a result of prohibiting the use of 2,4,5-T in 1977, the phenoxy acids, MCPA and 2,4-D, have seen increased use. The following paragraph suggests that this study will offer the possibility of specifically analyzing the potential effects of MCPA and 2,4-D. It is not clear how much use MCPA and 2,4-D had 10 years ago and before, when exposures relevant to the cancer cases in this study may have occurred.

Selection of Cases

Cases of malignant mesenchymal soft-tissue tumors were selected for study from all male cases which were diagnosed and reported to the National Social Welfare Boards' Cancer Register in the years 1974-1978. The authors do not indicate what percentage of all cancers are reported to the Register, nor do they discuss possible selection bias which could influence the reporting of cases. Thus, it is difficult to evaluate the representativeness of the sample. In any case-control study, it is imperative that the cases chosen for study are representative of all such cases or there is no unknown bias influencing their selection.

From Table VI, Histopathological Diagnosis in the Reviewed Material, the rather lengthy and diverse list of diagnoses included for study can be noted. Certainly, a sufficient number of cases of Leiomyosarcoma existed so that the study could have been restricted to individuals with such a diagnosis, and a more meaningful study may have resulted.

Selection of Controls

Controls must be selected from the same general population which gave rise to the cases. Any known bias which influenced the selection

of cases must be applied equally to the selection of the controls. The matching design employed in this study proved to be quite wasteful, the authors eventually discarded over 700 originally selected controls. It is unclear why 8 controls were initially matched for each living case and 10 controls were matched for each deceased case. For cases dying in 1978, controls who were deceased in 1977 were matched for ethical reasons. This may have created a systematic bias, since next of kin for controls may have had more difficulty recalling exposures due to the increased time since death.

The matching design was compromised as 12 controls were selected from municipalities which were separate and distinct from those which gave rise to the cases. If such areas are underrepresented by workers in the occupations of interest (farming, forestry work) then there is bias introduced.

Another source of possible systematic bias was introduced when controls were selected conditional upon gainful employment until five years before the subject's retirement or death. This condition was not stipulated for selection of the cases, and may have eliminated controls who worked in the occupations of interest. It is quite possible that the nature of occupation is related to the age at retirement.

Assessment of Exposure

In any case-control study, it is critical that information concerning possible exposures be gathered in a comparable manner for both cases and controls. Since the analysis is dependent upon a comparison of responses by the cases and controls, it is especially sensitive to the influence of bias in the reporting of exposure. There is a tendency for cases to recollect prior exposures better than controls, thus leading to a relatively higher reporting rate by cases.

Answers to questionnaires were studied and supplemented over the telephone. This can lead to a problem with the lack of comparability in the accuracy and completeness of responses by the cases and controls. If a greater proportion of cases than controls were contacted for supplementary information, there is the possibility that bias entered into the reporting and perhaps inflated the exposures

reported by cases. Unfortunately, the authors do not indicate what proportion of the study subjects were contacted for supplementary information, nor do they indicate the nature of the questions asked.

It is mentioned that employers, boards of agriculture, machine pools, neighbors and others were interviewed in order to elucidate possible exposures. The authors did not indicate how this information was used in the analysis, nor do they indicate whether it corroborated or contradicted information obtained from study subjects or next of kin.

The specific nature of the questionnaire mailed to study subjects is not provided. The authors feel the questionnaire masked its true intent, but it is unlikely that respondents knew or remembered which chemicals they were exposed to without some prodding on the part of the investigators. It is more probable, given the media attention to phenoxy herbicides and dioxin, that respondents were particularly alerted to questions about exposure to these chemicals.

Apart from whether or not the responses from cases and controls were obtained in an equally valid manner, is the rather vague nature of the exposure information. It is apparent that what this study is testing is not the risk associated with working with chlorophenols and phenoxy acids, but the risk associated with working in forestry and agriculture. These occupations are associated with exposure to a variety of physical, chemical and biological agents. It is impossible to single out one or even several of these agents as the cause of soft-tissue sarcoma based on the environmental data presented. The authors do not discuss the intensity or duration of exposure incurred by study participants nor do they discuss latency. Both of these factors made the conclusions drawn by Hardell in his earlier study incompatible with the relevant scientific literature on exposure to phenoxy acids and chlorophenols.

Statistical Methods

The statistical analysis employed is generally appropriate; however, the authors decided to dissolve the matching when it is generally recognized that more correct estimates of both risk and statistical significance are obtained when the analysis maintains the matching. The only motivation for dissolving the matching is the relatively simplified calculations which result.

Results

One control was excluded in the analysis stage and no justification for his exclusion was given. One could argue that the matched case and other control should have been dropped as well. The authors note the loss in efficiency resulting from dispersal of the matching (relative risk for matching retained = 5.1 versus relative risk for dissolved matching = 4.7), yet they drop the matching to simplify the analysis.

Table II presents exposure to phenoxy acids in cases and controls after exclusion of chlorophenols and dissolution of matching. The relative risk of 6.8 was statistically significant at a 95% confidence interval. The authors imply a dose-response relationship appeared in the division of the material, but to infer such a relationship is ludicrous. The difference between the exposure strata was one less control in the strata reporting exposure greater than 30 days.

Statistical significance was established for the risk associated with exposure to all of the herbicides analyzed. Although the relative risk associated with exposure to each of the agents was statistically greater than 1.0, this would tend to argue that the risk is associated with the occupations and not with any specific agent which could be singled out for analysis. The authors fail to see this logic and contend that exposure to all the agents examined resulted in an increased risk.

Table V provides evidence that the cases reported exposure to everything more often than did controls. This argues two points; one, the number of potentially harmful agents associated with working in forestry or agriculture precludes singling one or several agents out as the causative agent, and two, the cases were much more sensitive to questions concerning exposure and were more likely to report exposure to chemical agents than controls.

Discussion

It is apparent that either the living controls used were not checked against the National Cancer Register and excluded if they appeared, or that the Register is not a complete listing of cancer patients. The authors admit that a living control in fact had cancer,

and view their error as one of conservatism. If the Register is not a complete listing of cancer cases, one must question which factors influence the reporting of cases to the Register and how the distribution of this factor may differ amongst the cases and controls.

The authors state that, "No calculation of the risk for individual chemical controls other than phenoxy acids was considered meaningful since there were too few exposed cases and controls." One could argue that the paucity of subjects and controls exposed to other chemical pesticides is a direct result of an incomplete and incomparable effort to obtain information concerning exposure to other pesticides and other chemical agents.

The authors admit that it is conceivable that the cases attach more importance to questions concerning exposures than do the controls. They attempt to demonstrate that there was no distortion of the establishment of exposure to phenoxy acids with some questionable statistics in Table VII. The authors argue that if misreporting of exposure by cases were to occur, that this misreporting would occur independent of the persons' occupation. What is really at issue is whether or not cases within an occupational group recall specific exposures better than controls within the same occupational group. This requires a validity check on responses which is not provided in this study. Thus, the authors cannot assume that misreporting did not occur on the basis of the analysis they perform

Conclusion

Consistent findings across epidemiologic studies generally lend support to the findings; however, in this instance, since both studies were done by the same authors and therefore, probably replicated both the results and the errors in design, collection of data or analysis, little significance can be attributed to the consistency of the findings. Given there are several potential sources of bias in these studies and the validity of the exposure information is suspect, the association between soft-tissue sarcomas and prior occupational exposure to phenoxyacetic acids or chlorophenols suggested by this and the earlier study must be regarded suspiciously. Further studies of this association should address the plethora of exposure agents associated with the occupations (forestry and agriculture) which have been identified as being at an increased risk for soft-tissue sarcoma.

Perhaps a study design which is not case-control retrospective in nature, could be employed to obtain a better estimate of the risk associated with agricultural and forestry work. In any event, further studies must direct attention towards obtaining more complete and valid exposure data.

Gregory G. Bond, M.P.H.
Epidemiologist
U.S. Area Medical, H&ES

GGB/mp

References

1. T. Hardell, M. Eriksson, N. Berg, T. Moller and O. Axelson, 1979. Case-Control Study of Malignant Mesenchymal Soft-Tissue Tumors and Exposure to Chemical Substances. Submitted for publication.

2. T. Hardell, A. Sandstrom, 1979. Case Control Study: Soft-Tissue Sarcomas and Exposure to Phenoxyacetic Acids or Chlorophenols. British J. Cancer. 39:711-717.

3. Young, A.L., J.A. Calcagni, C.E. Thalken, J.W. Tremblay, 1978. The Toxicology, Environmental Fate, and Human Risk of Herbicide Orange and its Associated Dioxin. USAF OEHL Report TR-78-92.

M.S.D.S. DOCUMENTS LIST IN M.S.D.S. NUMBER SEQUENCE

MSDS #	LEVEL 70 CODE	PRODUCT NAME
0303	28745 maybe	ESTERON (R) 245 BRUSH AND WEED KILLER
0303	28750 Jun 75	ESTERON (R) 245 BRUSH AND WEED KILLER (PL & BULK)

DOW99223

MN066556

MSDS

27 Mar 72
01 Aug 76
01 apr 78
01 Jul 78
08 Jan 80

C0005783

DOW HEALTH AND ENVIRONMENTAL SCIENCES

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L. M. Wine KΣE

ESTERON 245, ESTERON Brush Killer and KURON have been approved for fencerows and industrial sites. Stamped labels are now on hand so packaging can proceed with the new labels.

FROM: MARGUERITE L. LENG
9008 Building
Phone (517) 636-3720

MN0729.93

DOW 21331180

8120

0008420

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DOW 212891

18 FEB 1980

Marguerite L. Leng, Ph.D.
Dow Chemical Company
P.O. Box 1706
Midland, MI 48640

Dear Dr. Leng:

Subject: Revised 2,4,5-T and Silvex Interim Amended Registration
for KURON LOW-VOLATILE BRUSH AND WEED HERBICIDE
EPA Registration No. 464-162
ESTERON BRUSH KILLER
EPA Registration No. 464-204
ESTERON 245 HERBICIDE
EPA Registration No. 464-205
Your letters of January 3, 1980, and January 21, 1980

The labeling referred to above, submitted in connection with registration under the Federal Insecticide, Fungicide and Rodenticide Act, as amended, is acceptable. A stamped copy is enclosed for your records.

Sincerely,

Willa Garner

Willa Y. Garner, Ph.D.
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (TS-767)

Enclosure: Stamped label

RECEIVED
FEB 15 1980
REGISTRATION

0001778

ACCEPTED
13 FEB 1980
Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide registered under E.P.A. Reg. No. 464-162

DOW

DOW212892

KUR

LOW-VOLATILE BRUSH AND

Contains Propylene Glycol Butyl E
Acid Equivalent: 4 pound

FOR THE CONTROL OF MANY WOODY
ANNUAL AND PERENNI

ACTIVE INGREDIENT:
Silvex, [2-(2,4,5-Trichlorophenoxy) propionic Acid]
Propylene Glycol (C_3H_6O to $C_9H_{18}O_3$) Butyl Ether Esters 69.2%
INERT INGREDIENTS: 30.8%
Silvex[2-(2,4,5-Trichlorophenoxy) propionic Acid]
Equivalent: 45.8%—4 pounds per gallon
E.P.A. Registration No. 464-162 E.P.A. Est. 464-MI-1

PRECAUCION AL USUARIO: Si usted no lee inglés, no use este producto hasta que la etiqueta le haya sido explicada ampliamente.
TRANSLATION: (TO THE USER: If you cannot read English, do not use this product until the label has been fully explained to you.)

HAR

18.93 L/5 g

86-1092 PRINTED IN U.S.A. IN JANUARY, 1980.
REPLACES SPECIMEN LABEL 86-1092 PRINTED IN SEPTEMBER, 1979.
DISCARD PREVIOUS SPECIMEN LABELS.
REVISIONS INCLUDE: USES ON INDUSTRIAL SITES AND FENCEROWS
REINSTATED BY EPA

8123

0001759

DOW

DOW212893

ESTE

BRUSH K

Low-Volatile Brush and

For the Control of Most Kinds of Unwanted Trees and Brush, as
on Rangelands, Fencerows, and Industrial Sites

ACTIVE INGREDIENTS:

2,4-Dichlorophenoxyacetic Acid, Propylene Glycol Butyl Ether Esters	36.0%
2,4,5-Trichlorophenoxyacetic Acid, Propylene Glycol Butyl Ether Esters	34.1%
INERT INGREDIENTS:	29.9%

2,4-D Acid Equivalent 22.2%—2 pounds per gallon
2,4,5-T Acid Equivalent 22.2%—2 pounds per gallon
E.P.A. Registration No. 464-204 E.P.A. Est. 464-MI-1

PRECAUCION AL USUARIO: Si usted no lee inglés, no use este producto hasta que la etiqueta le haya sido explicada ampliamente.
TRANSLATION: (TO THE USER: If you cannot read English, do not use this product until the label has been fully explained to you.)

18.93 L/5

86-1066 PRINTED IN U.S.A. IN JANUARY, 1980.
REPLACES SPECIMEN LABEL 86-1066 PRINTED IN SEPTEMBER, 1979.
DISCARD PREVIOUS SPECIMEN LABELS.
REVISIONS INCLUDE: USES ON INDUSTRIAL SITES AND FENCEROWS REINSTATED BY EPA.

0001786

DOW212894

ESTERO
HERBI

FOR THE CONTROL OF TREES, BR

Low-Volatile Brush and Weed Herbicide for Industr

ACTIVE INGREDIENT:

2,4,5-Trichlorophenoxyacetic Acid: Propylene Glycol Butyl Ether Esters	69.2%
INERT INGREDIENTS:	30.8%

2,4,5-Trichlorophenoxyacetic Acid Equivalent —45.0%
4 Pounds per Gallon

E.P.A. Registration No. 464-205 E.P.A. Est. 464-MI-1

PRECAUCION AL USUARIO: Si usted no lee ingles, no use este producto hasta que la etiqueta le haya sido explicada ampliamente.
TRANSLATION: (TO THE USER: If you cannot read English, do not use this product until the label has been fully explained to you.)

18.93 L

86-1064 PRINTED IN U.S.A. IN JANUARY, 1980.
REPLACES SPECIMEN LABEL 86-1064 PRINTED IN SEPTEMBER, 1979.
DISCARD PREVIOUS SPECIMEN LABELS.
REVISIONS INCLUDE: USES ON INDUSTRIAL SITES AND FENCEROWS REINSTATED BY EPA.

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NTP ASSIGNS MANAGERS FOR CHEMICALS IN TESTING SCHEDULE

Individuals, dubbed managers, are being designated by the National Toxicology Program to be responsible for individual chemicals, Dr. Richard Greisemer told two subgroups of the Clearinghouse on Environmental Carcinogens last week. The managers have met with interested personnel in other agencies to agree on objectives, clarify what needs to be done and design experiments. Some chemical selection is already in progress, Greisemer added.

Various selection processes span eight Federal agencies, he said, making it difficult to project progress for next year, since all the agencies have different needs. NTP will not test chemicals which it believes industry ought to test, he added. However, the agency will retest substances already tested by industry to review data or if the substance is high volume.

NTP's Board of Scientific Counselors met for the first time in January and formed three subcommittees: (1) to review chemical selection projects and evaluate ongoing activities; (2) to review data processing and management needs for test data management plans for automated data systems; and (3) a peer review of reports for release of data. In other organizational work, an office has been created to deal with industry and trade groups; it is headed by Dr. Thomas Cameron.

The government has sufficient lab facilities, Greisemer noted, since they were built in anticipation of the Toxic Substances Control Act and industry could build to meet its needs within a year; shortages do exist for toxicologists and industrial hygienists, however.

* * *

CALIFORNIA LAWSUITS CHALLENGE STATE PESTICIDE RULES

California's new pesticide rules are being challenged in court by both environmentalists and industry, one group charging that the state rules are not stringent enough and the latter group claiming that the standards conflict with Federal rules.

The suit filed by environmentalists, farm workers and labor officials claims that state laws based on Environmental Protection Agency standards underestimate the amount of hazardous substances present in foods in the state. Since Federal residue estimates are inaccurate, according to the suit, the state should enact more stringent rules to take the place of EPA laws.

Meanwhile, two trade groups and 13 agricultural chemical firms challenged the state's authority to register pesticides with the state since they already must be registered with EPA. The suit also attempts to prohibit the state from labeling pesticides, issuing permits, establishing lower tolerances than EPA and releasing trade secret data. Central to the industry lawsuit is whether individual states should be allowed to adopt differing pesticide regulatory programs preempted by the Federal EPA plan.

* * *

MONTANA WOMEN BLAME HERBICIDE 2,4-D FOR MISCARRIAGES

Out of 10 pregnant women in rural Condon, Montana, only one gave birth successfully in a 12-month period and residents are blaming the herbicide 2,4-D, which is used in the area to control weeds along roads. Nine women had miscarriages and the only successful birth was by a woman who had not lived in the area for most of her pregnancy.

County officials, however, claim that they have not used 2,4-D in the area where the 10 women live, although farmers in the area may be using the pesticide. The substance is used as an alternative to 2,4,5-T which was linked to miscarriages by Oregon women.

In interviews conducted by a county health nurse, it was noted that the victims and their families ate vegetables from their own gardens, drank milk from cows which grazed along roadsides and purchased their meat and dairy products from local producers.

Environmental Protection Agency recently approved the use of 2,4,-D for forest control in Oregon (TMN, Feb. 13, 1980, p. 55) claiming no significant impacts of its use.

7/6 2,4-D

Full Text

ENVIRONMENTAL PROTECTION AGENCY REVIEW AND CONCLUSIONS CONCERNING POTENTIAL HEALTH EFFECTS OF THE HERBICIDE 2,4-D

April 1980

2,4-D is one of the most widely used herbicides in the United States. There are approximately 1,500 products containing 2,4-D registered with EPA, and more than 70 million pounds of the active ingredient are distributed annually. The term "2,4-D" refers to the phenoxy herbicide 2,4-dichlorophenoxy acetic acid and its 35 derivative salt and ester forms. 2,4-D is used to control broadleaf weeds in a variety of places including home lawns, cereal and grain crops, commercial areas, commercial turf, rights-of-way, and forests.

Public concern about the potential adverse health effects of 2,4-D has intensified since the emergency suspension of 2,4,5-T and Silvex in March 1979. This concern stems primarily from (1) the chemical similarity of 2,4-D and 2,4,5-T as phenoxy herbicides, and (2) the question of 2,4-D dioxin-contamination, especially contamination with tetrachloro-dioxin, a manufacturing contaminant in 2,4,5-T, which causes cancer and miscarriages. Due to the chemical similarity of 2,4-D and 2,4,5-T, the public has expressed concern about the potential for cancer and miscarriages from the use of 2,4-D.

There is also concern because the controversial military defoliant Agent Orange, used in Viet Nam, was composed of 2,4,5-T and 2,4-D. Agent Orange was never registered by EPA for civilian use in the United States. Its use in Viet Nam by the U.S. military has resulted in claims of adverse health effects to American military personnel. The Veterans Administration is studying these claims.

Prompted by these concerns and EPA's need to resolve the questions surrounding the use of 2,4-D, the Agency initiated a review of the available information on the potential health effects of 2,4-D. This review was conducted in part to determine if the herbicide should be reviewed under the RPAR process (Rebuttable Presumption Against Registration) or if another regulatory action was appropriate.

II. *Agency Review and Conclusions*

Based on the results of this review, EPA has concluded that (a) the presently available information on the potential adverse health effects of 2,4-D does not support a regulatory action to remove 2,4-D products from the market; (b) information from scientifically valid studies does not indicate that the continued use of 2,4-D poses an imminent hazard or unreasonable adverse effect when used according to label precautions and direction for use; and c) the Agency should act quickly and vigorously to obtain better toxicological information on 2,4-D.

These conclusions are based on these following considerations:

1. There is no evidence available at this time that indicates 2,4-D contains any form of dioxin. This includes the tetrachloro-dioxin (TCDD), which is a manufacturing contaminant of 2,4,5-T and causes cancer and miscarriages.

TCDD is not theoretically expected to be found in 2,4-D. The manufacturing processes and starting chemicals from which 2,4-D and 2,4,5-T are made are not the same. Although other much less toxic dioxins are theoretically possible in 2,4,-D, they have not been found despite thorough chemical analyses.

2. Because products containing 2,4-D have been registered for use since the 1940's, most of the scientific data submitted to support the product registrations now on the market were developed many years ago. While some of these studies are scientifically valid, many others do not meet today's standards for scientific testing. As a result, there are significant information gaps in several areas including cancer-potential, reproductive effects, neurotoxicity, and metabolism in animals.

3. The studies most pertinent to the question of tumor-causing potential (oncogenicity) of 2,4-D were considered inadequate and inconclusive. No valid conclusions could be drawn one way or another from the data.

4. Almost all animal tests conducted on the potential reproductive effects of 2,4,-D show that, unlike 2,4,5-T with its contaminant TCDD, there is a no-effect level for injury to the fetus (fetotoxicity) from 2,4,-D. A no-effect level in animal studies is the dose level below the lowest dosage that produces observable adverse effects. At comparable dose levels, 2,4-D induces less serious fetotoxic effects than 2,4,5-T contaminated with TCDD.

In tests with rats, 2,4,5-T with its TCDD contamination caused resorptions of the fetus (dissolution of the unborn animal) at very low levels. This effect was virtually non-existent in rats fed 2,4-D at the same dose levels. Because of the significance of fetotoxic effects and because several of the reproductive tests on 2,4-D were found to be scientifically deficient, new tests will be needed before sound conclusions can be made.

5. The scientific evidence available at this time does not indicate the potential human exposure is sufficient to result in human health effects.

6. The most vigorous authority available to EPA under the pesticide law to fill information needs is a new section of FIFRA (Federal Insecticide Fungicide Rodenticide Act) passed in 1978. This provision, known as 3(c)(2)(B), allows EPA to request any additional data from pesticide registrants that is considered necessary to maintain the registration of existing products. The Agency can immediately require the manufacturer to develop the data where gaps exist. The registrants have 90 days to show that they are complying. Their product registrations may be summarily suspended if they fail to meet the Agency's conditions. No other action could obtain this information any faster.

EPA is putting the data requirements into final form and they will be issued to the registrants after review by our Scientific Advisory Panel. These scientific experts will review and comment on the data requirements to assure that they will provide the information EPA needs to more definitively answer the questions on potential health effects of 2,4-D.

7. Based on a review of the toxicology data (see section IV below), and a review of the risks of other pesticide chemicals now undergoing regulatory action, the Agency believes that the risks of several other pesticides are higher

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and better documented than those associated with 2,4-D. To put the review of these other higher priority chemicals aside in order to devote EPA resources to taking action against 2,4-D would not, in the Agency's opinion, best serve the public interest.

III. *Additional Actions*

In addition to requiring several important studies of the manufacturers on 2,4-D, EPA will also:

1. Conduct several tests on reproductive effects (through our Office of Research and Development) of several derivatives of 2,4-D in order to quickly get new information and have a good basis for comparison with the company-produced data.

2. Continue its ongoing review of forest pest control practices. This review will evaluate all chemical and non-chemical controls to identify the most environmentally protective ways to control forest pests. The Agency believes that a piecemeal approach to forest chemical regulation only leads to confusion, both to the industry and to the public. Unless we review the whole range of possible controls, examining one chemical at a time only gives rise to questions about the chemicals which would be used to replace those examined and prohibited from use.

3. Review all new data as it comes in to determine if a change in our regulatory posture is warranted. This includes evaluating the results of new animal tests as well as looking into reported incidents involving human exposure to the chemical.

4. Continue to support field tests to measure exposure to 2,4-D during the present growing season.

5. EPA is informing the Inter-Agency Work Group, established by the White House to study the possible long-term effects of Agent Orange, of the actions being taken. EPA will also share its scientific findings with this committee.

IV. *Toxicology Background*

The potential hazard of a chemical is usually measured in laboratory animal tests. Animals are given doses of a chemical over a specific time period. Scientists attempt to derive from most of these tests a "no observable effect level" (NOEL) — the dose level below the dosage where effects are first observed. From the animal tests and NOEL's, the potential effects on humans and other animals can be estimated. A set of brief definitions is provided below to permit better understanding of the subsequent discussion of toxicological findings.

A. *General terms*

1. *Acute oral toxicity (LD50)* — this test determines the dose level which produces death in half the test animals after a single oral dose (short-term test). Used to predict the near-term toxicity of the chemical immediately upon contact with people or other non-target animals.

2. *Chronic feeding tests* — animals are fed for most their life span (usually greater than 18 months in rodents) in order to determine the dose level which shows no toxic effect in test animals. This is the test from which the NOEL is (usually) derived.

3. *Oncogenicity testing* — animals fed relatively large doses of the test chemical for their life span (usually 18 months to 2 years in rodents) to try to induce tumors. These tests are used to predict whether the chemical may pose a cancer hazard.

4. *Reproductive testing* — these tests evaluate the effects of the chemical on the fertility of both the male and female parents by exposing the animals for a period of time before breeding. The tests also measure the possible effects of the chemical on the pregnant female and the fetuses through several generations. (The test with rodents through 3 generations runs approximately 14 months.)

5. *Teratology testing* — these tests evaluate the effects of the chemical on fetuses by exposing pregnant females during the short period of time that the fetus is most susceptible to congenital malformation. Teratogenic effects include cleft palate, central nervous system deformities, eye and limb deformities, and internal organ malfunction. These are considered to be life-threatening effects that put the animal at a disadvantage for surviving in its environment.

6. *Fetotoxicity* — fetotoxic effects can be seen in either the reproduction or teratology tests. Toxicity may be seen in the extreme form as fetal death or as less severe problems, such as delayed formation of bones, reduced body weights at birth, or edema (abnormal fluid accumulation in the tissue). Most fetotoxic effects appear to be reversible once exposure to the test chemical is curtailed. Therefore most fetotoxic effects are considered to be less serious than teratogenic effects, with the exception of fetal death.

B. *Summary of Toxicology Review*

Most of the data in EPA files on the potential health effects of 2,4-D are centered on the acid form, even though there are many derivatives, such as salts and esters. This is because the many forms of 2,4-D metabolize to the acid form in the environment and in the body. The discussion of animal data below, therefore, concerns the acid form of 2,4-D unless otherwise noted.

1. *Acute toxicity* — low to moderate. The potential for immediate poisonings from contact with the chemical is unlikely.

2. *Neurotoxicity* — There is little definitive information on the possible neurological effects of 2,4-D. In several reported cases of impaired nerve function, it was not known if the individuals were peculiarly sensitive to that type of effect or were exposed to other toxic materials.

3. *Reproductive effects* (effects on the unborn) — Tests have been conducted on rats, mice and hamsters to evaluate the possible reproductive effects of 2,4-D. In almost all tests, no observable effect level has been established. 2,4-D causes some of the less serious fetotoxic effects, such as edema (swelling of tissues) at the lower dose levels tested, and causes life-threatening birth defects (skeletal malformations) and cleft palates only at the very high levels tested.

Based on the no observable effect levels in the animal studies, EPA estimates that the level of exposure in a "worst case" situation (e.g., a person standing directly under a spray plane) would be 500 to 1000 times less than the dose level that might cause an effect.

Much of the data available to judge these effects was generated by old study protocols, has deficiencies in the test methods, and needs clarification by further study.

EPA also reviewed summaries of tests conducted in the Soviet Union which state that some derivatives of 2,4-D produced adverse effects on unborn animal fetuses at much lower levels than indicated by the data in EPA's files. These summaries could not be used in the Agency's review because the identity of the test material, and its impurities, was unclear, and because there were no numerical data to back up the summary conclusions. In some cases tests need to be done on specific derivatives of 2,4-D.

4. *Oncogenicity* (potential for causing tumors) — Several rodent studies have been conducted to date. The tests were conducted a decade ago and are considered to be inadequate and inconclusive by today's scientific standards. New studies on rodents are needed.

5. *Mutagenicity* (inheritable effects) — the vast majority of the mutagenicity studies conducted on 2,4-D are negative. However, there are three positive studies. Taken

as a group, the results of the studies can be described as inconsistent and inconclusive. A new series of tests being conducted by the Department of Health, Education, and Welfare will be reviewed by EPA when they are completed.

6. *Epidemiology* — No epidemiological studies of human health effects from 2,4-D exposure have been completed. However, EPA is currently investigating reports about alleged adverse effects from potential chemical exposure in several parts of the country. EPA will be looking at the results of those studies and will decide in the near future about additional field work.

V. *Exposure to 2,4-D*

There are at least three ways that the average citizen might come into contact with 2,4-D — through the diet, during home use, and drift of the herbicide from nearby use.

(a) *Diet*

The EPA has set tolerances for residues of 2,4-D in various food crops. The Food and Drug Administration (FDA) routinely samples a variety of foods (the Market Basket Survey) which FDA considers to be representative of the average American diet. Samples are analyzed for pesticide residues. During the period of 1974 to 1977, no 2,4-D residues were found in any of the products surveyed. However, during the 1965 to 1977 period, a variety of other food products were analyzed, of which about 1.1% were positive for 2,4-D in very minute quantities that were well below EPA's tolerance (allowable residue) levels.

(b) *Home use*

There are currently a number of registered home-use products which contain 2,4-D in a variety of formulations. Exposure to the herbicide in home-use situations will depend to some extent on the specific formulation used. If care is exercised by the homeowner in adhering to the directions for use and precautionary statement on the label, exposure to 2,4-D should be low.

(c) *Drift*

"Drift," the airborne transport of pesticide materials to a non-target area, is a common source of exposure. Sometimes, a pesticide will drift during application, depending on climatic conditions (temperature, wind speed), type of formulation used, terrain (forests, mountains), type of application method used (aerial, ground spray). Several States have imposed restrictions on 2,4-D use in order to cut down on drift potential.

Once on the ground or target crop, the herbicide may become airborne again by the process of vaporization. This particular type of drift has been the subject of intensive research by the producers of 2,4-D. Since the introduction of less volatile forms of the herbicide over the last few years, this kind of drift has become much less extensive. .

VI. *Environmental Persistence*

2,4-D is not a persistent pesticide. Breakdown of the herbicide begins almost immediately after application at a rate dependent on several environmental factors such as temperature, humidity and medium (air, soil, crop, water). The rate of loss (commonly referred to as the half-lie) is a measure of the time required for half of the substance to be degraded or lost.

On *sprayed vegetables*, the half-life varies from 1-3 weeks depending on geographic location, climatic conditions, vegetation type, application technique and formulation used.

In *soil*, the half-life varies from several days to 2 weeks, depending on acidity, soil type and amount of rain.

In *water*, the half-life varies from a few days to several months depending on factors such as oxygen concentration, acidity, light intensity, water temperature and formulation used.

CONGRESS

(For the Period April 23-30)

Senate Bills Introduced

April 24

RCRA — to amend the Solid Waste Disposal Act (the Resource Conservation and Recovery Act), S 2609, (Heinz) to Environment and Public Works.

House Committee Action

Interstate and Foreign Commerce, approved HR 7020, the Hazardous Waste Containment Act of 1980, April 30.

MEETINGS SCHEDULED

Government Institutes, Inc., environmental laws and regulation course, May 15-16, Washington, D.C. (Government Institutes, Inc., P.O. Box 5918, Washington, D.C. 20014, (301) 656-1090)

McGraw-Hill, conference on coping with Industry environmental costs, May 15-16, Arlington, Va. (McGraw-Hill Conference and Exposition Center, 1331 Ave. of the Americas, Room 3677, New York, N.Y., 10020.

Vanderbilt University, hazardous materials training course, May 19-23, Nashville, Tenn.; June 16-20, Seattle; July 28-August 1, Niagara Falls, N.Y. (Dr. R.D. Harbison, Vanderbilt Medical Center, Nashville, Tenn. 37232, (615) 322-4754).

Center for Energy and Environmental Management course on strategic planning for disposal of solid wastes, May 20-21, Chicago; June 2-3, Washington, D.C.; June 24-25, Pittsburgh; July 14-15, Denver (CEEM, P.O. Box 536, Fairfax, Va. 22030, (703) 250-5900).

CEEM, course on EPA's regulation of new chemical substances, May 22, Chicago; June 4, Washington, D.C.; June 26, Pittsburgh; July 16, Denver (CEEM, P.O. Box 536, Fairfax, Va. 22030, (703) 250-5900)

Cosmetic, Toiletry and Fragrance Association, Inc., seminars on regulatory and legislative issues relating to cosmetic manufacturers, May 22, Los Angeles; June 5, Deerfield Beach, Fla.; June 12, Rye, N.Y. (Margaret Smith or Debbie Alexander, CTFA, 1133 15th St., N.W., Washington, D.C. 20005, (202) 331-1770)

The Institute for Applied Pharmaceutical Sciences course on good clinical practices, May 22-23, East Brunswick, N.J. (Edith Webb, Registrar, P.O. Box 964, E. Brunswick, N.J. 08816, (201) 248-1400)

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2,4-D FACT SHEET

I. Background

2,4-D is one of the most widely used herbicides in the United States. There are approximately 1,500 products containing 2,4-D registered with EPA, and more than 70 million pounds of the active ingredient are distributed annually. The term "2,4-D" refers to the phenoxy herbicide 2,4-dichlorophenoxy acetic acid and its 35 derivative salt and ester forms. 2,4-D is used to control broadleaf weeds in a variety of places including home lawns, cereal and grain crops, commercial areas, commercial turf, rights-of-way, and forests.

Public concern about the potential adverse health effects of 2,4-D has intensified since the emergency suspension of 2,4,5-T and Silvex in March 1979. This concern stems primarily from 1) the chemical similarity of 2,4-D and 2,4,5-T as phenoxy herbicides, and 2) the question of 2,4-D dioxin-contamination, especially contamination with tetrachlorodioxin, a manufacturing contaminant in 2,4,5-T, which causes cancer and miscarriages. Due to the chemical similarity of 2,4-D and 2,4,5-T, the public has expressed concern about the potential for cancer and miscarriages from the use of 2,4-D. There is also concern because the controversial military defoliant Agent Orange, used in Viet Nam, was composed of 2,4,5-T and 2,4-D. Agent Orange was never registered by EPA for civilian use in the United States. Its use in Viet Nam by the U.S. military has resulted in claims of adverse health effects to American military personnel. The Veterans Administration is studying these claims.

Prompted by these concerns and EPA's need to resolve the questions surrounding the use of 2,4-D, the Agency initiated a review of the available information on the potential health effects of 2,4-D. This review was conducted in part to determine if the herbicide should be reviewed under the RPAR process (Rebuttable Presumption Against Registration) or if another regulatory action was appropriate.

II. Agency Review and Conclusions

Based on the results of this review, EPA has concluded that a) the presently available information on the potential adverse health effects of 2,4-D does not support a regulatory action to remove 2,4-D products from the market; b) information from scientifically valid studies does not indicate that the continued use of 2,4-D poses an imminent hazard or unreasonable adverse effect when used according to label precautions and direction for use; and c) the Agency should act quickly and vigorously to obtain better toxicological information on 2,4-D.

These conclusions are based on these following considerations:

1. There is no evidence available at this time that indicates 2,4-D contains any form of dioxin. This includes the tetrachloro-dioxin (TCDD), which is a manufacturing contaminant of 2,4,5-T and causes cancer and miscarriages.

TCDD is not theoretically expected to be found in 2,4-D. The manufacturing processes and starting chemicals from which 2,4-D and 2,4,5-T are made are not the same. Although other much less toxic dioxins are theoretically possible in 2,4-D, they have not been found despite thorough chemical analyses.

2. Because products containing 2,4-D have been registered for use since the 1940's, most of the scientific data submitted to support the product registrations now on the market were developed many years ago. While some of these studies are scientifically valid, many others do not meet today's standards for scientific testing. As a result, there are significant information gaps in several areas including cancer-potential, reproductive effects, neurotoxicity, and metabolism in animals.

3. The studies most pertinent to the question of tumor-causing potential (oncogenicity) of 2,4-D were considered inadequate and inconclusive. No valid conclusions could be drawn one way or another from the data.

4. Almost all animal tests conducted on the potential reproductive effects of 2,4-D show that, unlike 2,4,5-T with its contaminant TCDD, there is a no-effect level for injury to the fetus (fetotoxicity) from 2,4-D. A no-effect level in animal studies is the dose level below the lowest dosage that produces observable adverse effects. At comparable dose levels, 2,4-D induces less serious fetotoxic effects than 2,4,5-T contaminated with TCDD.

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In tests with rats, 2,4,5-T with its TCDD contamination caused resorptions of the fetus (dissolution of the unborn animal) at very low levels. This effect was virtually non-existent in rats fed 2,4-D at the same dose levels. Because of the significance of fetotoxic effects and because several of the reproductive tests on 2,4-D were found to be scientifically deficient, new tests will be needed before sound conclusion can be made.

5. The scientific evidence available at this time does not indicate the potential human exposure is sufficient to result in human health effects.

6. The most vigorous authority available to EPA under the pesticide law to fill information needs is a new section of FIFRA (Federal Insecticide Fungicide Rodenticide Act) passed in 1978. This provision, known as 3(c)(2)(B), allows EPA to request any additional data from pesticide registrants that is considered necessary to maintain the registration of existing products. The Agency can immediately require the manufacturers to develop the data where gaps exist. The registrants have 90 days to show that they are complying. Their product registrations may be summarily suspended if they fail to meet the Agency's conditions. No other action could obtain this information any faster. EPA is putting the data requirements into final form and they will be issued to the registrants after review by our Scientific Advisory Panel. These scientific experts will review and comment on the data requirements to assure that they will provide the information EPA needs to more definitively answer the questions on potential health effects of 2,4-D.

7. Based on a review of the toxicology data (see section IV below), and a review of the risks of other pesticide chemicals now undergoing regulatory action, the Agency believes that the risks of several other pesticides are higher and better documented than those associated with 2,4-D. To put the review of these other higher priority chemicals aside in order to devote EPA resources to taking action against 2,4-D would not, in the Agency's opinion, best serve the public interest.

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III. Additional Actions

In addition to requiring several important studies of the manufacturers on 2,4-D, EPA will also:

1. Conduct several tests on reproductive effects (through our Office of Research and Development) of several derivatives of 2,4-D in order to quickly get new information and have a good basis for comparison with the company-produced data.

2. Continue its ongoing review of forest pest control practices. This review will evaluate all chemical and non-chemical controls to identify the most environmentally protective ways to control forest pests. The Agency believes that a piecemeal approach to forest chemical regulation only leads to confusion, both to the industry and to the public. Unless we review the whole range of possible controls, examining one chemical at a time only gives rise to questions about the chemicals which would be used to replace those examined and prohibited from use.

8135

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5. EPA is informing the Inter-Agency Work Group, established by the White House to study the possible long-term effects of Agent Orange, of the actions being taken. EPA will also share its scientific findings with this committee.

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The potential hazard of a chemical is usually measured in laboratory animal tests. Animals are given doses of a chemical over a specific time period. Scientists attempt to derive from most of these tests a "no observable effect level" (NOEL) -- the dose level below the dosage where effects are first observed. From the animal tests and NOEL's, the potential effects on humans and other animals can be estimated. A set of brief definitions is provided below to permit better understanding of the subsequent discussion of toxicological findings.

A. General terms

1. Acute oral toxicity (LD50) - this test determines the dose level which produces death in half the test animals after a single oral dose (short-term test). Used to predict the near-term toxicity of the chemical immediately upon contact with people or other non-target animals.

2. Chronic feeding tests - animals are fed for most their life span (usually greater than 18 months in rodents) in order to determine the dose level which shows no toxic effect in test animals. This is the test from which the NOEL is (usually) derived.

3. Oncogenicity testing - animals fed relatively large doses of the test chemical for their life span (usually 18 months to 2 years in rodents) to try to induce tumors. These tests are used to predict whether the chemical may pose a cancer hazard.

4. Reproductive testing - these tests evaluate the effects of the chemical on the fertility of both the male and female parents by exposing the animals for a period of time before breeding. The tests also measure the possible effects of the chemical on the pregnant female and the fetuses through several generations. (The test with rodents through 3 generations runs approximately 14 months.)

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6. Fetotoxicity - fetotoxic effects can be seen in either the reproduction or teratology tests. Toxicity may be seen in the extreme form as fetal death or as less severe problems, such as delayed formation of bones, reduced body weights at birth, or edema (abnormal fluid accumulation in the tissue). Most fetotoxic effects appear to be reversible once exposure to the test chemical is curtailed. Therefore most fetotoxic effects are considered to be less serious than teratogenic effects, with the exception of fetal death.

B. Summary of Toxicology Review

Most of the data in EPA files on the potential health effects of 2,4-D are centered on the acid form, even though there are many derivatives, such as salts and esters. This is because the many forms of 2,4-D metabolize to the acid form in the environment and in the body. The discussion of animal data below, therefore, concerns the acid form of 2,4-D unless otherwise noted.

1. Acute toxicity - low to moderate. The potential for immediate poisonings from contact with the chemical is unlikely.

2. Neurotoxicity - There is little definitive information on the possible neurological effects of 2,4-D. In several reported cases of impaired nerve function, it was not known if the individuals were peculiarly sensitive to that type of effect or were exposed to other toxic materials.

3. Reproductive effects (effects on the unborn) - Tests have been conducted on rats, mice and hamsters to evaluate the possible reproductive effects of 2,4-D. In almost all tests, a NOEL has been established. 2,4-D causes some of the less serious fetotoxic effects, such as edema (swelling of tissues) at the lower dose levels tested, and causes life-threatening birth defects (skeletal malformations) and cleft palates only at the very high levels tested.

Based on the NOELs in the animal studies, EPA estimates that the level of exposure in a "worst case" situation (eg. a person standing directly under a spray plane) would be 500 to 1000 times less than the dose level that might cause an effect.

Much of the data available to judge these effects was generated by old study protocols, has deficiencies in the test methods, and needs clarification by further study.

EPA also reviewed summaries of tests conducted in Russia which state that some derivatives of 2,4-D produced adverse effects on unborn animal fetuses at much lower levels than indicated by the data in EPA's files. These summaries could not be used in the Agency's review because the identity of the test material, and its impurities, was unclear, and because there were no numerical data to back up the summary conclusions. In some cases tests need to be done on specific derivatives of 2,4-D.

3. Oncogenicity (potential for causing tumors) - Several rodent studies have been conducted to date, but none of these studies produced data that showed 2,4-D was oncogenic in test animals. The tests were conducted a decade ago and are considered to be inadequte by today's scientific standards. New studies on rodents are needed.

4. Mutagenicity (inheritable effects) - The vast majority of the mutagenicity studies conducted on 2,4-D are negative. However, there are three positive studies. Taken as a group, the results of the studies can best be described as inconsistent and inconclusive. A new series of tests being conducted by the Department of Health, Education, and Welfare will be reviewed by EPA when they are completed.

5. Epidemiology - No epidemiological studies of human health effects from 2,4-D exposure have been completed. However, EPA is currenlty investigating reports about alleged adverse effects from potential chemical exposure in several parts of the country. EPA will be looking at the results of those studies and will decide in the near future about additional field work.

V. Exposure to 2,4-D

There are at least three ways that the average citizens might come into contact with 2,4-D - through the diet, during home use, and drift of the herbicide from nearby use.

a) Diet

The EPA has set tolerances for residues of 2,4-D in various food crops. The Food and Drug Administration (FDA) routinely samples a variety of foods (the Market Basket Survey) which FDA considers to be representative of the average American diet. Samples are analyzed for pesticide residues. During the period of 1974 to 1977, no 2,4-D residues were found in any of the products surveyed. However, during the 1965 to 1977 period, a variety of other food products were analyzed, of which about 1.1% were positive for 2,4-D in very minute quantities that were well below EPA's tolerance (allowable residue) levels.

b) Home use

There are currently a number of registered home-use products which contain 2,4-D in a variety of formulations. Exposure to the herbicide in home-use situations will depend to some extent on the specific formulation used. If care is exercised by the homeowner in adhering to the directions for use and precautionary statement on the label, exposure to 2,4-D should be low.

c) Drift

"Drift", the airborne transport of pesticide materials to a non-target area, is a common source of exposure. Sometimes, a pesticide will drift during application, depending on climatic conditions (temperature, wind speed), type of formulation used, terrain (forests, mountains), and type of application method used (aerial, ground spray). Several States have imposed restrictions on 2,4-D use in order to cut down on drift potential.

Once on the ground or target crop, the herbicide may become airborne again by the process of vaporization. This particular type of drift has been the subject of intensive research by the producers of 2,4-D. Since the introduction of less volatile forms of the herbicide over the last few years, this kind of drift has become much less extensive.

VI. Environmental Persistence

2,4-D is not a persistent pesticide. Breakdown of the herbicide begins almost immediately after application at a rate dependent on several environmental factors such as temperature, humidity and medium (air, soil, crop, water). The rate of loss (commonly referred to as the half-life) is a measure of the time required for half of the substance to be degraded or lost.

On sprayed vegetables, the half-life varies from 1-3 weeks depending on geographic location, climatic conditions, vegetation type, application technique and formulation used.

In soil, the half-life varies from several days to 2 weeks, depending on acidity, soil type and amount of rain.

In water, the half-life varies from a few days to several months depending on factors such as oxygen concentration, acidity, light intesity, water temperature and formulation used.

April 22, 1980

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2,4-D FACT SHEET

I. Background

2,4-D is one of the most widely used herbicides in the United States. There are approximately 1,500 products containing 2,4-D registered with EPA, and more than 70 million pounds of the active ingredient are distributed annually. The term "2,4-D" refers to the phenoxy herbicide 2,4-dichlorophenoxy acetic acid and its 35 derivative salt and ester forms. 2,4-D is used to control broadleaf weeds in a variety of places including home lawns, cereal and grain crops, commercial areas, commercial turf, rights-of-way, and forests.

Public concern about the potential adverse health effects of 2,4-D has intensified since the emergency suspension of 2,4,5-T and Silvex in March 1979. This concern stems primarily from 1) the chemical similarity of 2,4-D and 2,4,5-T as phenoxy herbicides, and 2) the question of 2,4-D dioxin-contamination, especially contamination with tetrachlorodioxin, a manufacturing contaminant in 2,4,5-T, which causes cancer and miscarriages. Due to the chemical similarity of 2,4-D and 2,4,5-T, the public has expressed concern about the potential for cancer and miscarriages from the use of 2,4-D. There is also concern because the controversial military defoliant Agent Orange, used in Viet Nam, was composed of 2,4,5-T and 2,4-D. Agent Orange was never registered by EPA for civilian use in the United States. Its use in Viet Nam by the U.S. military has resulted in claims of adverse health effects to American military personnel. The Veterans Administration is studying these claims.

Prompted by these concerns and EPA's need to resolve the questions surrounding the use of 2,4-D, the Agency initiated a review of the available information on the potential health effects of 2,4-D. This review was conducted in part to determine if the herbicide should be reviewed under the RPAR process (Rebuttable Presumption Against Registration) or if another regulatory action was appropriate.

II. Agency Review and Conclusions

Based on the results of this review, EPA has concluded that a) the presently available information on the potential adverse health effects of 2,4-D does not support a regulatory action to remove 2,4-D products from the market; b) information from scientifically valid studies does not indicate that the continued use of 2,4-D poses an imminent hazard or unreasonable adverse effect when used according to label precautions and direction for use; and c) the Agency should act quickly and vigorously to obtain better toxicological information on 2,4-D.

These conclusions are based on these following considerations:

1. There is no evidence available at this time that indicates 2,4-D contains any form of dioxin. This includes the tetrachloro-dioxin (TCDD), which is a manufacturing contaminant of 2,4,5-T and causes cancer and miscarriages.

TCDD is not theoretically expected to be found in 2,4-D. The manufacturing processes and starting chemicals from which 2,4-D and 2,4,5-T are made are not the same. Although other much less toxic dioxins are theoretically possible in 2,4-D, they have not been found despite thorough chemical analyses.

2. Because products containing 2,4-D have been registered for use since the 1940's, most of the scientific data submitted to support the product registrations now on the market were developed many years ago. While some of these studies are scientifically valid, many others do not meet today's standards for scientific testing. As a result, there are significant information gaps in several areas including cancer-potential, reproductive effects, neurotoxicity, and metabolism in animals.

3. The studies most pertinent to the question of tumor-causing potential (oncogenicity) of 2,4-D were considered inadequate and inconclusive. No valid conclusions could be drawn one way or another from the data.

4. Animal tests conducted on the potential reproductive effects of 2,4-D show that, unlike 2,4,5-T with its contaminant TCDD, severe life-threatening effects were generally absent from 2,4-D treatments at moderate or high doses. However, new tests will need to be conducted at lower doses to clearly establish no-effects levels. In comparison, TCDD, which is present in 2,4,5-T and not in 2,4-D, produces serious life-threatening effects on the fetus at minute doses including the lowest dose tested in many studies.

5. The scientific evidence available at this time does not indicate the potential human exposure is sufficient to result in human health effects.

6. The most vigorous authority available to EPA under the pesticide law to fill information needs is a new section of FIFRA (Federal Insecticide Fungicide Rodenticide Act) passed in 1978. This provision, known as 3(c)(2)(B), allows EPA to request any additional data from pesticide registrants that is considered necessary to maintain the registration of existing products. The Agency can immediately require the

manufacturers to develop the data where gaps exist. The registrants have 90 days to show that they are complying. Their product registrations may be summarily suspended if they fail to meet the Agency's conditions. No other action could obtain this information any faster. EPA is putting the data requirements into final form and they will be issued to the registrants after review by our Scientific Advisory Panel. These scientific experts will review and comment on the data requirements to assure that they will provide the information EPA needs to more definitively answer the questions on potential health effects of 2,4-D.

7. Based on a review of the toxicology data (see section IV below), and a review of the risks of other pesticide chemicals now undergoing regulatory action, the Agency believes that the risks of several other pesticides are higher and better documented than those associated with 2,4-D. To put the review of these other higher priority chemicals aside in order to devote EPA resources to taking action against 2,4-D would not, in the Agency's opinion, best serve the public interest.

III. Additional Actions

In addition to requiring several important studies of the manufacturers on 2,4-D, EPA will also:

1. Conduct several tests on reproductive effects (through our Office of Research and Development) of several derivatives of 2,4-D in order to quickly get new information and have a good basis for comparison with the company-produced data.

2. Continue its ongoing review of forest pest control practices. This review will evaluate all chemical and non-chemical controls to identify the most environmentally protective ways to control forest pests. The Agency believes that a piecemeal approach to forest chemical regulation only leads to confusion, both to the industry and to the public. Unless we review the whole range of possible controls, examining one chemical at a time only gives rise to questions about the chemicals which would be used to replace those examined and prohibited from use.

3. Review all new data as it comes in to determine if a change in our regulatory posture is warranted. This includes evaluating the results of new animal tests as well as looking into reported incidents involving human exposure to the chemical.

4. Continue to support field tests to measure exposure to 2,4-D during the present growing season.

5. EPA is informing the Inter-Agency Work Group, established by the White House to study the possible long-term effects of Agent Orange, of the actions being taken. EPA will also share its scientific findings with this committee.

IV. Toxicology Background

The potential hazard of a chemical is usually measured in laboratory animal tests. Animals are given doses of a chemical over a specific time period. Scientists attempt to derive from most of these tests a "no observable effect level" (NOEL) -- the dose level below the dosage where effects are first observed. From the animal tests and NOEL's, the potential effects on humans and other animals can be estimated. A set of brief definitions is provided below to permit better understanding of the subsequent discussion of toxicological findings.

A. General terms

1. Acute oral toxicity (LD50) - this test determines the dose level which produces death in half the test animals after a single oral dose (short-term test). Used to predict the near-term toxicity of the chemical immediately upon contact with people or other non-target animals.

2. Chronic feeding tests - animals are fed for most their life span (usually greater than 18 months in rodents) in order to determine the dose level which shows no toxic effect in test animals. This is the test from which the NOEL is (usually) derived.

3. Oncogenicity testing - animals fed relatively large doses of the test chemical for their life span (usually 18 months to 2 years in rodents) to try to induce tumors. These tests are used to predict whether the chemical may pose a cancer hazard.

4. Reproductive testing - these tests evaluate the effects of the chemical on the fertility of both the male and female parents by exposing the animals for a period of time before breeding. The tests also measure the possible effects of the chemical on the pregnant female and the fetuses through several generations. (The test with rodents through 3 generations runs approximately 14 months.)

5. Teratology testing - these tests evaluate the effects of the chemical on fetuses by exposing pregnant females during the short period of time that the fetus is most susceptible to congenital malformation. Teratogenic effects include cleft palate, central nervous system deformities, eye and limb deformities, and internal organ malfunction. These are considered to be life-threatening effects that put the animal at a disadvantage for surviving in its environment.

6. Fetotoxicity - fetotoxic effects can be seen in either the reproduction or teratology tests. Toxicity may be seen in the extreme form as fetal death or as less severe problems, such as delayed formation of bones, reduced body weights at birth, or edema (abnormal fluid accumulation in the tissue). Most fetotoxic effects appear to be reversible once exposure to the test chemical is curtailed. Therefore most fetotoxic effects are considered to be less serious than teratogenic effects, with the exception of fetal death.

B. Summary of Toxicology Review

Most of the data in EPA files on the potential health effects of 2,4-D are centered on the acid form, even though there are many derivatives, such as salts and esters. This is because the many forms of 2,4-D metabolize to the acid form in the environment and in the body. The discussion of animal data below, therefore, concerns the acid form of 2,4-D unless otherwise noted.

1. Acute toxicity - low to moderate. The potential for immediate poisonings from contact with the chemical is unlikely.

2. Neurotoxicity - There is little definitive information on the possible neurological effects of 2,4-D. In several reported cases of impaired nerve function, it was not known if the individuals were peculiarly sensitive to that type of effect or were exposed to other toxic materials.

3. Reproductive effects (effects on the unborn) - Tests have been conducted on rats, mice and hamsters to evaluate the possible reproductive effects of 2,4-D. 2,4-D causes some of the less serious fetotoxic effects, such as edema (swelling of tissues) at the lower dose levels tested, and causes life-threatening birth defects (skeletal malformations) and cleft palates only at the very high levels tested.

Based on available animal studies, EPA estimates that the level of exposure in a "worst case" situation (eg. a person standing directly under a spray plane) would be 500 to 1000 times less than the dose level that might cause an effect.

Much of the data available to judge these effects was generated by old study protocols, has deficiencies in the test methods, and needs clarification by further study.

EPA also reviewed summaries of tests conducted in Russia which state that some derivatives of 2,4-D produced adverse effects on unborn animal fetuses at much lower levels than indicated by the data in EPA's files. These summaries could not be used in the Agency's review because the identity of the test material, and its impurities, was unclear, and because there were no numerical data to back up the summary conclusions. In some cases tests need to be done on specific derivatives of 2,4-D.

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6. Epidemiology - No epidemiological studies of human health effects from 2,4-D exposure have been completed. However, EPA is currenlty investigating reports about alleged adverse effects from potential chemical exposure in several parts of the country. EPA will be looking at the results of those studies and will decide in the near future about additional field work.

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c) Drift

"Drift", the airborne transport of pesticide materials to a non-target area, is a common source of exposure. Sometimes, a pesticide will drift during application, depending on climatic conditions (temperature, wind speed), type of formulation used, terrain (forests, mountains), and type of application method used (aerial, ground spray). Several States have imposed restrictions on 2,4-D use in order to cut down on drift potential.

Once on the ground or target crop, the herbicide may become airborne again by the process of vaporization. This particular type of drift has been the subject of intensive research by the producers of 2,4-D. Since the introduction of less volatile forms of the herbicide over the last few years, this kind of drift has become much less extensive.

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In water, the half-life varies from a few days to several months depending on factors such as oxygen concentration, acidity, light intesity, water temperature and formulation used.

April 22, 1980

IONS & ROUTING:

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Unless critical leave effective date blank
Systems by QA Office. This will be don

One person may sign for both Mark
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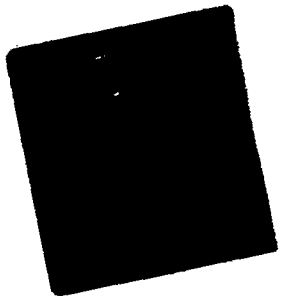

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2. To be completed by the Corporate Product Department. QA Office
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Record any objections to discontinuation.

Self-explanatory.

Names to be provided and notifications accomplished by Originator in the originating area.

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sponsibility of notification of discontinuation on receipt of completed form.

DOW CONFIDENTIAL INFORMATION

R & D REPORT

DOW CHEMICAL U.S.A.

R&D REPORTS SHOULD REMAIN ON THE PREMISES OF THE DOW CHEMICAL COMPANY

CRI NUMBER: K-66681-(40)
LABORATORY REPORT CODE: HET K-66681-(40)
DATE ISSUED: May 30, 1980
CRI

DEPARTMENT: TOXICOLOGY RESEARCH LABORATORY
LAB. NO. | PROBLEM NO.

TITLE: 2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN: ACUTE ORAL TOXICITY IN HAMSTERS

21 PAGES IN FULL REPORT

CRI NUMBER

AUTHOR(S): J. W. Henck, M. A. New and R. J. Kociba

AUTHOR(S) SIGNATURE(S): J. W. Henck 6/18/80 M. A. New 6/18/80 R. J. Kociba 6/19/80

REVIEWER'S SIGNATURE: K. J. Olson and K. S. Rao K. S. Rao 6/19/80

This report is: [ ] INTERIM [X] FINAL and mainly: [X] NEW [ ] REVIEW

8029R

DESCRIPTIVE SUMMARY WITH CONCLUSIONS:

The acute oral toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was evaluated in hamsters. Male hamsters (Engle Laboratory Animals, Inc., Farmersburg, Indiana) weighing 70-120g received 0 (corn oil only), 300, 600, 1000, 3000 or 6000 µg TCDD/kg body weight by single-dose oral gavage. To facilitate dosage, TCDD was fed as a 0.06% or a 0.16% suspension in acetone/corn oil (1:9). All hamsters were maintained for observation at least 55 days following dosage.

The 55-day single-dose oral LD_{50} was calculated by the moving average method of analysis to be 5051 µg (3878-18,487 µg/kg, 95% confidence interval). Initially, no hamsters exhibited adverse effects related to dosage with TCDD. However, 4-5 weeks following dosage, hamsters of the 1000, 3000 and 6000 µg/kg dose groups began to develop unkempt hair coats. A dose-related depression of mean body weight when compared to control weights was observed in hamsters of the 1000, 3000 and 6000 µg/kg dose groups by 3 weeks post-treatment.

At the termination of the study, all surviving hamsters were subjected to a gross pathologic examination. The following lesions were observed in hamsters dosed initially with 0, 300, 600, 1000 or 3000 µg/kg: a slight decrease in abdominal adipose tissue (300, 600 and 3000 µg/kg dose groups), a slight decrease in thymus size (600-3000 µg/kg dose groups), and sporadic instances of liver lesions (600 and 3000 µg/kg dose groups). Hamsters were dosed at a later date with 0, 1000, 3000 or 6000 µg/kg. One hamster of the 1000 µg/kg dose group exhibited pale, coalescing areas in the liver, all other lesions observed in the hamsters of this second group were felt to be spontaneous in nature and unrelated to treatment with TCDD. The hamsters dosed initially were subjected to a gross necropsy 16 days after the hamsters of the second group. It is possible that this 16-day time

DOW 2111697

8154

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FORM C-4300 PRINTED R-3-80

interval was sufficient for lesions to begin to develop; this may explain why no lesions were observed in hamsters of the 6000 µg/kg dose groups.

THE DOW CHEMICAL COMPANY

POST OFFICE BOX 1706
MIDLAND, MICHIGAN 48640

June 2, 1980

bcc: D. M. Frederick
M. L. Leng
A. J. Watson
Action File: 2,4,5-T, ESTERON 245

Mr. James M. Stone
Product Manager 23
Registration Division (TS-767)
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

DOW 2520593
MN061593

Dear Mr. Stone:

Subject: ESTERON* 245
EPA Registration No. 464-205
Application for Amended Registration

The accompanying application concerning the subject product is largely self-explanatory. Basically, we propose reinstatement of the foliage treatment inadvertently deleted from the label at the time of our initial compliance with the March 22, 1979 suspension order. In addition, some minor text changes are proposed to improve flow and/or clarity of the existing wording.

We believe that this application complies with the compensation exemptions cited under 40 CFR 162.9-1(b)(7), (b)(9), and (b)(17); consequently, an Offer-to-Pay and Certification Statment have not been included.

Your earliest possible consideration and approval of this application will be appreciated.

Sincerely,

Robert W. Morgan
Registration Supervisor
Product Registrations
Regulatory and Legislative Issues
Health and Environmental Sciences

er

Attachment

8157

0001826

*Trademark of The Dow Chemical Company

**** DOW CONFIDENTIAL **** 28750

THE DOW CHEMICAL COMPANY QUALITY ASSURANCE OFFICE

QACACI SPECIFICATION CONFIRMATION COPY

DATE PRINTED: 5 JUN 80 PAGE: 1

PRODUCT: 28750 QAC: 290 REVIEWED: 2 JUN 80 REPLACES: 28750 19 FEB 80

NAME: OBSOLETE - ESTERON (R) 245 BRUSH AND WEED KILLER (PL & BULK)

DESC: AMBER, OILY, EMULSIFIABLE LIQUID. PRODUCT NO LONGER PRODUCED AND DECLARED OBSOLETE 2 JUN 80.

MSD: 303

PROD'N PTS U.S. :MM DEPT:31

	PROD'N	DATA	TERM'L	RAW MAT'L	SALES	TEST METHOD
DATES :						
LATEST:	4 JUN 79					
PRIOR :	9 JAN 76					

PROD'N NOTE
PRODUCT DECLARED OBSOLETE 2 JUN 80.

RAW MAT'L NOTE
PRODUCT DECLARED OBSOLETE 2 JUN 80.

SALES NOTE
PRODUCT DECLARED OBSOLETE 2 JUN 80.

TERMINAL NOTE
PRODUCT DECLARED OBSOLETE 2 JUN 80.

APPROVERS: W.L. GOLD
J.M. FRASER

APPROVAL OF CHANGES INDICATED ABOVE:

APPROVERS OF INDIVIDUAL SPECS:
PRODN:
SALES:
RAW M:
TERML:

APPROVALS	DIV-DEPT	DATE	APPROVALS	DIV-DEPT	DATE

(R) INDICATES A REGISTERED OR TRADEMARK NAME OF THE DOW CHEMICAL CO.

**** DOW CONFIDENTIAL **** LAST PAGE

8159

0007491

MEDICAL INFORMATION

MATERIAL: ESTERON 245 BRUSH AND WEED KILLER — MATERIAL NO: [illegible]
SYNONYMS: M-3506 — SOLUBILITY: Emulsifiable in wat
COMPOSITION: SEE BACK * — PHYSICAL STATE: Liquid

TOXICOLOGY — ANTICIPATED HUMAN RESPONSE — BASED ON: 1 ANIMAL DATA 2 HUMAN DATA 3 STRUCTU 4 LITERATU

EYES: Slight to moderate pain, slight transient conjunctival inflammation and iritis.

SKIN: Prolonged contact, intact skin, unconfined: slight erythema. Repeated skin contact slight to moderate erythema and edema. Skin absorption capacity not evaluated (Based on minimal tox study).

ORAL: Moderate to low acute oral lethality (LD50 rats approx. 1 g/kg body weight. (Based on minimal tox study).

RESP. One hour exposure of 20 rats to an aerosol of M-3506 resulted in no adverse effects.

DOW 0899067

BY	DATE	REFERENCE
Pat Keeler	6-24-80 *Revised	

SUGGESTED — TREATMENT AND HUMAN EXPERIENCE

EYES: Stain for evidence of corneal abrasion or injury.

SKIN:

RESP.

NOTICE: POOR COPY DUE TO DEFICIENT ORIGINAL

ORAL: May cause reaction similar to petroleum or petroleum-like solvent. Product moderately toxic. Danger of chemical pneumonia must be weighed against toxicity. If lavage is performed suggest endotracheal and/or esophagoscopic control.

SYSTEMIC: Human effects not established. Probably could cause serious illness with spontaneous recovery. Based on minimal data.

BY	DATE	REFERENCE
J.M. Lanham	10-30-78	

SUGGESTED FIRST AID PROCEDURES

EYES: Irrigate with flowing water immediately and continuously for fifteen minutes. Refer to medical personnel.

SKIN: Wash off in flowing water. Decontaminate clothing and accessories before reuse. Good personal hygiene.

[illegible]: Remove to fresh air if effects occur. Consult medical personnel.

[illegible]: Do not induce vomiting. Call a physician and [illegible] facility.

8161 0000913

J.M. Lanham 10-30-78

1954

8162

1954

COMPOSITION

69.2 % 2,4,5-trichlorophenoxyacetic acid PGBE Esters
 0.9 % polyglycol 59-13
 2.6 % Emcol AC 31-2
27.3 % Bay refining PF Solvent

DOW 089068

[illegible]
[illegible] Company
[illegible]

8163

0000914

write this, then it had to be the EPA sending this to Dow outside the normal public channels telling them why they were cancelling their 2,4,5-T. In any event, it is a very damaging document to Dow.

190. 5/5/80 — Document entitled: "Product Discontinuation - For the Product Esteron 2,4,5 Herbicide".
Comment: Dow Chemical stops the use of Esteron 2,4,5 in the United States in PL and bulk sizes".

191. 5/16/80 — Dow R&D Report: "Picloram: Results of a 32-Day Toxicity Tolerance in Feed in Mice", with attached report.

192. 5/30/80 — J.W. Henck, et al., Dow R&D Report on 2,3,7,8-Tetrachlorodibenzo-P-DioxinAcute Oral Toxicity in Hamsters". This is a report summary.

193. 6/2/80 — Letter to Stone of the EPA from Morgan of Dow re: Esteron 2,4,5 Application for Amended Registration.

194. 6/5/80 — Dow Quality Assurance printout on Esteron 2,4,5 Brush and Weed Killer.
Comment: Esteron 2,4,5 has been declared obsolete on 6/2/80.

195. 6/24/80 — Dow form of medial information from Esteron 2,4,5 BRUSH AND WEED KILLER.
Comment: See exhibit 195a below.

195a. 6/24/80 — The back page of the document in exhibit 195 which is entitled: "Composition Listing Chemical Ingredients".
Comment: This states that Esteron 2,4,5 can cause serious illness (from a Dow medical sheet). If gives all chemicals in this product and they contain no ~~anerts~~ inerts! (In other words, nothing is hidden here in what Dow is actually putting in their product. They usually hide the deadly ingredients under ~~enerts~~ inerts and then list some percentage like 35% enerts. In this case we are getting to see for the first time everything that Dow puts in their Agent Orange product.)

APPENDIX E

ALL REGISTRANTS WITH MANUFACTURING-USE PRODUCTS FOR THE FOLLOWING:

2,4-Dichlorophenoxyacetic acid

148	Thompson-Hayward Chem. Co., Kansas City, KS 66106
264	Union Carbide Agric. Prod. Co., Ambler, PA 19002
359	Rhone-Poulenc Chem. Co., Monmouth Junction, NJ 08852
464	DOW Chemical USA, Midland, MI 48640
524	Monsanto Co., Wash., D.C. 20036
677	Diamond Shamrock Agric. Chem., Cleveland, OH 44114
2217	PBI-Gordon Corp., Kansas City, KS 66118
6305	Robeco Chem. Inc., New York, NY 10016
7173	Chempar Chem. Co. Inc., New York, NY 10016
7969	BASF Wyandotte Corp., Parsippany, NJ 07054
8997	Shepard Chem. Indust. Inc., New York, NY 10022
39335	Fallek-Lankro Corp., Tuscaloosa, AL 35404
39511	Vertac Chem. Inc., Memphis,TN 38137

Butoxypropyl ester of 2,4-D

464	DOW Chemical USA, Midland, MI 48640

Isopropyl ester of 2,4-D

524	Monsanto Co., Wash., D.C. 20036
677	Diamond Shamrock Agric. Chem., Cleveland, OH 44114
5481	Amvac Chem. Corp., Los Angeles, CA 90023

Isooctyl (ethylhexyl) ester of 2,4-D

148	Thompson-Hayward Chem. Co., Kansas City, KS 66106
228	Riverdale Chem. Co., Chicago Heights, IL 60411
359	Rhone-Poulenc Chem. Co., Monmouth Junction, NJ 08852
464	DOW Chemical USA, Midland, MI 48640
524	Monsanto Co., Wash., D.C. 20036
677	Diamond Shamrock Agric. Chem., Cleveland, OH 44114
2217	PBI-Gordon Corp., Kansas City, KS 66118
39511	Vertac Chem. Inc., Memphis, TN 38137
40831	Falls Chem. Inc., Great Falls, MT 59403

APPENDIX A

LIST OF YOUR COMPANY'S PRODUCTS CONTAINING SOME FORM OF 2,4-D

REGISTRANT	NAME AND ADDRESS
000464	DOW CHEMICAL U S A AGRICULTURAL PRODUCTS DIV 5176361000 PO BOX 1706 MIDLAND MI 48640

	PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00001	DOW FORMULA 40	072963	23	0376	3
	TYPE: 40 HERBICIDE				
	FORM: 15 SOLUBLE CONCENTRATE				

INGREDIENTS:
030010 59.7000 Alkanol amine 2,4-dichlorophenoxyacetate (salts of the ethanol and ispropanol series)

	PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00151	DOW DMA 6 WEED KILLER	072767	23	0375	2
	TYPE: 40 HERBICIDE				
	FORM: 15 SOLUBLE CONCENTRATE				

INGREDIENTS:
030019 69.5000 Dimethylamine 2,4-dichlorophenoxyacetate

	PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00159	ESTERON 99	021154	23	0173	3
	TYPE: 40 HERBICIDE				
	FORM: 12 EMULSIFIABLE CONCENTRATE (EC OR E)				

INGREDIENTS:
030072 41.0000 Propylene glycol butyl ether 2,4-dichlorophenoxyacetate

	PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00183	DOW BUTYL 265	022156	23	1274	3
	TYPE: 40 HERBICIDE				
	FORM: 12 EMULSIFIABLE CONCENTRATE (EC OR E)				

INGREDIENTS:

**COMPANY REGISTRANT 000464

PRODUCT 00183 DOW BUTYL 265

•INGREDIENTS•
030056 39.0000 Butyl 2,4-dichlorophenoxyacetate

********** PRODUCT NAME **********	•APDATE•	•PM•	•DATE•	•TOXICITY•
00184 DOW BUTYL 400	061270	23	0779	3
• •TYPE: 40 HERBICIDE				
• •TYPE: 46 HERBICIDE TERRESTRIAL				
• •TYPE: 77 UNCLASSIFIED				
• •FORM: 12 EMULSIFIABLE CONCENTRATE (EC OR E)				

•INGREDIENTS•
030056 55.4000 Butyl 2,4-dichlorophenoxyacetate

********** PRODUCT NAME **********	•APDATE•	•PM•	•DATE•	•TOXICITY•
00187 ESTERON FOUR LOW VOLATILE WEED KILLER	042471	23	0275	3
• •TYPE: 40 HERBICIDE				
• •FORM: 12 EMULSIFIABLE CONCENTRATE (EC OR E)				

•INGREDIENTS•
030055 72.8000 Butoxypropyl 2,4-dichlorophenoxyacetate

********** PRODUCT NAME **********	•APDATE•	•PM•	•DATE•	•TOXICITY•
00196 DMA 4 HERBICIDE	070572	23	0475	2
• •TYPE: 40 HERBICIDE				
• •FORM: 15 SOLUBLE CONCENTRATE				

•INGREDIENTS•
030019 49.3000 Dimethylamine 2,4 dichlorophenoxyacetate

CONFIDENTIAL REGISTRANT 000464

PRODUCT 00201 DMA 4 HERBICIDE

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00201 ESTERON 99 CONCENTRATE	092557	23	0875	3
TYPE: 40 HERBICIDE				
FORM: 15 SOLUBLE CONCENTRATE				

INGREDIENTS		
030072	72.8000	Propylene glycol butyl ether 2,4-dichlorophenoxyacetate

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00204 ESTERON BRUSH KILLER	020758	23	1075	3
TYPE: 40 HERBICIDE				
FORM: 12 EMULSIFIABLE CONCENTRATE (EC OR E)				

INGREDIENTS		
030072	36.0000	Propylene glycol butyl ether 2,4-dichlorophenoxyacetate
082072	34.1000	Butoxyethyl 2,4,5-trichlorophenoxyacetate
		Use code no. 082053

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00273 ESTERON 2 2	042561	23	0567	3
TYPE: 40 HERBICIDE				
FORM: 15 SOLUBLE CONCENTRATE				

INGREDIENTS		
030072	36.3000	Propylene glycol butyl ether 2,4-dichlorophenoxyacetate
082055	34.4000	Butoxypropyl 2,4,5 trichlorophenoxyacetate

** ONLINE REGISTRANT 000464

PRODUCT 00279 TYPPON 2 2

PRODUCT	NAME	APDATE	PM	DATE	TOXICITY
00279	DOW ESTERON 76 BF WEED KILLER	060267	23	0275	6
	TYPE: 40 HERBICIDE				
	FORM: 12 EMULSIFIABLE CONCENTRATE (EC OR E)				

INGREDIENTS
000056 79.2000 Butyl 2,4-dichlorophenoxyacetate

PRODUCT	NAME	APDATE	PM	DATE	TOXICITY
00289	VERTON CF WEED AND BRUSH KILLER	030669	23	0369	3
	TYPE: 40 HERBICIDE				
	FORM: 12 EMULSIFIABLE CONCENTRATE (EC OR E)				

INGREDIENTS
030072 36.0000 Propylene glycol butyl ether 2,4-dichlorophenoxyacetate
082055 34.1000 Butoxypropyl 2,4,5-trichlorophenoxyacetate

PRODUCT	NAME	APDATE	PM	DATE	TOXICITY
00306	TORDON 101 MIXTURE WEED AND BRUSH KILLER	061463	23	1070	3
	TYPE 40 HERBICIDE				
	TYPE 99 RESTRICTED				
	FORM 15 SOLUBLE CONCENTRATE				

INGREDIENTS
005102 10.2000 Triisopropanolamine picloram (4-amino-3,5,6-trichloropicolinic acid)
030035 39.6000 Triisopropanolamine 2,4-dichlorophenoxyacetate

**DOWELL REGISTRANT 000464

PRODUCT 00347 TORDON 101 MIXTURE WEED AND BRUSH KILLER

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00347 PICLORAM 6E HERBICIDE	112965	23	0375	3
TYPE: 40 HERBICIDE				
FORM: 12 EMULSIFIABLE CONCENTRATE (EC OR E)				

INGREDIENTS
000063 94.4000 Isooctyl(2 ethylhexyl) 2,4-dichlorophenoxyacetate

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00447 WEED KILLER 4D	122865	23	1274	3
TYPE: 40 HERBICIDE				
FORM: 12 EMULSIFIABLE CONCENTRATE (EC OR E)				

INGREDIENTS
000063 70.0000 Isooctyl(2 ethylhexyl) 2,4-dichlorophenoxyacetate

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00452 BRUSH KILLER 3 2	012566	23	0475	3
TYPE: 40 HERBICIDE				
FORM: 12 EMULSIFIABLE CONCENTRATE (EC OR E)				

INGREDIENTS
000063 34.7000 Isooctyl(2-ethylhexyl) 2,4-dichlorophenoxyacetate
082063 34.1000 2 Ethylhexyl 2,4,5 trichlorophenoxyacetate

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00461 DOW TORDON 212 MIXTURE HERBICIDE	081167	25	0468	3
TYPE: 40 HERBICIDE				
TYPE: 99 RESTRICTED				
FORM: 15 SOLUBLE CONCENTRATE				

INGREDIENTS

C0066215

DOWL 0862241

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**CONTINUE REGISTRANT 000464

PRODUCT 00361 DOW TORDON 212 MIXTURE HERBICIDE

•INGREDIENTS•
000102 18.1000 Triisopropanolamine picloram (4-amino 3,5,6 trichloropicolinic acid)
030035 37.7000 Triisopropanolamine 2,4 dichlorophenoxyacetate

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00382 LAWN WEED KILLER	110871	23	0275	3
• •TYPE: 40 HERBICIDE				
• •FORM: 12 EMULSIFIABLE CONCENTRATE (EC OR E)				

•INGREDIENTS•
030055 21.4000 Butoxypropyl 2,4-dichlorophenoxyacetate
082555 10.0000 Butoxypropyl silvex (2-(2,4,5-trichlorophenoxy)propionic acid)

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00423 VERTON 2D	052372	23	0375	6
• •TYPE: 40 HERBICIDE				
• •FORM: 12 EMULSIFIABLE CONCENTRATE (EC OR E)				

•INGREDIENTS•
030072 39.6000 Propylene glycol butyl ether 2,4-dichlorophenoxyacetate

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00454 2,4 D ACID FOR MANUFACTURING PURPOSES ONLY	012673	23	0375	3
• •TYPE: 40 HERBICIDE				
• •FORM: 01 TECHNICAL CHEMICAL				

•INGREDIENTS•
030001 99.0000 2,4 Dichlorophenoxyacetic acid

**CONTINUED REGISTRANT 000464

PRODUCT 00454 2,4 D ACID FOR MANUFACTURING PURPOSES ONLY

********** PRODUCT NAME **********	*APDATE*	*PM*	*DATE*	*TOXICITY*
00454 2,4 D ACID, DAMP FOR MANUFACTURING PURPOSES ONLY	012373	23	0275	3
*TYPE 46 HERBICIDE TERRESTRIAL				
*TYPE 77 UNCLASSIFIED				
*FORM 01 TECHNICAL CHEMICAL				

INGREDIENTS
030001 97.0000 2,4-Dichlorophenoxyacetic acid

********** PRODUCT NAME **********	*APDATE*	*PM*	*DATE*	*TOXICITY*
00456 2,4 D, BUTYL ESTERS	030673	23	0475	3
*TYPE 40 HERBICIDE				
*FORM 01 TECHNICAL CHEMICAL				

INGREDIENTS
030056 98.8000 Butyl 2,4-dichlorophenoxyacetate

********** PRODUCT NAME **********	*APDATE*	*PM*	*DATE*	*TOXICITY*
00457 DOW 2,4 D BUTOXY PROPYL ESTERS FOR MANUFACTURING USES ONLY	022673	23	0475	3
*TYPE 46 HERBICIDE TERRESTRIAL				
*TYPE 77 UNCLASSIFIED				
*FORM 01 TECHNICAL CHEMICAL				

INGREDIENTS
030055 99.0000 Butoxypropyl 2,4-dichlorophenoxyacetate

********** PRODUCT NAME **********	*APDATE*	*PM*	*DATE*	*TOXICITY*
00458 DOW 2,4-D ISOOCTYL ESTERS FOR MANUFACTURING USE ONLY	022673	23	0475	3
*TYPE 40 HERBICIDE				
*FORM 01 TECHNICAL CHEMICAL				

INGREDIENTS

**OFFICIAL REGISTRANT 000464

PRODUCT 00458 DOW 2,4 D ISOOCTYL ESTERS FOR MANUFACTURING USE ONLY

•INGREDIENTS•
030063 97.0000 Isooctyl(2 ethylhexyl) 2,4 dichlorophenoxyacetate

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00461 ESTERON 44 IMPROVED	070573	23	0175	6
•TYPE 40 HERBICIDE				
•FORM 12 EMULSIFIABLE CONCENTRATE (EC OR E)				

•INGREDIENTS•
030056 51.0000 Butyl 2,4 dichlorophenoxyacetate

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00467 DOW DMA 6 UNSEQUESTERED	041073	23	0779	6
•TYPE 40 HERBICIDE				
•TYPE 77 UNCLASSIFIED				
•FORM 02 FORMULATION INTERMEDIATE				

•INGREDIENTS•
030019 66.6000 Dimethylamine 2,4-dichlorophenoxyacetate

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00507 AMINE FOUR HERBICIDE	111874	23	1174	3
•TYPE 40 HERBICIDE				
•FORM 15 SOLUBLE CONCENTRATE				

•INGREDIENTS•
030010 57.1000 Alkanol• amine 2,4-dichlorophenoxyacetate •(salts of the ethanol and ispropanol series)

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
00510 DOW TORDON 101R FORESTRY HERBICIDE	022575	25	1179	2
•TYPE 40 HERBICIDE				
•TYPE 46 HERBICIDE TERRESTRIAL				
•FORM 16 SOLUTION READY TO USE				

•INGREDIENTS•

C000118

DOW-1 085244

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**[illegible] PRODUCT UPDATE 000464

PRODUCT 005510 DOW TORDON 101R FORESTRY HERBICIDE

•INGREDIENTS•
005102 5.4000 Triisopropanolamine piclorum (4-amino-3,5,6-trichloropicolinic acid)
030035 20.9000 Triisopropanolamine 2,4-dichlorophenoxyacetate

•••••••••• PRODUCT NAME ••••••••••	•APDATE•	•PM•	•DATE•	•TOXICITY•
005513 DOW 2,4-D, DIETHANOLAMINE SALT 5	052275	23	0575	3
• •TYPE: 40 HERBICIDE				
• •FORM: 15 SOLUBLE CONCENTRATE				

•INGREDIENTS•
030016 69.3000 Diethanolamine 2,4-dichlorophenoxyacetate

•••••••••• PRODUCT NAME ••••••••••	•APDATE•	•PM•	•DATE•	•TOXICITY•
005514 DOW 2,4-D, TRIETHANOLAMINE SALT-4	052275	23	0575	3
• •TYPE: 40 HERBICIDE				
• •FORM: 15 SOLUBLE CONCENTRATE				

•INGREDIENTS•
030033 64.8000 Triethanolamine 2,4-dichlorophenoxyacetate

•••••••••• PRODUCT NAME ••••••••••	•APDATE•	•PM•	•DATE•	•TOXICITY•
005515 DOW BUTOXY PROPYLESTER MIX NO.1	052275	23	0575	3
• •TYPE: 40 HERBICIDE				
• •FORM: 15 SOLUBLE CONCENTRATE				

•INGREDIENTS•
030055 66.8000 Butoxypropyl 2,4-dichlorophenoxyacetate
082555 31.1000 Butoxypropyl silvex (2-(2,4,5-trichlorophenoxy)propionic acid)

6179

[illegible] 052275

00066113

**COMPANY REGISTRANT 000464

PRODUCT 06866 DOW BRUSH KILLER X HERBICIDE

PRODUCT NAME		APDATE	PM	DATE	TOXICITY
06866 FORMULA 40 HERBICIDE	LA	010176	23	0176	3
TYPE: 40 HERBICIDE					
FORM: 15 SOLUBLE CONCENTRATE					

INGREDIENTS
030010 59.7000 Alkanol amine 2,4 dichlorophenoxyacetate (salts of the ethanol and ispropanol series)

PRODUCT NAME		APDATE	PM	DATE	TOXICITY
06868 FORMULA 40 HERBICIDE	III	010176	23	0176	3
TYPE: 40 HERBICIDE					
FORM: 15 SOLUBLE CONCENTRATE					

INGREDIENTS
030010 59.7000 Alkanol amine 2,4-dichlorophenoxyacetate (salts of the ethanol and ispropanol series)

PRODUCT NAME		APDATE	PM	DATE	TOXICITY
06897 DMA 4 HERBICIDE	III	010176	23	0176	9
TYPE: 40 HERBICIDE					
FORM: 15 SOLUBLE CONCENTRATE					

INGREDIENTS
030019 49.3000 Dimethylamine 2,4-dichlorophenoxyacetate

PRODUCT NAME		APDATE	PM	DATE	TOXICITY
06898 DMA 4 HERBICIDE	CA	010176	23	0176	9
TYPE: 40 HERBICIDE					
FORM: 15 SOLUBLE CONCENTRATE					

INGREDIENTS

**REGISTRANT 000464

PRODUCT 000618 DOW BUTOXY PROPYLESTER MIX NO 1

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
000619 DOW 2,4 D BUTOXY ETHANOL ESTER	071575	23	0779	3
TYPE: 40 HERBICIDE				
TYPE: 46 HERBICIDE TERRESTRIAL				
TYPE: 77 UNCLASSIFIED				
FORM: 01 TECHNICAL CHEMICAL				

INGREDIENTS

000053 95.6000 Butoxyethyl 2,4-dichlorophenoxyacetate

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
000619 DOW IOE MIX NO 1	071575	23	0775	3
TYPE: 46 HERBICIDE TERRESTRIAL				
TYPE: 77 UNCLASSIFIED				
FORM: 02 FORMULATION INTERMEDIATE				

INGREDIENTS

030063 66.0000 Isooctyl(2 ethylhexyl) 2,4-dichlorophenoxyacetate
082563 31.0000 Isooctyl(2 ethylhexyl) silvex (2-(2,4,5 trichlorophenoxy)propionic acid)

PRODUCT NAME	APDATE	PM	DATE	TOXICITY
000627 DOW BRUSH KILLER 7 HERBICIDE	101775	23	1075	3
TYPE: 40 HERBICIDE				
FORM: 12 EMULSIFIABLE CONCENTRATE (EC OR E)				

INGREDIENTS

030055 36.0000 Butoxypropyl 2,4-dichlorophenoxyacetate
082055 34.1000 Butoxypropyl 2,4,5-trichlorophenoxyacetate

**CONTINUE REGISTRANT 000464

PRODUCT 06898 DMA 4 HERBICIDE CA

•INGREDIENTS•
030019 49.3000 Dimethylamine 2,4-dichlorophenoxyacetate

•••••••••••••••• PRODUCT NAME ••••••••••••••••		•APDATE•	•PM•	•DATE•	•TOXICITY•
06898 DMA 6 WEED KILLER	HI	010176	23	0176	9
• •TYPE: 40 HERBICIDE					
• •FORM: 15 SOLUBLE CONCENTRATE					

•INGREDIENTS•
030019 69.5000 Dimethylamine 2,4-dichlorophenoxyacetate

•••••••••••••••• PRODUCT NAME ••••••••••••••••		•APDATE•	•PM•	•DATE•	•TOXICITY•
07083 TORDON (R) 101 MIXTURE WEED AND BRUSH KILLER	WA	010176	23	0176	9
• •TYPE: 40 HERBICIDE					
• •FORM 15 SOLUBLE CONCENTRATE					

•INGREDIENTS•
005102 10.2000 Triisopropanolamine picloram (4-amino-3,5,6-trichloropicolinic acid)
030035 39.6000 Triisopropanolamine 2,4-dichlorophenoxyacetate

•••••••••••••••• PRODUCT NAME ••••••••••••••••		•APDATE•	•PM•	•DATE•	•TOXICITY•
07084 TORDON (R) MIXTURE WEED AND BRUSH KILLER	OR	010176	23	0176	3
• •TYPE: 40 HERBICIDE					
• •FORM: 15 SOLUBLE CONCENTRATE					

•INGREDIENTS•
005104 10.2000 Potassium picloram (4-amino-3,5,6-trichloropicolinic acid)
030035 39.6000 Triisopropanolamine 2,4-dichlorophenoxyacetate

··CONFIDENTIAL REGISTRANT 000464

PRODUCT 07085 TORDON (R) MIXTURE WEED AND BRUSH KILLER OR

··· PRODUCT NAME ···		·APDATE·	·PM·	·DATE·	·TOXICITY·
07085 TORDON (R) MIXTURE WEED AND BRUSH KILLER	ID	010176	23	0176	9
· ·TYPE: 40 HERBICIDE					
· ·FORM: 15 SOLUBLE CONCENTRATE					

·INGREDIENTS·		
005102	10.2000	Triisopropanolamine picloram (4-amino-3,5,6-trichloropicolinic acid)
030035	39.6000	Triisopropanolamine 2,4-dichlorophenoxyacetate

··· PRODUCT NAME ···		·APDATE·	·PM·	·DATE·	·TOXICITY·
07086 TORDON (R) 101 MIXTURE WEED AND BRUSH KILLER	CA	010176	23	0176	9
· ·TYPE: 40 HERBICIDE					
· ·FORM: 15 SOLUBLE CONCENTRATE					

·INGREDIENTS·		
005102	10.2000	Triisopropanolamine picloram (4-amino-3,5,6-trichloropicolinic acid)
030035	39.6000	Triisopropanolamine 2,4-dichlorophenoxyacetate

···· NUMBER OF PRODUCTS LISTED: 43

APPENDIX A

EPA Product Registration Number: _____

Registrant's Name: _____

CERTIFICATION OF ENTITLEMENT TO EXEMPTION FROM SUSPENSION UNDER FIFRA Section 3(c)(2)(B)

As an authorized representative of the registrant of the product identified above, I hereby certify that:

(1) I have read and am familiar with the terms of a notice from EPA dated _____ concerning a requirement for submission of data under FIFRA Section 3(c)(2)(B) on an active ingredient in the class of 2,4-D compounds*/

(2) My firm requests that EPA not suspend the registration of our product, despite our lack of intent to submit the data in question, on the ground that the product is an end-use product and it will contain an active ingredient in the class of 2,4-D compounds solely as the result of the incorporation into the product (during formulation or packaging) of another product which contains that same active ingredient, which is registered under FIFRA Section 3, and which is purchased by us from another producer.

(3) An accurate confidential formula statement for the above-identified product, current as of the date of this Certification, is on file with EPA's Registration Division or attached to this certification. That formula statement indicates, by company name, registration number, and product name, the source of the specific 2,4-D compound in my firm's product. My firm will apply for an amendment to the registration prior to changing the source of that specific form of 2,4-D in our product.

(4) I understand, and agree on behalf of my firm, that if at any time any of the statements in this Certification are no longer true, or if my firm fails to comply with the undertakings made in this Certification, my firm's product's registration may be suspended in accordance with FIFRA Section 3(c)(2)(B).

Dated: _____ _____
Authorized representative of

Registrant's name: _____

Registrant's address _____

_____

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*/ The class of 2,4-D compounds includes the active ingredients listed in page 4 of this letter.

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APPENDIX C

STATEMENT OF WILLINGNESS TO ENTER
INTO AN AGREEMENT WITH OTHER REGISTRANTS
FOR DEVELOPMENT OF DATA

(1) I am duly authorized to represent the following firm(s) who are subject to the requirement of an Order and Notice dated _____ under FIFRA Section 3(c)(2)(B), 7 U.S.C. Section 136a(c)(2)(B), to submit data concerning 2,4-dichlorophenoxyacetic acid and related salt and ester forms:

Name of Firm | EPA Company Number

(This firm or group of firms is referred to below as "my firm".)

(2) My firm is willing to develop and submit the data as required by that Order and Notice, if necessary. However, my firm would prefer to enter into an agreement with one or more other registrants to develop jointly, or to share in the cost of developing, the following required items or data:

(3) My firm has offered in writing to enter into such an agreement, which included an offer to be bound by an arbitration decision under FIFRA Section 3(c)(2)(B)(iii) if agreement on all terms could not be reached otherwise. This offer was made to the following firm(s) on the following date(s):

Firm: | Date of offer:

However, my firm's offer was not accepted by any of those firm(s).

(4) My firm requests that EPA not suspend the registration(s) of my firm's product(s), if any of the firms named in paragraph (3) above have agreed to submit the data listed in paragraph (2) above in accordance with the Order and Notice. I understand EPA will promptly inform me whether my firm must submit the data to avoid suspension of its registrations under FIFRA Section 3(c)(2)(B).

Dated: _____ _____

for: Firm(s)

198A

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DEPARTMENTAL MANUAL

41D
cc:

TRANSMITTAL SHEET

PART	SUBJECT	RELEASE NUMBER
517 DM 1	ENVIRONMENTAL QUALITY	2295
FOR FURTHER INFORMATION, CONTACT: Office of Environmental Project Review	Pesticide Use Policy	DATE: SEP 23 1980

EXPLANATION OF MATERIAL TRANSMITTED:

This release completely revises and updates the Department's policies on the use of pesticides to reflect current statutes, regulations, research, and experience.

It abolishes the Departmental Pesticides Committee (formerly the Departmental Pesticides Working Group and its Advisory Group) which was chaired by the Director of the Office of Environmental Project Review and assigns functions to that Office.

Larry E. Meierotto
Assistant Secretary of the Interior

FILING INSTRUCTIONS:

Remove:	Insert:
517 DM 1 (1 sheet)	517 DM 1 (2 sheets)
Appendix 1-2 (1 sheet)	Appendix 1 (1 sheet)
517 DM 2 (1 sheet)	
Appendix 1 (1 sheet)	

TO: JOHN DONALDS - 9008 BUILDING

FROM: FRED MAC GOWAN - WASHINGTON, D.C.

8186

1.1 Purpose. This Chapter sets forth the Department's policies in the use of pesticides on lands and waters administered, or under programs funded by the Department, and for complying with the Federal Insecticide, Fungicide, and Rodenticide Act of 1972, as amended (FIFRA).

1.2 Policy. It is the policy of the Department:

A. To use pesticides only after full consideration of alternatives - based on competent analyses of environmental effects, effectiveness, safety, specificity, and benefit/cost - demonstrating that the use of the pesticide is the least hazardous among those available and meets essential management goals. The full range of alternatives including chemical, biological, and physical methods, and no action must be considered.

B. To utilize pest management research, control, education, and assistance programs to develop, support, and adopt integrated pest management (IPM) strategies wherever practicable.

C. To use only pesticides registered by the Environmental Protection Agency (EPA) in full accordance with FIFRA, as amended, and as provided in regulations, orders, or permits issued by EPA.

D. That the handling and use of restricted-use pesticides be conducted with caution and only by personnel who are either certified or under the direct supervision of a certified applicator.

E. To insure that all pesticides and pesticide containers are transported, stored, and disposed of in a manner that will safeguard human health, fish and wildlife, and prevent soil and water contamination.

F. To give full consideration at all times to safety to humans, fish and wildlife, and other non-target organisms.

G. To use pesticides in habitats involving endangered and threatened animal or plant species only after it is determined that such use will not adversely effect the species or its critical habitat. This determination will be made through the Endangered Species Act consultation process

(2) Is responsible for coordinating any program differences or conflicts between Assistant Secretaries.

B. Program Assistant Secretaries. Are responsible for compliance with FIFRA, EPA's implementing regulations (40 CFR 162), and with this Part for bureaus and offices under their jurisdiction.

C. Heads of Bureaus and Offices.

(1) Will comply with FIFRA, EPA's implementing regulations (40 CFR 162), and with this Part.

(2) Will evaluate, control, and monitor all pesticide programs and activities so as to protect and enhance the quality of the environment and bring into conformance all pesticide use with the intent, purpose, and procedures of FIFRA, NEPA, and ESA.

(3) Will provide technical support for Departmental pesticide review activities, as appropriate and requested.

D. Office of Environmental Project Review.

(1) Will exercise oversight review of pesticide programs, projects, procedures, and performance for the Assistant Secretary--Policy, Budget and Administration.

(2) Will review and recommend revision to pesticide policies of the Department as changing technical, procedural, or other conditions warrant.

(3) Will alert bureaus when new information or other environmental considerations require significant controls, advice, or warning concerning the use of pesticides that may pose an environmental threat.

(4) Will review and approve certain proposed Departmental pesticide use projects and activities.

(5) Will advise the Assistant Secretary--Policy, Budget and Administration on the policy aspects of pesticide use in Departmental programs.

517 DM 1
Appendix 1

USE OF PESTICIDES

1. Prohibited List

   A. All pesticides cancelled by EPA

   B. The following pesticides:

      2, 4, 5 - T
      2, 4, 5 - TP

2. Restricted List

   A. All pesticide use restricted by EPA

   B. The following pesticides:

      Endosulfan
      Lindane

8190

Received from the Environmental Protection Agency

Certified Mail # 188525

September 8, 1980

Copies to:

R. L. Charlton
J. H. Davidson
L. Castillo
L. N. Jordan
R. L. Gantz
C. H. Goodman
R. C. Hunter
R. J. Kociba, 1803
S. J. Gorzinski, 1803
M. L. Leng, 1803
A. H. Morgan, 1803
R. W. Morgan
R. D. Moss
M. G. Norris
J. K. Priddy
A. E. Schober, 1803
B. A. Schwetz, 1803
J. M. Theis
S. R. Vranish
C. S. Williams
J. W. Weseloh

from:

J. W. Weseloh
Product Registrations
Health and Environmental Sciences
9008
636-4770

8191

ORDER AND NOTICE

Dear Registrant:

EPA recently completed a review of the available scientific information on the potential health effects of 2,4-D.

On April 29, 1980, based on the findings of the review, the Agency announced that significant gaps exist in the data base for 2,4-D and that additional scientific information will be required from the registrants under Section 3(c)(2)(B) of Federal Insecticide Fungicide Rodenticide Act (FIFRA), 7 U.S.C. 136a(c)(2)(B). This provision allows the Administrator of EPA to request any additional data from pesticide registrants that is considered necessary to maintain the registration of existing products. Enclosed is a copy of the Fact Sheet on 2,4-D which outlines the results of the Agency's review of the scientific information and the decision to require new studies under Section 3(c)(2)(B). Since this Fact Sheet was prepared for the general public, it may contain information which you already know. However, we feel that the Fact Sheet will provide you with material which will clarify EPA's reasons for requesting additional data from you.

Our records indicate that you are the registrant of a pesticide product(s) containing one or more of the following active ingredients which we will refer to collectively as 2,4-D:

2,4-dichlorophenoxyacetic acid
lithium salt of 2,4-D
potassium salt of 2,4-D
sodium salt of 2,4-D
ammonium salt of 2,4-D
alkanol amine salt of 2,4-D

alkyl amine (C12) salt of 2,4-D
alkyl amine (C14) salt of 2,4-D
alkyl amine (fatty acids
of tall oils) salt of 2,4-D
diethanolamine salt of 2,4-D
diethylamine salt of 2,4-D
dimethylamine salt of 2,4-D
dimethyloleylamine of 2,4-D
ethanolamine salt of 2,4-D
heptylamine salt of 2,4-D
isopropanolamine salt of 2,4-D
isopropylamine salt of 2,4-D
morpholine salt of 2,4-D
oleyl propylenediamine salt of 2,4-D
octylamine salt of 2,4-D
triethanolamine salt of 2,4-D
triethylamine salt of 2,4-D
triisopropanolamine salt of 2,4-D
diethylethanolamine salt of 2,4-D
dimethyloleylo-linoleylamine salt
butoxyethoxypropyl ester of 2,4-D
butoxyethyl ester of 2,4-D
butoxypolyethoxypropyl ester of 2,4-D
butoxypropyl ester of 2,4-D
butyl ester of 2,4-D
isobutyl ester of 2,4-D
isooctyl (ethyl hexyl) ester of 2,4-D
isooctyl (ethyl methyl pentyl) ester of 2,4-D
isooctyl (octyl) ester of 2,4-D
isopropyl ester of 2,4-D
propylene glycol butyl ether ester (PGBE) of 2,4-D

A list of your products that contain any of these materials is shown as Appendix A. Also refer to Appendix H for state registrations under Section 24(c)(1) for special local need which are also covered by this letter.

I. REQUIREMENT FOR DATA SUBMISSION

As we have explained in the Fact Sheet, under the authority of Section 3(c)(2)(B) of FIFRA, EPA has determined that additional data, more fully described in Section II of this letter, are required to maintain your registration(s) in effect.

This letter notifies you that if you wish your registrations to be maintained in effect, you are required to take steps to produce and submit data to EPA in accordance with the schedule set forth in Section III of this letter.

Sections IV and V of this letter indicate two limited circumstances in which EPA will not act to suspend the registration of your products if you do not submit the required data. Section VI of this letter describes the procedures by which you may ask EPA to reconsider the requirements imposed by this letter.

In responding to the data requirements established by this letter, you must choose one of the following options. If you fail to exercise one of these options within the time period specified, EPA may take steps to suspend the registration of each product to which the required data are pertinent.

(A) You must notify EPA within 90 days of your receipt of this letter that you are willing to produce (if necessary) and submit the data yourself;

(B) You must notify EPA within 90 days of your receipt of this letter that you have entered into an agreement, with one or more of the other registrants who are subject to this notice's requirements, to jointly produce (if necessary) and submit the data, or to share in the cost of this work;

(C) You must provide to EPA, within 90 days of your receipt of this letter, the "Statement of Willingness to Enter Into an Agreement with Other Registrants for Development of Data", in accordance with Section V and Appendix C of this letter, which will allow EPA to exempt you from the consequences of not submitting some or all of these data under certain circumstances;

(D) You must provide to EPA, within 30 days of your receipt of this letter, the Certification described in Section IV of this letter, which will allow EPA to exempt you from the consequences of not submitting some or all of these data because each of your products is an end-use product and otherwise qualifies under that Section;

(E) You must file with EPA, within 30 days of your receipt of this letter, a request for a waiver of some or all of the data requirements imposed by this Order and Notice; or,

(F) You must file with EPA, within 90 days of your receipt of this letter, a request that the registration(s) for your products containing any or all forms of 2,4-D be voluntarily cancelled.

II. WHAT DATA ARE NEEDED

EPA has determined that significant gaps exist in the data base for pesticides containing 2,4-D compounds. In order to make further determinations concerning potential health effects of 2,4-D, the Agency has determined that data from the studies listed below are required to support the continued registration of all products containing the various forms of 2,4-D. The required studies must be conducted in accordance with the referenced sections of EPA's proposed pesticide registration guidelines,*/ or other approved test standards such as those which are adopted by the Organization for Economic Cooperation and Development (OECD) except as modified or supplemented below.**/

TOXICOLOGY DATA

The following section describes the tests to be conducted and the specific forms of 2,4-D to be tested. When performing studies to produce the required data, you should be very careful to follow every applicable test standard contained either in the section of the guidelines cited or other approved test standards, except as modified in the paragraphs below.

COMPOUNDS TO BE TESTED

Some of the data requirements relate to specific technical grade forms of 2,4-D, while other tests pertain to formulated products. Because the salt and ester forms of 2,4-D will degrade to the acid form and to the metabolite 2,4-dichlorophenol, registrants of products containing any salt or ester form will be responsible for all the required studies on technical grade 2,4-dichlorophenoxyacetic acid and on 2,4-dichlorophenol. (See Appendix G). The required studies on the other technical grade forms of 2,4-D are the responsiblity of those registrants whose products contain

*/ The Agency published proposed human hazard guidelines on August 22, 1978, 43 FR 37336. The required studies on 2,4-D (with the exception of subacute dermal neurotoxicity, standard metabolism in pregnant dogs, and dermal absorption) are described in this section. Copies of the proposed guidelines are available on request.

**/ Note: you may request EPA to review the use of a test method which may vary from the test standards listed above in order to produce the required data. The procedures for submitting such a request are described in Section VI of this letter.

those compounds as active ingredients. The required studies on each formulated product, regardless of the specific forms of 2,4-D it contains, are the responsibility of the registrant to whom that product is registered.

DATA REQUIREMENTS

1. Oncogenicity studies - standard oral exposure study in rats and mice (proposed Section 163.83-2, 43 FR 37379-82).

   Material to be tested:
   - technical grade (or purer) of 2,4-dichlorophenoxyacetic acid

   Note: All registrants are responsible for this data*/

2. Reproduction study - (proposed Section 163.83-4, 43 FR 37384-88).

   Material to be tested:
   - technical grade (or purer) of 2,4-dichlorophenoxyacetic acid

   Note: All registrants are responsible for this data*/

3. Teratogenicity studies - (proposed Section 163.83-3, 43 FR 37382-84) modified as follows: test to be done in the rat.

   Materials to be tested:
   - technical grade (or purer) of 2,4-dichlorophenoxyacetic acid
   - technical grade (or purer) of butoxypropyl ester of 2,4-D
   - technical grade (or purer) of alkanolamine salt of 2,4-D
   - technical grade (or purer) of isopropyl ester of 2,4-D
   - 2,4-dichlorophenol (metabolite of 2,4-D)

   Note: All registrants are responsible for the data on 2,4-D acid and the metabolite, 2,4-dichlorophenol. Registrants with products containing the salt and ester forms listed above are also responsible for the data on those forms of 2,4-D.*/

4. Neurotoxicity studies

   a) subchronic oral neurotoxicity - (proposed Section 163.82-3, 43 FR 37374-75) modified as follows: test to be done in the dog, rat, and chicken. Materials to be tested:

      - technical grade (or purer) of 2,4-dichlorophenoxyacetic acid
      - technical grade (or purer) of dimethylamine salt of 2,4-D

*/ Registrants of end-use products formulated from a registered technical material should consult Section IV for exemption from this requirement.

Note: All registrants are responsible for the data on 2,4-D acid. Registrants with products containing the dimethylamine salt of 2,4-D are responsible for the data on this form.*/

b) subacute dermal neurotoxicity in the dog - This study will be required for the two compounds described in (a) unless otherwise indicated by the results of the subchronic neurotoxicity study and the results of dermal absorption study on that compound. EPA will review the results of these tests when submitted and inform the registrants whether to proceed with (b). At that time, registrants will be notified of the protocol to be used in developing this data.

5. Metabolism studies

a) standard metabolism study - (proposed Section 163.85-1, 43 FR 37394-96) modified as follows: test to be done in the dog and rat. Materials to be tested:

- technical grade (or purer) of 2,4-dichlorophenoxyacetic acid
- technical grade (or purer) of isooctyl (ethylhexyl) ester of 2,4-D
- technical grade (or purer) of PGBE ester of 2,4-D

Note: All registrants are responsible for this data on 2,4-D acid. Registrants with products containing one of the two ester forms listed above are also responsible for the data on those forms.*/

b) standard metabolism study in the pregnant dog - This study will be required for the three compounds described in (a) unless otherwise indicated by the results in (a). EPA will review the results of this test when submitted and inform the registrants whether to proceed with (b). At that time, registrants will be notified of the protocol to be used in developing this data.

6. Acute oral toxicity studies - (proposed Section 163.81-1, 43 FR 37355-56). Materials to be tested:

- each manufacturing-use product and each end-use product containing any of the 2,4-D compounds (Refer to Appendix A for the list of your products

*/ Registrants of end-use products formulated from a registered technical material should consult Section IV for exemption from this requirement.

for which this data must be submitted). A registrant may cite acceptable studies previously submitted to support the registration of his product(s). In lieu of providing his own studies, a registrant may cite acceptable studies already on file with the Agency or submit studies on a substantially similar product, and offer to compensate for such studies.

7. Acute dermal toxicity studies - (proposed Section 163.81-2, 43 FR 37356-57). Materials to be tested:

- each manufacturing-use product and each end-use product containing any of the 2,4-D compounds (Refer to Appendix A). A registrant may cite acceptable studies previously submitted to support the registration of his product(s). In lieu of providing his own studies, a registrant may cite acceptable studies already on file with the Agency or submit studies on a substantially similar product, and offer to compensate for such studies.

Note: The Agency generally requires a series of acute toxicity tests to support the registration of manufacturing use and formulated products. Acute oral toxicity and acute dermal toxicity studies are required for each manufacturing use product and each formulated product. Acute inhalation toxicity, primary eye irritation, primary dermal irritation, and dermal sensitization studies may be required to support the registration of each manufacturing use product and each formulated product, as specified in the proposed pesticide registration guidelines.

While the Agency is requiring only acute oral toxicity and acute dermal toxicity studies at this time, the other acute studies may be required at a later date as appropriate. The data which are being required at this time are essential to provide the Agency with a more accurate and detailed picture of any potentially significant acute oral and/or chronic health effects of 2,4-D. The Agency feels that acute oral and dermal toxicity studies will make a substantial contribution to our understanding of the acute hazard that may be associated with the chemical.

8. Dermal absorption studies -

At this time the Agency does not feel an acceptable protocol has been developed for testing pesticides. Therefore, although this testing remains a requirement as outlined in this letter, you will be notified at a later date of the protocol to be used in developing this data.

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Materials to be tested:

- each end-use product formulated in liquid form or as an emulsifiable concentrate that contains any of the 2,4-D compounds. (Refer to Appendix B for the list of your products for which this data must be submitted).

III. SCHEDULE FOR SUBMITTING DATA

The required data must be submitted to the Agency on the following schedule. If progress reports are required, the schedule will specify the date on which the first progress report is due, and the frequency of progress reports thereafter. If required, progress reports must be provided as specified below. Note: You may request that EPA extend any of the following deadlines. The procedures for submitting such a request are described in Section VI of this letter.

1. Oncogenicity studies

Final report due by 12/1/83
Progress report due on 6/15/82

2. Reproduction studies

Final report due by 3/1/82
Progress report due on 1/1/82 (for the two litters of the first generation)

3. Teratogenicity studies

Final report due by 6/10/81

4. Neurotoxicity studies

a) subchronic oral neurotoxicity
Final report due by 9/1/81

b) subacute dermal neurotoxicity - Registrants will be notified of the due date when they are notified whether to proceed with this testing.

5. Metabolism studies

a) standard metabolism
Final report due by 5/10/81

b) standard metabolism in pregnant dog - Registrants will be notified of the due date when they are notified whether to proceed with this testing.

6. Acute oral toxicity studies

Final report due by 5/1/81

7. Acute dermal toxicity studies

Final report due by 5/1/81

8. Dermal absorption studies

Registrants will be notified of the due date at the same time they are notified to proceed with this testing according to the specified protocol.

IV. REGISTRANT RESPONSIBILITY FOR SUBMISSION OF DATA AND EXEMPTION FROM SUSPENSION SANCTION FOR CERTAIN END-USE PRODUCT REGISTRATIONS

The data described in Section II of this letter relates, in certain cases, to the safety of specific 2,4-D active ingredients (technical grade). According to Section 3(c)(2)(D) of FIFRA, an applicant for registration of an end-use product containing one or more of these forms of 2,4-D is not required to submit or pay compensation for those data as a condition of obtaining registration if that form of 2,4-D is present in his product solely as the result of his incorporation into his product (as part of the formulation or packaging processes) of another registered product, containing that form of 2,4-D, which he purchases from another producer.

The object of this provision is to simplify data compensation by making compensation for data on active ingredient safety an element of the market cost of registered manufacturing-use products, so that formulators or other registrants who purchase such products need not separately offer to pay for data on the safety of the active ingredient.

EPA has concluded that these principles should also apply in the closely analogous situation presented by this Section 3(c)(2)(B) requirement. However, principles of fairness to those who incur expenses of data production and submission require that a registrant may be exempted from data submission requirements only if the specific form of 2,4-D in his product (listed on the active ingredient statement) is purchased from a firm which does have a duty to submit (or to offer to share in the cost of obtaining) the data required by this letter. (Refer to Appendix E for a list of firms with registered manufacturing-use products).

If a registrant who is subject to this Order and Notice fails to comply with the data submission requirement, the Administrator may suspend his registration. However, this authority is discretionary, and the Administrator will not exercise it to suspend a registration if:

(1) The registration is for an end-use product (as opposed to a manufacturing-use product) (Refer to Appendices F and G); AND, */ **/

(2) The specific form of 2,4-D in the end-use product is present solely as the result of the incorporation into that product (during formulation or packaging) of another product which contains that form of 2,4-D which is registered under FIFRA and which is purchased by the registrant; AND,

(3) The registrant completes and executes a "Certification of Entitlement to Exemption from Suspension Under FIFRA Section 3(c)(2)(C)", in the form of Appendix E to this letter, for each of his registered products containing some form of 2,4-D and submits it to EPA not later than September 30, 1980; AND,

(4) One or more registrants actually undertake to submit, and do submit, all the data required by this Order and Notice.

It should be emphasized that while the above procedures provide certain categories of exemptions, those data requirements that specifically relate to end-use (formulated) products are the responsibility of the registrant to whom that product is registered. (See Appendices A and B).

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*/ Note: In the case of data requirements for technical grade forms of 2,4-D for which there are no registered manufacturing-use products, the registrants of the end-use products are responsible for the data.

**/ Note: Appendix F lists the company numbers for those registrants who have end-use products containing forms of 2,4-D for which there are no registered manufacturing-use products. Refer to Appendix G to obtain company names and addresses from the company numbers.

V. EXEMPTION FROM SUSPENSION SANCTION FOR REGISTRANTS WHO OFFER TO SHARE IN THE EXPENSE OF OBTAINING DATA

FIFRA Section 3(c)(2)(B) authorizes joint development of data by two or more registrants, and provides a mechanism by which parties can obtain an arbitrator's decision if they agree to jointly develop data but fail to agree on all the terms of the agreement. The statute does not compel any registrant to agree to develop data jointly.

In EPA's opinion, joint data development by all registrants who are subject to the requirements in this letter, or a cost-sharing agreement between all such registrants, is clearly in the public interest. Duplication of testing is not only wasteful in terms of money, but could tie up testing facilities unnecessarily.

As noted earlier, EPA has discretion not to suspend the registration of a product when a registrant fails to submit data required under FIFRA Section 3(c)(2)(B). EPA has concluded that it is appropriate to exercise its discretion not to suspend in ways which will discourage duplicative testing. Accordingly, if: (1) a registrant has informed us of its intent to develop and submit data required by this Notice and Order; and (2) a second registrant informs EPA that it has made a bona fide offer to the first registrant to share in the expenses of the testing (on terms to be agreed upon or determined by arbitration under FIFRA Section 3(c)(2)(B)(iii)); and (3) the first registrant has without good cause declined to agree to enter into a cost-sharing agreement, EPA will not suspend the second firm's registration. While the first firm is not required to agree to jointly develop data, EPA is not required to force the second firm to engage in economically inefficient duplicative testing in order to maintain its registration.

The format for informing EPA of the bonafide offer to the first registrant is shown as Appendix C.

VI. PROCEDURES FOR REQUESTING WAIVERS, CHANGES IN TESTING METHODOLOGY, AND EXTENSIONS OF TIME

EPA recognizes that you may disagree with our conclusions regarding the need for data, the appropriate ways to develop the required data, and how quickly the data must be submitted. We will give you the opportunity to state the basis for your disagreement and request that we change our requirements. We note that if you seek to challenge our requirements in court, a judge may

dismiss your lawsuit unless you have first presented your arguments to EPA according to the procedures described below.*/

If you think that EPA does not need the data required by this letter to determine whether your product causes unreasonable adverse effects on the environment, you may request a waiver. The waiver request must be submitted within 30 days of your receipt of this letter. The waiver request must be submitted in writing to the person specified at the end of this letter. The waiver request should state the reasons why you conclude that each particular kind of data is not needed. EPA will promptly review your request(s) and inform you whether the waiver has been granted.

If you want to use, or think that you should use, a test methodology which does not satisfy the test standards specified in Section II of this letter, you may ask EPA to review and approve that methodology. The request must be submitted in writing to the person specified at the end of this letter.

In most cases, EPA will not grant an extension of time to submit required data on the ground that you have requested Agency approval to change the required test methodology. Accordingly, you should submit the request as soon as possible.

If you want, or think that you will need, more time to produce the required data than is allowed by EPA's schedule, you must submit a request for an extension of time. The extension request must be submitted in writing to the person specified at the end of this letter. The extension request should state the reasons why you conclude that an extension is appropriate. No extensions will be granted based on the fact that the Agency is considering your request for an extension. Accordingly, you must continue to work diligently to meet the deadline for submitting the required data while EPA considers your request.

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*/ This letter constitutes "final Agency action" unless you submit a request for a waiver, a request for a modification in the required test methodology, or a request for extension of time. If any such request has been submitted, EPA's action with regard to the subject matter of the request does not become final until the Agency has acted on the request. The Agency thinks that a registrant must use the procedures described in this section of the letter in order to exhaust its administrative remedies.

VII. CONCLUSION

All responses to this notice should be submitted to:

Director, Special Pesticide Review Division (TS-791)
Office of Pesticide Programs
U.S. Environmental Protection Agency
401 M St., S.W. Washington, D.C. 20460

ATTN: 2,4-D Project Manager

If you have any questions regarding the requirements and procedures established by this letter, please contact:

Kevin Keaney, Chief, Chemical Review Branch #2, (703) 557-7716.

Sincerely yours,

Edwin L. Johnson
Deputy Assistant Administrator
for Pesticide Programs

Enclosures

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THE CARCINOGEN ASSESSMENT GROUP'S

RISK ASSESSMENT ON

(2,4,5-TRICHLOROPHENOXY)ACETIC ACID (2,4,5-T)

(2,4,5-TRICHLOROPHENOXY)PROPIONIC ACID (SILVEX)

2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD)

Roy E. Albert, M.D.
Chairman
September 12, 1980

PARTICIPANTS

Elizabeth L. Anderson, Ph.D.
Larry D. Anderson, Ph.D.
Steven Bayard, Ph.D.
David Bayliss, M.S.
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Chang S. Lao, Ph.D.
Robert McGaughy, Ph.D.
Charles Poole, M.P.H.
Dharm V. Singh, D.V.M., Ph.D.
Todd W. Thorslund, Sc.D.
Peter Voytek, Ph.D.

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SUMMARY AND CONCLUSIONS

QUALITATIVE RISK ASSESSMENT

(2,4,5-Trichlorophenoxy)Acetic Acid (2,4,5-T)

(2,4,5-Trichlorophenoxy)acetic acid, widely known as 2,4,5-T is used as a vegetation growth regulator and herbicide. "Agent Orange," a defoliant used extensively by the U.S. Army in Vietnam, is a mixture of equal amounts of 2,4,5-T and (2,4-dichlorophenoxy)acetic acid. In 1970, amid growing concern about the teratogenic effects of 2,4,5-T, the EPA cancelled the registration of the compound for uses "around the home, recreation areas, and similar sites" and "in crops intended for human consumption." Before some uses were suspended in 1979, it was used primarily to clear vegetation along powerlines, highways, pipelines, and railroad rights-of-way, and on range, pasture, and forestlands.

The commercial preparation of 2,4,5-T contains 2,3,7,8-tetrachlorodibenzo -p-dioxin (TCDD) as an unavoidable impurity present at a concentration of approximately 0.05 ppm. TCDD is considered extremely toxic.

2,4,5-T is readily absorbed by several mammalian species, including man, and is excreted unchanged - mostly in urine.

The available information about the mutagenic activity of 2,4,5-T is considered to be limited. 2,4,5-T is indicated to be a weak mutagen in Drosophila and, under acidic conditions, showed mutagenic effects in Saccharomyces cerevisiae.

Tests for the chronic carcinogenicity of 2,4,5-T were performed by several investigators. Two studies were carried out with Sprague-Dawley rats, one by the Dow Chemical Company (Kociba et al. 1979) and one by F. Leuschner (1979), Laboratorium fur Pharmakologie und Toxikologie, Hamburg, Germany. The Dow study showed an increased incidence of carcinoma of the tongue in male rats dosed with

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specially purified 2,4,5-T at 30 mg/kg/day. This incidence as reported by the authors of the study, is marginally statistically significant (P = 0.063) when compared to controls. In addition, there was a significant dose-related linear trend by the Cochran-Armitage test. When compared to historical controls, the incidence of this tumor, as reported by the authors, is statistically significant (P < 0.001); however, when the tongue tissues from this study were reexamined by Dr. Squire, he found one additional tongue carcinoma in male rats treated at the high dose with 2,4,5-T which increased the statistical significance to P = 0.025. In a recently completed study by F. Leuschner, an increased incidence of interstitial cell tumors of the testes was observed when compared with matched controls. However, this increase is not statistically significant when compared to historical controls. The results of the Kociba et al. study provide highly suggestive evidence of the carcinogenicity of essentially pure 2,4,5-T.

In mice, two studies by Muranyi-Kovacs et al. (1976, 1977) and two studies by Innes et al. (1969) (Bionetics Laboratories 1968) have not provided positive evidence of oncogenic effects of 2,4,5-T. However, several deficiencies in these studies make them inadequate to assess the lack of oncogenicity of 2,4,5-T.

In summary, the Dow study in rats provides highly suggestive evidence of the carcinogenicity of 2,4,5-T, while the Leuschner study showed only equivocal results. The mouse studies were too insensitive to be considered valid negative studies.

(2,4,5-Trichlorophenoxy)Propionic Acid (Silvex)

Silvex, like 2,4,5-T, contains the highly toxic TCDD. Uses of silvex are similar to those of 2,4,5-T. Chronic carcinogenicity studies have been performed on mice and rats and a 2-year study has been conducted on dogs. Innes

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et al. (1969) (Bionetics Laboratories 1968) conducted two studies using mice, one oral and the other subcutaneous. These studies were found to be inadequate to assess the carcinogenicity of silvex.

Dow Chemical Company performed two feeding studies, a 2-year feeding study on rats and a two year feeding study on dogs which were summarized by Mullison (1966) and Gehring and Betso (1978). These have been found to be inadequate to rule out the carcinogenicity of silvex.

2,3,7,8-Tetrachlorodibenzo-P-Dioxin (TCDD)

Probably one of the most toxic chemicals known to man is 2,3,7,8-tetrachlorodibenzo-p-dioxin. The major source of its environmental contamination is from the pesticidal uses of 2,4,5-T, 2,4,5-trichlorophenol, and silvex.

In small amounts, TCDD is a potent inducer of arylhydrocarbon hydroxylase in mammals. This is a complex enzyme system that consists of epoxidase, epoxidehydratase, and glutathione transferase. The enzyme epoxidase is known to mediate the formation of epoxides, which are potentially active carcinogenic metabolites. TCDD can be metabolized in mammalian species via the epoxide to dihydodiol and further conjugates with glutathione. Persistent residues of TCDD were found in liver and fat in a 2-year feeding study in rats. Significant covalent binding of TCDD to protein has been demonstrated by two investigators. Covalent binding of TCDD with DNA is less significant in liver cells.

Currently available studies on the mutagenicity of TCDD are inconclusive. Two bacterial systems, Escherichia coli and Salmonella typhimurium (without metabolic activation), exhibited positive mutagenic activity. However, in another study of Salmonella typhimurium (with and without metabolic activation), the results were negative.

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There are several cancer bioassay studies of TCDD: 1) a Dow Chemical Company (Kociba et al. 1978) study in male and female Sprague-Dawley (Spartan substrain) rats; 2) the Van Miller et al. (1977) study in male Sprague-Dawley rats; 3) the Toth et al. (1979) study in Swiss mice; 4) the National Cancer Institute (1980a, b) studies in rats and mice; 5) the Pitot et al. (1980) promotion study in rats; and 6) the Kouri et al. (1978) cocarcinogenicity study in mice.

The study by the Dow Chemical Company of male and female Sprague-Dawley rats fed TCDD in doses of 22 ppt, 210 ppt, and 2200 ppt revealed a highly statistically significant excess incidence of hepatocellular carcinomas in female rats at the highest dose level and hepatocellular carcinomas and hepatocellular hyperplastic nodules in female rats at the middle dose level, as compared to the controls. In addition, there was a significant increase in carcinomas of the hard palate/nasal turbinates in both high dose males and females, of the tongue in males, and of the lung in females. The Van Miller et al. study also showed some evidence of a carcinogenic response in the liver and lungs of male Sprague-Dawley rats at dosages of 1000 and 5000 ppt, even though the study used a relatively small number of animals. The Toth et al. study provides suggestive evidence that TCDD induced an increased incidence of liver tumors in male mice (females were not tested) receiving 0.7 ug/kg/week by gavage.

In the National Cancer Institute rat study (1980a), male and female Osborne-Mendel rats were administered TCDD by gavage at three dose levels 0.01, 0.05, and 0.5 ug/kg/week. TCDD induced statistically significant increases of hepatocellular carcinomas, subcutaneous fibrosarcomas, and adrenal cortical adenomas in high dose female rats. TCDD also induced significant increases in thyroid tumors at low, middle, and high doses in male rats.

In a companion mouse study by the National Cancer Institute (1980a), male and female B6C3F1 mice were given TCDD by gavage at dose levels of 0.01, 0.05, and 0.5 ug/kg/week for males and 0.04, 0.2, and 2.0 ug/kg/week for females. TCDD induced statistically significant increased incidences of hepatocellular carcinomas in the high dose males and females, and thyroid tumors, subcutaneous fibrosarcomas, and histiocytic lymphomas in females.

In a study by Pitot et al. (1980), TCDD has been shown to be a potent liver cancer promoter. In a study by Kouri et al. (1978), TCDD has been shown to be a cocarcinogen.

Epidemiologic Studies

Several epidemiologic studies have been conducted which are relevant to the assessment of the carcinogenicity of 2,4,5-T, silvex, and TCDD. Two Swedish epidemiological case-control studies (Hardell and Sandstrom 1979, Erikson et al. 1979) reported a very strong association between soft tissue sarcomas and occupational exposure to phenoxyacetic acid herbicides and/or chlorophenols. These studies indicated approximately five to sevenfold increases in the risk of developing soft tissue sarcomas among people exposed to phenoxyacetic acids only in comparison to people not exposed to these chemicals. Another Swedish case-control study (Hardell et al. 1980) provides suggestive evidence of an increased risk of developing lymphomas resulting from occupational exposure to phenoxyacetic acids.

Two cohort studies, one by Axelson et al. (1980) and the other by Thiess and Frentzel-Beyme (1977) provide suggestive evidence that phenoxyacetic acids and/or TCDD increases the risk of stomach cancer in humans.

Four other cohort studies by Ott et al. (1980), Riihimaki et al. (1978), Zack and Suskind (1980), and Cook et al. (1980) did not indicate an increased

risk of stomach cancer, but three of these studies were of relatively low statistical power, and the fourth (Riihimaki et al. 1977) has certain inconsistencies requiring clarification.

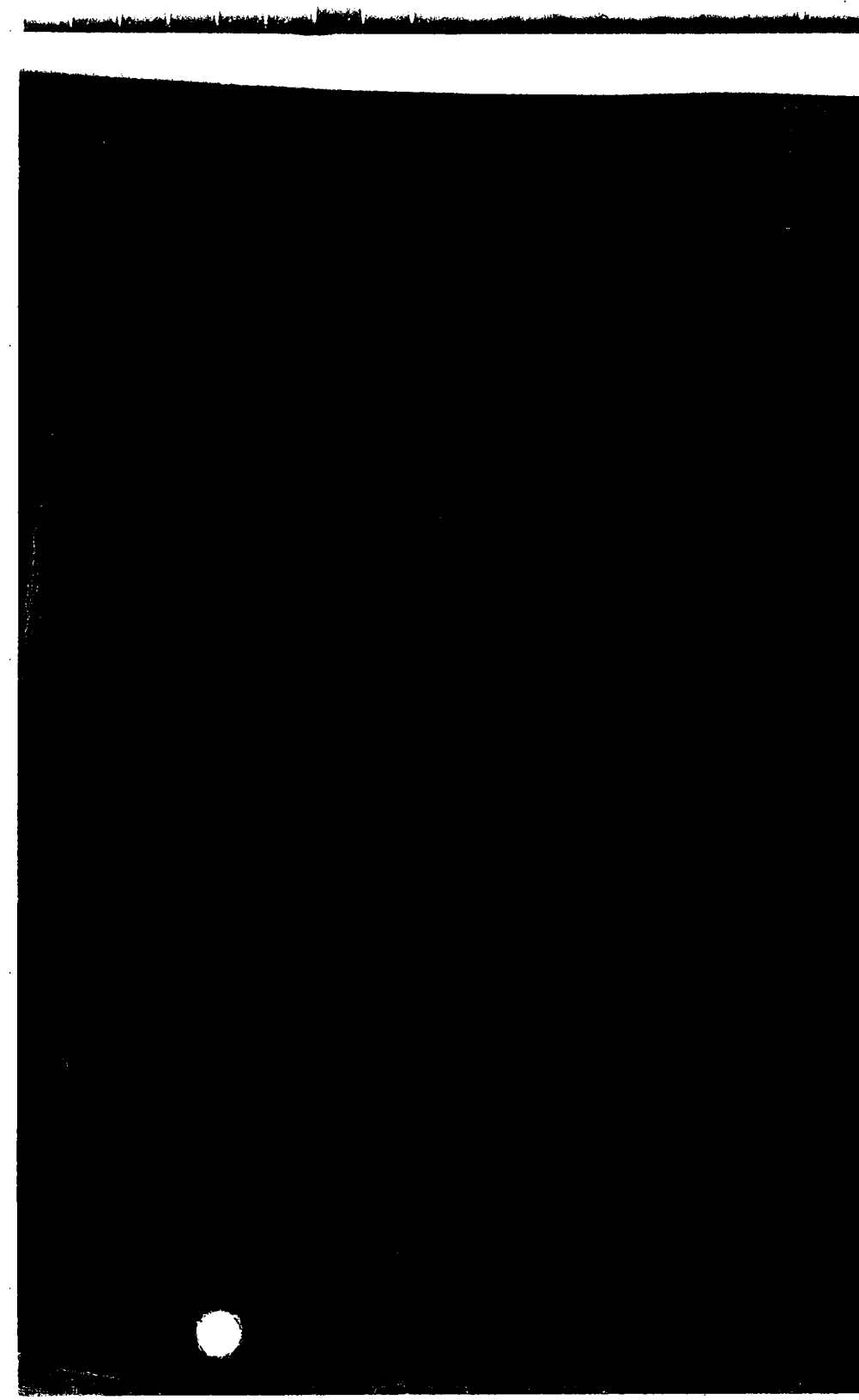
In summary, carcinogenic responses have been induced in mice and rats at very low doses of TCDD. In addition, TCDD has been shown to be a potent cancer promoter. These results, together with the strongly suggestive evidence in epidemiologic studies, constitute substantial evidence that TCDD is likely to be a human carcinogen. In addition, on the basis of the Dow study on TCDD, it appears that TCDD is a more potent carcinogen than aflatoxin B_1 which is one of the most potent carcinogens known. The levels of TCDD (contained as a contaminant of the 2,4,5-T) used in the 2,4,5-T studies apparently were too small to produce an observable response in those experiments. The lack of a statistically significant tumor incidence in most of the studies on the 2,4,5-T product may be attributed both to the very low levels of TCDD in the product relative to the levels at which it produces observable carcinogenic effects in rats and mice, as well as to the deficiencies of those studies. However, since TCDD is a carcinogen, any product containing TCDD, including 2,4,5-T and silvex, can be considered to pose a human carcinogenic hazard. In addition, a rat study on specially purified 2,4,5-T provides highly suggestive evidence that essentially pure 2,4,5-T may be a human carcinogen.

QUANTITATIVE RISK ASSESSMENT OF 2,4,5-T, SILVEX AND TCDD

A quantitative assessment has been calculated for the carcinogenic risk posed to humans by the use of the herbicides 2,4,5-T and silvex. While there is no evidence for carcinogenicity of silvex, the evidence for 2,4,5-T is highly suggestive, and that for the contaminant TCDD is substantial. Furthermore, TCDD is highly carcinogenic to animals.

The assessment of risk from TCDD exposure covers only the herbicide applicators and dietary exposure to beef, milk, deer, and elk. For unprotected workers, the upper limits of lifetime risk of induced cancers are in many cases as high as or in the 10^{-3} range. For the general population exposed to beef contaminated with TCDD, the upper limit of risk for the estimated exposure is 2.4×10^{-6}. For local populations consuming only beef which is contaminated with TCDD, the risk is much greater, as high as 1.9×10^{-4} for the estimated exposure. For local populations consuming only milk and other dairy products which are contaminated with TCDD, the risk is 4.7×10^{-4}. For deer and elk meat contaminated with TCDD, risks to the local population are no greater than 10^{-4} for 12 meals a year.

The upper limit of dietary risk associated with estimated exposures to 2,4,5-T in contaminated rice and milk were in the 10^{-7} range for a high consumer eating only contaminated rice or an average consumer drinking only contaminated milk.



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DOSE LEVELS OF 2,4-D IN FOREST WORKERS

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DOSE LEVELS OF 2,4-D IN FOREST WORKERS

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ABSTRACT

The dose level of 2,4-D absorbed by forest workers during the helicopter application of 2,4-D sprays has been determined. Three crews, each comprised of 6 workers, were engaged in 2 applications of ESTERON* 99*C herbicide. During the first application the workers used normal clothing and work practices. During the second application they were instructed to use more stringent protective measures to minimize exposure. Measurements of airborne 2,4-D during the spray applications revealed that the respiratory route contributes an insignificant proportion of the total potential for exposure. Total daily urine samples were collected from each worker on the spray application days and for 5 days thereafter. Analysis of total urinary 2,4-D provided reliable estimates of the total amount of 2,4-D absorbed. Fourteen of the 36 exposures did not reveal detectable quantities of urinary 2,4-D. Of the 22 exposures with detectable quantities of urinary 2,4-D, the maximum dose level was only 0.0557 mg/kg and the lowest was 0.00038

*Trademark of The Dow Chemical Company.

mg/kg. Those workers remote from the operations (supervisors and observers) received even lower dose levels than did those in closer contact with the sprays (pilots, mechanics, and batchmen). The low dose levels observed following spray operations using customary precautions (first application) were reduced following spray operations using more stringent precautions (second application). Computer simulation of predicted body burden of 2,4-D upon repeated daily exposures demonstrated a maximum accumulation of only seven- tenths of the daily dose. In conclusion, the very low exposure potential demonstrated by this study, coupled with the low toxicity of 2,4-D, supports the continued registration and use of 2,4-D herbicides.

INTRODUCTION

A reliable assessment of the potential risk to workers during pesticide applications in the field is dependent on accurate knowledge of the quantity of the pesticide absorbed into the body. This report concerns measurements of the amount of 2,4-D absorbed by applicators of 2,4-D formulations in the forest.

EXPERIMENTAL

In an experiment conducted by T. L. Lavy (1) eighteen different workers were each engaged in 2 separate forest applications of 2,4-D formulations (ESTERON 99C applied by helicopter at a rate of approximately 2 lb. acid equivalents per acre). In the first application (T1) all personnel followed normal work practices, followed label directions, and operated in compliance with regulatory requirements. During the second application (T2), in addition to the foregoing procedures, the workers all wore protective clothing (disposable coveralls, chemically impervious gloves and boots, and clean hats), were instructed to wash before rest stops and meals, and were instructed in further good hygiene practices by research personnel in the field.[1]

[1]Deviations from prescribed operating conditions are noted in the report by Lavy (1).

The applicators consisted of 3 crews of 6 persons each. Each crew was comprised of 1 helicopter pilot, 1 mechanic, 1 batchman-loader, 1 supervisor, and 2 observers. The members of crew number 1 were employees of Weyerhauser Company, and crews number 2 and 3 were comprised of commercial applicators. Details of the applicator personnel and specific operating conditions are given in the report by T. L. Lavy (1).

Three indicators of worker exposure to 2,4-D were monitored: analysis of ambient air concentration of 2,4-D esters; analysis of patch samples attached to the workers clothing for 2,4-D esters; and analysis of total voided urine samples for 2,4-D and 2,4-D conjugates. The analytical methods and their validation are fully discussed in the report by Lavy.

RESULTS AND DISCUSSION

Airborne 2,4-D. Only one of the 36 personnel air monitors showed a detectable level of 2,4-D esters, and since this airborne concentration could account for no more than 1% of the 2,4-D excreted in the urine of this worker (No. 33, T1) it was concluded that the inhalation route of exposure was negligible under these conditions. None of the 10 air monitors placed

near the batch trucks at the heliports revealed detectable levels of 2,4-D esters. Only 2 of the 5 air monitors placed directly in the spray areas revealed detectable concentrations of 2,4-D esters (equivalent to 0.033 and 0.167 µg 2,4-D per liter of air). Further corroboration of the negligible exposure hazard to phenoxy herbicides via the airborne route is given by similar results following both aerial and ground application of 2,4,5-T sprays in the forest (8).

Patch Sample 2,4-D. Widely varying quantities of 2,4-D were detected on the various patch samples. But the poor correlation between the estimated quantity of 2,4-D absorbed based on these data, and the amount excreted in the urine (see following section) shows that this indirect method of estimating the absorbed dose has little validity. In a similar study with 2,4,5-T spray applications in the forest, patch samples were shown to be inadequate indicators of the amount of 2,4,5-T actually absorbed (8).

Urinary 2,4-D. The analysis of total urinary 2,4-D (on a daily basis) on the application day and for 5 days thereafter showed detectable quantities of 2,4-D for 22 of the 36 exposures comprising the study. The total quantity of urinary 2,4-D excreted on the application day and for 5 days thereafter

was divided by the individual worker's body weight to yield an estimate of the absorbed dose in mg 2,4-D per kg body weight (mg/kg). These data for each worker are shown in Table 1 which is a condensation of the same data presented by Lavy (1).

The dose levels thus reported are believed to be reliable and realistic estimates of the total absorbed dose of 2,4-D for the following reasons:

Pharmacokinetic studies with 2,4-D in rats (2) have shown that orally ingested or intravenously administered 2,4-D is excreted primarily in the urine by a first order process with a half-life of approximately 2 hours. Thus, the rapid and efficient urinary excretion of 2,4-D appears to be essentially independent of the route of administration. Further studies (3) have shown that the PGBE esters of 2,4-D applied to the skin of rats are absorbed through the skin at a first order rate with a half-life of about 20 hours, and are then rapidly excreted as 2,4-D acid in the urine.

In human volunteers (4) given an oral dose of 5 mg 2,4-D per kg, virtually the entire dose (greater than 95%) was excreted

in the urine as 2,4-D and 2,4-D conjugates by a first order process with an average half-life of approximately 11 hours.[1]

The foregoing data demonstrate that urine is indeed the major excretory route for 2,4-D in both rats and humans, and that urinary excretion is an efficient process that can be described by first order kinetics at non-saturating dose levels (i.e., below approximately 50 mg 2,4-D per kg (2)). Therefore, the measurement of total urinary 2,4-D and its conjugates during the spray application day and for 5 days thereafter (as reported in Table 1 and Reference 1) is considered to be a realistic approximation of the total quantity of 2,4-D absorbed.

Further support for the reliability of urinary 2,4-D measurements in estimating the absorbed dose is derived from comparison with another closely related phenoxyacetic acid herbicide, 2,4,5-T. This compound is also excreted almost exclusively in the urine of rats, dogs and humans (5,6,7) by a first order process that is apparently independent of the route of exposure. And the PGBE esters of 2,4,5-T (10), like the PGBE

[1]Sauerhoff et al. (4) calculated the half-life for urinary excretion of unconjugated 2,4-D as 17.7 hours. However, the inclusion of urinary conjugates of 2,4-D with these data (subjects no. 1, 2 and 3, reference 4) indicate an average half-life of approximately 11 hours for the excretion of both conjugated and unconjugated 2,4-D.

esters of 2,4-D (3), are absorbed relatively slowly through the skin of rats and then efficiently excreted in the urine as the corresponding phenoxy acid.

Urinary 2,4,5-T has been shown to be a reliable indicator of the quantity of 2,4,5-T absorbed by forestry workers during application of 2,4,5-T sprays (8,9). In that study, urinary concentrations of 2,4,5-T were measurable for several days following the spray application in some of the workers, which enabled determination of the pharmacokinetic model parameters for the dermal absorption and urinary excretion of 2,4,5-T (9). Thus, the half-life for dermal absorption of 2,4,5-T esters in humans was shown to be approximately 18 hours.

In contrast to the 2,4,5-T study cited above, the levels of urinary 2,4-D in the present study could not be measured for a sufficient length of time (because the exposure levels were so low that the concentration of urinary 2,4-D was often below the analytical detection limit) to allow direct determination of the first order rate constant for the dermal absorption of 2,4-D esters in these workers. However, because of the close similarity between the pharmacokinetic profiles of 2,4-D and 2,4,5-T, the rate of dermal absorption of 2,4-D esters in humans may be similar to that for 2,4,5-T esters. This assumption is supported by the observation

that the half-life values for the dermal absorption of the PGBE esters of 2,4-D and 2,4,5-T in rats are similar, approximately 20 hours and 24 hours, respectively (3,10).

In order to calculate the pharmacokinetic fate of dermally absorbed 2,4-D in humans, numerical values for the rate constants of absorption and elimination are required. Based on the considerations above, the dermal absorption rate constant of 2,4-D esters in humans was assigned the same value as that for 2,4,5-T esters (half-life = 18 hours) (9). The urinary excretion rate constant of 2,4-D and conjugates was assigned the value previously determined in a human study (half-life = 11 hours) (4). These values then allowed the calculation of the amount of dermally absorbed 2,4-D that is excreted in the urine at any time following exposure (9). This calculation reveals that approximately 99% of a dermally absorbed dose of 2,4-D esters would be excreted in the urine as 2,4-D and conjugates during the exposure day and for 5 days thereafter.

These values for the rate constants were also used to obtain a computer simulation of the body concentration of 2,4-D that would result from repeated daily dermal exposures to 2,4-D esters. The results of this prediction are shown in Figure 1 in which the body burden of 2,4-D is given in units

of the dose that has been absorbed thru the skin. This simulation shows that the maximum body burden attained would be approximately 0.7 times the daily dose. In other words, if a dose of 0.050 mg 2,4-D per kg were absorbed through the skin each day the maximum concentration attained in the body after repeated daily exposures would be only 0.035 mg/kg. This bioaccumulation factor is less than might be expected (as calculated based on 1 dose per day) because the absorption rate constant in the pharmacokinetic model is less than the elimination rate constant (i.e., a flip-flop model). Furthermore, the simulation shows that over 90% of this maximum concentration would be reached after 4 daily exposures.

The quantitative precision of this prediction is limited by the underlying assumptions. However it is apparent that, as long as 2,4-D is not absorbed at saturating dose levels (orally administered doses of 5 mg 2,4-D/kg in humans show no evidence of saturation (4)), even repeated exposures to 2,4-D will not result in continually increasing accumulation in the body.

Exposure Comparisons. Based on the absorbed dose levels reported in Table 1, the following comparisons concern possible differences in exposure to applicators based on

usual (T1) versus more stringent (T2) application procedures, possible differences between application crews, and different job descriptions within all 3 crews.

Even though the dose levels received by the workers operating under usual conditions (T1) were very low, there was nevertheless a slight but statistically significant reduction ($p<0.05$, two-tailed Wilcoxon matched-pairs signed-rank test) in the dose levels received by these same workers when utilizing protective clothing (T2). Of the fifteen exposures in which urinary 2,4-D was detected in one or the other treatment (i.e., either T1 or T2), 11 exhibited a decrease in dose level during the second exposure (T2) whereas 4 showed an increase in urinary 2,4-D.

Among the 3 different crews, there was no statistically significant difference in dose levels when compared by a nonparametric analysis of variance. However a nonparametric t-test revealed that the workers of crew 1 received a significantly lower dose than did the workers of crew 3 ($p<0.05$).

As would be expected, those workers in closer contact with the sprays (pilots, mechanics, and batchmen) received a significantly greater dose level than did the workers more

remote (supervisors and observers) when compared by a non-parametric analysis of variance ($p<0.05$). A similar correlation between close contact with the spray mixtures and absorbed dose level was observed with crews applying 2,4,5-T sprays in the forest (9).

In conclusion, forest workers engaged in the aerial application of 2,4-D absorbed minimal quantities of 2,4-D based on total urinary excretion data. Of the 36 total exposures comprising this study, 14 did not result in detectable concentrations of urinary 2,4-D. Of the 22 exposures yielding detectable concentrations of urinary 2,4-D, the maximum dose level was only 0.0557 mg/kg, while the lowest was 0.00038 mg/kg. Repeated daily exposures to 2,4-D formulations are not expected to result in continually increasing accumulation in the body. The very low exposure potential demonstrated by this study, coupled with the low toxicity of 2,4-D, supports the continued registration and use of this herbicide.

DOSE LEVELS OF 2,4-D IN FOREST WORKERS

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TABLE 1

ABSORBED DOSE OF 2,4-D IN FOREST WORKERS
ESTIMATED FROM URINARY EXCRETION OF 2,4-D*

		mg 2,4-D/kg Body Weight**	
		Ordinary Precautions	Special Precautions
CREW 1 -	Pilot	0.00179	nd
	Mechanic	0.00044	nd
	Batchman	0.00215	0.00053
	Supervisor	nd	0.00038
	Observer	nd	0.00056
	Observer	0.00055	nd
CREW 2 -	Pilot	0.0557	0.0237
	Mechanic	0.00232	0.00516
	Batchman	0.0189	0.0196
	Supervisor	nd	nd
	Observer	nd	nd
	Observer	nd	nd
CREW 3 -	Pilot	0.00206	0.00192
	Mechanic	0.0136	0.00388
	Batchman	0.0377	0.0219
	Supervisor	0.00692	nd
	Observer	0.0011	nd
	Observer	0.0013	nd

*From T. L. Lavy (1), Table 21, p. 48.

**nd = not detectable at a detection limit of 0.04 ppm 2,4-D in urine.

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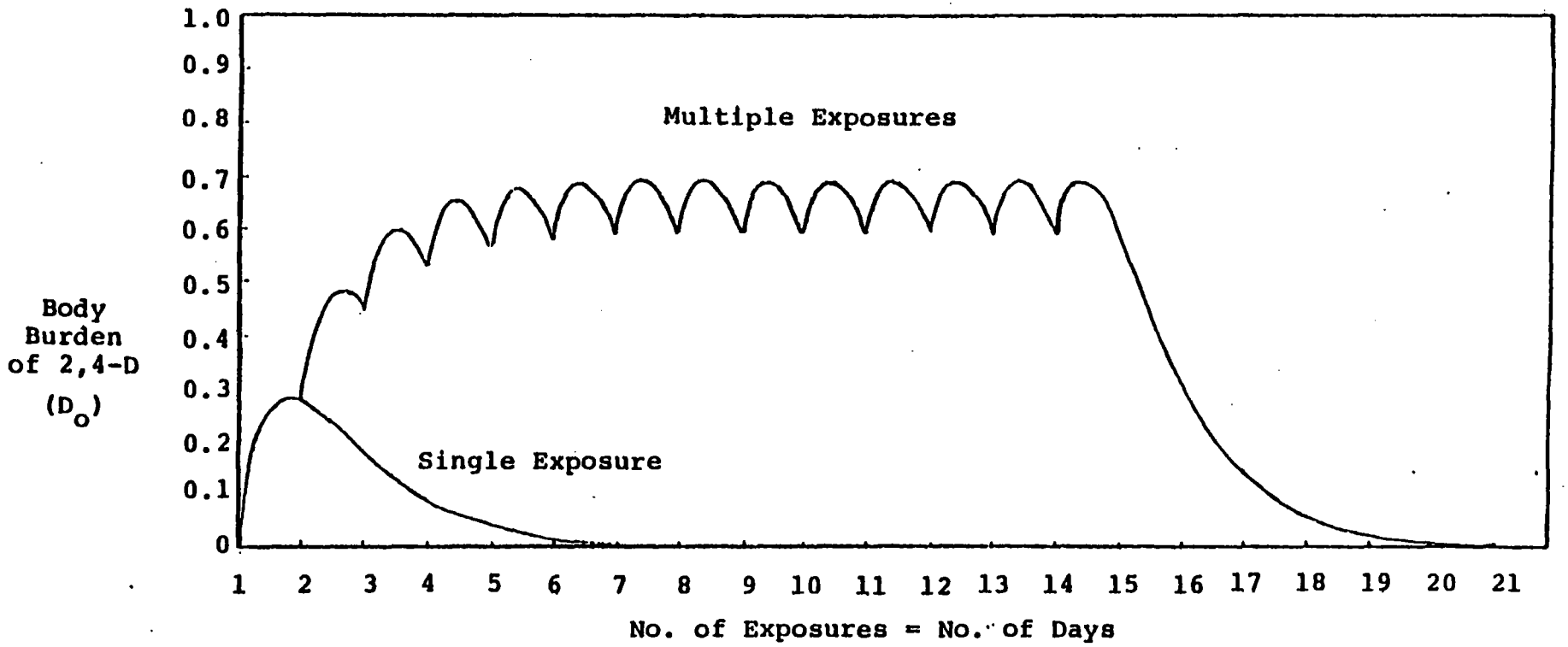

FIGURE 1. Simulated body burden of 2,4-D in humans after a single dermal exposure and after repeated (daily) dermal exposures. The body burden is expressed in units of the dose level applied to the skin (D_o). Digital computer simulation based on assumptions described in the text.

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Subject: 2,4-D TESTS

OTTAWA, October 23, 1980 -- Agriculture Minister Eugene Whelan today announced that tests conducted by Agriculture Canada have identified previously unrecognized contaminants in some samples of the herbicide 2,4-D.

Scientists in Agriculture Canada's Food Production and Inspection Branch, using state-of-the-art technology, have found that some 2,4-D products contain dioxin contaminants.

It has generally been believed that 2,4-D products are dioxin-free. The majority of world tests have focussed on what is recognized to be the most acutely toxic member of the dioxin family, the 2,3,7,8-TCDD isomer. This dioxin has never been identified in 2,4-D.

The intensive Agriculture Canada tests just completed have again confirmed the absence of 2,3,7,8-TCDD in 2,4-D. Other dioxin contaminants were, however, identified in some 2,4-D products, while no dioxin contamination was detected in other 2,4-D samples tested.

"We are now assessing these results in concert with officials in Health and Welfare Canada who work in co-operation with us in pesticide regulation.

"A decision on how our new findings will affect the permitted uses of 2,4-D will be made before the 1981 growing season," Mr. Whelan said.

The herbicide 2,4-D is used to control broad-leaf weeds in everything from lawns to cereal fields. About eight million pounds of 2,4-D is used in Canada each year. This represents about 25 per cent of total herbicide use.

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"These findings clearly identify dioxin contaminants in some, but not all, 2,4-D samples examined. Work is continuing to gain a broader and more detailed understanding of these new findings."

"When some pesticide products were registered, today's highly-sophisticated testing equipment did not exist. The investment my department has made in high-priced laboratory equipment and in highly-trained scientists is paying off with results like these.

"My main concern is about the safety of all pesticide products used in Canada.

"I can guarantee the public that Agriculture Canada will continue to work hard in keeping agricultural chemicals under constant review and to provide answers to concerns that may arise as a result of the review process," Mr. Whelan said.

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For more information, media may contact:

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CBC "Radio Noon" October 27, 1980 12:16 to 12:20 p.m.
Prof Steve Safe, U of Guelph, Re Dioxin levels in 24-D and 245-T (4 minutes)

* * *

Professor Steve Safe says dioxin found by Agriculture Canada in 24-D samples is relatively non-toxic. Late last week A. D. St. Clair, President of the Canadian Agricultural Chemicals Association, said he was pleased the Federal test of 24-D showed none of the highly-toxic dioxin found in the banned herbicide 245-T. Dr. Safe explains the difference between that lethal form of dioxin and the type of dioxin found in 24-D.

SS There are major differences. It turns out with 245-T, the expected by-product turns out to be the most toxic dioxin in the whole series. There are a number of different dioxins. With 24-D the expected by-products which have been identified are relatively non-toxic and it turns out it's because of the starting material -- in one case it's 24 Diplorafino; in the other case it's 245 Trichlorofino. So we tend to get lower chlorinated dioxins because of their structure. They're much less toxic, although certainly more work has to be done on them, and in addition they're probably much less persistent.

Q When you say less toxic, is there some kind of an example you could use to compare them to that very seriously toxic dioxin?

SS Well, the easiest example is that in any case where they've been studied, and they haven't been studied in detail, but the major one, I think, is the 27 Dichloral dioxin, and there's no data as far as I know in the literature indicating that it's a toxic chemical. It is relatively non-toxic. It's, I would expect or predict, several orders of magnitude less toxic, and certainly much less because it would be expected to

(SS) be broken down pretty quickly in the environment.

Q It would seem that if dioxin, including the either lethal ones or the relatively safe ones occur in the manufacturing processes of some of these herbicides, that we should ask some questions about how they do occur and how we can be assured that minimal amounts will be there when they are manufactured.

SS Yeah, I think the fact that the dioxins have been isolated is important. They were not isolated in comperable preparations, in all preparations, or in many preparations from Europe, and they were looked for by good people before. I think they can be made to minimize or eliminate those dioxins, and it does turn out that the dioxins that have been identified and that you would predict would be present are relatively non-toxic. So the 24-D, luckily, we went out.

Q Since they are relatively innocuous in 24-D, why then is the Federal Government doing these sample tests?

SS Well, I think they're doing the tests because they're as sensitized as everyone else is to dioxins, and I think, I have a feeling, and I know some of the people that are doing the work, and I think the government wants to know. They want to know, and, if necessary, advise the companies and perhaps advise the public, and perhaps it can be changed. I think there are methods to produce 24-D, to eliminate or almost eliminate the dioxin by-products.

Q Steve Safe, Professor of Biochemistry at the University of Guelph.

* * *

WAYNE ORMEROD DOES NOT MENTION RATES OF TOXICITY IN HIS PRESS RELEASE. IF ASKED ABOUT TOXICITY, HE INTENDS TO REPLY AS FOLLOWS:

1. IN CONJUNCTION WITH THE HEALTH PROTECTION BRANCH OF THE DEPT. OF HEALTH AND WELFARE, THE DIOXINS IDENTIFIED AS BEING IN SOME 2,4-D PRODUCTS ARE NOT THE HIGHLY TOXIC 2,3,7,8 TCDD ASSOCIATED ONLY WITH 2,4,5-T.

2. THERE ARE THREE TYPES OF DIOXINS THAT HAVE BEEN IDENTIFIED. THESE ARE THE DIPOLYCHLORINATED DIBENZOPARADIOXINS (PCDD), THE TRI PCDD'S AND THE TETRA PCDD'S.

3. ACUTE TOXICITY TESTS FROM PUBLISHED TOXICOLOGICAL INFORMATION INDICATES THAT THE DIDI-ISOMERS OF PCDD ARE ONE MILLION FOLD LESS TOXIC THAN 2,3,7,8 TCDD.

4. ACUTE TOXICITY TESTS OF THE TETRA ISOMERS OF PCDD INDICATES THAT THEY ARE 50,000 TIMES LESS TOXIC THAN 2,3,7,8 TCDD.

5. ACUTE TOXICITY TESTS OF THE TRI ISOMERS OF PCDD ARE 15,000 TIMES LESS TOXIC THAN 2,3,7,8 TCDD.

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PLEASE NOTE NUMBER THREE, LINE TWO, SHOULD READ DI-ISOMERS.

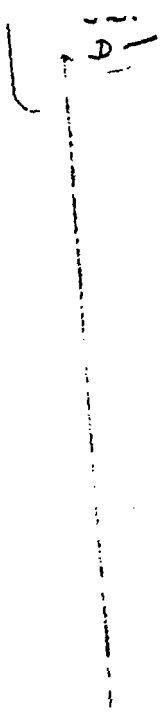

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Exhibit 895

Determination of 2,4-D Exposure Received by Forestry Applicators Spring 1980

Principal Investigator:
Terry L. Lavy, Ph.D.
University of Arkansas

In Cooperation With
Dow Chemical, U.S.A.

October, 1980

Sponsored by:

National Forest Products Association

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National Forest
Products Association

John F. Hall
Vice President,
Resource and Environment

Forest Industries Building • 1619 Massachusetts Avenue, N.W.
Washington, D.C. 20036 • 202/797-5858

November 14, 1980

Mr. Edwin L. Johnson
Deputy Assistant Administrator
for Pesticide Programs
Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Dear Ed:

The National Forest Products Association submits the attached research report entitled "Determination of 2,4-D Exposure Received by Forestry Applicators, Spring 1980" for EPA use in its Forest Chemicals Use Project and in response to EPA's FIFRA Section 3(c)(2)(B) notice in connection with 2,4-D registrations. This study was conducted with the cooperation and assistance of the Dow Chemical Company and the enclosed report includes a Dow paper entitled "Dose Levels of 2,4-D in Forest Workers."

This study confirms that forest workers absorb only low doses of 2,4-D during aerial application of this herbicide. Resulting safety factors for exposed workers are substantial -- ranging from 1,212 to 48,980 in relation to the Scientific Advisory Panel's 500 ppm NOEL for reproductive toxicity -- even without special precautions during the loading and application process. The study also indicates that still lower exposure and larger safety factors can be achieved when special precautionary measures are taken including applicator use of disposable coveralls, chemically impervious gloves and boots, and strict personal hygienic practices. Safety factors, under these special circumstances, range from 1,714 to 266,667.

The study is similar to NFPA's "Measurement of 2,4,5-T Exposure of Forest Workers" submitted to EPA in February, 1979. You may recall that NFPA's February 14, 1979 cover letter accompanying the 2,4,5-T study proposed a follow-up investigation which would have examined the effects of added precautions during the 2,4,5-T application process. Since EPA declined to allow the use of 2,4,5-T for the post-suspension experiment, NFPA elected to conduct the follow-up study using 2,4-D.

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The enclosed study, like its predecessor study, was conducted by T.L. Lavy, Ph.D. of the Altheimer Laboratory, University of Arkansas. The protocol for this study, developed by Dr. Lavy and a committee of forest industry scientists, was submitted to EPA for review and comment before the study was undertaken. NFPA is grateful for the assistance rendered by EPA personnel and found that their comments substantially contributed to a better research project.

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NFPA would welcome more extensive EPA involvement in future research activities of this sort. The forest industry believes that cooperative scientific effort involving both the regulatory agency and the regulated public is a more fruitful way of resolving the controversies that arise concerning pesticide use than the adversarial proceedings which have marked the history of pesticide regulation.

I. GENERAL STUDY DESCRIPTION

A. Crews

The enclosed exposure study investigates the dose level of 2,4-D absorbed by forest workers as a consequence of the helicopter application of 2,4-D sprays. Three spray crews, each comprised of six workers, participated in the study. Each crew consisted of a pilot, a mechanic, a batchman-loader, a supervisor, and two forest observers. Observers were included in the study to enable measurement of whatever 2,4-D dose is received by individuals not involved in the spray application but who are proximate to the spray site.

Each of the three helicopter crews participated in two different application tests. In the first test, designated T1, measurements were taken on crew members performing their duties in the customary manner using ordinary application precautions. Crew members were instructed to dress and to perform their duties in a normal fashion. The second test, designated T2, was conducted following conclusion of T1. During T2, the workers are outfitted with special protective clothing including disposable coveralls, chemically impervious gloves and boots, and clean hats. In addition, crew members were instructed to wash before rest stops and meals and were instructed to observe other stringent hygienic practices by research personnel in the field.

B. Location

Three different spray locations were selected for these studies, so as to represent the range of site conditions encountered in Pacific Northwest forestry. Crew 1 operated near Raymond, Washington in a forest site typical of the moderately steep slopes of the Washington Coast Range. Crew 2 operated near Gardiner, Oregon, in an area representative of the highly dissected topography of the Oregon Coast Range. Crew 3, operated near Cottage Grove, Oregon in the western foothills of the Oregon Cascade Range.

Two sites within 10 miles of each other at each geographic location were chosen for T1 and T2 treatments with 2,4-D. Each site consisted of approximately 100 acres of Douglas-Fir which required release from competing vegetation.

II. TEST METHODS

Lavy, et al. used three methods to estimate crew exposure to 2,4-D: (1) air samples, (2) denim patches, and (3) urine samples. The detailed analytical results for each test method appear in tables 10 (air monitors), 14A-14B (patches), and 16A-18B (urinalysis). Analysis of those data, confirm Lavy et al.'s findings in the 2,4,5-T Exposure Study, that (1) airborne 2,4-D is an insignificant exposures avenue for forest workers and (2) that patch data is not a reliable means of estimating absorbed dose. These data also confirm that measurement of urinary 2,4-D content is the most reliable means of estimating absorbed dosages. Accordingly, only the urinanalysis data are discussed below.

III. RESULTS

Table 21, reproduced in modified fashion below, summarizes the estimated maximum initial dose received by each crew member for both T1 (regular precautions) and T2 (special precautions) utilizing measurements of total urinary 2,4-D.

ABSORBED DOSE OF 2,4-D IN FOREST WORKERS
ESTIMATED FROM URINARY EXCRETION OF 2,4-D

		mg 2,4-D/kg Body Weight	
		Ordinary Precautions	Special Precautions
CREW 1 -	Pilot	0.00179	nd*
	Mechanic	0.00044	nd
	Batchman	0.00215	0.00053
	Supervisor	nd	0.00038
	Observer	nd	0.00056
	Observer	0.00055	nd
CREW 2 -	Pilot	0.0557	0.0237
	Mechanic	0.00232	0.00516
	Batchman	0.0189	0.0196
	Supervisor	nd	nd
	Observer	nd	nd
	Observer	nd	nd
CREW 3 -	Pilot	0.00206	0.00192
	Mechanic	0.0136	0.00388
	Batchman	0.0377	0.0219
	Supervisor	0.00692	nd
	Observer	0.0011	nd
	Observer	0.0013	nd

*nd = not detectable at a detection limit of 0.04 ppm

Fourteen of the thirty-six exposures did not result in detectable quantities of urinary 2,4-D. Of the 22 exposures with detectable quantities, the dose level ranged from 0.00038 mg/kg (T2) to a maximum level of 0.0557 mg/kg (T1).

Although the dose levels received by crew members employing usual precautions in T1 were quite low, the same workers generally experienced a statistically significant reduction in dose, or none at all, when utilizing special precautions in T2. Six workers who received some dose in T1 received no dose in T2. Of the fifteen crew members who received some dose in T1 or T2, eleven exhibited a decreased dose during T2. Four crew members, however, showed an increased dose during T2.

As might be expected, intuitively, those crew members with the higher values were most intimately connected with the spray operation. Pilots, mechanics, and batchman received a significantly greater dose level than supervisors and observers who were more removed from the spray operation. Since this latter observation confirms a similar conclusion drawn by Lavy et al. in the 2,4,5-T Exposure Study, one can confidently conclude that spray crew dose levels represent a worst-case situation and that "involuntary" exposure opportunities for the general population diminish as a function of distance from the actual spray operation.

IV. Safety Factors

Although EPA has sought some additional toxicological information concerning 2,4-D through a section 3(c)(2)(B) notice, general agreement in the scientific community already exists on a no-observable effect level for 2,4-D reproductive toxicity. EPA's April 22, 1980 "2,4-D Fact Sheet" accompanying the Agency's announcement of its 3(c)(2)(B) actions acknowledged that "almost all animal tests conducted on the potential reproductive effects of 2,4-D show that . . . there is a no-effect level for injury to the fetus (fetotoxicity) from 2,4-D." Fact Sheet, Section II. 4. The Fact Sheet also stated that "based on the NOELs in the animal studies, EPA estimates that the level of exposure in a "worst case" situation (e.g. a person standing directly under a spray plane) would be 500-1,000 times less than the dose level that might cause an effect." Fact Sheet, Section IV, B.3.

These conclusions were confirmed by the FIFRA Scientific Advisory Panel's review of 2,4-D literature to determine what further tests EPA should require pursuant to its Section 3(c)(2)(B) authority. The SAP unanimously

concluded that, "In our opinion 500 ppm should be considered as a no observed effect level (NOEL) for reproductive toxicity in rats exposed to 2,4-D and should be used in estimating the potential reproductive toxicity to 2,4-D to humans exposed to this compound." Scientific Advisory Panel Report at 4.

The table, below, displays the safety factors for crew member by job classification using the SAP's 500 ppm NOEL converted to mg 2,4-D per kg body weight*

SAFETY FACTORS

BY JOB CLASSIFICATION

	Estimated Average Initial Dose of 2,4-D in mg/kg		SAP NOEL For Reproductive Toxicity	Safety Factor	
	T1	T2		T1	T2
Pilots	.0198	.00854	24 mg/kg*	1,212	2,810
Mechanics	.00545	.00301	24 mg/kg	4,404	7,973
Batchmen	.0198	.0140	24 mg/kg	1,212	1,714
Supervisors	.00231	.00013	24 mg/kg	10,390	184,615
Observers	.00049	.00009	24 mg/kg	48,980	266,667

T1 (ordinary precautions) safety factors for crewmen ranged from 1,212 to 48,980. Pilots, mechanics, and batchmen who received the highest 2,4-D doses have ample margins of safety even in T1 when ordinary safety precautions were observed. Supervisors' and observers' safety factors were so large in T1 (10,390-48,980), that further improvement could only be of academic interest.

In T2, the already substantial safety factors found in T1 were further improved and ranged from 1,714 to 266,667.

It appears then, that the 500-1000 fold "worst case" safety margins announced by EPA in Section IV B.3. of its April 22, 1980 2,4-D Fact Sheet, are quite conservative. The Exposure Study clearly demonstrates that actual field applications without extraordinary precautions (i.e. T1), can substantially exceed the 500 to 1000 fold safety margins EPA found adequate in its April 22 document. Although crew safety factors were substantially improved by the special pre-

* The SAP's 500 ppm NOEL for 2,4-D reproductive toxicity was converted to 24 mg 2,4-D per kg body weight as follows:

500 ug/g 2,4-D in feed X 12g feed/day = 6000 ug or 6 mg 2,4-D dose per day.

$$\frac{\text{6 mg 2,4-D per day}}{\text{0.25 kg body weight}} = \text{24 mg 2,4-D/kg/day}$$

cautions observed in T2, there seems to be little point in adopting the T2 special precautions day-to-day field operations since the safety margins in T1 were already substantial.

The National Forest Products Association would be pleased to discuss both the methodology and results of the 2,4-D Exposure Study with EPA representatives. In addition, NFPA would be pleased to furnish EPA with an aliquot of the remaining urine samples so that the Agency can run confirmatory analyses.

As always, we remain committed to providing EPA with useful information about forest use chemicals. We believe that the enclosed exposure study significantly advances the current state of knowledge concerning forest worker exposure to 2,4-D following aerial application of that herbicide. NFPA hopes that EPA will increase its level of participation with the forest industry in these dispassionate scientific inquiries so that future regulatory decisions about forest chemicals can be based on the best information available.

Respectfully submitted,

John F. Hall

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Toxics law could stimulate innovation

The 1976 Toxic Substances Control Act, long decried by the chemical industry as a hindrance to innovation, may, in fact, stimulate the development of new and safer chemicals. So finds a study prepared for EPA by Massachusetts Institute of Technology's Center for Policy Alternatives. The study concludes that although the impact of the law is not predictable, the agency can do much to thwart any negative effects. Among the suggestions to offset any discouraging effects are generic premanufacturing notifications for selected classes of new chemicals, "fast-track" premanufacturing reviews for safe chemicals or major innovations, and government subsidy of the testing and compliance costs of new chemical development. To complement this report, EPA has begun a three-year study analyzing innovation in the chemical industry. The MIT report can be obtained from EPA's Industry Assistance Office in Washington, D.C.

Industrial boilers destroy PCB's safely

EPA has found that polychlorinated biphenyls (PCB's) can be destroyed safely by burning them in high-efficiency industrial boilers. Tests were performed last May at the Chevrolet plant in Bay City, Mich. A mixture of PCB-containing oil and No. 6 fuel oil was burned having a final PCB concentration of about 50 ppm. Monitoring of the emissions found no PCB's or other toxic substances, meaning that at least 99.99% of the PCB's had been destroyed. Finding a safe method for disposal of PCB's has been a problem for EPA since it was given the task in the 1976 Toxic Substances Control Act. These findings suggest that many industrial boilers throughout the U.S. can be used to destroy PCB-containing wastes without risk to health or the environment.

Park service halts use of 2,4-D

The National Park Service is suspending use of the herbicide 2,4-D in its 325 parks and recreation areas. Park service spokesman Duncan Morrow says that this action comes on the heels of pressure from environmental groups, which cited spontaneous abortions and birth defects as adverse reactions to the weed killer. One of the major manufacturers of 2,4-D, Dow Chemical, says that in 30 years of marketing there has been "absolutely no problem associated with the chemical." EPA is studying 2,4-D. So far the agency says the evidence of adverse health effects is inconclusive, and it has no plans to ban the herbicide's use.

Two California air standards overturned

Under a special procedure to hear the petroleum industry's lawsuit against the California Air Resources Board, retired state judge Eugene Sax ruled in a memorandum of intended decision that the board must rescind its strict sulfur dioxide and sulfate standards. In his ruling, Judge Sax declares that the board adopted the standards without adequate procedures and without careful consideration of economic impacts. Further, he says, the standards went beyond the recommendations of the state health department. The Air Resources Board has indicated that it will appeal this ruling, and will particularly challenge the contention of economic impact. A board spokesman tells C&EN that standards, as opposed to regulations, are based on health, not economic considerations.

House wrangling over committee seats

The 33 seats the Republicans snatched from the Democrats in the recent election mandate a change in the number of members of each party who sit on each of the House's 22 committees. But Republicans are already crying "foul." Rep. Bud Shuster (R.-Pa.), chairman of the Republican Policy Committee, charges that Speaker Tip O'Neill (D.-Mass.) is trying to stack the three most important committees in the House—Appropriations, Rules, and Ways & Means—by maintaining the current ratio of Republicans to Democrats on those three committees, while changing the ratio on all other committees to approximate the overall ratio in the House. According to the Republicans' calculations, they should pick up a total of 12 seats among those committees, which would make it harder for the Democrats to garner the majority vote needed to move legislation out of committee.

Gulf refutes council's pricing charges

Gulf Oil Chemicals Co. has issued a strong denial of charges by the Council on Wage & Price Stability that the company did not comply with the voluntary price guidelines in the third quarter of 1979. During the entire first year the guidelines were in effect, October 1978 through September 1979, the company says that its profits were about $60 million less than those permitted by the council's original rules. According to the company, eight months after the program began the council changed the rules and imposed a "condition" that the company was not to raise its average prices during the quarter except to pass through specified cost increases. Gulf says it complied but that later the council changed the rules again, interpreting the "condition" to mean that Gulf had to lower its prices, with the result that the company would lose money during the quarter. Gulf says it "finds this interpretation unacceptable."

Washington roundup

- The Justice Department's antitrust division, without any action, has closed a five-year-old investigation of alleged improper pricing practices and communications in the aluminum industry.
- The American Arbitration Association says it stands ready to provide arbiters to help resolve disputes between pesticide manufacturers arising from the use of technical data produced by one and used by another.
- After months of wrangling, the House and Senate have agreed on a binding budget resolution setting federal outlays for fiscal 1981 at $632.4 billion and revenues at $605 billion, leaving a deficit of $27.4 billion. It is unlikely that any of those figures will hold up.

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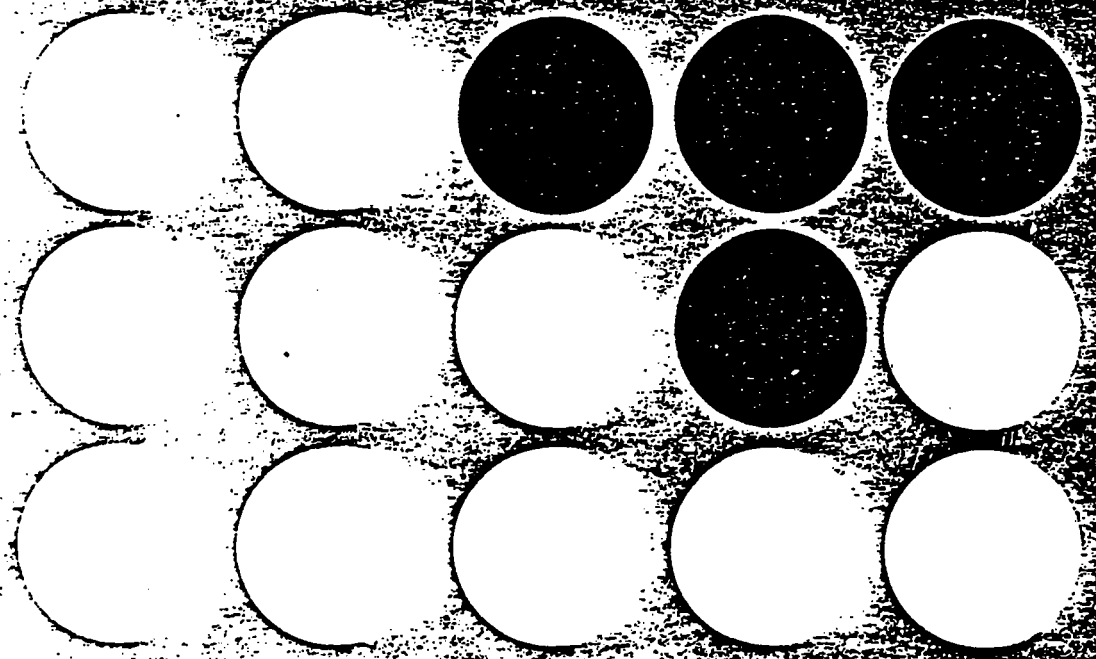

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Toxicology, 15 (1980) 135—144

ROLE OF THE ENDOCRINE SYSTEM IN THE ACTION OF 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD) ON THE THYMUS

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SUMMARY

Several experiments were conducted to study the involvement of the adrenal and the pituitary gland in the acute toxic effects of TCDD.

Adrenalectomized or hypophysectomized rats were treated with a single oral dose of 10 or 20 μg of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)/kg body weight. The reduced growth rate, the hepatotoxic effects and thymic involution induced by TCDD were not prevented by the adrenalectomy.

The pituitary gland did not appear to be involved in causing thymic involution. In fact, the thymic effects of TCDD intoxication were even somewhat increased in hypophysectomized rats. Treatment with growth hormone failed to prevent thymic involution or the influence of TCDD on the liver.

INTRODUCTION

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is an extremely toxic compound which has been found as an impurity in chlorinated phenols and other chemicals derived from chlorophenols. Trace amounts of TCDD and other dioxins, e.g. 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin, were isolated from animal fat which was mixed into the food of chickens resulting in the death of millions of broiler chickens from a syndrome referred to as chick edema disease [1,2]. The reported oral LD_{50} ranges from 0.6 μg/kg body wt in male guinea pigs to 115 μg TCDD/kg in rabbits. The LD_{50} for rats is about 50 μg TCDD/kg [3]. In rats given TCDD 5 days/week for 13 weeks, the no-toxic

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effect level based on liver enlargement was between 0.01 and 0.001 μg TCDD/kg body wt. In a chronic study in rats the incidence of some types of neoplasms were increased, whereas the incidence of other types were decreased at dose levels of 0.01 μg/kg body wt [4,5]. At higher doses TCDD induced a reduction in growth rate, progressive wasting disease, severe thymic involution and immune suppression [6--8]. Stress induced release of glucocorticoids was not considered to be responsible for atrophy of the thymus. In TCDD-exposed rats, decreased eosinophilia was observed in acidophilic cells in the adenohyphophysis, whereas the serum levels of growth hormone (GH) were increased. These changes may indicate a disturbance caused by TCDD in the relationship between the pituitary gland and the thymus, either by blockade of the GH receptor sites on the thymus or by a disturbed secretion by thymus epithelial cells [8].

To test the forgoing hypothesis, experiments were carried out using adrenalectomized or hypophysectomized rats. The interaction between TCDD and GH was studied also.

METHODS

The 2,3,7,8-TCDD utilized in these studies was supplied by Dow Chemical Company, Midland, MI, U.S.A. and was 99% pure. It was dissolved in reagent grade acetone and subsequently diluted with corn oil. The stock solution was calculated to contain 10 μg TCDD/ml. The TCDD-acetone-corn oil solution was administered via gastric intubation; the dose being calculated according to the weight of each rat (specific pathogen free female Fischer 344, Charles River, Wilmington, MA, U.S.A.). The volume given was either 0.1 or 0.2 ml/100 g body wt. Control animals were gavaged with an acetone corn oil mixture. Bovine growth hormone, NIH-GH-B17 (National Institutes of Health, Bethesda, MD, U.S.A.) was dissolved in 0.9% sodium chloride solution immediately prior to injection. All rats except those hypophysectomized were individually housed in suspended wire cages in animal quarters maintained under a rigid sanitary regimen. Temperature was maintained at 21 ± 1°C and relative humidity at 50 ± 5%. Four to 5 hypophysectomized rats were housed in each plastic cage to diminish body heat loss. Water and food (Wayne Sterilizable Lab-Blox, Allied Mills, Inc., Chicago, IL. U.S.A.) were available at all times.

Dorsal adrenalectomy or hypophysectomy by the parapharyngeal approach was performed by the supplier. Surgical procedures were carried out at least 1 week before the administration of TCDD. Adrenalectomized rats were given 1% sodium chloride in their drinking water; the hypophysectomized rats received 5% glucose in their drinking water.

Body weights were recorded at least twice a week. All rats were anesthetized with CO_2 gas and blood specimens obtained via cardiac puncture. Serum sodium and potassium concentrations were measured by the flame photometric method. Tissue samples for histopathologic evaluation were fixed in neutral buffered 10% formalin, paraffin-embedded, sectioned 6 μm

thick and stained with hematoxylin and eosin. Statistical analysis of the numerical results was preformed by the Student's *t*-test.

In the first experiment, groups of 10 normal and 10 adrenalectomized rats were given a single gavage of 10 μg TCDD/kg body wt in corn oil. Similar groups of 10 normal and 10 adrenalectomized rats received corn oil only. Five rats from each of the 4 groups were killed 3 and 10 days later. The following tests were performed on blood samples: serum sodium and potassium concentrations, packed cell volume, hemoglobin content, erythrocyte count, total and differential leukocyte counts. Lung, heart, spleen, liver, kidneys, thymus, adrenals, ovaries, uterus, brain, thyroid and pituitary gland were removed, trimmed, and weighed. Specimens were then retained for histopathologic evaluation.

In a second experiment, 2 groups of 5 normal rats received either corn oil or 20 μg TCDD/kg body wt, 1 group of 5 adrenalectomized rats were given corn oil and one group of 10 adrenalectomized rats 20 μg TCDD/kg body wt. Ten days later, the rats were killed, organ weights recorded, and the liver, thymus, and adrenals retained for histopathologic evaluation.

In the first hypophysectomy experiment, 8 normal rats received corn oil, and 9 hypophysectomized rats received 20 μg TCDD/kg body wt. Ten days later, the rats were killed, and the liver, spleen, thymus and adrenals were weighed. These tissues were also saved for histopathologic evaluation.

In the second experiment with hypophysectomized rats, the effect of GH was evaluated. Ten normal and 19 hypophysectomized rats were injected subcutaneously with 0.25 mg GH in 0.25 ml saline for 11 consecutive days. Similar numbers of normal and hypophysectomized rats received 0.25 mg saline daily. One day after the first injection with either GH or saline, one-half of the number of rats in each group received 20 μg TCDD/kg body wt. The other rats were given corn oil only. After 10 days, all rats were killed, the organ weights recorded, and specimens of the liver and thymus retained for histopathologic evaluation.

RESULTS

Adrenalectomized rats

First experiment

The body weight gain, serum sodium and potassium concentrations and relative weight of the thymus are presented in Table I. After 3 days there was a decrease in body weight gain caused by TCDD in both normal and adrenalectomized rats which persisted at the 10-day observation period. In fact the effect of TCDD on the body weight decrease of adrenalectomized rats was even more pronounced. The serum potassium concentration in adrenalectomized control rats was higher when compared to normal controls, probably due to the absence of aldosterone. The relative weight of the thymus of both the normal and adrenalectomized TCDD-treated rats was lower when compared with the control animals.

TABLE I

BODY WEIGHT GAIN, SERUM SODIUM AND POTASSIUM CONCENTRATION AND THYMUS/BODY WEIGHT RATIO OF NORMAL OF ADRENALECTOMIZED RATS RECEIVING A SINGLE ORAL DOSE OF 10 μg TCDD/kg BODY WEIGHT

The rats were killed after 3 or 10 days. Values presented are means ± S.D.

Parameter	Normal rats		Adrenalectomized rats	
	Corn oil	TCDD	Corn oil	TCDD
Killed after 3 days				
Number of rats	5	5	4	5
Body weight gain (g)	10 ± 2	4 ± 1**	13 ± 3	2 ± 7*
Sodium conc. (mmol/l)	145 ± 7	147 ± 3	134 ± 3	140 ± 8
Potassium conc. (mmol/l)	5.5 ± 1.0	5.2 ± 0.5	6.8 ± 0.7	8.3 ± 2.7
Relative weight of the thymus	0.26 ± 0.02	0.22 ± 0.02*	0.31 ± 0.05	0.26 ± 0.04
Killed after 10 days				
Number of rats	5	5	5	4
Body weight gain (g)	27 ± 3	20 ± 2**	31 ± 4	9 ± 3**
Sodium conc. (mmol/l)	138 ± 3	140 ± 6	134 ± 3	128 ± 5
Potassium conc. (mmol/l)	4.4 ± 0.1	5.0 ± 1.2	6.2 ± 0.6	7.2 ± 0.7*
Relative weight of the thymus	0.22 ± 0.01	0.14 ± 0.02**	0.34 ± 0.02	0.19 ± 0.03**

Values marked with asterisks differed significantly from appropriate control values: $^{**}P < 0.01$; $^{*}P < 0.05$.
Significance calculated by comparing TCDD to corn oil in both normal and adrenalectomized rats.

There was no significant effect on the leukocytes, hemoglobin concentration, packed cell volume and the number of erythrocytes.

Second experiment

The results of the second experiment with adrenalectomized rats are given in Table II. The effects of 20 μg were more pronounced than the effects of 10 μg TCDD in the first experiment. Not only the thymus to body weight ratio, but also the relative weight of the uterus decreased, whereas the relative liver weight was higher. There was no significant effect ($P < 0.05$) on the weight of the other organs. The increase of the weight of the lungs in the adrenalectomized rats is thought to be due to a decreased glucocorticoid level in the blood [9].

TABLE II

BODY WEIGHT GAIN AND ORGAN WEIGHTS, EXPRESSED IN PERCENTAGE OF THE BODY WEIGHT OF NORMAL OR ADRENALECTOMIZED RATS, RECEIVING A SINGLE DOSE OF 20 μg TCDD/kg BODY WEIGHT

The rats were killed 10 days after dosing. Values presented are means ± S.D.

Parameter	Normal rats		Adrenalectomized rats	
	Corn oil	TCDD	Corn oil	TCDD
Number of animals	5	5	4	10[a]
Initial body weight (g)	117 ± 4	115 ± 6	106 ± 5	110 ± 6
Body weight gain				
after 3 days (g)	9 ± 2	5 ± 2*	10 ± 4	−1 ± 6**
after 10 days (g)	23 ± 2	14 ± 5**	29 ± 4	9 ± 11*
Relative organ weights				
Lungs	0.70 ± 0.11	0.69 ± 0.03	0.83 ± 0.10	0.82 ± 0.09
Liver	4.43 ± 0.09	6.36 ± 0.14**[b]	4.34 ± 0.21	5.43 ± 0.85*
Spleen	0.25 ± 0.01	0.23 ± 0.01*	0.28 ± 0.03	0.30 ± 0.03
Adrenals	0.034 ± 0.004	0.034 ± 0.002	—	—
Thymus	0.23 ± 0.02	0.11 ± 0.01**	0.28 ± 0.02	0.11 ± 0.02**
Ovaries	0.052 ± 0.005	0.048 ± 0.005	0.056 ± 0.016	0.045 ± 0.007
Uterus	0.20 ± 0.11	0.11 ± 0.02	0.22 ± 0.10	0.12 ± 0.03
Brain	1.19 ± 0.02	1.28 ± 0.07*	1.29 ± 0.05	1.38 ± 0.14
Pituitary	0.006 ± 0.002	0.006 ± 0.001	0.007 ± 0.001	0.006 ± 0.001*

[a] Three animals died after 5 and 1 after 6 days respectively.
[b] Average of 4 animals only.
Values marked with asterisks differ significantly from appropriate control values: $^{**}P < 0.01$; $^{*}P < 0.05$.
Significance calculated by comparing TCDD to corn oil in both normal and adrenalectomized rats.

Histopathologic evaluation

Microscopic changes in the thymus of normal or adrenalectomized rats examined 3 and 10 days after a single dose of 10 μg TCDD were not remarkable. However, there was an indication of an increased number of mitotic figures and slight swelling of hepatocytes in TCDD-treated rats.

Rats treated with a dose of 20 μg/kg TCDD had a slight to moderate swelling of hepatocytes, hyperchromatism of individual cells and single cell necrosis in the liver as well as a slight involution of thymus. These effects were accentuated in the adrenalectomized rats treated with 20 μg/kg TCDD. The thymuses of these rats were moderately involuted. Special staining of the adrenals with Oil Red O for lipid did not reveal significant differences between the normal and the TCDD-treated rats.

Hypophysectomized rats

First experiment

In the course of the study, the hypophysectomized rats treated with 20 μg TCDD lost 5 ± 6 g body wt, whereas the control hypophysectomized rats gained 2 ± 2 g. The relative weights of the thymus were 0.05 ± 0.02 and 0.12 ± 0.03, respectively. Apparently hypophysectomy does not protect against body weight loss and enhances the thymus involution caused by TCDD. The relative weights of the liver, spleen and adrenals from TCDD treated rats were not different from those of the control hypophysectomized animals.

Second experiment

Daily injections of GH had a marked positive influence on the body weight in hypophysectomized animals, but there was no clear protection against TCDD in either the normal or hypophysectomized rats (Table III). The relative weight of the liver, thymus, spleen and adrenals are given in Table IV. The effect of TCDD on the thymus is even more pronounced in hypophysectomized rats, in comparison to the controls. Regular injections with GH failed to significantly prevent the thymic involution. In hypophysectomized rats TCDD did not significantly increase the relative weight of the liver unless there was GH stimulation, and even then the increase was minimal compared to normal rats given the same amount of TCDD. TCDD caused an increase in the relative weight of the spleen independent of GH injection in hypophysectomized rats only.

Histopathologic evaluation

TCDD injected in normal rats caused only a slight depletion of thymocytes from cortical region. The liver of these rats showed slight to moderate swelling of the hepatocytes.

The thymus of hypophysectomized rats treated with TCDD was markedly affected. There was a marked depletion of cellular elements from the cortex, dilatation of the blood vessels, and occasional hemorrhages. The liver of these animals showed random single cell necrosis and moderate swelling of the hepatocytes. There were also focal areas of centrolobular congestion in the liver. The microscopic appearance of the thymus and liver of TCDD-treated normal rats did not differ from those rats which had been given

TABLE III

INFLUENCE OF TCDD (20 μg TCDD/kg body wt) ON THE BODY WEIGHT GAIN OF NORMAL OR HYPOPHYSECTOMIZED RATS

Starting 1 day before the TCDD administration the rats were given daily s.c. injections of either saline or 0.25 mg growth hormone (GH). Values presented are means ± S.D.

Treatment	Normal rats				Hypophysectomized rats			
	Number of animals	Initial body wt	Body wt gain after		Number of animals	Initial body wt	Body wt gain after	
			3 days	10 days			3 days	10 days
Corn oil saline daily	5	117 ± 6	6 ± 2	22 ± 3	9[a]	101 ± 7	−1 ± 2	−2 ± 4
TCDD saline daily	5	117 ± 3	1 ± 2**	9 ± 4**	8[b]	101 ± 5	−7 ± 2**	−14 ± 6**
Corn oil GH daily	5	118 ± 3	8 ± 2	25 ± 4	9	105 ± 4	4 ± 3	16 ± 4
TCDD GH daily	5	118 ± 3	2 ± 2**	16 ± 3**	9	105 ± 4	0.4 ± 2**	8 ± 5**

[a] One animal died after 5 days.
[b] One animal died after 8 days.
Values marked with asterisks differ significantly from appropriate control values; $^{**}P < 0.01$; $^{*}P < 0.05$. Significance calculated by comparing TCDD to corn oil in both normal and hypophysectomized rats.

additional injections with GH. TCDD had only a slight to moderate effect on the thymus in hypophysectomized rats injected with GH. Six out of those 9 showed swelling of hepatocytes, occasional single cell necrosis, and some degenerative changes in the liver.

DISCUSSION

Glucocorticoid administration is known to produce a striking involution of the thymus and a less pronounced atrophy of the lymph nodes and spleen [10-12]. The atrophy of the thymus caused by TCDD dose not seem to result from an enhanced secretion of adrenocorticosteroids, since involution also occurred in our experiments with adrenalectomized rats. If the adrenal-thymus axis was involved in the TCDD action, one might also expect an atrophy of the spleen and a hypertrophy of the adrenals. However, in the present studies no influence on the spleen or the adrenals was noted, whereas in earlier TCDD studies, an increase in spleen weight and a decrease in adrenal weight was found [6]. In rats corticosteroid effects on the lymphoid system are associated with lymphopenia, eosinopenia, and an increase in

TABLE IV

ORGAN WEIGHTS, EXPRESSED IN PERCENTAGE OF THE BODY WEIGHT OF NORMAL OR HYPOPHYSECTOMIZED RATS, RECEIVING A SINGLE DOSE OF 20 μg TCDD/kg BODY WEIGHT

Starting 1 day before the administration of TCDD the rats were given daily s.c. injections of either saline or 0.25 mg growth hormone (GH). The rats were killed 10 days after dosing. Values presented are means ± S.D.

Treatment	No. of rats	Relative weight of the			
		Liver	Thymus	Adrenals	Spleen
Normal rats					
Corn oil saline daily	5	4.51 ± 0.31	0.22 ± 0.02	0.027 ± 0.005	0.258 ± 0.02
TCDD saline daily	5	6.28 ± 0.34**	0.10 ± 0.01**	0.023 ± 0.005	0.246 ± 0.01
Corn oil GH daily	5	4.37 ± 0.41	0.22 ± 0.01	0.027 ± 0.003	0.292 ± 0.05
TCDD GH daily	5	5.98 ± 0.35**	0.10 ± 0.01**	0.024 ± 0.001	0.258 ± 0.03
Hypophysectomized rats					
Corn oil saline daily	8	4.56 ± 0.29	0.16 ± 0.02	0.013 ± 0.002	0.200 ± 0.03
TCDD saline daily	7	4.33 ± 0.97	0.04 ± 0.02**	0.014 ± 0.004	0.258 ± 0.02**
Corn oil GH daily	9	4.14 ± 0.20	0.22 ± 0.03	0.013 ± 0.003	0.242 ± 0.02
TCDD GH daily	9	4.99 ± 0.24**	0.09 ± 0.02**	0.014 ± 0.002	0.286 ± 0.04**

Values marked with asterisks differ significantly from control values: $^{**}P < 0.01$; $^{*}P < 0.05$.
Significance calculated by comparing TCDD and saline to corn oil, TCDD and GH to corn oil and GH in both normal and hypophysectomized rats.

circulating polymorphonuclear leukocytes [13,14]. The experiments reported in this paper and previous investigations in which rats were injected with 10 μg TCDD for 10 to 14 consecutive days [15] failed to show a significant decrease in peripheral blood lymphocytes accompanied by an increase in circulating polymorphonuclear leukocytes.

In both mice and guinea pigs, the sensitivity of the lymphoid system to the action of TCDD is even greater than with rats. In these animal species

there was also no evidence in favor of a stress induced release of glucocorticoids by TCDD [8]. This postulate was confirmed in an experiment with chemically (Metapyrone) adrenalectomized guinea pigs in which involution of the thymus caused by TCDD was equivalent to that found in intact treated guinea pigs (unpublished data, 1975).

Mineralocorticoids regulate the electrolyte balance of the blood by favoring potassium excretion and sodium retention. An aldosterone deficiency present in adrenalectomized rats results in a lower serum sodium and higher potassium concentration than in control animals. TCDD did not alter the serum electrolyte concentration in normal rats, another indication that (at least in rats) involvement of the adrenals is of minor importance in the toxic effects produced.

After hypophysectomy, thymus weight markedly decreased. In our experiments, TCDD was able to evoke further atrophy of the thymus. This does not support major involvement of the hypothalamus-pituitary-thymus axis in the action of TCDD. The weight of the pituitary gland in TCDD treated animals also did not differ from the controls. The observed decrease in eosinophilia of acidophilic granules in the anterior lobe of the pituitary gland is not in direct agreement with the foregoing findings [8]. Pierpaoli and Sorkin [16] have shown that thymectomy of the newborn mice provoked a degranulation of the acidophilic cells of the anterior pituitary gland. One cannot totally rule out that TCDD-induced atrophy of the thymus may contribute to the observed alterations in the adenohypophysis.

Regular injections of GH reversed the involution of the thymus which occurs in hypophysectomized rats; the impact on the body weight is even more impressive. However, GH was ineffective both in normal and hypophysectomized rats receiving TCDD in preventing the involution of the thymus. Since GH did not prevent the body weight gain retardation also, interference with GH action would not explain the toxic effects of TCDD.

As thymosin injections did not increase thymus weight and mitogenic responsiveness of thymocytes an involvement of a reduced production of thymosin, caused by TCDD is also very unlikely [17].

Thyroidectomy also evokes an atrophy of the thymus [18]. The involution of the thymus therefore, may be secondary to an influence of TCDD on the thyroid gland. However, until now, no substantial effect on the weight or the histology of the thyroid was observed.

It has been known for some time that the administration of either androgenic or oestrogenic hormones produce atrophy of the thymus in normal or castrated animals [19]. Hence, the acute involution of the thymus caused by TCDD could be due to enhanced endogenous secretion of gonadal hormones. However, since TCDD evokes thymus atrophy in fetal and juvenile rats, it seems unlikely that TCDD effects are exerted through effects on the gonads.

From the present experiments it can be concluded that the effect of TCDD on the thymus is not mediated by the adrenals or pituitary gland.

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ECOTOXICOLOGY AND ENVIRONMENTAL SAFETY 4, 346–356 (1980)

Accidental Release of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) at Sèveso, Italy

VI. TCDD Levels in Atmospheric Particles

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TCDD in atmospheric dust was monitored in the Sèveso area between 1977 and 1979 using both dustfall jars and high-volume samplers. Apart from the sampling site in Subzone A1, sporadic TCDD levels were detected at different times and different sites throughout the contaminated area. Variable amounts of TCDD were constantly detected at the sampling site located in the most heavily contaminated subzone. All findings were in the range of 0.06–2.1 ng of TCDD/g of dust, for dustfall jar specimens, and 0.17–0.50 ng of TCDD/g of dust, for samples from high-volume samplers.

I. INTRODUCTION

Continuous monitoring of atmospheric dust in the Sèveso area was carried out to establish to what extent air-borne TCDD could contribute to contaminating nearby areas. Breathing in contaminated dust was also suspected as representing a potential health hazard for inhabitants residing near heavily contaminated areas. Moreover it was of interest to clarify the dynamics of mechanisms responsible for TCDD mobility in the environment.

Due to expectably low levels of TCDD in atmospheric dust, and to the sensitivity capabilities of presently available analytical methods, it was necessary to collect dust samples amounting to hundreds of milligrams. This was achieved using both dustfall jars and high-volume samplers. Some attempts to use electrostatic precipitators were performed, but these devices offered a number of inconveniences including poor reproducibility, low tolerance to atmospheric moisture, and special location and care requirements to prevent accidents. Preliminary findings have been previously reported by Viviano *et al.* (1).

II. EXPERIMENTAL

Dustfall jars (Fig. 1) were 10-liter glass vessels topped by a plastic metal screen-lidded funnel with a collecting cross-section of approximately 0.11 m^2. The top of the funnel was approximately 160 cm above the soil. Samples were collected for one month or the time needed for the vessel to be filled with meteoric water and sediment. This sampling methodology enables dust particles smaller than 500 μm, most of which are >10 μm, to be collected (2–4). A relatively small amount of soluble particles was dissolved in the liquid phase, whereas most

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TABLE 5

TCDD IN DUST SAMPLED WITH HIGH-VOLUME SAMPLERS (POOLED SAMPLES)

Sampling site[a]	Sampling duration (hr)	Air volume sampled (m^3)	Dust weight (g)	Dust per air volume ratio (mg/m^3)	TCDD per dust weight (ng/g)	TCDD per air volume (pg/m^3)
A	161	1.58×10^4	2.19	0.139	0.432	0.060
B	151	1.45×10^4	1.66	0.115	0.504	0.058
C	161	1.51×10^4	1.79	0.119	≤0.168[b]	≤0.02

[a] For site locations, see text.
[b] ≤ indicates uncertain detection.

were pooled and analyzed (Table 5). The sensitivity of the method used was, in this case, equal to 0.2 ng of TCDD/g of dust.

IV. DISCUSSION

The data reported show that both dustfall jars and high-volume samplers can be used to monitor TCDD levels in atmospheric particles. TCDD levels ranged from 0.06 to 2.1 ng of TCDD/g of dust from dustfall jars and from 0.17 to 0.50 ng of TCDD/g of dust from high-volume samplers. These findings suggest that the different dimensions of the particles sampled with the two devices are of minor significance for TCDD contamination levels. Moreover, it can be observed that TCDD levels detected in some dust samples are considerably high and, if expressed with the units used for soil contamination (7), correspond to TCDD levels in the range of 10–300 $\mu g/m^2$ of soil surface.

A comparison of TCDD levels in dust and soil samples taken at the same locations, indicates that air-borne TCDD does not significantly affect TCDD levels in the soil top layer. Moreover, data from dustfall jars show that TCDD levels in the dust decrease with increasing distance from Subzone A1 moving along the main diffusion pathway of the toxic cloud generated by the accident. TCDD levels found in some samples suggest that some TCDD diffusion into adjoining areas may have been propagated by dust originating from contaminated areas. Calculations based on TCDD levels detected in atmospheric particles may provide a rough estimate of the amount of TCDD breathed in by a person exposed to TCDD-containing dust for a given period of time. For instance, assuming a dust concentration in the air of 0.14 mg/m^3 and a TCDD level in the dust of 1 ppb (an approximate average of the levels detected at different times in Subzone A1), it can be estimated that an exposed individual, inhaling an average of 10 m^3 of air in 24 hr, would also take in 1.4 pg of TCDD.

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THE TORONTO STAR Sunday October 26, 1980

Dioxins found in 2,4-D alarm Ottawa

By Ross Howard Toronto Star

Dioxins discovered in 2,4-D, the most widely used vegetation killer in Canada, didn't include dioxin TCDD, one of the most deadly man-made chemicals, says Sharon McKay of the federal agricultural ministry.

"But all dioxins are a problem and the discovery of at least three different dioxins in 2,4-D is a surprise and a cause for concern," she said in an interview.

The dioxins were discovered within the last month by federal researchers in tested samples of 2,4-D.

Until now, most scientists and the chemical industry believed 2,4-D to be completely free of dioxins and relatively safe for widespread use.

As little as six units of dioxin TCDD in one trillion units of another substance, such as water, can cause human death, cancers or birth defects.

Federal agriculture and health officials won't say which three of 75 different kinds of dioxin they found, or exactly how dangerous they are, but said concentrations ranged as high as four parts per million.

The dioxins discovery is expected to bring new pressure for limits on the use of 2,4-D, with sweeping implications for agriculture.

Almost 4 million kilograms of 2,4-D are used annually in Canada for controlling broad-leafed weeds and brush in farmers' fields, along roadways, power line right-of-ways, and public parks and school yards.

A similar chemical, 2,4,5-T, already known to contain dioxin TCDD, has been banned in Ontario and several other provinces because of health risks.

Until now, environmentalists have unsuccessfully opposed 2,4-D's widespread use only on the grounds of other suspected dangerous ingredients.

A federal health ministry scientist said yesterday the dioxins findings and a rating of their dangers will be reviewed quickly and the results made public.

"We'll have to make some decisions before Christmas, because after that it's too late for manufacturers to prepare approved products, with labelling about risks, in time for their use during the growing season," the spokesman said.

The 2,4-D herbicide is used most in western Canada but nearly 1 million kilograms are used annually in Ontario, particularly by government agencies, according to Ontario agriculture ministry reports.

Telecopy to Don Stephenson

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THE SARNIA OBSERVER Wednesday October 29, 1980

Massive rise in cancer deaths predicted

EDMONTON (CP) — There will be a massive increase in cancer deaths as the effects of the chemical age start to catch up to North Americans, a U.S. professor said Monday.

Dr. Samuel Epstein said cancer rates are increasing as a result of exposures to large quantities of cancer-causing chemicals put into the environment in the 1950s. He is a professor of occupational and environmental medicine at the University of Illinois in Chicago.

Statistics from the National Cancer Institute in the United States and other U.S. sources show the cancer rate among 100,000 people rose between one and two per cent annually between 1969 and 1976.

"Within the last decade the increase in cancers has been equal to the increase in the entire 35 years between 1935 and 1970," Epstein told 140 delegates at a seminar on cancer at the University of Alberta.

'CANCER RATE UP'

"We now have good evidence that we are going up steeply in cancer rates. We are beginning to see the emergence of very significant trends in a disease that is killing many of us."

Cancer kills about one in five North Americans, a figure that will seem trivial in 20 to 30 years when the cancerous effects of chemicals now in use become apparent, Epstein said.

He said the environment can be cleaned without a loss of jobs in the chemical industry, which is using three strategies in trying to keep government regulations from clamping down on cancer-causing chemicals.

"The strategy is to deny there is a risk, control data on health effects and blame the victim and his lifestyle for cancers that do show up."

Blaming cigarette smoking as a cause of cancer is part of this "blame-the-victim" strategy, said Epstein. Recent studies in the U.S. show a "greater link to occupationally-induced lung cancers than to smoking."

EVERYONE AT RISK

He said workers in chemical plants, farmers and forestry workers who apply pesticides and people who live near chemical plants face the greatest risk. But everyone is a potential victim of cancer caused by chemicals dumped into the environment.

"We just have a little more time than the chemical workers."

Epstein criticized industry's use of economics to defeat regulations and controls, using the risk-benefit ratio in arguments for continuing the use of dangerous chemicals.

"The cost of regulation will be seen now. But the benefits from those regulations won't be seen for 20 or 30 years. And then it will be in the form of an absence of disease.

"The benefits are benefits for industry. But the risks are to the public or the workers, and there are no matching benefits."

High cancer-death rates can be avoided only by stiff safety regulations and controls over new petrochemical plants, he said.

THE GLOBE AND MAIL Thursday October 30, 1980

Employers withhold truth about toxics, MD warns workers

By ROBERT STEPHENS

Workers exposed to toxic and carcinogenic substances are little more than guinea pigs, and their employers are purposely withholding information about the very real risks of industrial cancer, a expert on occupational health has warned.

Dr. Samuel Epstein, professor of occupational and environmental medicine at the University of Illinois, told a conference in Toronto yesterday that workers who are exposed to hazardous substances "are the throwaway segment of society."

He condemned the governments of the United States, Canada and Britain for failing to regulate toxic substances in the workplace. While regulations controlling the use of seven designated substances were proposed in Ontario more than two years ago, these regulations are yet to be passed.

Dr. Epstein said the incidence of cancer is increasing among the general population at an alarming rate that reflects the huge growth in the production of synthetic organic chemicals beginning 30 years ago.

He said the worker is being sacrificed by government and industry because "they believe that economic growth is paramount." And he charged that industry was engaged in a massive coverup to keep its employees ignorant of the risks of cancer in the workplace.

Dr. Epstein said one of the favorite strategies of industry was to "blame the cancer victim himself" by linking his disease to smoking, diet, and even his genetic makeup. "Industry tries to deny the evidence for occupational cancer."

He said industry also frequently resorts to the argument that the costs of complying with exposure regulations will result in plant shutdowns and higher unemployment.

He said chemical companies in the United States had fought regulations on vinyl chloride for years, and that their spokesmen had claimed the costs of compliance would be $90-billion and 2.2 million lost jobs.

"But when BF Goodrich came under the regulations in the spring of 1975 — its cost was $35-million — it actually began to make money on the recovery of vinyl chloride, and then, complaining of unreasonable government interference, it had the nerve to raise its prices," Dr. Epstein said.

One of the delegates at the conference asked what workers could do to protect themselves from exposure to dangerous substances in the absence of government regulation, and Dr. Epstein replied: "If you have an option, I'd say get the hell out of hazardous workplaces."

BOB CARLTON

Park Service to Stop 2,4-D Weedkiller Use On All Its 325 Areas

By Joanne Omang
Washington Post Staff Writer

The National Park Service is to call a halt next week to the use of the nation's most popular weedkiller, 2,4-D, in its 325 parks and recreation areas.

The chemical, one of the constituents of the herbicide Agent Orange that was sprayed in Vietnam, is in common commercial use, and tons of it are used every year nationwide to kill weeds along highways, on golf courses and on millions of lawns. Figures were unavailable on how much the Park Service used nationally last year, but some 60 pounds were used to control dandelions on the Mall, the White House grounds and other park lands here.

The Environmental Protection Agency is studying the chemical, but officials there said evidence of its health effects is inconclusive so far and there are no plans to curtail its use.

Park Service Director Russell Dickenson confirmed that he had written a memorandum to all park superintendents ordering them to halt use of the herbicide immediately. Future use is to be allowed only if the superintendents convince their regional directors that no alternative methods are available to accomplish indispensable weed control.

A spokesman for the park service, Duncan Morrow, said this was "nearly but not quite" a ban on 2,4-D, "but it will halt its use for now and in the long run . . . it will substantially reduce its use."

Morrow said the action followed pressure from environmental groups, many in the Washington area, which argued that the herbicide had been found to cause spontaneous abortions, bleeding of fetuses and birth defects.

"It's a matter of considerable controversy, and the evidence is inadequate to make any firm judgment," Morrow said. "Therefore [Dickenson] decided that it's better to err on the side of conservatism and protect [possibly] ..."

farmers and other large-scale users under several manufacturers' brand names, including Weedone, Estron, Weed-Rhap and Brush-Rhap, and to homeowners as Weed-B-Gon and Formula 40.

Although it was one of the constituents of Agent Orange, 2,4-D was not the controversial part. That was 2,4,5-T, which was found to be contaminated with deadly dioxins and has subsequently been banned from most uses in the United States.

Hundreds of Vietnam veterans have filed suit and have sought compensation for a wide range of illnesses they claim resulted from their exposure to Agent Orange. The EPA is holding hearings on whether to ban all remaining uses of 2,4,5-T.

L.D. Blanchard of EPA's Pesticides Division said dioxins of the Agent Orange sort have so far never been detected in 2,4-D. While tests have shown that large doses of 2,4-D are toxic to animals, he said, small doses appear to have no effect. The agency has asked 2,4-D manufacturers for additional tests, but conclusive results are not expected for two years, Blanchard said.

An April fact sheet on the issue said EPA "believes the risks of several other pesticides are higher and better documented than those associated with 2,4-D." Blanchard said the EPA is eager to see any new evidence the park service may have. "If we receive anything that makes us believe suspension is warranted, we'll act quickly," he said.

Erik Jansen of Friends of the Earth, one of those instrumental in persuading Dickenson of the need for his action, said existing literature "is already overwhelming" in providing evidence of spontaneous abortions and fatal bleeding. "There's absolutely no doubt it's a problem chemical," he said.

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THE HAMILTON SPECTATOR Wednesday October 22, 1980

Amputee continues his fight for a precedent

Story and picture
by BRUCE STEWART
Spectator Staff

CALEDONIA — Peter Ward lost his arm to cancer earlier this year and has since lost a bid to link his problem to weedkiller he used at work.

But the 44-year-old Caledonia area truck driver isn't giving up his fight as he feels a victory would help both him and others who have been exposed to chemicals at work.

In April, Mr. Ward had his arm amputated about four inches (10 centimetres) below the shoulder after doctors discovered a malignant tumor.

Since then Mr. Ward, who works for the town of Haldimand roads department, has been trying to get compensation from the Workmen's Compensation Board.

Although his request has been denied by the board's review branch, and he has lost an appeal of that decision, he is ready to launch a final appeal, with the help of the Canadian Union of Public Employees (CUPE).

"I would like to be able to set some kind of a precedent with the Workmen's Compensation Board as there are many other people using these types of chemicals," he said.

"If we can get our nose in the door and get them to recognize this type of claim, it may help others."

Wages

Mr. Ward is now able to carry out a number of functions with the hook attached to the stump of his arm. He hopes to be able to return to work soon, and resume most of his old duties.

He feels he should be reimbursed for the wages he has lost while off work and compensated for the loss of his arm.

Mr. Ward said he now thinks his tumor may have been caused by a combination of an earlier injury at work and later exposure to weedkiller at work. He says the tumor could have also been caused by either the earlier injury or the weedkiller exposure alone.

His upper arm was injured when he was cutting down a tree while working for the old township of Seneca on March 11, 1974, he said. The tumor developed in the same spot that was injured in the 1974 mishap.

"I was hit by a chain in the upper arm while cutting down a tree and thought I had broken something," he said. "But it turned out I hadn't, although my arm was in a sling for a while. But it got better, although it bothered me a little in the winter."

A few years after the accident, he spent three weeks spraying roadside weeds for the town of Haldimand, which replaced the old township of Seneca.

He believes the weedsprays included the herbicide 2,4,5-T, which has now been banned in Ontario. It may have also included the controversial herbicide herbicide 2,4-D, he said. The herbicide 2,4,5-T has been the subject of controversy because it contains dioxin, an extremely toxic compound linked to brith defects and considered cancer causing.

It was one of two herbicides in Agent Orange, which was used to defoliate forests during the Vietnam war. But the 2,4,5-T used in Vietnam contained as much as 50 parts per million, while Canadian regulations limited it to less than 0.1 parts per million.

"I was breathing in weedspray some of the time and noticed that my sandwiches tasted funny," Mr. Ward said. "I had a mask but couldn't wear it all the time because it was too hot and my glasses would fog up."

Mr. Ward wants his doctor to search the medical literature for research and experimental data which would establish a link between the weedkiller and the tumor or the earlier accident and the tumor.

Dr. Kenneth McKenzie said yesterday he would be willing to try to set up a computer search of the medical literature to try to establish some link between the tumor and the weed killer or the tumor and the njury.

"There might be some link but I don't know, it is a very hazy area and it would have to be looked into," he said. "I told Mr. Ward that if he or the union were ready to pay for the search, I could set it up."

"The type of tumor he had could have been caused by anything. It could be a virus," he said. "In his particular case the tumor was in an area of the arm where they usually don't occur too often. But it might be a coincidence."

"Or it could be caused by the trauma of an earlier injury. But short of going through hundreds of years to literature to support it, we really don't have a leg to stand on, unfortunately."

Dr. McKenzie said he hoped to meet union officials about Mr. Ward's case and the possibility of a records search.

Meanwhile, Jack White, a national representative for the Canadian Union of Public Employees, said tests in Sweden and New York have proven that neither herbicide 2,4,5-T nor 2,4,5-TP cause cancer.

He said the onus should be on the Workmen's Compensation Board, however, to prove that Mr. Ward's earlier injury didn't cause the tumor.

Mr. White has written to Mr. Ward, asking him to obtain information from both of his doctors on what they believe caused the problem before an appeal is made to the Appeal Board.

Workmen's Compensation Board officials were not available for comment yesterday.

THE HAMILTON SPECTATOR Wednesday October 22, 1980

Peter Ward won't give up his battle for compensation

Edmonton Journal, October 24, 1980

Herbicide's use in jeopardy

Killer chemical found in 2,4-D

By ALLAN MAYER

A herbicide widely used in Alberta and found in surface waters throughout western Canada contains dioxin, one of the most deadly chemicals, say federal agriculture officials.

Department testers have found the extremely toxic dioxin in some samples of the herbicide 2,4-D, Agriculture Minister Eugene Whelan said Thursday.

About 2 million pounds of the weed-controlling herbicide is used in Alberta annually.

"If this is true then we're in real trouble," Keith Price, head of Alberta Agriculture's weed control branch said Thursday night. "There's nothing to replace it. I don't know what the farmers would do other than let the weeds grow."

2,4-D is used to control broad-leaf weeds in everything from lawns to cereal fields. About eight million pounds of it is used in Canada each year. This represents about 25 per cent of total herbicide use.

Agriculture and health department officials in Ottawa are investigating the situation further and a decision will be made on 2,4-D use before next year's growing season.

The only Canadian plant manufacturing 2,4-D is Uniroyal near Sherwood Park.

Glenn Martin, Uniroyal plant manager, said he couldn't disclose how much 2,4-D is made at the Sherwood Park plant because "that's something our competitors would love to know."

The Energy and Chemical Workers' Union is conducting a major medical survey at the plant in an attempt to pinpoint any correlation between workers' illnesses and their exposure to herbicide products.

Ray Senkiw, Alberta Federation of Labor health and safety director, said a royal commission is needed to examine society's use of chemicals.

He described the federal government's method of approving chemicals as a "bloody disaster."

Mr. Price said Uniroyal is the sole Canadian manufacturer since Dow Chemicals in Fort Saskatchewan phased out 2,4-D production this summer. He said 2,4-D is also imported from the United States and Europe.

The popular and cheap herbicide has been used extensively in this country since the late 1940s.

"It's supposed to be impossible to have dioxin in 2,4-D," Mr. Price said, "unless there's some contaminant."

EDMONTON JOURNAL, [illegible] 83

Dioxin levels in 2,4-D low— official

By ALLAN MAYER

The toxicity of dioxin found in samples of the herbicide 2,4-D is not as great as other types of the chemical, say federal agriculture officials.

Clarifying a press release issued a day earlier, Wayne Ormrod, associate director of the department's pesticides division, compared different kinds of dioxin with spiders.

"There's about 1,500 different kinds of spiders in Canada. Some are harmless and some are not," said Mr. Ormrod. "It's the same as dioxin, some kinds are more toxic than others."

He said the most toxic form of dioxin, 2,3,7,8-2,C.C.D., was not found in 2,4-D. The dioxins found were much less toxic.

But department officials are continuing to explore the situation and will decide by next spring if adjustments should be made with the product, used to control broad-leaf weeds in everything from lawns to cereal fields. About eight million pounds of 2,4-D is used in Canada annually with 1.5 million pounds used in Alberta.

Traces of 2,4-D have been found in surface waters throughout Western Canada.

Mr. Ormrod said that 12 of 25 2,4-D products tested by his department showed levels of dioxin [illegible] 2,3,7,8-2,C.C.D., which has been linked with birth defects.

He said that as far as he knows, it's the first time anyone has found any dioxin in 2,4-D.

He said levels of dioxin in 2,4-D ranged from four parts per million to five parts per billion.

Keith Price, head of Alberta Agriculture's weed control branch, said he doesn't think the federal government's finding will present any difficulty to farmers in Alberta.

He said the dioxins found by Agriculture Canada were 15 [illegible] less toxic than 2,3,7,8-2,C.C.D. which has been linked with birth defects.

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THE OTTAWA CITIZEN Friday October 24, 1980

Weedkiller has deadly chemical

By The Canadian Press

Agriculture department testers have found dioxin, one of the most deadly of chemicals, in some samples of the herbicide 2,4-D, it was announced Thursday.

Agriculture and health department officials are investigating the situation further and a decision will be made on 2,4-D use before next year's growing season.

The herbicide 2,4-D is used to control broad-leaf weeds in everything from lawns to cereal fields. About eight million pounds of 2,4-D is used in Canada each year. This represents about 25 per cent of total herbicide use.

Agriculture Minister Eugene Whelan said "These findings clearly identify dioxin contaminants in some, but not all, 2,4-D samples examined. Work is continuing to gain a broader and more detailed understanding of these new findings.

"When some pesticide products were registered, today's highly sophisticated testing equipment did not exist. The investment my department has made in high-priced laboratory equipment and in highly trained scientists is paying off with results like these.

"I can guarantee the public that Agriculture Canada will continue to work hard in keeping agricultural chemicals under constant review and to provide answers to concerns that may arise as a result of the reviewing process," Mr. Whelan said in a news release.

THE SUDBURY STAR Saturday October 18,1980

Union charges Uniroyal workers endangered by toxic chemicals

EDMONTON (CP) — Workers at the Uniroyal Ltd. herbicide plant are being contaminated by toxic chemicals, the Energy and Chemical Workers Union charged Friday.

"We've noticed an abnormal number of people who have had to take time off because of colds and lung problems," said Reg Basken, national representative of the union.

He said one of the 25 Uniroyal employees has uncontrollable tremors, another has problems with his memory and several others have experienced muscle weakness in their arms.

He said the company has not done enough to prevent exposure to the herbicides.

Among the chemicals produced at the plant are 2,4-D, MCPA, pentachlorophenol, tetrachlorophenol and 2,4,5-T — a highly toxic chemical used by the American military as a defoliant during the Vietnam War.

The production of 2,4,5-T and pentachlorophenol produces small quantities of the dioxin TCDD, one of the most deadly chemicals.

Basken said the union obtained a copy of a study done last year by the Alberta labor department which showed abnormally high levels of pentachlorophenol and dichlorophenol in the urine of workers.

Those two chemicals can cause birth defects if passed on in sperm, he said.

DETECT PHENOL

Dave Gibson, director of the hygiene branch of the labor department, said the report did find "some of the urine samples of a minority of the workers indicated higher phenol levels than we want to see."

But air tests showed no problems, he added, and the only potential exposure came from absorbing the phenols through the skin.

Basken said the workers were not told of the test results.

The union has started a medical survey of all former and current employees at the plant to determine what kind of hazards exposure to the chemicals might cause.

The survey will study a number of potential health problems including cancer, liver damage and nerve disorders. It will also look into the number of birth defects among the workers' children and miscarriages among the workers' wives.

NO COMPLAINTS

Glenn Martin, manager of the Uniroyal plant, said his company has not received any complaints about medical problems.

He said some monitoring and testing had been done by the Alberta government but the company has not been given detailed information of the findings.

"We are going to talk to the workers and see what they are up to," Martin said.

He dismissed allegations about poor safety standards, saying workers are supplied with masks, gloves, work clothes and rubber-soled shoes. And all workers trained in how to handle the chemicals.

Basken said the company has installed washing machines for the employees' clothes and a sauna to sweat the chemicals out of the workers' skin, but most of the men are still contaminated.

"We notice that they tend to buy less weedkiller than most people — they just go home and throw their shirt on the lawn," the union official said.

"I'm not kidding. I'll bet a survey of these guys' homes would show none of them can grow houseplants because of the stuff they take home in their skin and clothes."

Basken said conditions at the plant have improved in recent years but remain far from being safe.

THE EDMONTON JOURNAL Tuesday

Farm chemicals safety tests 'faulty'

(First in a series)

Report By Allan Mayer

The federal government can no longer vouch for the safety of the chemicals used on agricultural chemicals because of faulty test results at a U.S. laboratory.

The pesticides were all tested for safety by Industrial Biotest Laboratories (IBT) of North Brook, Ill., once the largest commercial safety testing company in the U.S.

Both the Canadian and American governments have accused the companies of making up test results and tinkering with studies.

Both governments had relied on the tests to approve the sale of the chemicals.

In Alberta, there have been incidents involving the chemicals.

Social Credit leader Bob Clark was at home in Olds last spring spraying his garden raspberries with a weed killer when he suddenly developed bad chest pains.

He felt sick for about two weeks and didn't feel like himself for another month. Mr. Clark was using a chemical known as Paraquat.

Debby Bullock of Lacombe was applying Eater's *Plant Doctor* on a house plant this summer when she became extremely nauseous.

She began suffering from severe hallucinations and was in hospital for a week and away from work for six weeks. The chemical in the plant doctor was Disulfoton.

A worker at Uniroyal's herbicide plant near Sherwood Park spilled some pentachlorophenol on his arm and jacket.

He washed the chemical off his arm but put his jacket back on. The chemical got in his skin and, according to an Energy and Chemical Workers' Union official, the worker's arm is "just about useless."

While the three victims survived their run-ins with pesticides, there is no long-term guarantee that their experiences might catch up with them in later years.

All the pesticides were originally approved by Industrial Biotest Laboratories.

About half of the 106 pesticides now under suspicion are used in Alberta.

Canadian officials maintain the firm substituted live rats for dead ones in long-term safety tests.

Other results were juggled to show fewer birth defects and genetic mutations between laboratory animals that were fed chemicals and those that were not.

The problem is a massive one for federal government officials, who have known about the situation for three years.

None of the affected chemicals have been withdrawn from the market and little has been done to inform the public.

Chemicals on the list are used in products such as "No Pest" strips, home and garden insecticides, and Lanate, a major insecticide used to control *Heetha* army worms.

A major fungicide, Captan, which is still used in the province, underwent 14 tests in IBT labs. Thirteen of those tests have now been ruled invalid.

Captan is suspected of causing cancer. As much as 800,000 pounds of Captan is used in Alberta each year.

Dr. Alex Morrison, head of the federal government's health protection branch, says his department has ordered re-examination of 450 studies done by IBT, two-thirds of which are suspected of being invalid.

It may cost manufacturers $100 million to retest suspected chemicals, said Dr. Morrison. The federal government has spent $500,000 so far in investigating the IBT situation.

IBT first came under suspicion of the US food and drug administration in 1976.

A spokesman for the environmental protection agency in Washington said about eight safety reports were shredded once the company heard of the suspicions.

The Canadian government issued a news release in August, 1977, outlining the bare bones of the problem but did not say what chemicals were involved.

This summer, Health Minister Monique Begin issued a list of 97 pesticides under suspicion only after pressure from the Saskatchewan government and opposition members of Parliament.

Jack Cookson, Alberta's environment minister, says his government "relies on the federal government to make the recommendations."

The senior health consultant with Saskatchewan's environment department, Dr. David Penman, is demanding more information from Ottawa.

October 21, 1980

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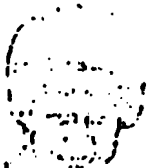
[illegible] JOURNAL, Thursday, October 23, 1980 A7



June Sheppard

On Aug. 29, I criticized the practice of having decisions about what chemical pesticides shall be allowed on the market in Canada on test results from laboratories hired by the chemical industry.

The column was prompted by Health and Welfare Minister Monique Begin's announcement early in the summer that two-thirds of the tests done by one lab — Industrial Biotest of Illinois — for the second time *because the first were so faulty) had also proven unreliable.*

I wrote that dissatisfaction with the lab had existed for some time but hadn't been revealed to Canadians until this year. I have a letter from Don Carlson, regional public relations officer for health and welfare in Edmonton, saying that in fact the former minister, Marc Lalonde, announced in 1977 that investigation had begun into the American lab's toxicity tests. Carlson attaches the news release from Lalonde corroborating this.

While I'm pleased to clear up this one error, the more important points in the column remain unanswered.

Mr. Carlson writes: "With regard to the testing by independent laboratories, I can also assure you that there are very good and valid reasons for this approach and although no system may be completely fail-safe, it has nevertheless proven extremely successful for many years. The Industrial Biotest experience far from being the norm, is in fact very much the exception to the rule."

Surely in an area as crucial as public safety and [illegible] such reasons should be spelled out for all to know. [illegible] is no assurance whatsoever in simply being told [illegible] exist by a public relations department. And there [illegible] the question of duration — just what [illegible] "independent" mean, for instance?

Of course, no system is completely "fail-safe." [illegible] things they involve humans and that effectively rul[illegible] perfection, a fact amply demonstrated by the runa[illegible] nuclear reactor field.

While I'm quite prepared to believe that the Indu[illegible] Biotest experience may not be the "norm," I wo[illegible] more convincing that it is the "exception to the [illegible] There's now considerable literature about faulty t[illegible] conflict-of-interest in testing, carelessness, suppress[illegible] manipulation of test data, etc. etc. in the U.S. W[illegible] much of Canada's economy being of the branch [illegible] variety, it's hard to believe that we were not affect[illegible] these matters.

The environmental protection agency in the U[illegible] revealed that it is looking into test results from more [illegible] other laboratories because of suspicions that their [illegible] is also careless or deliberately invalid.

But even if it were proven true that only Indu[illegible] Biotest is untrustworthy, the fact that this one [illegible] handled the testing of more than 100 pesticides now [illegible] on the Canadian market is hardly cheering news.

Mr. Carlson assures me that Health and Welf[illegible] "indeed deeply concerned over this matter and [illegible] others which might adversely affect the healt[illegible] Canadians." I don't doubt the sincerity of [illegible] statement.

But I'd feel more reassured if I hadn't heard Dr. [illegible] Mortensen, head of the federal health protection br[illegible] say on national TV that if it is Agriculture C[illegible] which makes the decisions about what pesticides w[illegible] permitted on this country — and that the decisions [illegible] made, not on the basis of safety, but on what he c[illegible] "agri-economics."

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THE EDMONTON JOURNAL Wednesday October 22,

Doctored chemical tests raise questions about wide-ranging dishonesty in labs

This is the second in a series of articles. The first appeared in the Journal Tuesday, Oct. 21. The last is on Page A17 today.

By Allan Mayer

Industrial Biotest Laboratories (IBT) has been an embarrassment to both the Canadian and United States governments and raises questions about the way in which pesticides are approved for use.

When it was discovered in 1976 that IBT had been doctoring both long-term and short-term safety studies on pesticides used internationally, the U.S. government was taken aback.

IBT is still in operation but only *for re-evaluation of* the suspect safety tests. Two of the IBT's three labs have been sold and a buyer is being sought for the remaining lab in Northbrook, Ill. The lab is also facing numerous lawsuits.

Dr. Alex Morrison, head of the Canadian government's health protection branch, admits that IBT was doctoring chronic toxicity studies on a grand scale for the last decade.

"But was IBT the only company doing this? That's the nightmare," says Dr. Morrison. "If IBT is just a rogue company which for some reason went crooked then you can deal with that. But if IBT is the tip of the iceberg and there is widespread chicanery going on in commercial laboratories then we have a very serious problem where you cannot trust information given by the private sector to government supporting the use of chemicals.

"We don't know how big the problem is yet. We've been trying to concentrate on IBT but there is no doubt that we will be going back to look at other laboratories to see whether or not we have monkey business going on there."

Since the IBT affair began, the U.S. Food and Drug Administration has initiated a whole inspection cycle which includes data audits and on-site inspection of commercial testing labs.

But in Canada, Dr. Richard Prentice, co-ordinator of Agriculture Canada's crop protection research branch, maintains the existing process of registration is adequate.

"Do you put into suspect every bit of data you didn't find yourself?" he says. "The existing review process isn't cavalier."

Under that process, pesticide products are examined by Agriculture Canada, Health and Welfare Canada, Environment Canada and Fisheries Canada. Final approval rests with Agriculture Canada which doesn't necessarily have to ask for health department input.

In non-communist countries, the principle responsibility for the safety of chemicals has fallen upon

(1 of 2 pages)

the manufacturer, who then submits the data to governments for approval. Governments don't do the testing.

And in the case of IBT, all the Canadian government saw were synopses of the raw data.

"If you can't trust the private sector then that leads you into certain difficult policy decisions," says Dr. Akerstrom. "The first one is to do without chemicals, but our society runs on chemicals. The second one is for the government to do all the testing. Well, there's a bill for about $1 million every time a new chemical comes up. If we do all of that testing on several hundred chemicals a year then you're looking at a bill of several hundred million dollars a year. Governments don't have that kind of money.

"The third option is to audit the people who do it, go back into their laboratories, look every week on what they're doing so they can't cheat on you and get away with it."

But federal NDP science critic Simon de Jong (Regina East) doesn't buy the fact that the government can't do its own testing.

"There's just too many conflicts of interests involved here and the stakes are pretty high," he says. He proposes the creation of government toxicology centres, spread across the country, which would examine agricultural chemicals used in the different regions.

Mr. de Jong says there are so many "don't knows" concerning IBT data that the country is using farmers and our environment as testing grounds.

The Saskatchewan environment department is the only provincial agency that's put pressure on the federal government for more information. Dr. David Pennak, the environment department's senior health consultant, has asked Agriculture Canada for health reports on IBT-approved chemicals Vitavax, dichlorvos and pentachlorophenol but was told to get that information from the manufacturers.

He says he's particularly concerned about Vitavax because a Manitoba farmer who was handling the chemical this spring died shortly afterwards from kidney failure.

In Alberta, Environment Minister Jack Cookson says he's content to let the federal government decide what's safe and what isn't in the IBT affair.

"To pull everything off the shelves would be a highly irregular thing to do with no evidence to back it up," says Mr. Cookson.

Joe Gocha, head of the province's crop protection and pest control branch, says Alberta's agriculture department doesn't have the staff, laboratories or mechanisms to carry out the tests required in this case.

"If we pulled some of these chemicals off the market right now, Lorsban for instance, there would be no rapeseed crop. The Bertha army worm would destroy it. Our rapeseed oil extraction plants on the province would have to be shut down," he says.

"The rest of the world is stuck with this too. It's the federal government's responsibility and we have confidence in them."

Mr. Gocha admits that the Alberta government has no idea of the quantity of pesticides used in this province and other government officials admit that they don't know how many people get sick from pesticides each year.

Dr. Stanley Greenhill, chairman of the University of Alberta's community health department, is concerned about the easy access to these chemicals.

He warns that organophosphate pesticides, such as Diazinon (which is on the IBT list), are slightly modified nerve gases and that the purchase of these pesticides over the counter are ridiculously easy. He says the seller often has no knowledge of the potency of the product.

To combat this, the province recently approved new agricultural chemicals regulations which will force dealers to complete a correspondence course on pesticide safety. Chemicals have been classified under different headings regarding their potency and farmers will have to sign for some of the chemicals they use. Under the

regulations, it will be illegal to display pesticides [illegible] metres of food products, as in case on Wednesday in Lethbridge. It will be illegal to purchase any pesticide of source unless you've used the regulations, [illegible] keeping track of the amount of pesticides sold in the province starting immediately this fall.

"People have become complacent about pesticides [illegible] are afraid to use chemicals it's very easy to overuse them," [illegible] Jim McKinley, licensing supervisor with Alberta Environment's pesticide chemicals branch. "A farmer has to see his name on the [illegible] buys a chemical, maybe he'll be more careful.

When Ed Mandrake, [illegible] Farmers Union representative [illegible] Edmonton, heard about the Vitavax case in Manitoba he sent out questionnaires to Alberta farmers asking them to report any ill effects they've suffered from [illegible] chemicals. The questionnaires were sent out last May but so far he's had no response.

Harry Spalling, spokesman for Alberta's Christian Farmers Federation, says his group urges farmers to use pesticides [illegible] discretion because there's [illegible] information on the long term effects of the chemicals.

"Pesticides are being used on a trial and error basis in the human environment."

It could take some years to know for sure how safe agricultural chemicals really are

By ALLAN MAYER
(Last in a series)

It will be at least three years before a federal government team of toxicologists can say whether 10s commonly used agricultural chemicals are safe.

Between then and now, the toxicologists will have to pour over thousands of pages of raw data supplied by Industrial Bionet Laboratories (IBT) of Northbrook, Illinois, in an effort to ascertain which studies are valid and which studies are not.

"We've found flaws in both short-term and long-term studies," says Dr. Alex Morrison, head of the federal government's health protection branch. "Right now we can't judge whether the chemicals are safe or unsafe."

To find out, the toxicologists will have to go over about 900 studies done by IBT. After examining 450 studies, health department officials have ruled two-thirds of them invalid.

The government has six toxicologists on staff now with plans to add another four as soon as they can be found. They will all be PhD-level scientists.

"We check to see if a given animal is followed through a study, whether the protocol for the study was followed. If a 24-month study was conducted, did it carry on that long or was it only 20 months, or 18 months," says Dr. Morrison. "Can you account for dead animals? Sometimes we find that there were more animals at the end of a study than at the beginning."

"Because they might have done the study in part, they might have made it all up, they may have done it in a different way than they said they had done it. They often seem to have done these studies for less time than they claim."

Dr. Morrison says that IBT-approved chemicals are used on four to five billion dollars worth of food products sold in this country each year.

He says until his officials know more about the IBT data, the department has to be careful that "we don't err in term of public advice."

"We have no evidence to demonstrate that these pesticides represent a health hazard to users or as residues in food," says Health Minister Monique Begin. "If evidence becomes available that these products do represent a health hazard, immediate action to protect the public will be taken."

But neither Ms. Begin nor any of her officials can vouch for long-term health effects. And until they can, the federal government will spend thousands of dollars, in addition to $[illegible] spent already, in clearing up the situation.

Replacement studies for invalid IBT data will have to be conducted by chemical manufacturers and some of these studies will take as long as three years.

A lifetime study on a rat takes about two years with another year analyzing the data, says Dr. Morrison. If you're using monkeys or dogs it may take four or five years.

Details about how the tests are flawed remain sketchy, but Dr. Morrison provided a few examples for agricultural chemicals used in Alberta.

•Pulvaram, an extensively used herbicide, was the subject of four IBT studies. No original data on three long-term studies. A two-year study on a dog was invalid.

•Endosulfan, a moderately used insecticide. Thirteen IBT studies done, four invalid, two valid and seven the government has no information on right now. Teratology studies (study of monsters) and reproductive studies invalid.

•Captan, an extensively used fungicide. Fourteen IBT studies done. 10 are invalid. Replacement studies under way for carcinogen studies for rats and mice as well as a teratology replacement study.

Altogether, Dr. Morrison says, there are probably 2,000 formulations that result from IBT chemicals on the market in Canada, and each formulation can be used in a number of products.

Following is a list of the chemicals under suspicion by the federal government: Acephate, Alachlor, Alanap, Alar, Allidochlor, Amitraz, Amtor, Atrazine, Azodrin, Bacillus Thuringiensis, Larbon, Bifenox, Binapacryl, Bromofenoxim Bux, Captan, Captafol, Carbofuran, Chlorbenzuron, Chloropropham, Chlorpyrifos, Chlorthalonil, Cyadrin, Cyanazine, Cypazine, Dacthal, Delnav, Desmedipham, Diallate, Dalitaz, Diazinon, Dibrom, Dichlobenil, Difenzoquat, Dimetramine, Dinoseb, Diquat, Disulfoton, Dyanap, Edifenphos, Embark, Endosulfan, Enkthall, Ethodate, Ethion, Fenitrothe, Fenamiphos, Fenitrothion, Fensulfothion, Fenton Hydroxide, Fensulcate, Folpet, Fumetonate Hydrochloride, Glyphosate, Glyphosine, Harvade, Hexazinone, Igrasan, Merphos, Metabromuron, Methamidophos, Methidathion, Methocarb Methomyl, Methoprene, Monolachlor, Metribuzin, Nurea, Nicotine Sulphate, Omite, Oxamyl, Oxydemeton Methyl, Paraquat, Pennap L, Pennap M, Pentachlorophenol, Permethrin, Phenmedipham, Phosphamidon, Polaram, Polyram, Profenofos, Prometon, Propham, Profluralin, Propachlor, Propanil, Prowl, Pyrethrins, Simazine, Sinazine, Simothrin, TCMTB, Terbufos, Terbuthylazine, Tetrahydrophthalimide, Tetrasan, Telvon, Tetrachlorvinphos, Thiodicarb, Thiophanate, Treallate, Tuvax, Vapona, Vegadex, Vendex, Vitavax.

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HEALTH&SAFETY Alert

NUMBER THREE

BEWARE OF THE WEED KILLER 2,4,5,T and 2,4,5,TP

BANNED

On April 15, 1980, the Ontario Minister of Environment banned the use of the herbicides 2,4,5,T and 2,4,5,TP. Studies have shown that the substances can cause irreversible health effects. This ban follows similar bans in the USA, New Brunswick and British Columbia. Other provinces are considering whether to place a ban on its use.

USES

These chemicals are used extensively as a control for broad leafed weed and bush and hardwoods. They are sprayed on the sides of highways, on hydro right-of-ways and in forest areas.

CUPE members that may have possible exposure include Hydro workers, municipality workers and school board employees. The justification for this spraying is purely economic; spraying is cheaper than cutting.

Municipalities, Provincial Governments and Hydro authorities are the largest users of these chemicals.

HEALTH EFFECTS

The problem that exists with these chemicals is that after spraying the substances tend to decompose very quickly. They leave behind however, an extremely toxic substance known as DIOXIN.

Dioxin is one of the most toxic substances known to man. It is estimated that one-twelve hundredth of one drop of dioxin is fatal to a human. The explosion at Sevesso in Italy caused dioxin to pollute the surrounding countryside turning it into a waste area. Military personnel who were exposed to it in Vietnam, where it was used as a defoliant in the jungles, are now experiencing many health problems.

Studies have shown that where there is exposure to 2,4,5,T and TP there is an increase in cancers of the muscle and of the tissue. Reports from a town in Oregon indicate that there was an abnormally high rate of miscarriages among pregnant women approximately six weeks after spraying occurred in the area. Swedish studies have shown a link between increased levels of cancer and exposure to the chemicals.

The residue dioxin that is left behind can get into the food chain and cause prolonged exposure in the general public.

ACTION REQUIRED

Wherever spraying of herbicides is conducted insist on knowing the type of chemical that you are using. Ask the following questions:

i) What is the name of the chemical, both the generic name (this will indicate the type of chemical e.g. 2,4,5,T and 2,4,5,TP are the generic names) and the trade name (silvex is a common trade name for these chemicals).

ii) Obtain the name of the manufacturer.

iii) If it is confirmed that it is the above chemicals, then refuse to use them.

iv) Report all uses, and/or all areas where it is stored, to your union.

v) If you have these present at your worksite and they are being sold or transported elsewhere, find out where and report it to your union.

vi) Where there is any chance of exposure, insist on protective clothing, self-contained breathing apparatus and decontamination after exposure.

vii) Report any employer who is using these materials in the provinces where a ban exists, to the Ministry of Labour and the Ministry of the Environment.

NOTE: All reports to local unions should be acted upon - inform your Staff Representative and the National Office. Complain to your provincial government.

2, 4, 5, T and 2, 4, 5, TP ARE HEALTH HAZARDS THAT MAY EFFECT YOU OR YOUR CHILDREN - DON'T USE THEM!

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Evaluation of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) toxicity in C57BL/6 mice:

Reproduction and Fertility in Treated Male Mice and Evaluation of Congenital Malformations in Their Offspring

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ABSTRACT

This study was undertaken to determine the effects of mixtures (simulated Agent Orange) of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on reproduction and fertility of treated male mice.

Male C57BL/6 mice were given feed containing varying concentrations of 2,4-D, 2,4,5-T and TCDD such that daily doses of approximately 40 mg/kg 2,4-D, 40 mg/kg 2,4,5-T and 2.4 µg/kg TCDD (Group II) or 40 mg/kg 2,4-D, 40 mg/kg 2,4,5-T and 0.16 µg/kg TCDD (Group IV) or 20 mg/kg 2,4-D, 20 mg/kg 2,4,5-T and 1.2 µg/kg TCDD (Group III) would be achieved. Controls (Group I) were given a diet with only the corn oil vehicle added to the feed. In the treated animals, dose-related liver and thymus toxicity were found and body weight gain was significantly reduced. Liver and thymus toxicity showed significant or complete recovery when the mice were returned to a control diet. Sperm concentration, motility and percent sperm abnormalities were evaluated and no significant effect was noted during or after the dosing period.

At the conclusion of an eight week dosing period treated males were mated to untreated virgin females (three per male per week for eight weeks). Mating frequency, average fertility, percent implantation and resorption sites and percent fetal malformations were all measured in relation to the treatment. No significant decrement in fertility or reproduction was noted in the study. There was no evidence of germ cell toxicity. Survival of offspring and neonatal development were apparently unaffected by paternal exposure to the simulated mixtures of Agent Orange.

INTRODUCTION

Chlorinated phenoxyacetic acid compounds are used extensively as herbicides in forestry and agriculture. The Department of Defense tested and used a number of different herbicides containing chlorinated phenoxy acids in Vietnam as defoliants; these included Herbicide Orange, Herbicide White, Herbicide Purple, Herbicide Pink and Herbicide Green (Young et al., 1978). The herbicide most extensively used was Herbicide Orange, a 1:1 mixture of the n-butyl esters of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). It has been estimated that 107 million pounds were sprayed with the majority used in the years 1967 to 1969 (77% of total herbicide sprayed) (Young et al., 1978).

During the synthesis of 2,4,5-trichlorophenol (TCP) and subsequently 2,4,5-T, but not 2,4-D, a highly toxic contaminant is formed. This contaminant, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), has been found in Herbicide Orange at an average concentration of 2 ppm with individual analysis of up to 47 ppm reported (Young et al., 1978). Occupational or environmental exposure to humans to TCDD has been associated with a number of clinical disorders (Firestone, 1977; IARC, 1978). The heaviest exposures have involved industrial accidents which occurred in plants synthesizing TCP. The most consistently documented clinical manifestation has been chloracne, a severe form of pustular folliculitis which is most frequently observed on the face, neck and upper extremities. Other less common clinical findings following TCDD exposure include porphyria cutanea tarda, central and peripheral nervous system disorders, depression and irritability, hepatic dysfunction and altered serum lipid concentrations (Firestone, 1977; IARC 1978; Young et al., 1978).

A number of Vietnam Veterans have expressed concern as to health effects that may have resulted from exposure to Herbicide Orange either through application of the herbicide or through inhabiting defoliated areas (Holden, 1979; Rawls, 1979). A particular concern is that Herbicide Orange exposure may be related to reported decreases in both libido and fertility (low sperm counts and abnormal sperm forms) and that it may also be responsible for birth defects observed in offspring sired by veterans who were exposed to Agent Orange (Bogen, 1979; Holden, 1979).

The toxicity of TCDD and the phenoxy acids 2,4-D and 2,4,5-T has been studied in some detail. The biological effects of these chemicals are well documented in a number of mammalian test systems (Gehring and Betso, 1978; Moore, 1978). 2,4-D, 2,4,5-T and TCDD have all been investigated for teratogenicity and fetotoxicity when given to pregnant females. 2,4-D acid and 2,4-D esters show signs of fetotoxicity and embryotoxicity in hamsters and rats at high dose levels, but it is unclear whether the compounds are actually teratogenic (Collins and Williams, 1971; Khera and McKinley, 1971; Schwetz et al., 1971). Exposure of mice to 2,4,5-T during pregnancy results in congenital malformations (Courtney and Moore, 1971; Neubert and Dillman, 1972; Hood et al., 1979). Studies in rats (Sparschu et al., 1971) and monkeys (Dougherty et al., 1975), indicate that the teratogenicity of 2,4,5-T may be a species-dependent phenomenon, since gestational exposure to this compound produced fetotoxic but not teratogenic effects (Gehring and Betso, 1978).

Early studies with 2,4,5-T samples which were contaminated with 30 ppm of TCDD indicated that the herbicide was teratogenic in rats (Courtney et al., 1970). Subsequent studies by Courtney and Moore (1971), using

purified 2,4,5-T, showed that both 2,4,5-T and TCDD were teratogenic in three strains of mice but in rats only TCDD was fetotoxic and possibly teratogenic. TCDD has been shown by other laboratories to be teratogenic and/or embryotoxic in mice at levels above 0.1 µg/kg/day (Smith et al., 1976) and rats at 0.125-2.0 µg/kg/day (Sparschu et al., 1971).

Although fetotoxicity and teratogenicity associated with gestational exposures to these compounds have been extensively studied, there is a paucity of data as to the effects of male exposure on fertility and development of their offspring. Investigations in male rats undertaken to determine whether dominant lethal mutations could be caused by TCDD were negative. However, the incidence of fertile matings was decreased but it was not determined whether this was due to the systemic toxicity of TCDD or a direct effect on reproduction (Khera and Ruddick, 1971). Other studies that have considered reproductive competence in males have generally been multigeneration studies of animals treated during their entire lives with one of the compounds of interest. In those studies neither 2,4-D (Hansen et al., 1971) nor 2,4,5-T (Smith et al., 1978) significantly reduced fertility when males and females were given feed containing the herbicides. Three-generation studies with TCDD demonstrated that ingestion of levels greater than 0.1 µg/kg/day decreased fertility and litter survival in the f_0 generation; exposure to 0.01 µg/kg/day decreased fertility in the f_1 and f_2 generations, but not the f_0 generation (Murray et al., 1979). In that case, an increase in the percentage of resorbed implantation sites could be related to female exposure to TCDD, but not to male exposure (Murray et al., 1979).

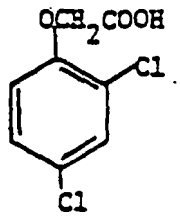
The consequences of chemical toxicity on male reproductive capabilities might include loss or decrease in fertility, abnormal sperm morphology, decreased sperm concentration and/or motility, or lesions in the reproductive tract and accessory sex glands (Gomes, 1970; Manson and Simons, 1980). In addition to effects on reproduction or fertility, chemical exposure might cause genetic mutations in the male germ cells which could be expressed in the offspring as an inherited anomaly, or embryo and fetal death (Joffe, 1979; Manson and Simons, 1980). Another mechanism to explain fetal effects via the male would be that the chemical might actually be transmitted to the female in the seminal plasma which could then result in a direct exposure of the ova.

The dominant lethal (Epstein, 1973; Generoso, 1973) and sperm morphology (Wyrobek, 1979) assays, used routinely in mice to evaluate potential chemical mutagenicity in male germ cells, were employed in this study. Both of these test systems involve chemical exposure followed by fertility testing or sperm evaluation of the animals for the duration of the spermatogenic cycle (approximately 35 days in mice). This approach is necessary since male germ cells are constantly dividing and differentiating during transit from spermatogonia to spermatozoa with each developmental stage varying in its sensitivity and susceptibility to chemical toxicity or mutagenicity. Experimental designs which are directed at determining male germ cell toxicity must consider this sperm maturation process to assure that all stages of development are tested.

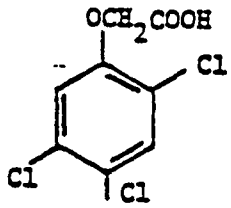
The following investigations were undertaken to determine if composite exposure to 2,4-D, 2,4,5-T plus TCDD (i.e., Herbicide Orange), could affect reproductive function in male mice.

MATERIALS AND METHODS

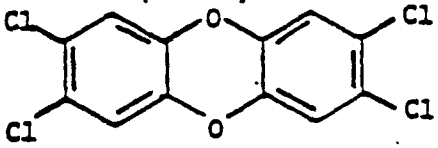
Test Chemicals and Purity



2,4-dichlorophenoxyacetic acid (2,4-D)



2,4,5-trichlorophenoxyacetic acid (2,4,5-T)



2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)

2,4-dichlorophenoxyacetic acid (2,4-D) (AGR 171114, 98.5% pure) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (AGR 133711, 98.7% pure) were supplied by the Dow Chemical U.S.A., Midland, Michigan. Both samples were analyzed by Dow Chemical for TCDD contamination who reported no TCDD or other dioxin detected in the samples (Tables 1 and 2).

The free acid was used to eliminate the volatility problem associated with the butyl ester which would compromise quantification of dose administered and pose an exposure risk to laboratory personnel. The free acid form is readily absorbed from the gastrointestinal tract.

2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was synthesized by the Environmental Chemistry Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. The TCDD was reported to be of greater than 98% purity by gas chromatographic analysis

TABLE 1

Analysis of 2,4-D Sample for Dioxins

	Concentration	Detection Limit
2,3,7,8-Tetrachlorodibenzo-p-dioxin	Not detected	1 ppb
Hexachlorodibenzo-p-dioxin	Not detected	1 ppb
Heptachlorodibenzo-p-dioxin	Not detected	20 ppb
Octachlorodibenzo-p-dioxin	Not detected	5 ppb

TABLE 2

Analysis of 2,4,5-T Sample for Dioxins

	Concentration	Detection Limit
2,3,7,8-Tetrachlorodibenzo-p-dioxin	Not Detected	0.5 ppb
Hexachlorodibenzo-p-dioxins	Not detected	0.03 ppm
Octachlorodibenzo-p-dioxin	Not detected	0.3 ppm

performed by NIEHS. The principal contaminate was 2,3,7-trichlorodibenzo-p-dioxin.

Animals and Husbandry

Four week old male and 10 week old female C57BL/6N inbred mice (Cesarean-Originated, Barrier Sustained) were purchased from the Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Upon arrival the mice were eartagged and housed in plastic cages with stainless tops (males, one per cage; females, ten per cage). Absorb-dri hardwood bedding (Barnes Supply, Durham, NC) was used, and cages were cleaned once each week. The animals were kept in constant temperature (20 ± 2°C) and humidity (R.H. 50 ± 10%) on a fixed cycle of 12 hours light-12 hours darkness. The mice were allowed food and water ad libitum. The powdered diet was open formula NIH-31 prepared by Zeigler Bros. Co. of Gardners, Pa.

Preparation of Diets

Stock solution of the test chemicals were prepared in a corn oil vehicle. The calculated and analytical values are given in Table 3. The test diets were prepared each week for 8 weeks by adding the appropriate stock solution into the feed (2% vol/wt). The concentration of chemicals in the feed was not changed during the 8 week exposure period study. Feed consumption (gm/mouse) was measured once a week. Approximate dose levels were projected using consumption of 5 gm feed/day by a mouse weighing 25 gm. The controls (Group I) were given a diet containing 2% corn oil. Group II consisted of mice that received about 40 mg/kg/day of 2,4-D, 40 mg/kg/day of 2,4,5-T and 2.4 µg/kg/day of TCDD for a total dose of 2.24 gm/kg of 2,4-D and 2,4,5-T each and 0.13 mg/kg of TCDD over the entire 8 weeks. Group III mice were treated at a rate of 40 mg/kg/day

TABLE 3

2,4-D, 2,4,5-T and TCDD

Concentrations in Stock Corn Oil Solutions*

and Projected Dosages in Feed

Treatment Group	2,4-D[1] ppm*	2,4-D[1] mg/kg/day**	2,4,5-T[1] ppm*	2,4,5-T[1] mg/kg/day**	TCDD[2] ppb*	TCDD[2] µg/kg/day**
I (Control)	0(0)	0	0(0)	0	0(0)	0
II	10,000(9380)	40	10,000(9590)	40	600(505)	2.4
III	10,000(9310)	40	10,000(9480)	40	40(39)	0.16
IV	5,000(4880)	20	5,000(4830)	20	300(271)	1.2

*Calculated prepared concentrations and in ( ) amounts detected by analysis.

**Dose levels based on ideal concentrations in feed and an average feed consumption of 5 gm feed/day/25 gm mouse.

[1]Samples of oil collected for 2,4-D and 2,4,5-T analyses were extracted with ethyl ether, derivatized with diazomethane, extracted with hexane and analyzed on an electron capture gas chromatograph (ECGC) by the Midwest Research Institute.

[2]Samples of oil collected for TCDD analysis were saponified in ethyl alcohol and potassium hydroxide, then extracted with hexane and analyzed with an ECGC by the Midwest Research Institute.

of 2,4-D and 40 mg/kg/day of 2,4,5-T (same as Group II), but received only 0.16 µg/kg/day of TCDD; the total dosages of 2,4-D and of 2,4,5-T were 2.24 gm/kg and 0.009 mg/kg of TCDD. The mice in Group IV received 20 mg/kg/day of 2,4-D, 20 mg/kg/day 2,4,5-T, and 1.2 µg/kg/day of TCDD, resulting in a total 8 week exposure of 1.12 gm/kg of 2,4-D and of 2,4,5-T and 0.067 mg/kg of TCDD. After the 8 week exposure period all mice were fed standard pelleted NIH 31 diet.

Experimental Design

Two hundred male mice were weighed and sorted (by weight) into eight groups (25 per group). One half of the male mice (4 groups of 25 each) were used for toxicity evaluation, while the other half (4 groups of 25 each) were used for fertility and reproductive studies.

All males were then acclimatized on NIH-31 laboratory chow for three weeks before the chemical exposures were begun. Chemical exposure began when the males were eight weeks old. Body weights and food consumption were recorded on a weekly basis. The males were assigned to experimental and control groups such that weight differences between groups were minimized. The mice were then treated with one of the three treated or control diets for eight consecutive weeks.

Toxicopathology

One hundred of the mice were studied during and after the 8 week feeding period. Four animals from each of the four dose groups were killed by decapitation at 1, 4, 5, 8, 12 and 16 weeks after first receiving treated feed. Each mouse received a gross autopsy examination; body and organ (brain, liver, spleen, kidney, thymus and testis/epididymis) weights were measured. These organs as well as lung, duodenum, ear,

prostate, seminal vesicle, coagulating gland and urinary bladder were fixed in 10% neutral buffered formalin, dehydrated and embedded in paraffin blocks. Six μm histologic sections were prepared and stained with hematoxylin and eosin. The tissues were examined for evidence of histopathologic change.

Also at sacrifice, the vas deferens were removed and spermatozoa milked into a 1.0 ml volume of 0.9% saline. The concentration of sperm per vas deferens was estimated with a hemocytometer immediately after collection. Additionally, the percent motile (any movement vs. no movement) sperm was enumerated. The sperm sample was then stained with 0.25% eosin Y for 30 minutes. The sperm were evenly distributed within the staining solution using a Pasteur pipette and four slide preparations were prepared from each sample. The smears were allowed to air dry, were cover slipped and were examined at 400 X magnification. Three hundred sperm were studied for each sample and sperm were classified as normal or abnormal using the criteria of Wyrobek and Bruce (1975) and Soares et al (1979).

Fertility and Reproduction

Fertility and reproduction assessments were conducted on the remaining 100 mice (four groups of 25).

After the male mice had been treated with the test chemicals for eight weeks they were returned to control feed. Beginning the next day, each male was housed with three virgin female mice (fourteen weeks of age) for up to 5 days each week for eight weeks. Each female was examined each morning for evidence of mating by detection of a vaginal plug (Day 0 of pregnancy). Each mated female was removed from the cage, weighed and placed in a cage with other mated females in that group. Females which did not appear to have mated during the 5-day cohabitation period

were observed for three more weeks to permit detection of possible pregnancies for which vaginal plugs were not observed. Apparent failure of a female to mate or conceive was verified three weeks after cohabitation by killing the animal, removing the uterus, and staining it with ammonium sulfide to better identify the presence of implantation sites (Kopf et al., 1964).

For each weekly mating trial one female bred to each male was put in a group to be sacrificed on day 18 of pregnancy for teratology examination. A second bred female from each male was placed in a group which was allowed to deliver and rear her offspring. All remaining dams found to have plugs were placed in a "teratology backup group" to be subjected to teratological evaluation if the dam selected for day 18 sacrifice was found not to have any live fetuses. The above pregnant mice were systematically distributed to the teratology, postnatal or "backup" groups such that no one group was biased with dams which mated first, second or third. However, if less than three dams had mated, priority was generally given to the teratology group. All mated dams were weighed on days 0, 7, 11, 15 and 18 of gestation.

On day 18 of gestation, the dams designated for teratology examination were coded to permit identification only by number so that laboratory personnel conducting the teratogenic analysis did not know the test group. The mice were killed by cervical dislocation and their reproductive status was determined. Implantation sites in each uterine horn were counted and the general condition of each conceptus was recorded. The detection of implantation sites in the uteri of apparently nonpregnant females was achieved through use of ammonium sulfide (Kopf et al., 1964). Live fetuses were weighed individually, sexed internally (surgical incision below navel), and examined for external malformations. Live

fetuses weighing <0.5 g, or weighing less than two-thirds the mean of their larger littermates, were designated as being "stunted". At least one-half of the fetuses of each litter, all "stunted" fetuses and fetuses having external malformations, were examined for visceral alterations (Staples, 1974). The bodies of all fetuses were then processed for skeletal examination (Staples and Schnell, 1964). The heads of each fetus subjected to visceral examination (with the exception of any fetuses which had external head malformations) were cut off at the base and examined by the free-hand sectioning technique described by Wilson (1965).

The remaining dams (postnatal group) were allowed to deliver their litters. Live and dead offspring as well as birth weight were recorded (day 0). The pups were reweighed on days 4, 7 and 21 and viability also was recorded. The dams and their offspring were killed on day 21.

The above procedures were repeated weekly for eight weeks resulting in a total of eight sets of data. Four weeks after the conclusion of the breeding study, (week 20 of the experiment), the male mice were killed and autopsied in a manner identical to that described for the males sacrificed for toxicopathologic evaluation.

Statistical Evaluation

Statistical evaluations of possible pairwise treatment-control differences in food consumption, body weights, organ weights, fertility, mating efficiency, and sperm number, motility and abnormalities were made by Dunnett's test (Miller, 1966). Analysis of variance procedures were employed to assess the significance of differences among groups, week-to-week variability, and week by group interactions. Analyses of abnormalities among the offspring were carried out employing pairwise

comparison of control versus treated groups with the Mann Whitney U test. The analysis of malformations considered the average percent malformed fetuses per litter.

RESULTS

Feed Consumption and Body Weight

The projected food consumption of 35 gm/week (5 gm/day) proved to be a conservative estimate in all groups throughout the period of chemical exposure (Figure 1). Lower food consumption for all groups is indicated in week-2 because only a fraction of the week (5 days) was measured. The addition of 2,4-D, 2,4,5-T or TCDD did not significantly decrease feed consumption during the full eight week dosing period in any treatment group, as compared to the controls. Statistically significant changes in feed consumption were only found in sporadic cases and no general trend of decreased feed consumption could be attributed to the addition of either phenoxy acids or TCDD.

Body weight and weight gain, however, showed significant reductions in the treated animals when compared to controls (Figures 2 and 3). This reduction in body weight was most pronounced in group II (2.4 µg TCDD/kg/day and 80 mg phenoxy acid/kg/day) from weeks 3 through 8 of the study. The Group II animals recovered most of their weight deficit when returned to control diet.

Generally all of the mice appeared healthy throughout the course of the study. Only two animals died during the twenty weeks, one in group IV at 5 weeks and one in group II at 19 weeks. Their death did not appear to be treatment-related.

Organ Weights and Histopathology

The mean organ weights of animals killed on weeks 1, 4, 5, 8, 12, 16, and 20 are shown in Figures 4-9. Statistically significant increases in liver weight (Figure 4) were observed in all treated groups and was positively correlated with the amount of TCDD exposure (i.e., 2.4 > 1.2

> .16 µg/kg TCDD/day, groups II, IV and III respectively). After conclusion of exposure the liver weight returned toward normal, although Groups II and IV continued to show significantly elevated values even at week 20. The livers of treated mice were enlarged, lighter in color than normal and mottled. The thymus was decreased in weight, which also appeared to be a function of the level of TCDD rather than phenoxy acid exposure (Figure 5). Although the thymus weights were significantly ($p<.01$) reduced in Groups II and IV relative to controls throughout the treatment period (weeks 1-8), thymic recovery appeared complete and weights were not statistically different from the controls by 4 weeks after the last exposure. No significant treatment-related effects were observed in the spleen (Figure 6), testis (Figure 7), kidney (Figure 8), or brain (Figure 9). Histopathological evaluation showed no treatment-related changes in any organs, with the exception of the liver. Even the thymus, which had decreased in size to as much as one-third that of the control thymus, appeared histologically normal. The mild toxic effects observed in the liver included hepatocellular swelling, scattered single cell necrosis, increased numbers of mitotic figures, excess extramedullary hematopoiesis, and leukocytic infiltration. These changes were most apparent in group II (2.4 µg/kg/day TCDD; 80 mg/kg/day phenoxy acids) and least apparent in Group III (0.16 µg/kg/day TCDD; 80 mg/kg/day phenoxy acid). These signs of toxicity diminished substantially by the end of the twelfth week of the study (four weeks after chemical exposure was concluded).

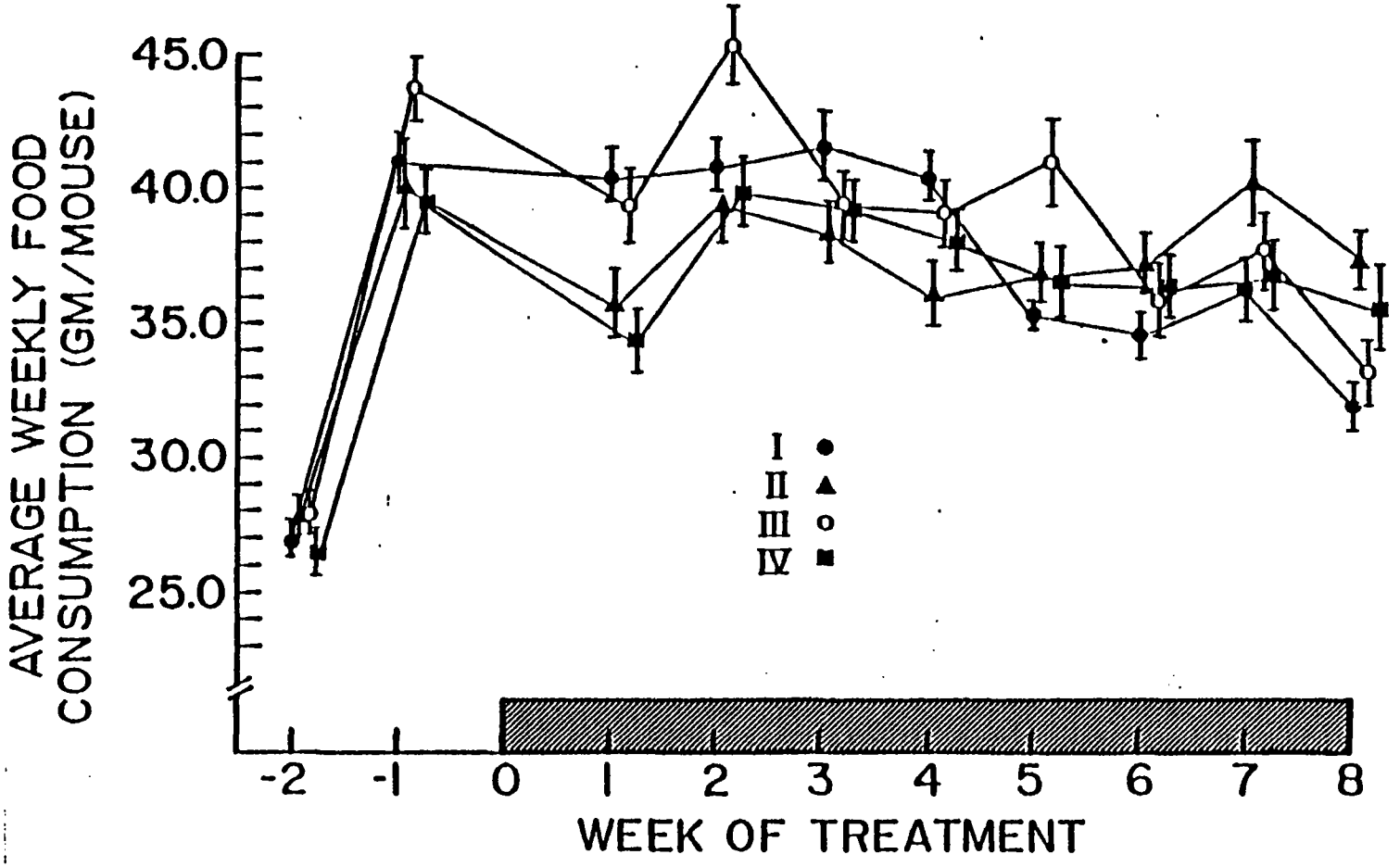


Figure 1. Average weekly food consumption before and during the treatment period of the study for the males. Values are mean ± S.E.M.

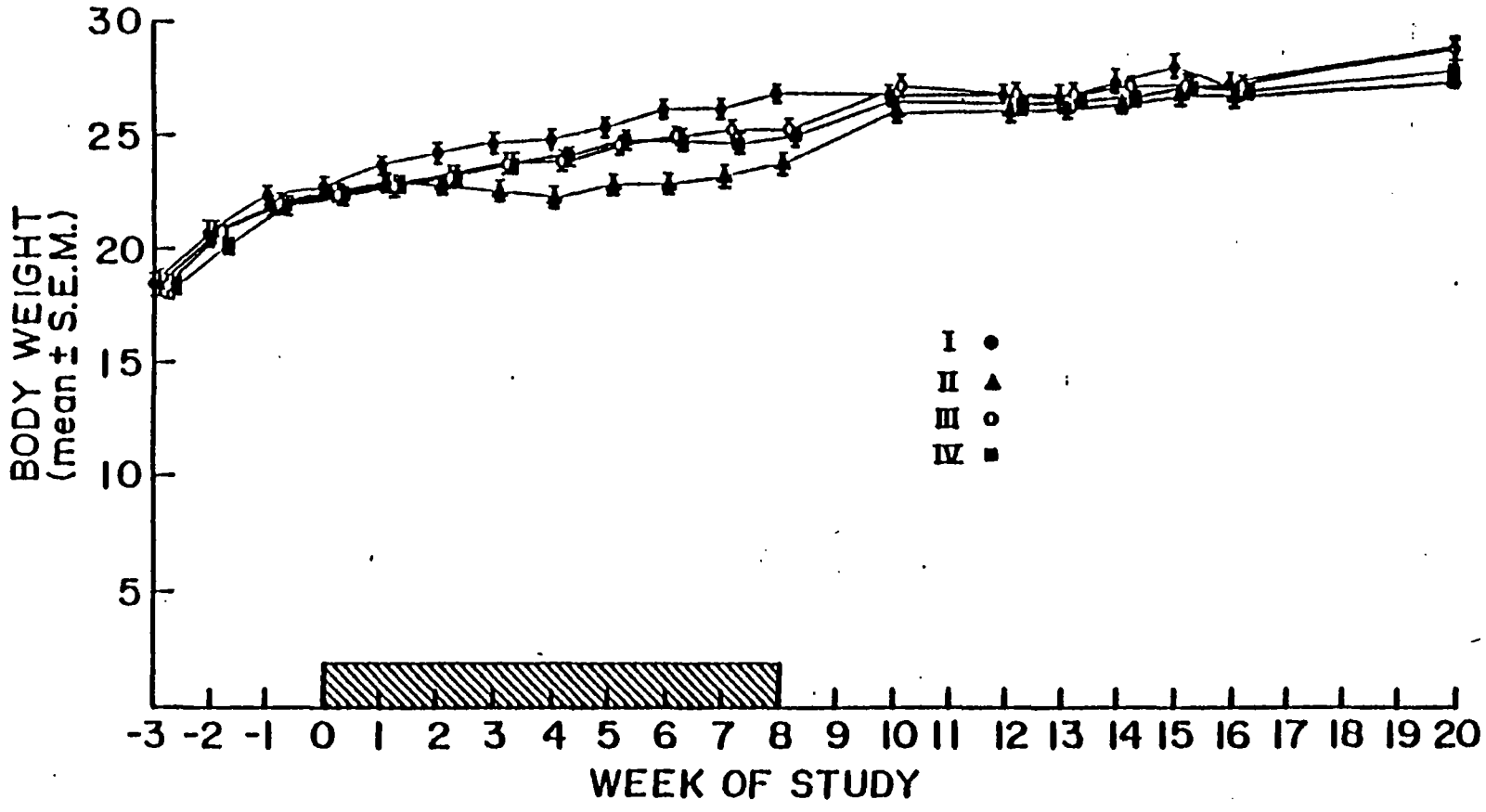


Figure 2. Mean body weights for male mice in all four treatment groups. Significant reductions ($p<0.05$) in weight, as compared to control, for groups II and III were present in weeks 3-8, group IV in weeks 6-8. Values are mean ± S.E.M.

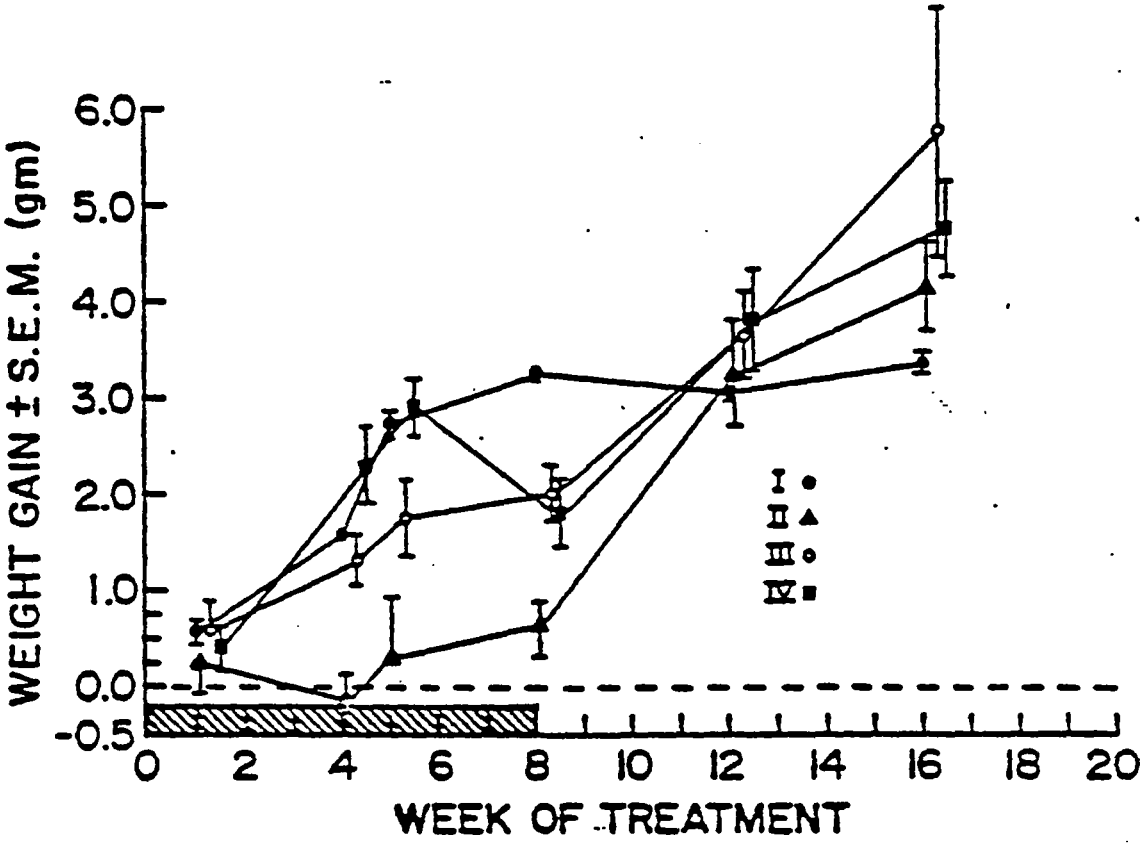


Figure 3. Average weekly weight gain. Weight gain was significantly ($p<0.01$) reduced in Group II relative to control during weeks 4, 5 and 8. Rapid recovery was observed such that no significant difference was present by week 12 in these animals. Values are mean ± S.E.M., n = 4 per group.

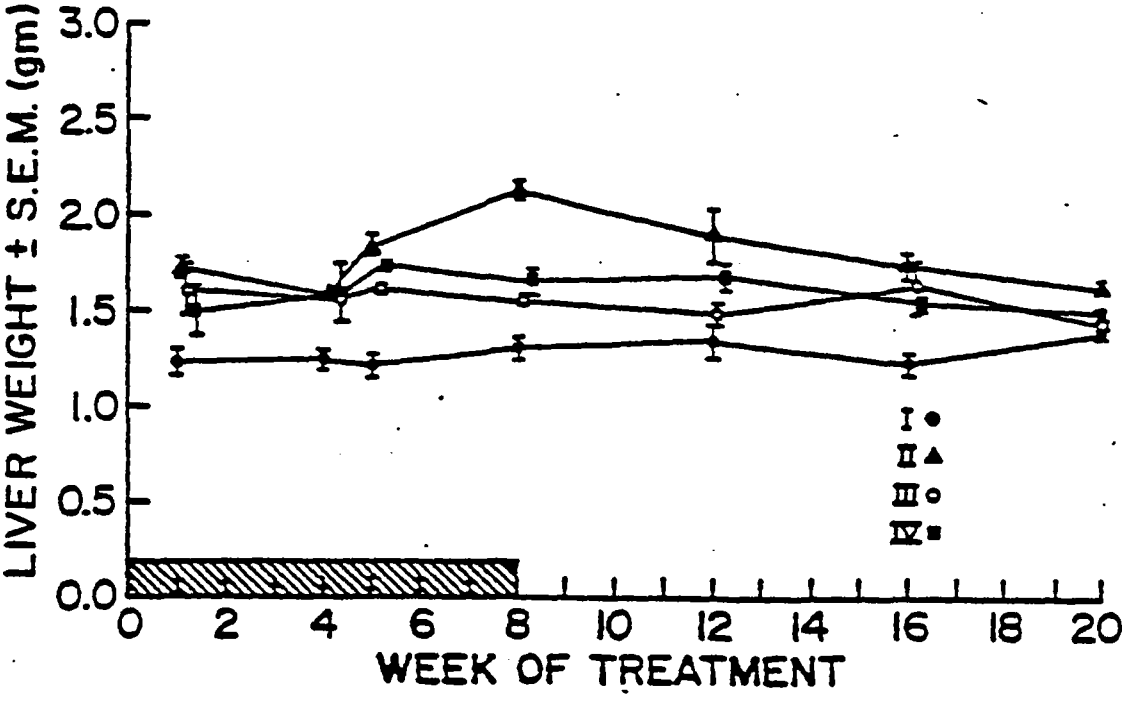


Figure 4. Average liver weight. Liver weight was significantly ($p<.05$) increased in Group II (weeks 1-20), Group III (weeks 1-5, week 16) and Group IV (weeks 4-20) relative to controls. Values are mean ± S.E.M., n = 4 per group, weeks 1-16, n = 25 per group in week 20.

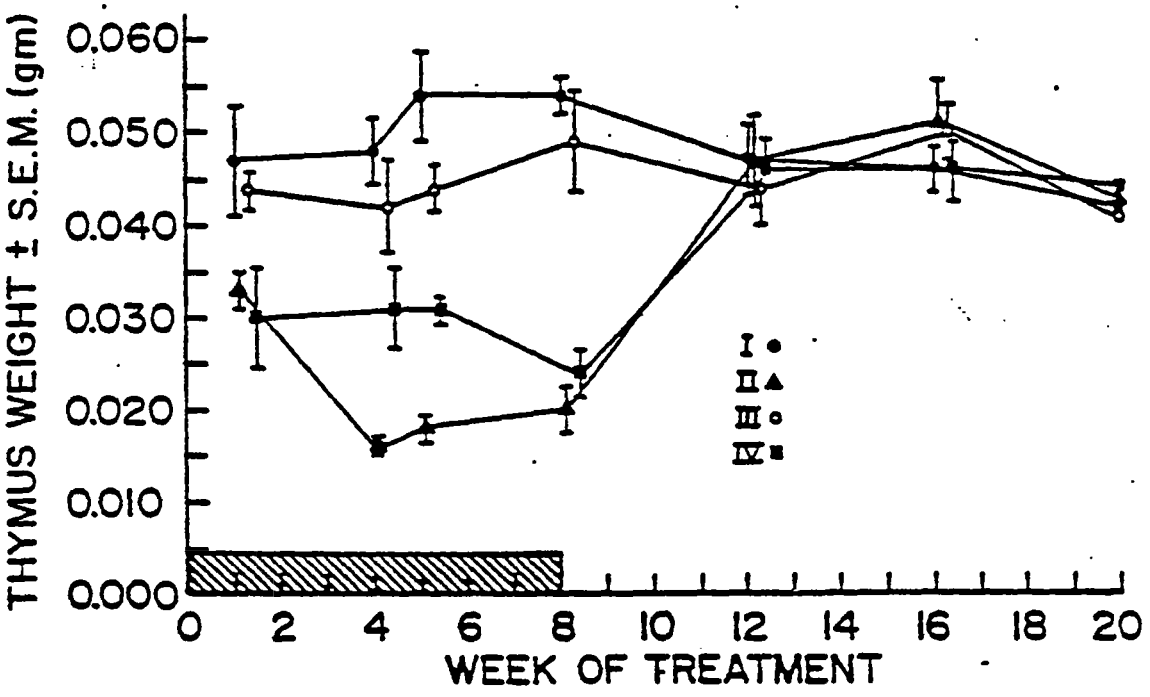


Figure 5. Average thymus weight. Thymus weight was significantly ($p<.01$) reduced in Groups II and IV relative to controls (weeks 1-8). Complete recovery was observed in all groups by week 12. Values are mean ± S.E.M., n = 4 per group on week 1-16, n = 25 per group in week 20.

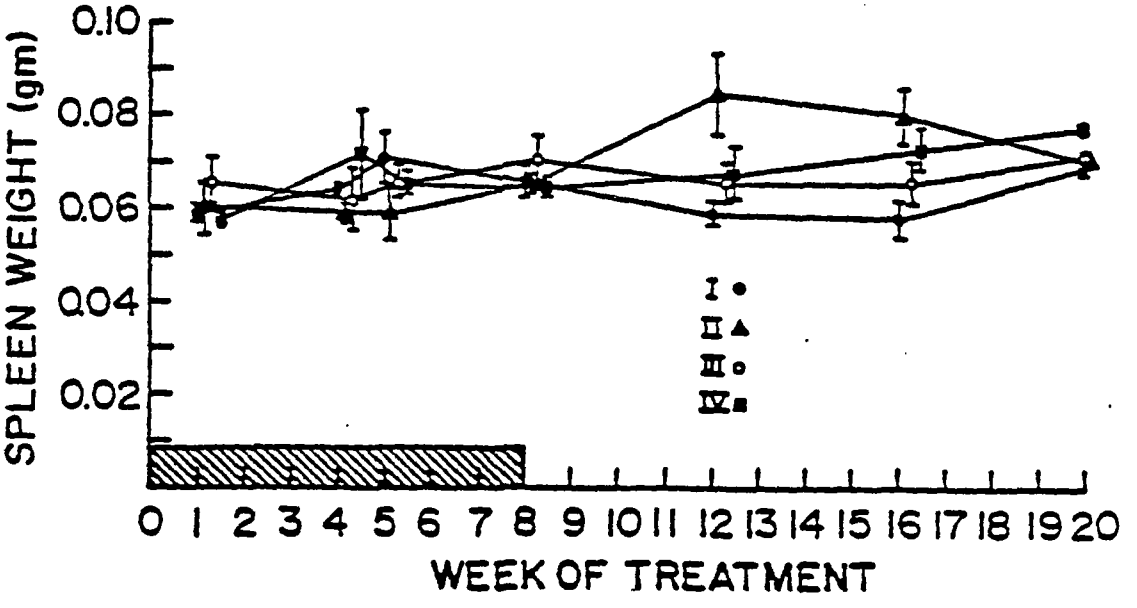


Figure 6. Average spleen weight was not significantly changed by treatment. Values are mean ± S.E.M., n = 4 per group in weeks 1-16, n = 25 per group in week 20.

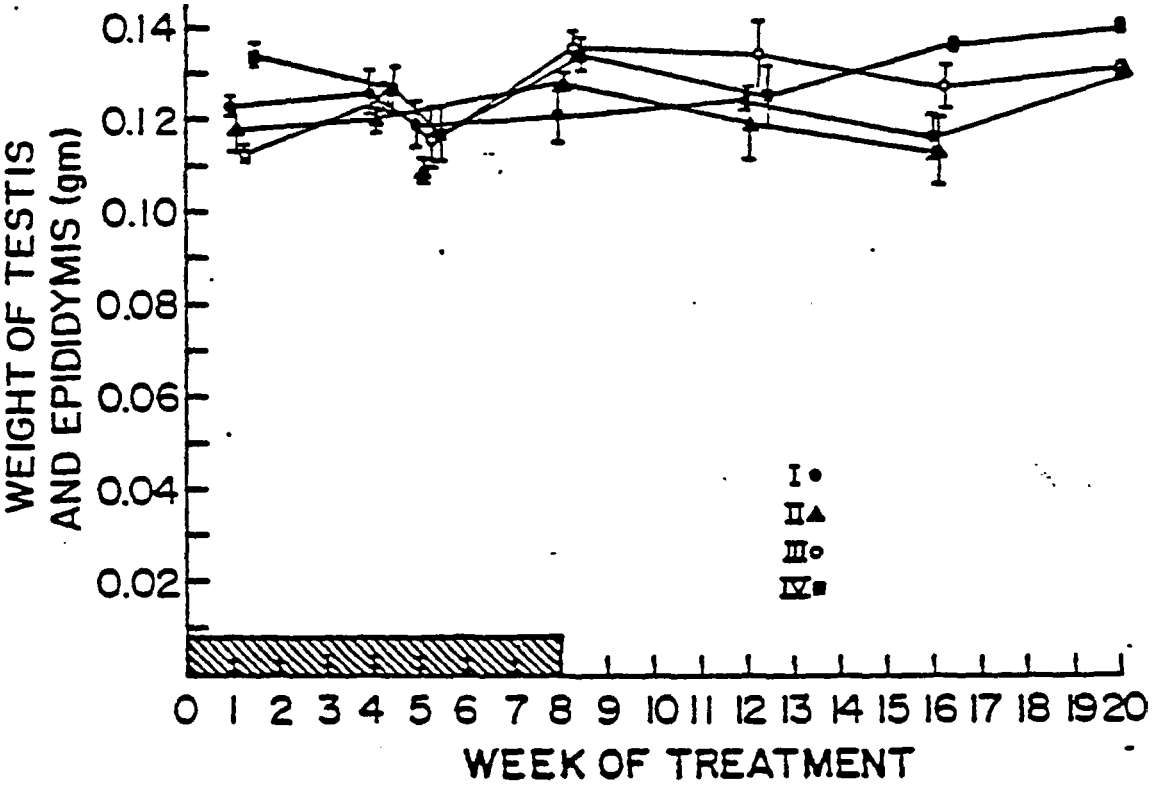


Figure 7. Average testis and epididymis weight was not significantly affected by treatment. Values are mean ± S.E.M., n = 4 per group in weeks 1-16, n = 25 per group in week 20.

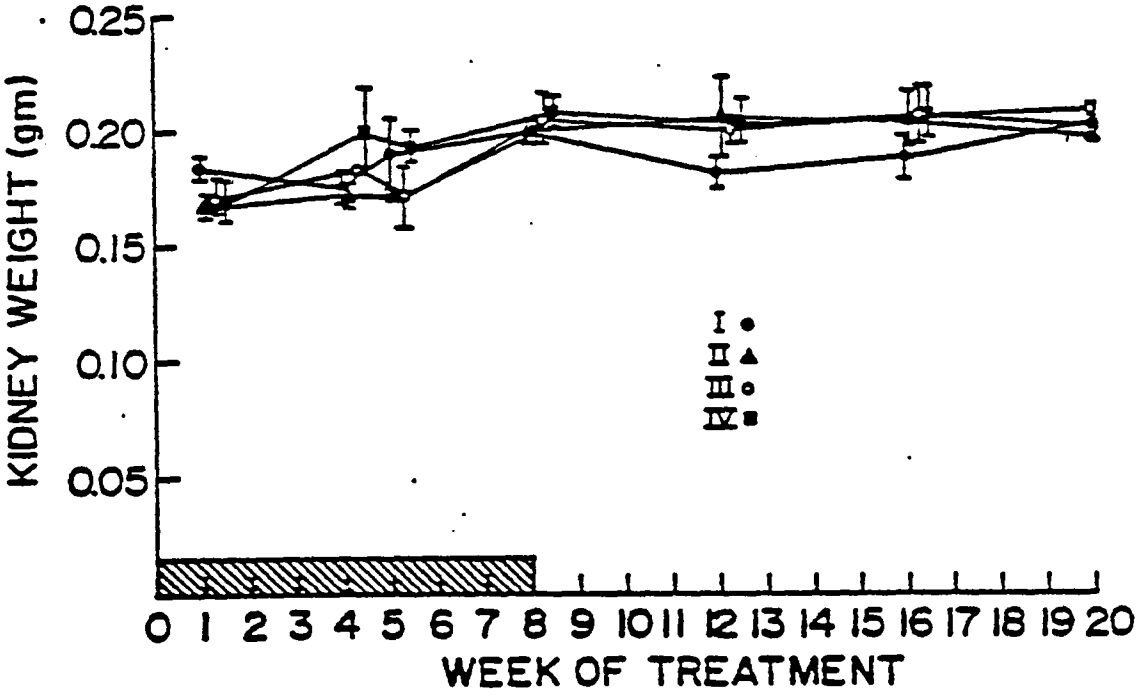


Figure 8. Average kidney weight was not significantly changed by treatment. Values are mean ± S.E.M., n = 4 per group in weeks 1-16, n = 25 per group in week 20.

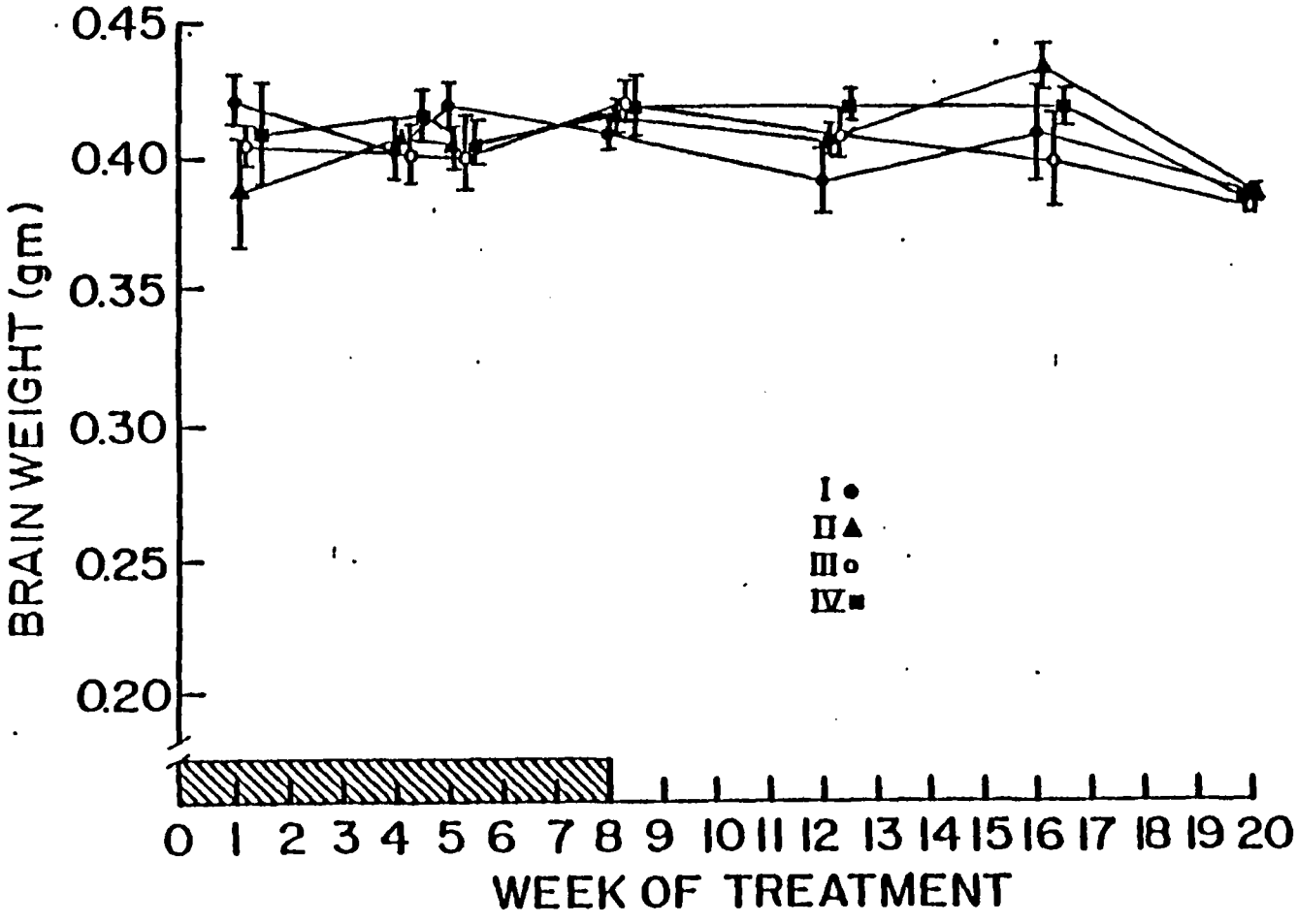


Figure 9. Average brain weight was not significantly altered by chemical treatment. Values are mean ± S.E.M., n = 4 per group in weeks 1-16, n = 25 per group in week 20.

Fertility

The average percent matings and overall fertility of the males through 8 weeks of the study are given in Table 4. There was a significant reduction in the mating frequency in males from group III (80 mg/kg/day phenoxy acid, 0.16 µg/kg/day TCDD). This effect was not significant in Group II whose phenoxy acid exposure was similar and whose TCDD exposure was 15-fold greater. Therefore, no dose-related effect could be attributed to this decrease. Also, the percent fertile matings and total fertility were not significantly reduced in Group III or in any group when compared to the control.

When fertility was evaluated on a week by week basis, no treatment-related changes were observed. Fertility was also studied on an individual per male basis and no significant changes were detected within treated males as compared to controls. At the conclusion of the study sperm concentration and motility and percent abnormal sperm were measured (week 20, Figures 10-12). These values were analyzed, on an individual male basis, to determine whether any correlation existed between low fertility performance (plug frequency, percent fertile matings and total fertility) and low values for sperm quality (concentration, motility, percent abnormal). In all groups there was no correlation between the parameters measured. This would indicate that, even though there was considerable variability within these parameters, variations in fertility could not generally be attributed to specific changes in sperm quality. The values for sperm concentration (Figure 10) and sperm motility (Figure 11) fluctuated considerably from week to week. Percent abnormal sperm were less variable (Figure 12). No treatment-related changes were observed in these parameters. The marked reductions in sperm concentration (Figure 10) and increase in sperm motility (Figure 11) which were

TABLE 4

Fertility and Mating Efficiency in Treated and Control C57Bl/6 Mice
8 Week Total

Treatment Group[1]	Mating[2] Frequency	Fertile Matings (percent)[3]	Total[4] Fertility (percent)
I(Control)	74.6 ± 1.6	56.2 ± 2.2	42.0 ± 1.9
II(80;2.4)	70.3 ± 2.4	58.3 ± 2.9	41.0 ± 2.6
III(80;0.16)	67.8 ± 2.4*	55.3 ± 2.3	37.7 ± 2.2
IV(40;1.2)	73.0 ± 2.0	60.8 ± 2.9	44.2 ± 2.3

[1]Calculated daily exposure is given in parentheses as total mg phenoxy acids/kg/day; μg TCDD/kg/day
[2]Percent plugs observed/total females housed with males.
[3]Percent fertile matings/females with plugs.
[4]Percent fertile matings/total females housed with males.
*P<.05 relative to controls

Values are mean ± standard error of the mean, n = 25 per group.

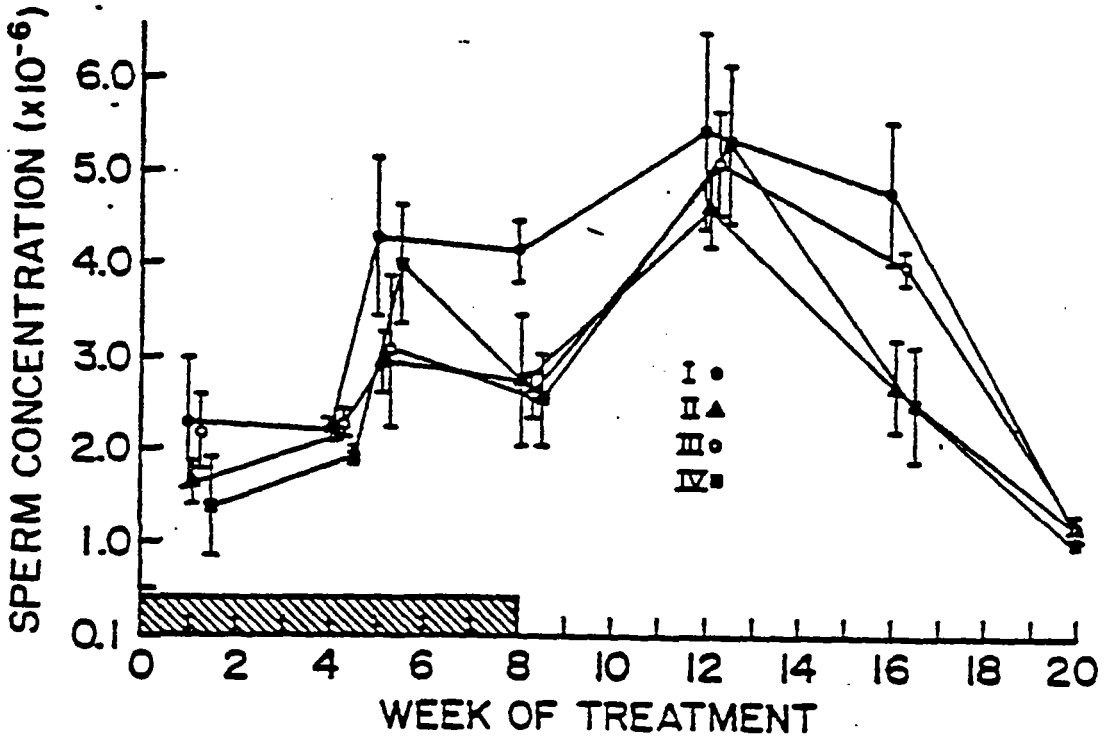


Figure 10. Average sperm concentration. Sperm concentration was quite variable and the only significant reduction relative to controls was in week 16 ($p<.05$, Group II; $p<.01$, Group IV). The marked reduction in all groups at 20 weeks may have been related to the mating of those animals. Values are mean ± S.E.M., n = 4 per group in weeks 1-16, n = 25 per group in week 20.

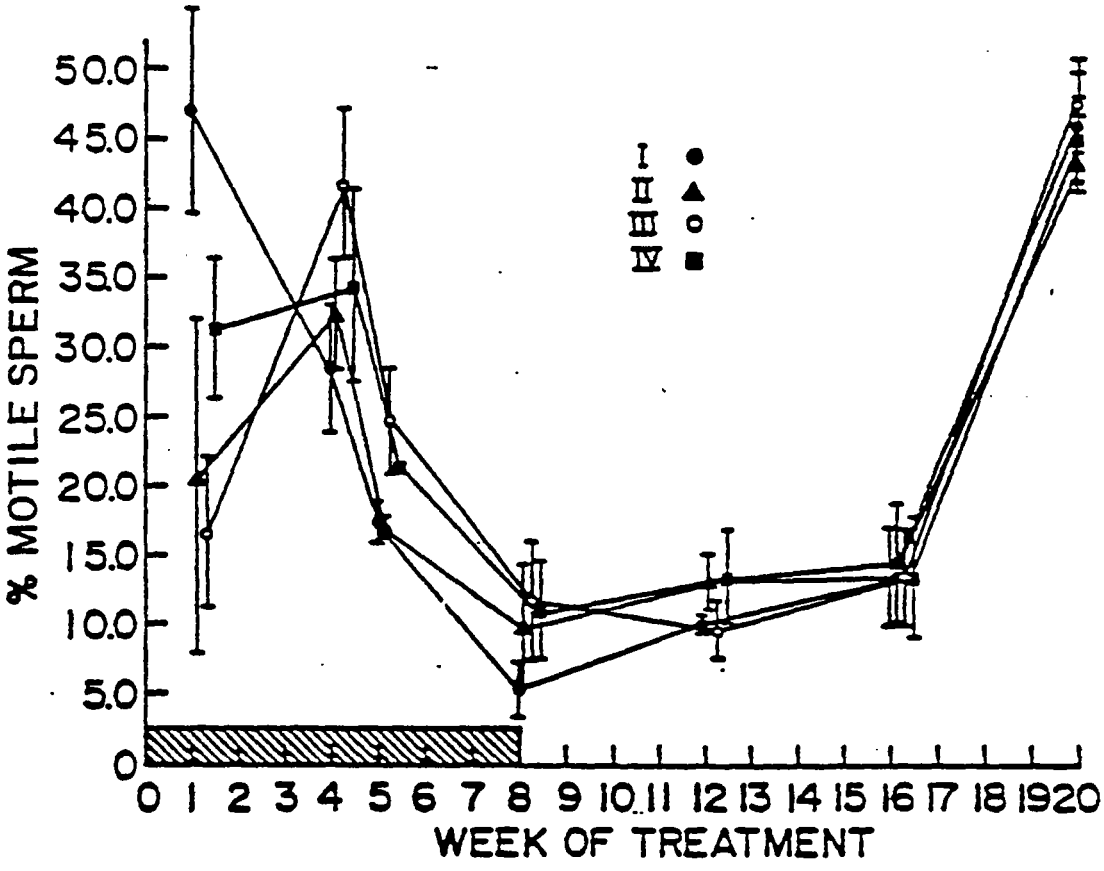


Figure 11. Average percent motile sperm. No significant change was observed in the percent motile sperm ($p<0.05$) when treated and control values were compared. The drop in motility seen from week 4 to week 16 may have resulted from not breeding those males; in contrast, the week 20 (mated) values were much higher. Values are mean $\pm$ S.E.M., n = 4 per group in weeks 1-16, n = 25 per group in week 20.

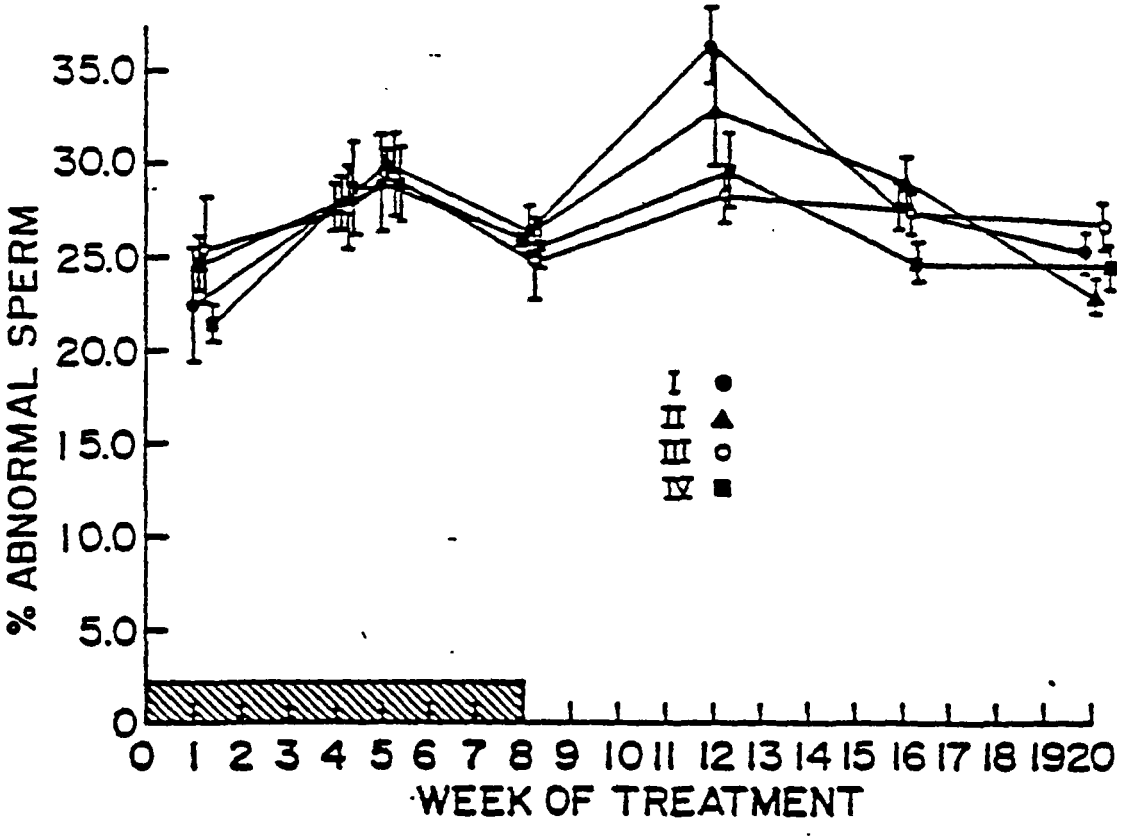


Figure 12. Average percent abnormal sperm. Treatment had no significant influence on the percent abnormal sperm ($p<0.05$). Values are mean ± S.E.M., n = 4 per group in weeks 1-16, n = 25 per group in week 20.

observed from weeks 16 to 20 of the study might be at least partly explained by the fact that the males whose sperm were checked on week 20 had been through an 8-week intensive mating program whereas the males monitored in the earlier weeks were virgins.

Teratological Examinations

The results of the teratology examination of the dams mated with treated or control males for each group by week are detailed in Tables 5-8. A comparison of the tables indicates that the average number of implants per litter, average number of resorptions per litter or average number live fetuses per litter (Tables 5-8) were unaffected by the male's chemical exposures. For example, the mean values for control and Group II (most heavily exposed) were 7.1 vs 7.4 implant sites per litter; also in Groups I and II there were 4.9 vs 5.0 live fetuses per litter and 2.18 vs 2.37 resorptions per litter. The average fetal weight was significantly ($p<0.05$) greater in all treatment groups as compared to controls. The total number of dead fetuses (i.e., offspring which weighed more than 0.3 gm; offspring weighing <0.3 gm were listed as a resorptions) was 1 in Group I, 2 in Group II, 1 in Group III and 0 in Group IV for the entire 8 week study. The ratio of male to female fetuses was also determined; no treatment group exhibited any significant change ($p<0.10$) in this ratio as compared to the control.

Congenital malformations were not significantly increased in the offspring of treated versus control males (Tables 5-10). Visceral malformations were observed with less frequency than external and skeletal malformations in all groups. The incidences of the most frequently observed malformations are summarized in Table 9: eye defects (anophthalmia and microphthalmia), jaw anomalies (agnathia, micrognathia), were observed in 1.4 to 2.4 percent and 1.2 to 1.6 percent of the fetuses,

Table 5

Effect of 2,4-D, 2,4,5-T and TCDD on Fetal Development
Group 1 Control

	Week of Study								Total 8 weeks
	1	2	3	4	5	6	7	8	
Number of females examined	19	22	22	25	23	19	22	19	171
Maternal weight gain	13.1 ± 1.0	12.8 ± 0.7	12.7 ± 0.7	12.0 ± 0.8	10.0 ± 0.7	10.1 ± 0.7	11.4 ± 0.8	12.1 ± 0.8	11.8 ± 0.3
Number of implants per litter	8.1 ± 0.5	7.7 ± 0.4	8.0 ± 0.4	7.4 ± 0.6	5.4 ± 0.5	5.8 ± 0.4	7.2 ± 0.5	6.6 ± 0.6	7.1 ± 0.2
Number of resorptions per litter	2.16 ± 0.38	2.41 ± 0.32	2.18 ± 0.32	2.16 ± 0.25	2.39 ± 0.25	2.16 ± 0.33	2.27 ± 0.3	1.68 ± 0.30	2.18 ± 0.11
Number of live fetuses per litter	5.9 ± 0.7	5.3 ± 0.5	5.9 ± 0.5	5.2 ± 0.6	3.0 ± 0.5	3.7 ± 0.4	4.9 ± 0.5	4.9 ± 0.6	4.9 ± 0.2
Average fetal weight per litter	1.04 ± 0.03	1.06 ± 0.02	1.05 ± 0.03	1.00 ± 0.02	1.03 ± 0.02	1.04 ± 0.03	0.99 ± 0.03	1.01 ± 0.03	1.03 ± 0.01
Male/female	59/52	47/68	63/64	69/60	38/32	32/38	52/53	42/52	404/419
Visceral Malformations:									
Number of fetuses examined	60	62	68	73	39	39	62	52	455
Number with visceral malformations	0	0	0	1	1	0	0	0	2
Skeletal and External Malformations:									
Number of fetuses examined	113	117	129	129	70	70	108	94	830
Number with malformations	2	3	4	4	4	0	4	5	26

Values are mean ± standard error of the mean.

Table 6

Effect of 2,4-D, 2,4,5-T and TCDD on Fetal Development
Group II

	Week of Study								Total 8 weeks
	1	2	3	4	5	6	7	8	
Number of females examined	19	18	21	17	22	20	17	14	148
Maternal weight gain	14.1 ± 0.5	12.7 ± 0.9	12.2 ± 0.8	11.5 ± 1.0	10.8 ± 0.7	10.4 ± 0.9	12.6 ± 0.9	12.0 ± 1.0	12.0 ± 0.3
Number of implants per litter	9.2 ± 0.4	7.4 ± 0.6	8.2 ± 0.4	6.2 ± 0.6	7.1 ± 0.4	6.2 ± 0.5	7.5 ± 0.4	7.0 ± 0.7	7.4 ± 0.2
Number of resorptions per litter	2.37 ± 0.27	1.94 ± 0.37	2.71 ± 0.40	1.76 ± 0.22	2.55 ± 0.36	2.30 ± 0.45	1.88 ± 0.38	3.43 ± 0.71	2.37 ± 0.14
Number of live fetuses per litter	6.8 ± 0.3	5.5 ± 0.7	5.6 ± 0.5	4.5 ± 0.7	4.5 ± 0.4	3.9 ± 0.6	5.6 ± 0.6	3.6 ± 0.7	5.0 ± 0.2
Average fetal weight per litter	1.00 ± 0.02	1.14 ± 0.03	1.08 ± 0.03	1.09 ± 0.02	1.02 ± 0.03	1.11 ± 0.03	1.02 ± 0.02	1.10 ± 0.03	1.08 ± 0.01
Male/female	62/67	39/60	61/48	36/39	45/54	43/34	42/54	28/20	356/376
Visceral Malformations:									
Number of fetuses examined	66	53	61	42	54	42	47	28	393
Number with visceral malformations	0	0	0	0	0	0	2	0	2
Skeletal and External Malformations:									
Number of fetuses examined	129	99	115	78	100	77	96	50	744
Number with malformations	2	6	4	0	5	1	7	1	26

Values are mean ± standard error of the mean.

53

Table 7

Effect of 2,4-D, 2,4,5-T and TCDD on Fetal Development
Group III

	Week of Study								Total 8 weeks
	1	2	3	4	5	6	7	8	
Number of females examined	18	15	21	17	19	22	21	12	145
Maternal weight gain	12.9 ± 0.9	12.9 ± 0.9	11.9 ± 0.7	12.0 ± 0.9	10.7 ± 0.8	10.9 ± 0.8	10.2 ± 0.6	12.2 ± 1.1	11.6 ± 0.3
Number of implants per litter	8.4 ± 0.6	7.6 ± 0.5	7.5 ± 0.4	6.6 ± 0.6	7.2 ± 0.5	6.6 ± 0.6	6.8 ± 0.4	7.0 ± 0.6	7.2 ± 0.2
Number of resorptions per litter	2.65 ± 0.58	2.27 ± 0.44	2.14 ± 0.35	1.65 ± 0.28	2.84 ± 0.37	2.14 ± 0.34	2.05 ± 0.30	2.33 ± 0.72	2.26 ± 0.1
Number of live fetuses per litter	5.7 ± 0.7	5.4 ± 0.6	5.3 ± 0.5	5.0 ± 0.5	4.3 ± 0.4	4.5 ± 0.5	4.8 ± 0.4	4.7 ± 0.7	4.9 ± 0.2
Average fetal weight per litter	1.06 ± 0.03	1.11 ± 0.02	1.15 ± 0.02	1.09 ± 0.03	1.09 ± 0.02	1.05 ± 0.03	1.00 ± 0.02	1.09 ± 0.03	1.08 ± 0.01
Male/female	47/50	41/39	58/53	33/50	46/35	51/47	51/49	29/26	356/349
Visceral Malformations:									
Number of fetuses examined	53	44	60	44	47	58	56	32	394
Number with visceral malformations	1	3	0	0	0	0	0	1	5
Skeletal and External Malformations:									
Number of fetuses examined	97	81	112	85	82	98	100	56	711
Number with malformations	2	1	4	2	5	0	5	1	20

Values are mean ± standard error of the mean.

Table 8

Effect of 2,4-D, 2,4,5-T and TCDD on Fetal Development
Group IV

	Week of Study								Total 8 weeks
	1	2	3	4	5	6	7	8	
Number of females examined	18	23	20	24	21	21	18	19	164
Maternal weight gain	11.6 ± 0.8	12.9 ± 0.8	11.5 ± 0.7	12.2 ± 0.8	9.9 ± 0.8	9.9 ± 0.8	11.9 ± 0.8	11.9 ± 0.9	11.5 ± 0.3
Number of implants per litter	8.9 ± 0.7	7.3 ± 0.6	7.0 ± 0.6	7.6 ± 0.5	6.0 ± 0.5	6.5 ± 0.5	7.5 ± 0.6	5.9 ± 0.7	7.0 ± 0.2
Number of resorptions per litter	4.00 ± 0.50	1.77 ± 0.29	1.30 ± 0.28	1.88 ± 0.30	1.95 ± 0.37	2.43 ± 0.35	2.39 ± 0.48	1.58 ± 0.30	2.11 ± 0.14
Number of live fetuses per litter	4.9 ± 0.6	5.6 ± 0.6	5.7 ± 0.5	5.8 ± 0.6	4.1 ± 0.5	4.1 ± 0.4	5.1 ± 0.6	4.9 ± 0.7	5.0 ± 0.2
Average fetal weight per litter	1.12 ± 0.04	1.16 ± 0.03	1.09 ± 0.02	1.11 ± 0.02	1.10 ± 0.03	1.07 ± 0.03	1.05 ± 0.03	1.07 ± 0.03	1.10 ± 0.01
Male/female	33/45	59/69	58/54	63/75	45/41	40/46	42/46	36/44	376/420
Visceral Malformations:									
Number of fetuses examined	41	67	62	77	50	50	50	46	443
Number with visceral malformations	0	2	1	1	1	0	0	0	5
Skeletal and External Malformations:									
Number of fetuses examined	78	129	113	139	86	86	92	82	805
Number with malformations	2	5	5	3	2	0	4	4	25

Values are mean ± standard error of the mean.

respectively. Cleft palate and heart or major blood vessel anomalies were observed in all groups in somewhat lower incidences (Table 9). The total percent malformed fetuses (Table 10) ranged from 3.1 to 3.6 percent and the weekly percentage did not show any treatment-related increases in congenital malformations. A comprehensive listing of malformations observed during the study has been included (Appendix Table 1).

Postnatal Litter Examinations

When females were allowed to carry their litters to term, the survival and development of their offspring were studied. The number of live pups and their mean body weight were compared in treated and control offspring (Tables 11-14). The lack of a toxic effect is graphically demonstrated by comparing values for control (Group I) animals to those for the animals exposed to the highest dose of phenoxy acid and TCDD (Group II). There was a marked reduction in the number of litters from day 0 to day 4 in all groups. In group I the number of litters fell from 80 to 44 and in group II from 90 to 60. This was accounted for in all groups by cannabalism by the mothers. After day 4, the loss of litters was greatly decreased. Other parameters show little difference between Groups I and II; on day 0, the number of live pups per litter were 4.40 and 4.19, number of dead pups per litter was 0.92 in both groups, and the average pup weights were 1.37 and 1.39. At day 21 the number of live pups per litter were 5.15 and 4.59 and the average pup weights were 7.48 and 7.60, respectively, for groups I and II. No effect on postnatal viability or growth could be attributed to the exposure of the adult male mice to phenoxy acids or to TCDD.

The pups were examined externally on day 0 for malformations (Tables 15 and 16). During the entire eight weeks the total malformation

TABLE 9

Summary of Most Frequently Occurring Defects in
Fetuses Sired by Males Treated with 2,4-D, 2,4,5-T and TCDD

	Treatment Group			
	I	II	III	IV
Anopthalmia/ micropthalmia	1.4(12/830)	1.9(14/744)	2.0(14/711)	2.4(19/805)
Agnathia/micrognathia	1.3(11/830)	1.2(9/744)	1.4(10/711)	1.6(13/805)
Cleft Palate	0.6(5/830)	0.7(5/744)	0.7(5/711)	0.7(6/805)
Heart/Vessels Anomalies	0.2(1/455)	0.5(2/393)	1.0(4/394)	0.7(3/443)

Values are percent incidence of specific anomalies; no. specific malformations per no. observed is given in parentheses.

TABLE 10

Percent Malformed Fetuses Sired by Males Treated with 2,4-D, 2,4,5-T and TCDD

Week	Treatment Group I	II	III	IV
1	1.8(2/113)	1.6(2/129)	3.1(3/97)	2.6(2/78)
2	2.6(3/117)	6.1(6/99)	3.7(3/81)	5.4(7/129)
3	3.1(4/129)	3.5(4/115)	3.6(4/112)	5.3(6/113)
4	3.1(4/129)	0.0(0/78)	2.4(2/85)	2.2(3/139)
5	5.7(4/70)	5.0(5/100)	6.1(5/82)	3.5(3/86)
6	0.0(0/70)	1.3(1/77)	0.0(0/98)	0.0(0/86)
7	3.7(4/108)	8.3(8/96)	5.0(5/100)	4.3(4/92)
8	5.3(5/94)	2.0(1/50)	1.8(1/56)	4.9(4/82)
Total	3.1(26/830)	3.6(27/744)	3.2(23/711)	3.6(29/805)

Values are percent malformed fetuses, number malformed per number observed is given in parentheses.

No values are significantly different from controls ($p<0.05$).

Table 11

Effect of 2,4-D, 2,4,5-T and TCDD on Postnatal Development of Offspring of Treated Males
Group 1 Control

	Week of Study								Total 8 weeks
	1	2	3	4	5	6	7	8	
Day 0:									
Number of litters	17	15	15	10	5	10	5	3	80
Number live pups per litter	3.94 ± 0.70	4.67 ± 0.80	6.00 ± 0.62	2.60 ± 0.85	4.00 ± 1.10	3.70 ± 0.91	5.40 ± 0.51	5.00 ± 2.51	4.40 ± 0.32
Number dead pups per litter	1.47 ± 0.43	1.33 ± 0.45	0.20 ± 0.20	1.10 ± 0.41	1.00 ± 0.78	0.44 ± 0.18	0.20 ± 0.20	1.33 ± 1.33	0.92 ± 0.16
Average pup weight	1.39 ± 0.03	1.34 ± 0.02	1.37 ± 0.48	1.41 ± 0.02	1.36 ± 0.04	1.38 ± 0.05	1.33 ± 0.03	1.30 ± 0.03	1.37 ± 0.01
Day 4:									
Number of litters	8	5	10	4	4	6	5	2	44
Number live pups per litter	5.00 ± 1.20	6.60 ± 0.93	5.30 ± 0.75	5.50 ± 0.50	4.75 ± 0.75	4.00 ± 0.78	5.40 ± 0.51	7.50 ± 0.50	5.30 ± 0.33
Average pup weight	1.87 ± 0.10	2.22 ± 0.19	2.04 ± 0.15	2.43 ± 0.10	2.71 ± 0.24	2.32 ± 0.28	2.35 ± 0.19	2.25 ± 0.29	2.22 ± 0.07
Day 7:									
Number of litters	8	5	9	4	4	5	5	2	42
Number live pups per litter	4.29 ± 0.99	6.60 ± 0.93	5.78 ± 0.64	5.50 ± 0.50	4.75 ± 0.75	4.00 ± 0.95	5.40 ± 0.51	7.50 ± 0.50	5.32 ± 0.31
Average pup weight	3.13 ± 0.29	3.64 ± 0.33	3.60 ± 0.19	4.07 ± 0.18	4.71 ± 0.39	4.67 ± 0.26	4.03 ± 0.24	3.59 ± 0.35	3.83 ± 0.12
Day 21:									
Number of litters	8	4	9	4	4	5	5	2	41
Number live pups per litter	4.75 ± 0.98	6.00 ± 0.91	5.78 ± 0.64	5.25 ± 0.63	3.50 ± 1.04	4.00 ± 0.95	5.40 ± 0.51	7.50 ± 0.50	5.15 ± 0.32
Average pup weight	6.43 ± 0.51	7.02 ± 0.75	7.34 ± 0.32	8.74 ± 0.21	8.62 ± 0.54	7.71 ± 0.65	8.07 ± 0.51	6.41 ± 0.12	7.48 ± 0.21

Values are mean ± standard error of the mean.

Table 12

Effect of 2,4-D, 2,4,5-T and TCDD on Postnatal Development of Offspring of Treated Males
Group II

	Week of Study 1	2	3	4	5	6	7	8	Total 8 weeks
Day 0:									
Number of litters	17	16	14	5	16	11	6	5	90
Number live pups per litter	4.76 ± 0.53	4.88 ± 0.68	5.29 ± 0.74	2.80 ± 1.20	3.35 ± 0.59	1.55 ± 0.74	3.67 ± 0.92	4.00 ± 1.41	4.19 ± 0.29
Number dead pups per litter	0.88 ± 0.40	1.06 ± 0.30	0.64 ± 0.27	1.00 ± 0.78	0.79 ± 0.26	1.25 ± 0.45	1.33 ± 0.80	1.00 ± 0.45	0.92 ± 0.14
Average pup weight	1.39 ± 0.03	1.39 ± 0.04	1.33 ± 0.02	1.47 ± 0.05	1.42 ± 0.03	1.42 ± 0.09	1.38 ± 0.07	1.36 ± 0.04	1.39 ± 0.01
Day 4:									
Number of litters	11	11	11	3	14	3	3	4	60
Number live pups per litter	4.63 ± 0.46	5.25 ± 0.56	5.36 ± 0.61	4.67 ± 0.67	4.64 ± 0.58	4.50 ± 0.50	3.67 ± 0.33	4.25 ± 1.44	4.79 ± 0.25
Average pup weight	2.21 ± 0.11	2.30 ± 0.14	2.11 ± 0.06	2.59 ± 0.19	2.47 ± 0.10	2.44 ± 0.18	2.36 ± 0.18	2.47 ± 0.21	2.33 ± 0.05
Day 7:									
Number of litters	11	11	11	3	14	3	3	4	60
Number live pups per litter	4.20 ± 0.44	4.73 ± 0.65	5.36 ± 0.61	4.67 ± 0.67	4.64 ± 0.58	3.67 ± 0.88	3.33 ± 0.68	4.25 ± 1.44	4.58 ± 0.25
Average pup weight	3.61 ± 0.19	3.65 ± 0.25	3.58 ± 0.10	4.12 ± 0.29	4.08 ± 0.22	3.03 ± 0.90	4.19 ± 0.21	4.04 ± 0.24	3.79 ± 0.09
Day 21:									
Number of litters	10	10	10	3	13	3	3	4	56
Number live pups per litter	4.00 ± 0.49	5.00 ± 0.58	5.10 ± 0.64	4.67 ± 0.67	4.92 ± 0.55	3.67 ± 0.88	3.33 ± 0.67	4.25 ± 1.44	4.59 ± 0.25
Average pup weight	7.28 ± 0.48	7.71 ± 0.24	7.20 ± 0.39	8.11 ± 0.45	8.43 ± 0.21	5.30 ± 0.14	8.43 ± 0.11	7.58 ± 0.52	7.60 ± 0.16

Values are mean ± standard error of the mean.

Table 13

Effect of 2,4-D, 2,4,5-T and TCDD on Postnatal Development of Offspring of Treated Males
Group III

	Week of Study								Total 8 weeks
	1	2	3	4	5	6	7	8	
Day 0:									
Number of litters	14	11	12	9	10	11	11	3	81
Number live pups per litter	5.64 ± 0.52	3.91 ± 1.01	5.67 ± 0.85	6.11 ± 1.03	3.80 ± 0.80	2.73 ± 0.75	3.82 ± 0.89	1.67 ± 1.67	4.44 ± 0.32
Number dead pups per litter	0.57 ± 0.34	1.55 ± 0.43	0.27 ± 0.14	0.11 ± 0.11	0.60 ± 0.34	0.50 ± 0.27	0.90 ± 0.41	1.00 ± 0.58	0.67 ± 0.13
Average pup weight	1.32 ± 0.02	1.39 ± 0.06	1.37 ± 0.27	1.36 ± 0.04	1.32 ± 0.06	1.39 ± 0.05	1.37 ± 0.02	1.38	1.36 ± 0.01
Day 4:									
Number of litters	12	3	8	4	8	5	7	1	48
Number live pups per litter	5.30 ± 0.47	4.33 ± 0.67	5.25 ± 0.10	5.25 ± 0.75	4.25 ± 0.49	4.60 ± 0.40	5.57 ± 0.53	5.00	4.91 ± 0.25
Average pup weight	2.03 ± 0.09	1.76 ± 0.89	2.19 ± 0.16	2.25 ± 0.16	2.50 ± 0.10	2.79 ± 0.08	2.73 ± 0.07	2.81	2.37 ± 0.06
Day 7:									
Number of litters	12	3	8	4	8	5	7	1	48
Number live pups per litter	5.00 ± 0.44	4.33 ± 0.67	5.13 ± 1.04	5.25 ± 0.75	4.25 ± 0.49	4.60 ± 0.40	5.57 ± 0.53	5.00	4.92 ± 0.24
Average pup weight	3.25 ± 0.21	2.79 ± 0.17	3.52 ± 0.93	3.67 ± 0.23	4.16 ± 0.13	4.67 ± 0.14	4.54 ± 0.13	4.66	3.82 ± 0.12
Day 21:									
Number of litters	12	3	7	4	8	5	6	1	46
Number live pups per litter	5.00 ± 0.44	4.00 ± 0.58	5.43 ± 0.97	5.00 ± 0.71	4.25 ± 0.49	4.60 ± 0.40	5.50 ± 0.62	4.00	4.87 ± 0.23
Average pup weight	6.83 ± 0.22	7.43 ± 0.64	7.12 ± 0.37	8.39 ± 0.25	8.15 ± 0.18	7.66 ± 0.24	8.59 ± 0.28	10.31	7.67 ± 0.15

Values are mean ± standard error of the mean.

Table 14

Effect of 2,4-D, 2,4,5-T and TCDD on Postnatal Development of Offspring of Treated Males
Group IV

	Week of Study								Total 8 weeks
	1	2	3	4	5	6	7	8	
Day 0:									
Number of litters	19	23	14	11	15	10	11	5	108
Number live pups per litter	4.84 ± 0.64	5.35 ± 0.68	5.29 ± 0.83.	3.82 ± 1.06	3.67 ± 0.56	2.60 ± 1.19	4.45 ± 0.71	3.80 ± 1.66	4.41 ± 0.29
Number dead pups per litter	0.95 ± 0.29	0.74 ± 0.20	0.79 ± 0.38	1.09 ± 0.32	0.79 ± 0.28	1.50 ± 0.50	0.27 ± 0.14	0.80 ± 0.49	0.84 ± 0.11
Average pup weight	1.36 ± 0.02	1.36 ± 0.03	1.39 ± 0.03	1.44 ± 0.05	1.39 ± 0.03	1.43 ± 0.05	1.38 ± 0.03	1.43 ± 0.06	1.39 ± 0.01
Day 4:									
Number of litters	10	10	8	4	9	4	8	3	56
Number live pups per litter	5.57 ± 0.43	5.40 ± 0.67	6.00 ± 0.66	6.25 ± 1.03	3.33 ± 0.50	5.75 ± 1.49	4.88 ± 0.55	4.67 ± 0.88	5.13 ± 0.27
Average pup weight	2.24 ± 0.16	2.41 ± 0.08	2.60 ± 0.97	2.30 ± 0.13	2.40 ± 0.19	2.94 ± 0.50	2.54 ± 0.16	2.38 ± 0.28	2.41 ± 0.08
Day 7:									
Number of litters	10	10	8	4	9	4	8	3	56
Number live pups per litter	5.00 ± 0.47	5.40 ± 0.67	6.00 ± 0.66	6.00 ± 1.08	3.33 ± 0.50	5.75 ± 1.49	4.88 ± 0.55	4.67 ± 0.88	5.04 ± 0.26
Average pup weight	3.28 ± 0.31	4.08 ± 0.15	4.06 ± 0.18	3.88 ± 0.24	3.98 ± 0.41	3.80 ± 0.33	4.24 ± 0.25	3.99 ± 0.46	3.94 ± 0.10
Day 21:									
Number of litters	10	10	8	4	9	4	8	3	56
Number live pups per litter	5.00 ± 0.47	5.30 ± 0.63	5.75 ± 0.59	6.00 ± 1.08	3.33 ± 0.50	5.75 ± 1.49	4.75 ± 0.59	4.67 ± 0.88	4.96 ± 0.25
Average pup weight	6.99 ± 0.34	8.15 ± 0.33	7.53 ± 0.40	8.20 ± 0.09	8.53 ± 0.68	6.66 ± 0.74	8.34 ± 0.37	7.38 ± 0.97	7.80 ± 0.18

Values are mean ± standard error of the mean.

TABLE 15

Summary of Malformation Rates (%) in Postnatal Study[1]

Week	Treatment Group I	II	III	IV
1	5.4(5/92)	2.1(2/96)	1.1(1/87)	1.9(2/105)
2	2.2(2/90)	3.2(3/95)	5.0(3/60)	0.0(0/140)
3	1.1(1/93)	6.0(5/83)	6.6(5/76)	2.4(2/85)
4	0.0(0/37)	5.3(1/19)	8.9(5/56)	13.0(7/54)
5	4.0(1/25)	1.1(1/88)	4.5(2/44)	2.7(2/73)
6	2.2(1/45)	0.0(0/32)	2.1(1/48)	2.1(1/47)
7	7.1(2/28)	13.3(4/30)	3.8(2/53)	3.8(2/52)
8	5.3(1/19)	8.0(2/25)	0.0(0/8)	4.3(1/23)
Total	3.0(13/429)	3.8(18/468)	4.4(19/432)	2.9(17/579)

[1]All fetuses (live or dead) were assumed to be at risk.

TABLE 16

Summary of Specific Malformations in Postnatal Study

	I	II	III	IV
Anophthalmia/ micropthalmia	1.9(8/429)	2.6(12/468)	2.5(11/432)	1.7(10/579)
Agnathia/micrognathia	1.4(6/429)	1.3(6/468)	1.9(8/432)	1.4(8/579)
Cleft Lip/palate	0.2(1/429)	0.4(2/468)	0.0(0/432)	0.0(0/579)
All else	0.0(0/429)	0.0(0/468)	0.5(2/432)[a]	0.0(0/579)

[a]One exencephaly; one clubbed right hind limb.

rate in these mice was between 2.9 and 4.4 percent. The only individual values which approach statistical significance are the malformation rates for week four group IV (40 mg/kg/day phenoxy acid, 1.2 µg/kg/day TCDD) (Table 15) versus control. In that case the control animals had no malformations and the treated had 13% malformations; all of these were either eye or jaw anomalies.

As seen in the prenatal evaluations, eye and jaw malformations accounted for the majority of the defects noted (Table 16). Anopthalmia or micropthalmia were seen in 1.7 to 2.6 percent of the pups and agnathia or micrognathia were seen in 1.3 to 1.9 percent of the pups for all treatment groups.

DISCUSSION

In these studies we have evaluated the toxicity of three mixtures of 2,4-D, 2,4,5-T and TCDD on reproduction in male mice. Mating frequency, fertility, germ cell mutagenesis, and fetal or postnatal development were all considered in the selection of toxicological endpoints. Male mice were continuously exposed to high doses of 2,4-D plus 2,4,5-T mixed with 2 or 30 ppm TCDD in the phenoxy acid for 8 weeks. These TCDD levels represent average and high contamination levels within Herbicide Orange used in Vietnam (Young et al., 1978).

This study employed the free acids of 2,4-D and 2,4,5-T rather than the butyl esters which were components of Herbicide Orange because of the lower volatility of the acids. The esters are rapidly metabolized to the free acid in both plants and animals, and therefore, the systemic toxicity can be attributed to the free acid (Gehring and Betso, 1978) and should be comparable on a molar basis. The dose levels employed exhibited moderate to low direct toxicity in exposed male mice as evidenced by decreased body weight gain, changes in thymus and liver weights and morphologic changes in the liver. The mortality, however, was quite low. The severity of these toxic effects appeared to be primarily related to the TCDD content of the simulated "Herbicide Orange" mixture.

Despite the use of continuous, moderately toxic, chemical exposures throughout the complete period of spermatogenesis, no significant increase in reproductive abnormalities in the 2,4-D, 2,4,5-T or TCDD exposed groups were observed. TCDD has previously been demonstrated to alter spermatogenesis in C57BL/6 mice (McConnell et al., 1978), however, that study used a single high (lethal range) dose of TCDD. Additionally,

testicular lesions were only found in clinically ill animals, as opposed to those which survived exposure to similar doses (McConnell et al., 1978). Altered spermatogenesis has also been reported in rats (Kociba et al., 1976), guinea pigs (McConnell et al., 1978), and monkeys and chickens (Norback and Allen, 1973), although these were again toxic exposures. In the present study, morphological changes were not observed in the testis of treated mice. Throughout this study testis weight was not affected, nor was sperm motility or percent abnormal spermatozoa. Mean sperm concentration, however, was slightly reduced after five and eight weeks of dosing, although the effect was not statistically significant ($p>0.10$).

The levels of TCDD chosen for this study were within the range that had already been shown to result in cleft palate and kidney anomalies when given to pregnant C57BL/6 female mice (Moore et al., 1973). Mixtures of phenoxy acids plus specific levels of TCDD were used in order to better mimic human exposures to Herbicide Orange. Additionally, previous investigators (Neubert et al., 1973) showed that adding as little as 0.1 µg/kg TCDD to 2,4,5-T increased the teratogenicity in mice of 2,4,5-T in offspring of exposed mothers above that expected by a simple additive effect. The dose of TCDD in this study is at or above the 0.1 µg/kg/day level. Also, it should be emphasized that human exposures involved mixtures of 2,4-D, 2,4,5-T and TCDD (Herbicide Orange).

Certain chemicals, when given to adult males, can cause fetal death or alter normal development in offspring sired by those males (Joffe, 1979; Manson and Simons, 1980), however, such effects were not elicited in the experiments we report by exposing male mice to the 2,4-D, 2,4,5-T and TCDD mixtures. As evidenced by the numbers of implants and resorptions, neither embryo toxicity nor dominant lethal mutations could be

attributed to exposure to these chemicals. The unaffected values for percent abnormal sperm, which is a test for mutagenicity (Wyrobek, 1979) also leads one to the conclusion that the chemicals, as given, were not mutagenic towards the male germ cells. This correlates well with previous multigeneration studies (Murray et al., 1979) and dominant lethal assays (Khera and Ruddick, 1971).

The values for percent malformed fetuses also indicated that 2,4-D, 2,4,5-T and TCDD had no influence on the offspring of exposed males. The study was designed such that, if the overall percent malformed fetuses (3%; see Appendix Table 1) was doubled in one of the experimental groups, there was a 90% chance that it would have been detected. There was a 70-80% chance of detecting a four-fold increase in congenital defects in any one week. For any specific malformation or class of malformations the corresponding powers would be somewhat less. For example, for visceral defects (background rate 0.44%; see Table 5) the experiment had approximately a 90% chance of detecting an overall rate as high as 3% in any particular treatment group. The only variation which we could find elevated in treated versus control offspring, in the entire study, was the incidence of fused sternebrae (Appendix Table 2). In that case, we observed a statistically significant ($p<0.05$) increase in fused sternebrae in Group III at week 3 and in Group IV at week 4. The incidence in the controls at those times, however, was unusually low (0 in both weeks 3 and 4). This type of skeletal variation has been described as occurring as often as 5-15% or more in offspring from untreated pregnancies in mice and although it is frequently observed, the incidence is quite variable and this anomaly is considered a variation and not a malformation (Wilson, 1973).

APPENDIX TABLE 1

Summary of All Malformations Observed in Fetuses Sired by Males Treated with 2,4-D, 2,4,5-T and TCDD

	Treatment Group			
	I	II	III	IV
Visceral Malformations[1]				
Heart/Vessels Anomalies	0.2(1/455)	0.5(2/393)	1.0(4/394)	0.7(3/443)
Kidney Agenesis	0.2(1/455)	0.0(0/393)	0.3(1/394)	0.0(0/443)
Liver-two lobes only	0.0(0/455)	0.0(0/393)	0.0(0/394)	0.2(1/443)
Lung-lobes 2/3 normal size	0.2(1/455)	0.0(0/393)	0.0(0/394)	0.0(0/443)
Right kidney-1/2 normal size	0.0(0/455)	0.0(0/393)	0.0(0/394)	0.2(1/443)
Skeletal and External Malformations[1]				
Anopthalmia/micropthalmia	1.4(12/830)	1.9(14/744)	2.0(14/711)	2.4(19/805)
Agnathia/micrognathia	1.3(11/830)	1.2(9/744)	1.4(10/711)	1.6(13/805)
Cleft palate	0.6(5/830)	0.7(5/744)	0.7(5/711)	0.7(6/805)
Cleft lip/nose	0.0(0/830)	0.0(0/744)	0.3(2/711)	0.0(0/805)
Open eye	0.5(4/830)	0.0(0/744)	0.0(0/711)	0.0(0/805)
Exencephaly/hydrocephaly	0.2(2/830)	0.4(3/744)	0.1(1/711)	0.2(2/805)
No tongue	0.0(0/830)	0.0(0/744)	0.1(1/711)	0.0(0/805)
Umbilical hernia	0.1(1/830)	0.3(2/744)	0.3(2/711)	0.1(1/805)
Ribs fused/missing	0.1(1/830)	0.3(2/744)	0.0(0/711)	0.0(0/805)
Spinal centra doubled/misaligned	0.1(1/830)	0.0(0/744)	0.1(1/711)	0.0(0/805)
Spinal arches fused	0.0(0/830)	0.0(0/744)	0.1(1/711)	0.0(0/805)
Mandibles fused	0.0(0/830)	0.0(0/744)	0.1(1/711)	0.0(0/805)
Skull bones missing	0.0(0/830)	0.1(1/744)	0.1(1/711)	0.0(0/805)
Eye bones missing	0.0(0/830)	0.1(1/744)	0.0(0/711)	0.0(0/805)
Facial bones fused	0.2(2/830)	0.5(4/744)	0.4(3/711)	0.0(0/805)
Kinked Tail	0.1(1/830)	0.0(0/744)	0.0(0/711)	0.0(0/805)
Total Malformations[2]	5.2(43/830)	5.8(43/744)	6.6(47/711)	5.7(46/805)
Total Malformed Fetuses[2]	3.1(26/830)	3.6(27/744)	3.2(23/711)	3.6(29/805)

[1] Values are percent incidence of specific anomalies; no. specific malformations per no. observations is given in parentheses.

[2] Values are percent incidence of malformations or malformed fetuses; no. malformations or malformed fetuses per no. observations is given in parentheses.

APPENDIX TABLE 2

Incidence of Fused Sternebrae in Feruses Sired by Males Treated with 2,4-D, 2,4,5-T and TCDD

Week	Treatment Group I	II	III	IV
1	0.9(1/113)	1.6(2/129)	1.0(1/97)	1.3(1/78)
2	1.7(2/117)	3.0(3/99)	3.7(3/81)	1.6(2/129)
3	0.0(0/129)	0.9(1/115)	7.1(8/112)*	2.7(3/113)
4	0.0(0/129)	2.6(2/78)	2.4(2/85)	5.0(7/139)*
5	1.4(1/70)	2.0(2/100)	3.7(3/82)	2.3(2/86)
6	1.4(1/70)	5.2(4/77)	3.1(3/98)	3.5(3/86)
7	3.7(4/108)	2.1(2/96)	0.0(0/100)	2.2(2/92)
8	2.1(2/94)	2.0(1/50)	0.0(0/56)	1.2(1/82)
Total	1.3(11/830)	2.3(17/744)	2.8(20/711)	2.6(21/805)

*$p<.05$ vs. controls.

Certain anomalies are associated with embryotoxicity, not teratogenicity or mutagenicity. However, with chemical exposure only to the males, not pregnant females, embryotoxicity would not be expected in their offspring. If exposure of the embryo directly to the chemicals had occurred, via seminal plasma or sperm, one would expect to observe increased embryotoxicity in the first weeks of the study, when the chemical levels in the body (or ejaculate) were the highest. One would have also anticipated that during the first weeks of the teratology study germ cell toxicity would most likely have been detected, because the spermatozoa that were evaluated in the first week of mating had been exposed to the chemicals throughout all stages of the spermatogenic process. If the spermatogonia had been affected by the exposure, the effect would have been most apparent in the last weeks of the mating, because at that time, we were evaluating spermatozoa which were spermatogonia during the entire 8 week dosing period and only began to proceed through the spermatogenic cycle near the end of chemical exposure.

Thus, there does not appear to be a residual or transient effect of 2,4-D, 2,4,5-T and TCDD at the concentrations in this study, on the fertility of exposed male mice. In addition, exposure to these chemicals did not appear to influence the fetal or neonatal development or the viability of offspring sired by these mice.

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Absorption of 2,4-dichlorophenoxyacetic acid through the skin.
AUTHOR: Senczuk, Witold

TRANSLATOR: Lilienheim
DATE: November 1981

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Witold Senczuk, Halina Pogorzelska, Monika Debska

ABSORPTION OF 2.4-DICHLORPHENOXYACETIC ACID THROUGH THE SKIN

Texicology Department of the Institute of Bicanalysis and medium analysis of the Medical Academy of Poznan
Director: Prof. Dr. W. Senczuk

Percutaneous absorption of 2.4-dichlorphenoxyacetic acid by indirect method was investigated, determining the amount of 2.4-D in the urine of rats.

The production of pesticides and their application give rise to wide possibilities of poisoning with these compounds (1,2,3,5), and this prompted the determination of the degree of percutaneous absorption of one of most frequently used protective agents, namely 2.4-dichlorphenoxyacetic acid (2.4-D).

Experimental Part

Material and Method

The tests were carried out on 28 rats of the Wistar species, weighing each 200 g ± 10g. The animals were divided into seven groups of four rats each group.

Commercial preparation "Pielik"(2.4-dichlorphenoxyacetic acid: translator) containing about 85% of sodium salt of 2.4-dichlorphenoxyacetic acid was used for the tests. The preparation was used in the form of aqueous solutions of different 2.4-D concentrations.

Results of Determinations

1. Determination of 2.4-D acid in the urine depending on the concentration of the tested compound in the solution

The tests were carried out with the use of aqueous solutions of "Pielik" containing 0.5, 1, 2, 4 and 5% of 2.4-D acid. After six hours there was determined the amount of 2.4-D acid excreted with urine. The results are shown in table 1 and in Fig. 1.

2. Determination of 2.4-D acid in urine depending on the period of exposure

The influence of the exposure period (2, 4 and 6 hours) on the excretion of 2.4-D with urine was determined by using aqueous solution of "Pielik" containing 4% of the tested acid. The results of the determination of 2.4-D acid in the collected portions of urine are shown in table II. Fig. 2 graphically

illustrates the results

Table 1. Results of the determination of 2.4-D acid in urine depending on the concentration of the compound in the solution

Solution %	Animal No	Amount of 2.4-D acid in urine (mg) 1st day (24 hours)	2nd day	3rd day	jointing after three days
0.5	1	0.9	1.4	1.2	3.5
	2	1.0	1.5	1.0	3.5
	3	1.0	2.8	1.0	4.8
	4	1.0	1.6	1.1	3.6
average	Sredniia	0.97	1.77	1.07	3.81
1.0	1	3.4	2.4	1.0	6.8
	2	1.0	1.6	1.2	3.8
	3	7.6	2.2	0.0	9.8
	4	2.5	1.0	0.0	3.5
average	Sredniia	3.62	1.80	0.55	5.97
2.0	1	1.2	5.1	1.8	8.1
	2	2.0	8.7	1.7	12.4
	3	1.6	4.8	2.6	9.0
	4	2.5	1.8	1.1	5.4
average	Sredniia	1.82	5.10	1.80	8.72
4.0	1	6.0	4.8	7.2	18.0
	2	5.0	5.8	2.6	13.4
	3	4.8	2.1	2.7	9.6
	4	2.0	3.3	2.7	8.0
average	Sredniia	4.45	4.00	3.80	12.25
5.0	1	3.5	4.7	4.9	13.1
	2	2.7	2.6	2.1	7.4
	3	3.6	5.8	6.8	16.2
	4	4.8	6.8	7.2	18.8
average	Sredniia	4.10	4.97	5.25	14.32

Table II. Results of the determination of 2.4-D acid in urine depending on the exposure period

Period of Exposure	Animal No	Amount of 2.4-D acid in urine (mg) 1st day (24 hours)	2nd day	3rd day	jointing after three days
2	1	1.6	0.8	0.9	3.3
	2	4.7	3.8	1.7	10.2
	3	2.5	1.7	0.8	5.0
	4	3.0	1.6	0.8	5.4
average	Sredniia	2.95	1.97	1.05	5.97
4	1	1.8	1.3	1.4	7.5
	2	1.4	3.3	1.5	8.2
	3	1.9	2.5	2.2	6.6
	4	3.2	10.5	4.0	17.7
average	Sredniia	2.07	5.15	2.27	9.40
6	1	6.0	4.8	7.2	18.0
	2	5.0	5.8	2.6	13.4
	3	4.8	2.1	2.7	9.6
	4	2.0	3.3	2.7	8.0
average	Sredniia	4.45	4.00	3.80	12.25

Discussion of the Results

It has been determined that the amount of the substance excreted with urine is proportional to the 2.4-D concentration in the tested solutions(Fig.1). As the 2.4-D concentration increased, the amount of this compound excreted with urine, as compared with the preceding group, i.e. of lower 2.4-D concentration of 2.4-D increased by about 50%. This related to 0.5 to 4% concentrations, but after exposure to 5% concentration, in comparison with the group of animals exposed to 4% solution, 17% less 2.4-D acid were excreted with urine.

Also the period of exposure influenced the amount of 2.4-D acid absorbed by skin. This relation was proportional for 2, 4 and 6 hour exposure (Fig. 2). This can provide a basis for further research in determining the biochemical absorption index.

Figure1. Excretion with urine of 2.4-D acid depending on the concentration of the compound in the solution

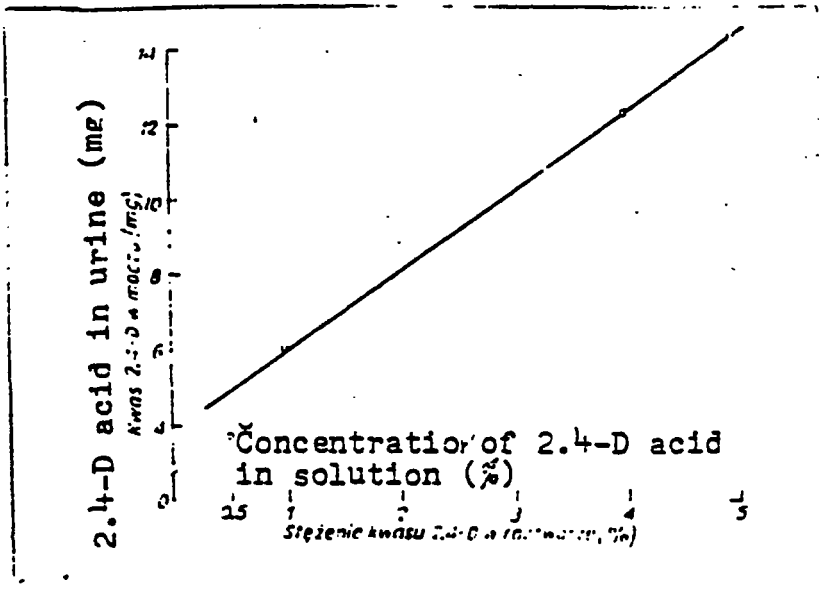
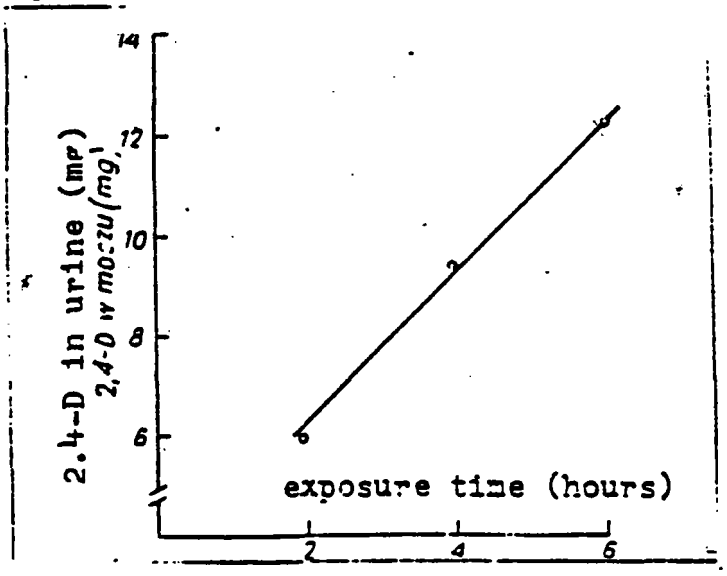


Figure 2. Excretion with urine of 2.4-D acid depending on the period of exposure.



A Russian summary corresponds to the following English summary.

W. Seneczuk, H. Pogorzelska, M. Dębska

ABSORPTION OF 2,4-DICHLORPHENOXYACETIC ACID THROUGH THE SKIN

Summary

The degree of percutaneous absorption of one of the most frequently used herbicides -- 2,4-dichlorphenoxyacetic acid — was investigated. The investigations were carried out with different concentrations of this acid in aqueous solutions of „Pielika" and in relation to the duration of exposure. Wistar rats were used in these experiments.

The dermal exposure was done by the tail method. The urinary excretion of the acid was determined by gas chromatography after previous extraction of the acid from urine and its estrification.

PIŚMIENNICTWO

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5. Poisoning with 'Pielik', Occupational Medicine

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WITOLD SENCZUK, HALINA POGORZELSKA, MONIKA DĘBSKA

WCHŁANIANIE KWASU 2,4-DWUCHLOROFENOKSYOCTOWEGO PRZEZ SKÓRĘ

Zakład Toksykologii Instytutu Bioanalizy i Badania Środowiska
Akademii Medycznej w Poznaniu
Kierownik: prof. dr hab. W. *Seńczuk*

Zbadano wchłanianie przez skórę kwasu 2,4-dwuchlorofenoksyoctowego metodą pośrednią oznaczając ilość 2,4-D w moczu szczurów.

Produkcja pestycydów i ich stosowanie stwarza duże możliwości zatrucia tymi związkami [1, 2, 3, 5], stąd celowym było określenie stopnia wchłaniania przez skórę, jednego z częściej używanych środków ochrony roślin, a mianowicie kwasu 2,4-dwuchlorofenoksyoctowego (2,4-D).

CZĘŚĆ DOŚWIADCZALNA

Materiał i metodyka

Badania wykonano na 28 szczurach, szczepu *Wistar*, o masie ciała 200 g ± 10 g. Zwierzęta podzielono na 7 grup po 4 szczury.

Do badań użyto preparatu handlowego „Pielik" zawierającego około 85% soli sodowej kwasu 2,4-dwuchlorofenoksyoctowego. Preparat używano w postaci roztworów wodnych o różnych stężeniach 2,4-D.

Ogony zwierząt po dokładnym umyciu i obliczeniu powierzchni, zanurzano w probówkach zawierających około 20 cm³ badanego roztworu o temp. 37- 40°C. Po określonym czasie ekspozycji (p. niżej) zwierzęta przenoszono do klatek metabolicznych typu „Simax", po czym przez 72 godziny zbierano dobowe porcje moczu. Dwa razy dziennie podawano zwierzętom sondą do żołądka po 5 cm³ wody. Zawartość kwasu 2,4-D w moczu określano metodą chromatografii gazowej, po uprzednim wyekstrahowaniu badanego związku z moczu i jego estryfikacji [4].

WYNIKI OZNACZEŃ

1. Oznaczanie kwasu 2,4-D w moczu w zależności od stężenia badanego związku w roztworze

Badania wykonano przy użyciu wodnych roztworów „Pielika" zawierających 0,5, 1, 2, 4 i 5% kwasu 2,4-D. Po 6 godzinach określano ilość wydalonego z moczem kwasu 2,4-D. Wyniki przedstawiono w tabeli 1 oraz na rycinie 1.

2. Oznaczanie kwasu 2,4-D w moczu w zależności od czasu ekspozycji

Wpływ czasu ekspozycji (2, 4 i 6 godzin) na wydalanie z moczem 2,4-D określono stosując wodny roztwór „Pielika" zawierający 4% badanego

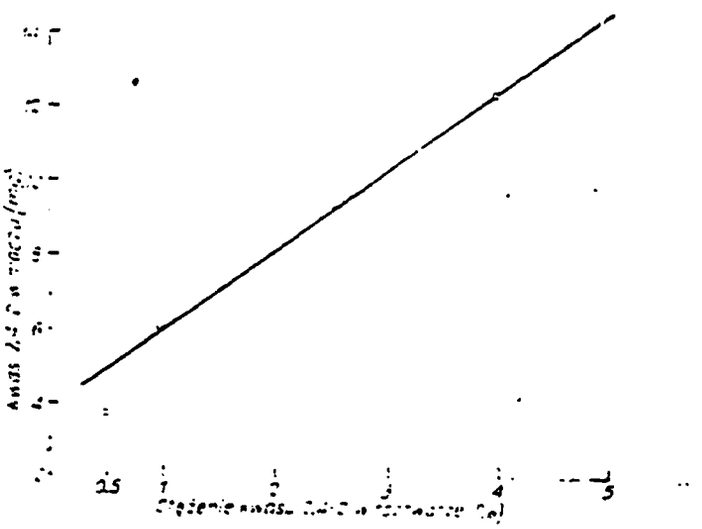
Tabela 1. Wyniki oznaczania kwasu 2,4-D w moczu w zależności od stężenia związku w roztworze

Roztwór %	Zwierzę Nr	Ilość kwasu 2,4-D w moczu (mg) I doba	II doba	III doba	Łącznie po trzech dobach
0,5	1	0,9	1,4	1,2	3,5
	2	1,0	1,5	1,0	3,5
	3	1,0	2,8	1,0	4,8
	4	1,0	1,6	1,1	3,6
	Średnia	0,97	1,77	1,07	3,81
1,0	1	3,4	2,4	1,0	6,8
	2	1,0	1,6	1,2	3,8
	3	7,6	2,2	0,0	9,8
	4	2,5	1,0	0,0	3,5
	Średnia	3,62	1,80	0,55	5,97
2,0	1	1,2	5,1	1,8	8,1
	2	2,0	8,7	1,7	12,4
	3	1,6	4,8	2,6	9,0
	4	2,5	1,8	1,1	5,4
	Średnia	1,82	5,10	1,80	8,72
4,0	1	6,0	4,8	7,2	18,0
	2	5,0	5,8	2,6	13,4
	3	4,8	2,1	2,7	9,6
	4	2,0	3,3	2,7	8,0
	Średnia	4,45	4,00	3,80	12,25
5,0	1	5,5	4,7	4,9	15,1
	2	2,7	2,6	2,1	7,4
	3	3,6	5,8	6,8	16,2
	4	4,6	6,8	7,2	18,6
	Średnia	4,10	4,97	5,25	14,32

kwasu. Wyniki oznaczania kwasu 2,4-D w zebranych porcjach moczu przedstawiono w tabeli II. Ilustracją graficzną wyników jest rycina 2.

OMÓWIENIE WYNIKÓW

Stwierdzono, że ilość substancji wydalonej z moczem jest proporcjonalna do stężenia 2,4-D w badanych roztworach (ryc. 1). W miarę wzrostu stężenia 2,4-D ilość tego związku wydalonego z moczem, w porównaniu z grupą poprzednią, tzn. o niższym stężeniu 2,4-D wzrastała o ok. 50%. Dotyczyło to stężeń od 0,5 do 4%; natomiast po ekspozycji na roztwór 5%, w porównaniu z grupą zwierząt eksponowanych na roztwór 4%, z moczem wydaliło się o ok. 17% mniej kwasu 2,4-D.

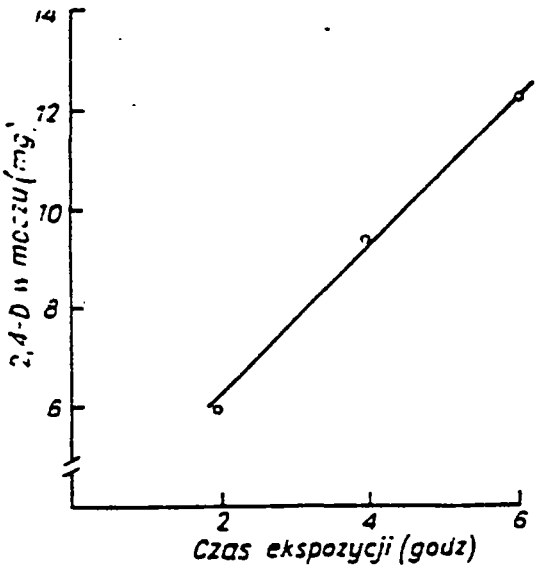


Ryc. 1. Wydalanie z moczem kwasu 2,4-D w zależności od stężenia związku w roztworze.

Czas ekspozycji wpływał również na ilość kwasu 2,4-D wchłoniętą przez skórę. Zależność ta była proporcjonalna dla 2, 4 i 6 godzinnej ekspozycji (ryc. 2). Może to stanowić podstawę do dalszych badań nad opracowaniem biochemicznego wskaźnika wchłaniania.

Tabela II. Wyniki oznaczania kwasu 2,4-D w moczu w zależności od czasu ekspozycji

Czas ekspozycji (h)	Zwierzę Nr	Ilość kwasu 2,4-D w moczu (mg)			
		I doba	II doba	III doba	Łącznie po trzech dobach
	1	1,6	0,8	0,9	3,3
	2	4,7	3,8	1,7	10,2
2	3	2,5	1,7	0,8	5,0
	4	3,0	1,6	0,8	5,4
	średnia	2,95	1,97	1,05	5,97
	1	1,8	1,3	1,4	7,5
	2	1,4	3,3	1,5	8,2
4	3	1,9	2,5	2,2	6,6
	4	3,2	10,5	4,0	17,7
	średnia	2,07	5,15	2,27	9,40
	1	6,0	4,8	7,2	18,0
	2	5,0	5,8	2,6	13,4
6	3	4,8	2,1	2,7	9,6
	4	2,0	3,3	2,7	8,0
	średnia	4,45	4,00	3,80	12,25



Ryc. 2. Wydalanie z moczem kwasu 2,4-D w zależności od czasu ekspozycji.

В. Сеньчук, Х. Погожельска, М. Дембска

РЕЗОРБЦИЯ ЧЕРЕЗ КОЖУ 2,4-ДИХЛОРФЕНОКСИУКСУСНОЙ КИСЛОТЫ

Резюме

Определялась степень резорбции через кожу одного из наиболее часто применяемых гербицидов, 2,4-дихлорфеноксиуксусной кислоты (2,4-D).

Исследования проводились в зависимости от концентрации этой кислоты в водном растворе препарата „Щелик" а также от времени экспозиции хвоста применяемых животных (крыс линии Вистар) на действие 2,4-D.

Количество выделяемого с мочой 2,4-D определяли методом газовой хроматографии после его экстракции из мочи и этерификации.

W. Seńczuk, H. Pogorzelska, M. Dębska

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Pharmacokinetics and Ecodisposition of Polyhalogenated Hydrocarbons: Aspects and Concepts

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8366

I. INTRODUCTION: THE FATE OF XENOBIOTICS*

Early physiological and pharmacological studies clearly demonstrated that many drugs and foreign compounds when administered are not excreted unchanged and have to be metabolized in order to be eliminated. In fact, before the end of the 19th century all the major pathways of drug metabolism had been discovered [1, 2] and were at that time considered to be detoxication mechanisms. Owing to the fundamental work of R. T. Williams and B. B. Brodie, a better understanding of the fate of foreign compounds was reached in the middle of the 20th century and subsequently became important for pharmacology, pharmacotherapy, and drug development. Williams not only systematized xenobiochemistry [2], but also deduced the general principles governing the fate of foreign compounds in the body. It became clear that only hydrophilic compounds can be excreted in urine and bile owing to the peculiarities of the major excretory organs. In contrast, lipophilic compounds are metabolized to polar metabolites. Thus, elimination of a xenobiotic can be achieved by excretion, metabolism, or both. Typically, a drug will be eliminated from the body by processes following first-order kinetics. Metabolism of xenobiotics does not lead to chemical degradation but rather to formation or unmasking of functional groups at selected metabolically vulnerable positions of a molecule. These Phase I reactions (oxidations, reductions, hydrolyses) are unable to biotransform highly lipophilic xenobiotics such as hydrocarbons, thereby increasing their polarity. Once functional

*The following abbreviations are used:

ADI	acceptable daily intake
6-CB	2,4,5,2',4',5'-hexachlorobiphenyl
DDA	2,2-bis-(p-chlorophenyl)-acetic acid
DDE	2,2-bis-(p-chlorophenyl)-1,1-dichloroethylene
DDT	2,2-bis-(p-chlorophenyl)-1,1,1-trichloroethane
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
MC	3-methylcholanthrene
PB	phenobarbital
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzodioxin
PCDF	polychlorinated dibenzofuran
PCP	pentachlorophenol
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TCDF	2,3,7,8-tetrachlorodibenzo-furan

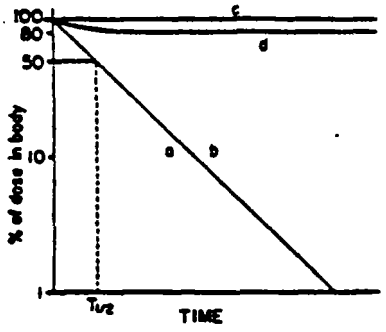

FIG. 1. Types of pharmacokinetic behavior: (a) "ordinary" xenobiotics, e.g., drugs ($T_{1/2}$ = hours or days); (b) persistent xenobiotics, e.g., DDT ($T_{1/2}$ = months or years); (c) ideal unmetabolizable lipophilic xenobiotic; and (d) unmetabolizable lipophilic xenobiotic, e.g., 2,4,5,2',4',5'-hexachlorobiphenyl (6-CB) [64, 102].

groups are present, Phase II reactions (conjugations) may take over, giving rise to the formation of highly polar and excretable metabolites.

Brodie, on the other hand, was more concerned with the enzymes catalyzing Phase I reactions and with physicochemical and evolutionary aspects of drug metabolism. In a series of classic papers [3-5], Brodie and his early associates summarized a decade of research and came to conclusions and outlooks which seem to have withstood the test of time and a flood of additional information. Thus, since lipophilic drugs have been shown not to be excreted unchanged to any significant degree, they must of necessity be metabolized. Otherwise, a lipophilic drug (like quinacrine) with a volume of distribution as high as 1000 L/kg and a renal clearance as low as 1 mL/min would have a half-life of some 90 years [6]. The liver microsomal drug-metabolizing enzyme system, which was discovered by Brodie and his associates, could be characterized as extremely nonspecific yet highly selective for lipophilic xenobiotics. As we are now witnessing in the case of opioid and other receptors, the question then arose: What can the natural substrates for this enzyme system be? According to Brodie's hypothesis, a great number of lipophilic organic compounds such as steroids, alkaloids, and terpenes, present in food, would gradually accumulate, perhaps to toxic levels, in the body unless mechanisms were present to dispose of them. In the process of evolution, development of the microsomal oxidative enzymes must therefore be considered as one of many biochemical adjustments that made possible the conquest of land by formerly marine forms of life. In conclusion, the microsomal drug-metabolizing enzymes

prevent higher organisms from being gradually poisoned by lipophilic (natural or synthetic) compounds and thus are an essential protective system, comparable perhaps with the immune system.

This fascinating theory has drawn little opposition, which may be due to the fact that it has not been possible to challenge it experimentally [7], for these hepatic and extrahepatic enzymes can neither be surgically removed nor can they be blocked by inhibitors, at least not for long enough to allow for accumulation of lipophilic xenobiotics and observation of the appearance of deleterious effects.

The aim of this review is to show that the simplistic scheme of hydrophilic-excretable and lipophilic-metabolizable organic compounds has been disturbed by the advent of DDT-like persistent compounds and must now be enlarged by a third group, that of lipophilic-unmetabolizable compounds. The last-named type of xenobiotic exhibits a new kind of pharmacokinetic behavior and has certainly accentuated the problem of global ecodisposition. Finally, this new class also contains members of extreme toxicity which have added or could add to the severity of the universal ecotoxicological condition. Old and new facts will be used to discuss and assess new aspects, concepts, and outlooks rather than merely reporting recent findings and progress in one limited field. Thus the quotations for the time before, say, 1970 will be drawn largely from the review literature, and the list of recent original works quoted will not be exhaustive. Our literature search was concluded in early 1980.

II. THE APPEARANCE OF DDT

A. New Compounds and Properties

In 1939 DDT came out of a screening procedure for insecticidal activity. The compound, dichlorodiphenyl-trichloroethane (chlorophenothane) had in fact gathered dust on a shelf for almost 70 years before it had been rediscovered and put to worldwide use. The success of DDT became immediately clear during its use in World War II, the first war in history not to be followed by devastating epidemics. The postwar years and the 1950s added further to DDT's success story owing to its worldwide use in the fight against vector-borne diseases like typhus, yellow fever and, particularly, malaria which was being eradicated in vast areas. It has been estimated that 50 million lives have been saved and 1 billion cases of illness averted by DDT, thus this "drug" can be second only to penicillin and other antibiotics. This aspect must not be forgotten in an era ready uncritically to ban and damn DDT and other pesticides.

noticeable residues in human tissues simply reflects the low level of exposure as compared with, say, DDT or PCBs. However, large-scale monitoring and improved analytical sensitivity may reveal TCDD residues in humans tomorrow. If so, what would residues at the ppt level mean? A cautious assumption would be that with compounds like TCDD, any residues may be harmful. Such a statement is based on facts like extreme species differences in toxic sensitivity which do not allow an extrapolation to humans of even the LD_{50} value. Furthermore, it is based on documented long-term effects like teratogenicity and carcinogenicity in animals and, finally, on our ignorance with respect to a no-effect level. Thus, in the absence of hard disproving data, it seems wiser for the time being to assume that TCDD is unmetabolizable, that it has entered the biosphere, and that humans do have tissue residues. Results of epidemiological studies of directly exposed people are still controversial [236, 237] but will certainly provide useful information in the future.

There is even more to this than just the problem of TCDD and TCDF. It has taken a long time to detect both the existence and the toxicity of these chemicals, years during which individuals and populations were exposed to them. The disturbing question therefore arises of whether such a situation can recur. Owing to one particular fact this does not seem to be too unlikely. This fact is the erratic structure-toxicity relationships which exist within the series of polychlorinated dibenzodioxins or dibenzofurans (Table 2), i.e., the general possibility of the appearance of excessively toxic members within chemical families of relatively harmless compounds. This is indeed one of the most important lessons that the TCDD story has taught us. Dispersion of high-toxicity compounds camouflaged by a harmless "carrier" can happen again in the manufacture and use of some other chemical product at any time. After all, polyhalogenated compounds have surprised us more than once by creating ecotoxicological hazards which are becoming increasingly difficult to cope with by traditional technical and legislative means.

VI. CONCLUSIONS

1. Lipophilic xenobiotics cannot be excreted but are eliminated by being metabolized. Hence, according to Brodie, these compounds remain in the body or accumulate in the absence of metabolism, so that drug-metabolizing enzymes must be regarded as a protective system against the accumulation of lipophilic xenobiotics, such as those contained in natural food.

2. If metabolically vulnerable groups of a lipophilic organic molecule are blocked by halogen atoms, the compound may become

persistent, i.e., very slowly metabolized. Owing to their lipophilicity, persistence, and lipid storage, compounds like DDT and related insecticides have become subject to global ecodisposition and bioconcentration.

3. Polychlorinated biphenyls (PCBs), another class of polyhalogenated hydrocarbons, have also undergone global ecodisposition and concentration in the biosphere, even though these industrially used compounds had never been intentionally introduced into the environment. Their appearance in human and animal residues has revealed unsuspected pathways of ecodisposition.

4. By blocking all metabolically vulnerable groups of a molecule according to established criteria, a persistent compound may become an unmetabolizable one. Studies with model compounds like 2,4,5,2',-4',5'-hexachlorobiphenyl have shown that its metabolism is indeed negligible, that total excretion (mainly in the feces) of unchanged material accounts for only a small fraction of the administered dose, and that the major part is stored in the adipose tissue where it is not available for elimination. These unmetabolizable lipophilic compounds thus represent a new class of pharmacokinetic behavior. In addition to its potential for ecodisposition and bioconcentration, this class of compounds also proves Brodie's hypothesis in demonstrating accumulation and retention of lipophilic compounds which cannot be substrates of the drug-metabolizing enzymes.

5. The herbicide 2,4,5-T, the wood preservative pentachlorophenol, and PCBs contain traces of the extremely toxic polyhalogenated compounds TCDD and TCDF. As contaminants of widely used products, they have already entered the global ecosystem. By being persistent or even unmetabolizable, they have the potential to enter food chains and undergo bioconcentration. Finally, by being excessively toxic they have opened a new dimension in ecotoxicology.

Acknowledgments

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Strictly Confidential

AN EPIDEMIOLOGICAL FEASIBILITY STUDY ON THE EFFECTS OF 2.3.7.8.-TETRACHLORODIBENZO-PARA-DIOXIN (TCDD) ON FINNISH FORESTRY, ROAD AND RAILWAY WORKERS

Preliminary findings

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INTRODUCTION

During several occasions human populations have been exposed to compounds, which contain as a contaminant small amounts of 2.3.7.8.-tetrachlorodibenzo-para-dioxin (TCDD). Such compounds include herbicides such as 2.4.5.-trichlorophenoxy acetic acid (2.4.5T) and an antiseptic compound, hexachlorophene.

It is now known that TCDD is one of the most toxic compounds ever synthetized, and its acute toxicity is for instance of the same magnitude as that of many well known toxins, such as diphteria toxin or tetrodotoxin. TCDD has received worldwide attention as a potential health hazard for humans because it was noticed that many widely used herbicides contained small amounts of TCDD and when on several occasions large numbers of wild and domestic animals were killed after acute exposure to TCDD.

Although the acute and chronic toxicity of TCDD has been extensively studied, little is so far known of its longterm effects on humans. The present study was undertaken to test whether it is possible to make epidemiological and clinical field studies on Finnish persons exposed to TCDD-containing herbicides for long periods. Also it was the purpose of the present study to examine whether there were any clear-cut differences in the anamnestic and clinical health status of the exposed persons as compared to control persons living in the same areas and belonging to similar social groups. This study was carried out with persons who had spread TCDD-containing herbicides, such as 2.4.5T, for many weeks each year during several years. It is interesting that according to two Swedish studies, higher than average numbers of malignant tumors were found among the same kind of workers.

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MATERIAL AND METHODS

The study was carried out with 31 exposed persons from Finnish forestry, road and railway workers living in Central Finland around the city of Jyväskylä. All of the exposed persons were Finnish Government employees and most of them had been exposed to herbicides during several summers. The average exposure time varied each year from one to three months and the herbicides were in most cases spread manually during five days a week. The amounts of exposure for each person are shown in Table 1. The herbicides used were mostly 2.4.5T and 2.4D until 1976 when it was replaced by MCPA in about half of the cases. The use of protective clothing, respiratory masks or gloves were almost negligible; About half of the exposed persons had used gloves and paper masks only occasionally during the last three years or so.

The control group consisted of 28 railway workers employed by the Finnish Railways from the same area as the exposed persons. Similarly to the exposed workers, these persons worked out of doors throughout the year. The control group was matched to the exposed group by age. The smoking habits of both groups were quite similar as seen in Table 1.

The epidemiological study consisted of interviews with each person (one hour per person) by a work health nurse. For the anamnestic interviews, three different questionnaires were used. One was an occupational health questionnaire used by the Finnish Railways, another was designed to ask exposures and symptoms mediated by air, and the third questionnaire was designed for tracking exposures and symptoms caused by toxic chemicals.

Detailed medical records were available from all control persons as well as about half of the exposed persons. Half of the exposed forestry workers did not have organized occupational

health care and there were little or no written records on their previous health status or on their exposure to chemicals. The exposed and control persons were examined by the same physician. The examination of the dermatological status was made by a dermatologist.

The laboratory tests (Table 2) included blood haemoglobin, haematocrite, sedimentation rate, total leucocyte count, total thrombocyte count, serum glucose, serum creatinine, SGOT, SGPT, SDH, serum LDH isoenzyme pattern, quantitation of immunoglobulin classes (A,G,M), relative amounts of T and B (K) cells in the blood, urine colour, urine albumine, urine glucose, urine pH and urine sediment. In addition, vitalograph was taken. Chest X-rays were studied by a radiologist.

In 1970-76 the most widely used herbicude was Vesakon Tuho Special manufactured by Kemira Co. It contains 2.4.5T 750 g/l. In 1976 the content of TCDD in 2.4.5T was 0.04-0.07 ppm.

RESULTS AND CONCLUSIONS

The major anamnestic results are shown in Table 1. There were no significant differences in the age of the exposed and control persons, nor their smoking habits or their consumption of alcohol. The average time since the first exposure was ten years and the average total exposure in weeks was forty-nine, thus making an annual mean exposure time of 4.9 weeks.

Anamnestically the exposed group had about twice the number of cardiovascular, respiratory and skin diseases and respiratory allergies (Table 3). On the other hand, it was found that approximately half of the exposed persons were tranferred from heavy to easier forestry work (includung the spreading of the herbicudes) because of health problems, such as cardiovascular or musculoskeletal diseases.

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One of the exposed persons had a mentally retarded child as compared to none in the control group (Table 3). In the physical examination

including the palpation of the abdominal organs, respiratory and cardiac auscultation, dermatological, neurological and ophthalmological examinations, no clear-cut differences were found between the groups (Table 4). Anamnestic symptoms of acute toxicity in the exposed group are shown in Table 5. For statistical conclusions, this material is, however, far too small.

As shown in Table 4 elevated blood pressure was found in six exposed persons and in seven control persons. The heart was radiologically enlarged in four out of fifteen exposed persons and in three control persons. In vitalographic findings and in radiological examination of the lungs, no differences were observed between the two groups.

In the dermatological examination done by a dermatologist, no skin lesions typical to chloracne were found.

The results of the blood analyses showed no obvious differences between the two groups. There were, however, two exposed persons, who had the lowest B lymphocyte values: 6.5 % and 6.1 %. One of these persons had also the lowest thrombocyte value 133 $x10^9/l$. However, the immunoglobulin amounts of these persons were in normal range. In the urine analyses, no obvious differences were found between the groups.

Summarizing, this study shows that it is possible to get both anamnestic and epidemiological as well as clinical data on the past and present health status of Finnish employees exposed for long periods to herbicides containing TCDD. In this study no obvious or significant differences were found between the exposed and control groups. It is, however, evident that this material is far too small to make any conclusions in this respect.

It is also suggested that this type of approach could be one possibility to further evaluate the potential and so far undocumented chronic effects of TCDD on humans.

Table 1.

CHARACTERISTICS OF THE CONTROL AND EXPOSED GROUPS

Persons		Controls Number	Controls Mean	Exposed Number	Exposed Mean
Persons studied	Age (years)		45		43
	Tobacco	15/28		21/31	
	Alcohol	16/28		16/31	
	Cancer	0/28		1/31	
Exposure	Time since first exposure (years)				9
	Number of weeks exposed				43
	Annual exposure time (weeks)				4.8

Table 2.

LABORATORY TESTS

Haemoglobin (g/l)	Blood glucose (mmol/l)
Haematocrite (%)	Serum creatinine (umol/l)
SR (mm/h)	Serum GOT (U/l)
Total leucocytes ($x10^9$/l)	Serum GPT (U/l)
Leucocyte differential	Serum LDH (U/l)
count (%)	Serum LDH/HBD (U/l)
Thrombocytes ($x10^9$/l)	Serum LDH_{1-5} isoenzymes (enzyme fraction)
T and B lymphocytes (%)	Serum immunoglobulins A,G,M (g/l)

Table 3.

ANAMNESTIC FINDINGS

Diseases	Controls Number	%	Exposed Number	%
Cardiovascular	5/28	18	13/31	42
Lung	1/28	4	5/31	16
Respiratory allergies	0/28	0	8/31	26
Gastrointestinal	7/28	25	8/31	26
Skin	8/28	29	11/31	35
Mental retardation (Children)	0/64[X]	0	1/31	3

[X] Number of children

Table 4.

ABNORMALITIES FOUND IN CLINICAL EXAMINATION

Organ (system)	Controls	Exposed
Cardiovascular	7	6
Lung	7	7
Liver	0	2
Skin	2	5
Neurological	1	2
Eye	1	2

Table 5.

ANAMNESTIC SYMPTOMS OF ACUTE TOXICITY

Organ (system)	Number	%
Respiratory	9/31	29
Gastrointestinal	6/31	19
Neurological	13/31	42
Skin	12/31	39

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Editorial

The Burial of the Two Million Dollar Teaspoon

EPA has reportedly contracted for the disposal of 30 million pounds of lawn fertilizer containing silvex. The cost of the "grave"? $2.1 million.

The EPA release reads, "This contract involves disposal of dry fertilizer-based products which contain no more than 1.5 percent of the active ingredient, silvex, which the Agency estimates to contain about 25 parts per billion or less of the toxic contaminant dioxin (TCDD). Over 95 percent of the material being disposed of consists of inert carriers for the fertilizer and weed-killer (such as corn cob grits or vermiculite)." Registrants of the products are to transport the materials to the disposal site and that could increase the cost considerably.

According to my calculations, the whole "kitten caboodle" contains about 5 grams of dioxin – one teaspoonful. Boy, are we ever a bunch of scaredy-cats, spending over $2 million to bury a teaspoonful of anything.

The grave, referred to as a "single burial cell," will reportedly hold 240,000 cubic yards. According to figures from the local trainmaster, that's about 1,500 box cars. With 100 cars per train, that's 15 trainloads.

Perhaps what we should do for slow-learners is park them by a railroad crossing to watch a 100-car train pass by – at the speed they usually do for you – then another, and another, until 15 trainloads have passed by. And in all that time, one itsy bitsy teaspoonful would have passed before their eyes – not in one car, not in one train, but in all 15 trainloads. Just think of the time, effort, energy and cost – to dispose of such a tremendous trifle – one teaspoonful. What should we call it, "Blum's folly"?

But that's just part of the story. There are about four million containers of various sizes with almost a million gallons of liquid silvex. EPA has considered having these containers emptied and rinsed and the material incinerated at sea. According to one estimate, the silvex going to sea would contain about two teaspoons of dioxin.

One EPA official reportedly estimated the total cost to taxpayers for silvex disposal and indemnities at $30 million. So that's $30 million to dispose of three teaspoons – one by land and two by sea. Wouldn't Paul Revere turn over in his grave if he could see what foolishness the bureaucracy of his great country is up to.

And what really gets your goat is the way we squander money frivolously, and needlessly on such regulatory activities while funding for educational programs for pesticide applicator training are being cut. Who will pick up the burden for that program initiated by the feds? You guessed it, the feds would like to dump it in the states' laps. And where will the states get the funds – the most likely place is by charging those who are being regulated and never asked for the program in the first place.

2 + 2 = 4

We certainly don't have anything against education. In fact, some good old arithmetic for some of those folks in EPA might be a good place to start.

The average mind probably hasn't caught up yet with terms like parts per trillion. If you say 10 parts per something – well, 10 sounds like a fairly big number. But 10 parts per trillion is like 10 seconds in 320 centuries.

Come on EPA, get your rear in gear and do your homework. You're supposed to provide some responsible leadership instead of catching butterflies with bear traps.

2,4-D

What concerns many of us now is EPA's domino game. They suspended many uses of 2,4,5-T and silvex just before the RPAR decision was ready. The major basis for their decision has been largely shown to be faulty. But perhaps their math book says 1 wrong + 1 wrong = 1 right. They acknowledged that dioxin had not been found in 2,4-D, but now 2,4-D is under scrutiny and subject to guilt by association.

2,4-D provides one of the lowest cost, most efficient methods for controlling weeds. If you are truly concerned about water quality, remember that the trend is toward reduced tillage – to save soil and energy. As we reduce tillage, 2,4-D, still our major postemergence herbicide, will become all the more essential.

I like Steve Jellinek's story about the G.I. who walked into a French village after the American's had bombed it to drive out the Germans. He said, "Boy, we sure liberated the h____ out of this place." At the rate EPA is going, that's about how our farmers and even the food consumer will feel if EPA continues their bombardment.

If EPA wants to listen to the potheads who want to get rid of any chemical that kills marihuana, or to the mafia, that's their privilege, as long as that's all they do is listen. But remember that the Good Lord doesn't let man discover a 2,4-D very often. And if we fritter away the discoveries he does allow us, we know not when he will let man use his mind for such great discoveries again.

"The concern for man and his destiny must always be the chief interest of all technical effort. Never forget it among your diagrams and equations."

––Albert Einstein

"When a country chooses its technology, it chooses its future."

––E. F. Schumacher

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"EPA, yours is a grave responsibility. Don't dig one for 2,4-D."

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DEPARTMENT: Toxicology Research Laboratory

LAB. NO.: 1,9,5 | PROBLEM NO.: 3,1,3,7,2,2,2

TITLE: TECHNICAL GRADE 2,4-DICHLOROPHENOXYACETIC ACID (2,4-D): RESULTS OF A 13-WEEK SUBCHRONIC DIETARY TOXICITY STUDY IN THE CDF FISCHER 344 RAT

77 PAGES IN FULL REPORT

AUTHOR(S): S.J. Gorzinski, C.E. Wade, D.C. Morden, D.G. Keyes, E.L. Wolfe, D.A. Dittenber, R.V. Kalnins, D.J. Schuetz and R.D. Kociba

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This report is: [ ] INTERIM [X] FINAL and mainly: [X] NEW [ ] REVIEW

DESCRIPTIVE SUMMARY WITH CONCLUSIONS:

Groups of 15 male and 15 female 6-week old CDF Fischer 344 rats were given diets formulated to provide doses of 0 (control), 15, 60, 100 or 150 mg/kg/day of technical grade 2,4-dichlorophenoxyacetic acid (2,4-D) herbicide for 13 weeks. Data were obtained on the following parameters: overt signs of toxicity, body weights, food consumption, food conversion, clinical evaluations (clinical biochemistries, hematology, urinalyses), organ weights, organ to fasted body weight ratios, gross examination at necropsy and histopathological examination of tissues.

Growth retardation and decreased food intake were evident for males and females given 150 mg/kg/day of 2,4-D. Food conversion was also slightly reduced in the top dose males and females. Serum glutamic pyruvic transaminase activity (SGPT) was statistically significantly increased in both sexes fed 150 mg/kg/day and females fed 100 mg/kg/day; total thyroxine (T_4) values were reduced significantly for females at the highest 2 dose levels whereas T_4 values for males were unaffected at any dose level.

Hematological values and urinalyses were not affected at any dietary level of test compound. The absolute (g) and relative (g/100g) kidney weight values were statistically significantly increased in all experimental groups of males fed 60 mg/kg/day and greater. Males given 15 mg/kg/day had a significant increase in the relative but not absolute kidney weight. Relative kidney and liver weights were increased for females given 150 mg/kg/day whereas only the relative kidney weight was increased at 100 mg/kg/day. Minor histopathological alterations of the liver were noted in both sexes given 100 or 150 mg/kg/day. At 60, 100 and 150 mg/kg/day both males and females had dose-related microscopic changes of the convoluted tubules of the kidneys. These slight changes of the renal tubules were not seen in male or female rats given 15 mg/kg/day.

(continued)

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In conclusion, the results of this study with technical grade 2,4-D indicate the primary target organ to be the kidney. Dose levels of 60 mg/kg/day and higher exceeded the maximum tolerated dose as evidenced by morphologic changes in the kidneys of both sexes. The 15 mg/kg/day dose level was interpreted as a no observable effect level (NOEL) in the female rats whereas in male rats this dose level produced only a slight increase in relative kidney weight.

TECHNICAL GRADE 2,4-DICHLOROPHENOXYACETIC ACID (2,4-D): RESULTS OF A 13-WEEK SUBCHRONIC DIETARY TOXICITY STUDY IN THE CDF FISCHER 344 RAT

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DISCUSSION

The growth retardation observed in males and females fed 150 mg/kg/day was associated with a slight decrease in food consumption and food efficiency (both sexes); this may suggest a degree of unpalatability of the experimental diets and treatment-related systemic toxicity.

Increased SGPT activity for males and females given 150 mg/kg/day and females given 100 mg/kg/day was considered treatment-related and suggests an effect possibly on the liver. The decreased serum alkaline phosphatase activity in the top dose females appears to be caused by non-specific decreases in food intake. Osihi (1979) has reported decreases associated with restriction of diet. Thus, the reduced value seen only in the top dose females may be related to the decreased feed intake where consumption was approximately 2 g/rat/day less than that of the concurrent controls. Serum T_4 values were decreased in female rats of the highest 2 dose levels. This is interpreted as a treatment-related effect consistent with a previous literature report by Florsheim and Velcoff (1962) of decreased serum levels of protein bound iodine in rats given higher dose levels of 2,4-D. None of the other clinical biochemistry results were considered to be the result of treatment with 2,4-D based on the reason included in the results section.

Organ weight data indicated that the kidney was the primary target organ with dose/treatment-related effects at all dose levels in male rats and at the highest dose level in the female rats. Histopathologic examination

also identified the kidney to be the most sensitive target organ with minor kidney alterations in male and female rats given the highest three dose levels of 60, 100 or 150 mg/kg/day; these effects seen on the kidney may be related to saturation of the elimination mechanism.

In conclusion, the results of this study identified the kidney, and to a lesser extent the liver, as target organs for rats ingesting up to 150 mg/kg/day of 2,4-D with the kidney being the more sensitive index for toxicity. Dose levels of 60 mg/kg/day exceeded the maximum tolerated dose as evidenced by cellular alterations in the kidneys of both sexes. The 15 mg/kg/day dose level was interpreted to be a no-observed effect dose level (NOEL) for female rats whereas in male rats this dose level produced no effects except for a slight increase in relative kidney weight.

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To: John Wesnalon, 3000 Bldg. Midland
AG CANADA STATEMENT - FURTHER CLARIFICATION TO FOLLOW
From: D.E. Weber

Text of TT from Ottawa January 27, 1981

Press release Re 2,4-D to be released Jan. 27 noon. Text follows:

2,4-D measures outlined:
Ottawa Jan. 27/81 - Agriculture Minister Eugene Whelan today outlined measures aimed at phasing out some 2,4-D herbicide products. Last October, Mr. Whelan announced that Agric. Canada scientists had discovered that some types of the popular weedkiller were contaminated with dioxins. There are many different forms of dioxin. The most toxic form - 2,3,7,8-TCDD - was not found in any 2,4-D samples tested. The measures outlined today are:

- an immediate ban on the sale by basic manufacturers of technical esters of 2,4-D that have been shown to contain dioxins.
- a phasing out of all sales of a volatile form of ester-based 2,4-D called butyl ester. Dept'l studies have identified concerns over rapid evaporation and drift of such products, leading to possibl damage to non-target crops.
- action to ensure that all 2,4-D material is free of dioxin contamination by 1982.

'We are extremely encouraged by the compliance already shown by industry with our measures', Mr. Whelan said. 'Basic manufacturers have already responded with a voluntary withdrawal of all technical esters to permit a more detailed evaluation.'

'We realize that these measures will not ensure that only dioxin-free 2,4-D is used this season', Mr. Whelan said. 'Our aim is to phase into completely uncontaminated products by next year. In the interim, users must recognize this new situation. It simply is not physically possible to phase into completely dioxin-free 2,4-D this year.

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'I can't emphasize enough the value of 2,4-D to Canadian Agriculture' he said. 'About eight million pounds is used in Canada each year, the bulk of it to control weeds that would otherwise drastically reduce our crop yields'.

Mr. Whelan explained that because Agric. Canada was first agency in world to discover dioxin contamination of 2,4-D, there was incomplete info available on what the presence of dioxins means in terms of health. Scientists in Agric. Canada's food production and inspection branch made the discovery, using state-of-the-art technology. The finding was made public at an international conference on dioxins in Rome last October.

Based on present knowledge, Health and Welfare Canada experts believe that the types of dioxin found are much less toxic than the 2,3,7,8-TCDD recently found in herring gull eggs and considered to be extremely dangerous.

'We are anxious to do all we possibly can to make sure that all 2,4-D products are free of dioxin contamination as quickly as possible', Mr. Whelan said. 'We have worked in consultation with federal colleagues in Health and Welfare Canada and Environment Canada as well as Provincial Agriculture, Environment and Health Depts.'

Agriculture Canada tests found that 2,4-D products based on basic material called esters are often contaminated with dioxins. The majority of the more common products based on materials called amines are dioxin-free, the tests showed. Most 2,4-D used in agriculture is amine based. All home-and-garden products are based on amine material. Labels clearly identify whether the product is amine or ester based.

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'I realize that these measures will not please everybody.' Mr. Whelan said. 'It simply is not possible to phase into completely dioxin-free 2,4-D this year. We do however have every confidence that this objective will be reached next year.'

'A complete ban on contaminated forms of 2,4-D would have resulted in drastic shortages of the weedkiller, and that in turn would have jeopardized our farmers' ability to produce food. We feel that these measures effectively respond to the new info that emerged last fall, while at the same time ensuring continued levels of crop production', Mr. Whelan said. 'As with all pesticides, all users are reminded to carefully follow label directions when using 2,4-D products.

For more info media may contact
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EPA

weekly report from OPP

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Canada To Phase Out Some 2,4-D Products

In a telegram to DAA Ed Johnson dated 1/27/81, Canadian Agriculture Minister Eugene Whelan outlined measures that his Government is taking aimed at phasing out some products containing the herbicide 2,4-D. Agriculture Canada's measures are: (1) an immediate ban on the sale by basic manufacturers of technical esters of 2,4-D that have been shown to contain dioxins; (2) a phasing-out of all sales of a volatile form of the ester-based 2,4-D called butyl ester (Department studies have identified concerns about rapid evaporation and drift of such products, the telegram states); and (3) action to ensure that all 2,4-D material is free of dioxin contamination by 1982. "We realize that these measures will not ensure that only dioxin-free 2,4-D is used this season," Whelan said. "Our aim is to phase into completely uncontaminated products by next year."

These actions are based on the Canadian findings, announced last fall, of three types of dioxins in 2,4-D product samples taken in the Canadian marketplace. The dioxins found are: 2,7 dichlorodibenzo-p-dioxin; 1,3,7 trichlorodibenzo-p-dioxin; and 1,3,6,8 tetrachlorodibenzo-p-dioxin. Some of the samples tested were free of dioxins, but when the contaminant was present concentrations ranged from 5 parts per billion (ppb) to approximately 8,000 ppb. None of the samples tested contained the highly toxic 2,3,7,8 tetrachlorodibenzo-p-dioxin which is often present in 2,4,5-T.

EPA is coordinating its review activities on 2,4-D with Agriculture Canada, but the Agency says that there is no justification for regulatory action to change current uses of 2,4-D in the United States because products tested here were either dioxin-free or contained extremely low levels (less than 100 ppb.) EPA has a number of review activities under way to assess the safety of 2,4-D. More details are contained in a fact sheet on 2,4-D issued 1/23/81. Copies of the telegram and fact sheet are being sent to the Regions. For more information or copies of the fact sheet, contact Jan Wine, 703-557-7973.

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The Development and Prognosis of Chronic Intoxication by Tetrachlordibenzo-p-dioxin in Men

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ABSTRACT. During 1965 to 1968, 80 workers who had been engaged in the production of 2, 4, 5-sodium trichlorphenoxyacetate and butylester of trichlorphenoxyacetate acid became ill. The cause of the illness was 2, 4, 7, 8-tetrachlordibenzo-*p*-dioxin. A 10-yr study has been conducted for 55 exposed individuals. The majority of the patients developed chloracne, and 11 manifested porphyria cutanea tarda. Approximately one-half of the patients suffered from metabolic disturbances, i.e., pathologically elevated lipids with abnormalities in the lipoprotein spectrum, and two-fifths of the patients had pathological changes in the glucose tolerance test. One-third of the patients had biochemical deviations indicative of a mild liver lesion. Histological examination revealed light steatosis, or periportal fibrosis, or activation of Kupffer cells. Fluorescence of the liver tissues was present in ultraviolet light. In 17 persons symptoms of nervous system focal damage existed, with predominance of peripheral neuron lesion of the lower extremities (verified by EMG examination). The majority of patients suffered from various psychological disorders. As of this date, two patients have died of bronchogenic lung carcinoma; one of liver cirrhosis; one of a rapidly developed, extremely unusual type of atherosclerosis precipue cerebri; and two patients have died in traffic accidents. The conditions of most other patients have improved.

PERHAPS THE most potent man-made toxin presently known is 2, 3,7,8-tetrachlordibenzo-*p*-dioxin (TCDD), a solid substance that is insoluble in water and slightly soluble in fats and chlorinated solvent. It is a heat-stable, amphoteric substance, and exerts its biological effects at extremely low concentrations. TCDD is not translocated in plants, and has a half-life in soil of about 1 yr. Microbial degradation of TCDD is reported to rarely occur in nature. Irradiation of TCDD in water produces few changes after 14 days.[1] Due to its extreme toxicity, its chemistry has not been fully evaluated. There are considerable differences in species susceptibility, but in all laboratory animals the lethal effect is slow and ensues several days or weeks after a single dose.[2]

TCDD is formed as a by-product during the synthesis of 2,4,5-trichlorphenol, which involves the hydrolysis of 1,2,4,5-tetrachlorbenzene using methanol and caustic soda at atmospheric pressure. TCDD is formed in the distillate by the condensation of two molecules of sodium trichlorphenolate influenced by the highly exothermic decomposition of sodium-2-hydroxyethanol. Trichlorphenoxyacetic acid (2,4,5-T), a herbicide produced commercially prior to 1965, contained 30 mg/kg TCDD. Currently, 2,4,5-T, containing < 0.05 mg/kg TCDD is produced in several countries and is available in commercial quantities.[1]

Several accidents have occurred during the industrial synthesis of 2,4,5-trichlorphenol and 2,4,5-T, the consequences of which are well described in the literature.[2-7]

The most recent large-scale TCDD intoxication that occurred in Seveso, Italy in 1976 renewed the interest of specialists and the general public. Since we have acquired considerable information during the 10 years we have observed patients with chronic TCDD intoxication, we have chosen to present our findings in this study.

Table 1.—Physiologic, Neurologic, Psychiatric, and Dermatologic Observations for Fifty-Five Males with TCDD Intoxication*

	Percent of patients (N = 55)
Medical lesions	
Porphyria cutanea tarda	20
Only uroporphyrinuria	21
Hypercholesterolemia	56
Hyperlipemia	67
Hyperphospholipemia	42
Diabetes mellitus	8
Low glucose tolerance test value	19
Hepatic lesions	20
Increased total blood proteins	13
Increased plasma	
γ globulins	36
α_1 globulins	44
Decreased plasma albumin	33
Neurological lesions	
Pathological changes without any connection with exposure exposure to TCDD	8
Polyneuropathy	23
Encephalopathy	7
Psychiatric changes	
Severe neurotic symptoms and signs with disorders of vegetative nervous system	64
Neurasthenia syndromes with depressive component	11
Depressive syndromes with endogenous component	8
Pseudeoneurasthenia syndromes in patients with arteriosclerosis of central nervous system	14
Skin lesions	
Chloracne of different severity	95

*All results were obtained at the beginning of intoxication.

MATERIALS AND METHODS

The Department of Occupational Diseases University Hospital in Prague admitted 55 males for the first time in 1968 and 1969 suffering from chronic TCDD intoxication, who had been engaged in the production of sodium 2,4,5-trichlorphenoxyacetate and butyl ester of 2,4,5-trichlorphenoxyacetate acid. This incidence of mass intoxication occurred during a time when alkaline hydrolysis of tetrachlorbenzene at atmospheric pressure was used to increase and shorten reaction time, and probably during the same time the mother liquor, which was originally disposed of, was put back into production. The concentration of TCDD in the work atmosphere was never measured; however, TCDD was found in the final product—Arboricide E—and several years later, was also found in the building and on wall paintings.

Originally, 80 of 400 persons who were engaged in this production became ill. Only 55 of those persons have been observed on a long-term basis; the remaining 25 persons either refused to be examined in our hospital or moved, leaving no address. Those who moved were usually foreigners who returned home. The mean age of the 55 intoxicated individuals was 36.3 [standard error (SE) = 11.2] at the time the outbreak of illness occurred. We do not provide any further details about production conditions and the course of the illness during the initial 3 to 4 yr in this article, since these were described in our 1974 report;[7] therefore, we shall only provide the most important data required for understanding the development of the illness.

RESULTS

The first symptoms of intoxication which occurred at the time of exposure were: gradual, but rarely sudden, formation of chloracne; a feeling of sickness; fatigue; weakness in the lower extremities; and frequently, pain under the right coastal arch. In 10 patients, however, the first symptoms of intoxication appeared several months after work with TCDD was completed. The intoxication affected several organs and systems (Table 1). It should be noted that only the most severely affected patients exhibited all of the above-listed symptoms, and the extent of organ damage was not uniform for these patients. The severity of illness was not related to the duration of exposure, job status, or age.

Table 2.—Cause of Death for Six Patients with TCDD Intoxication

	Age (yr)	Duration of Exposure	Duration of Intoxication	Severity of TCDD Intoxication Cause of Death and Post-Mortem Findings
1.	57	9 mo	2 yr	Severe type of TCDD intoxication. Unusual type of very severe arteriosclerosis of cerebri, liver, pancreas, and kidneys. Dementia cerebri. Immediate cause of death: bronchopneumonia.
2.	59	3 yr	2 yr	Severe type of TCDD intoxication. Bronchogenic carcinoma.
3.	47	2, 5 yr	3 yr	Severe type of TCDD intoxication. Bronchogenic carcinoma.
4.	31	15 shifts	4 yr	Slight signs of TCDD intoxication. Traffic accident—comminuited fractures of lower extremities. Immediate cause of death: fat embolisation to lungs.
5.	63	7 mo	5 yr	Severe chloracne and slight signs of lipid metabolism disorder. Traffic accident—fractura coli femoris. Cause of death: bronchopneumonia hypostatica.
6.	40	32 shifts	9 yr	Severe type of TCDD intoxication; about 3 yr before death; complicated with hepatitis epidemica, type B. Macronodular cirrhosis with signs of portal hypertension, ascites. Cause of death: hepatic coma.

The progression of illness was not linear. In some patients, symptoms and signs of intoxication that were present from the very beginning of the illness, became more severe during the 3-4 yr that followed intoxication. In others, however, organs and systems that were functionally normal during the beginning of illness later became impaired. Deterioration occurred suddenly, the eliciting factors sometimes being intercurrent illness, stress, or unusual physical exertion. In other patients, however, deterioration could not be ascribed to specific factors, but was probably attributable to the spontaneous course of the illness proper. Deterioration and subsequent improvement did not occur consistently in individual organs and systems. During 5 yr of intoxication, the health status of most patients was stabilized; some patients' status even improved. During this time 6 patients died, the causes of which are listed in Table 2, and 5 refused our systematic medical care. The authors are therefore providing medical care to 44 of the original 55 patients; all patients' conditions have improved, but no patient is entirely healthy. Most of these individuals gradually re-entered the workforce, and established themselves in society. During their illness, 18 healthy children were born. The wives of two patients had spontaneous abortions in their third month of pregnancy, but the cause is not known because the fetuses were not autopsied.

The impact of the intoxication varies. There are still pathological deviations in lipid metabolism in most of the patients. Figure 1 shows mean values of total cholesterol measured when the illness was first noted and "to-date" values, both compared with a control group. Figure 2 shows similar results for phospholipid measurements. At the beginning of intoxication, lipid values were pathologic in more than one-half of the patients (mean = 13.85 g/L). Currently, the mean values of lipids do not significantly differ from controls. Lipoproteins could be examined only in recent years; we found elevated mean values in the pre-beta fraction [VLDL (Fig. 3)]. In the blood protein spectrum, pathologically increased alpha 1 and gamma globulin levels have normalized, but there are still elevated mean values of total blood proteins in comparison to controls: 7.5404 (SE = 0.5499) against 7.0296 [SE = 0.4462 (P = .01)]. For all internal examinations we used the Student's t test for statistical evaluation.

Currently, one-fifth of the patients has a pathological diabetic glucose tolerance test and another one-fifth has a pathological flat glucose tolerance test. Pathologically high excretion of uroporphyrins, together with other signs of porphyria cutanea tarda, were present at the outset of intoxication in one-fifth of the patients. The same fraction had a slightly increased uroporphyrin excretion in urine (to 100 μg/24 hr) without any skin manifestations. Excretion of coproporphyrin in urine was, only rarely, substantially affected; mean values of delta-aminolevulinic acid in

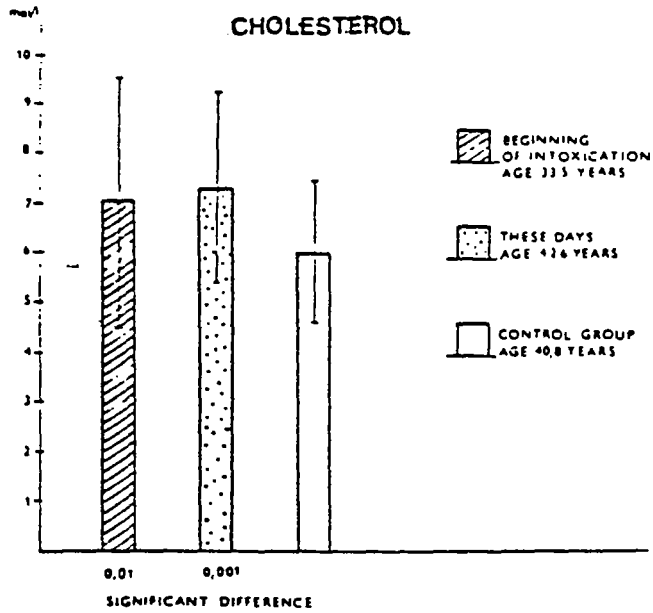

Fig. 1. Values of cholesterol in serum of patients at the "beginning of intoxication" and "these days" in correlation with "control group."

urine were, during the first years of intoxication, significantly higher than in controls. At present, pathological excretions of uroporphyrins and skin manifestations of porphyria cutanea tarda are very rare. Similarly, functional liver tests (i.e., bilirubin, thymol pyruvic transaminase in serum, bromsulphalein test) are seldom pathological, whereas in the beginning of the illness, one-fifth of the patients had mild hepatic lesions. Liver necropsy and biopsy showed that even for the most severe forms of intoxication, only slight morphological deviations in terms of mild steatosis or periportal fibrosis occurred; even when most severely affected patient, who was the first victim of intoxication, showed only slight activation of Kupffer cells. Only one patient, who died in hepatic coma attributable to concommitant infectious hepatitis B (HBAG positive), displayed large-nodule active cirrhosis with manifestations of portal hypertension and ascites.

In all decreased patients and for those in whom liver biopsy was performed, liver tissue fluorescence in ultraviolet (UV) light was present, even in cases where repeated examinations revealed normal values of urinary porphyrins. Throughout the entire observation period of the whole patient group, goal-directed examinations did not indicate any signs of toxic lesions in the myocardium or kidneys, and hemopoiesis was not affected. There were no pathological values of phosphatase alkaline serum and iron in serum, nor ophtalmological impairments that could be attributed to the effect of TCDD.

The results of repeated neurological examinations are presented in Table 3. During the initial 3-4 yr of illness, the lesion in the peripheral neuron of the lower extremities deteriorated, which in most patients, was present from the onset of intoxication. In some cases, polyneuropathy appeared only during the course of the illness; in these patients it could be reliably documented that clinical and electromyographic examinations were normal at the

Table 3.—Results of Neurological Examinations for Individuals Exposed to TCDD

	Onset (N = 55)	At Present (N = 44)
Normal neurological examination	62%	51%
Pathological changes without any connection with exposure to TCDD	8%	9%
Polyneuropathy	23%	31%
Encephalopathy	7%	9%

outset of intoxication. In addition, in four patients there was peripheral lesion N VII, which occurred either in connection with polyneuropathy of the lower extremities, or was isolated. After 4 yr of illness, the neurological picture stabilized; three patients even showed improvement. Encephalopathy sometimes develops in persons aged 50-65 yr, accompanied by organic psychosyndrome on the basis of atherosclerosis of cerebral arteries. Very rarely is ischemic heart disease concurrently present. The patient who presently has the most severe form of the illness is also afflicted with paroxysms of temporal epilepsis and

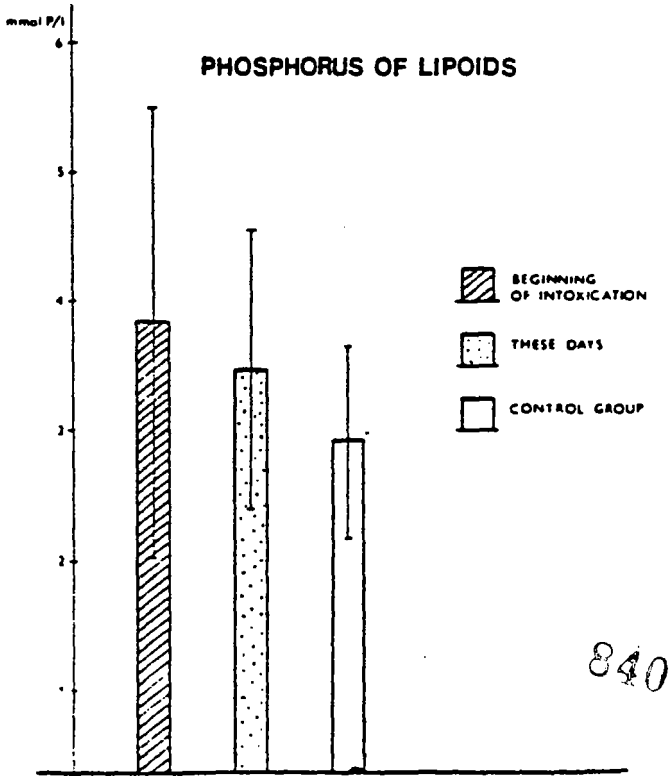

Fig. 2. Phosphorus of lipoids in serum at the "beginning of intoxication" and "these days" in correlation with "control group."

Table 4.—Psychiatric Changes Observed in TCDD-Exposed Individuals

Beginning of Intoxication (N = 55)	At Present (N = 44)
Neurotic symptoms, neurasthenia syndromes with depressive component, depressive syndromes with endogenous component	Neurotic symptoms without any depressive symptoms and anxiety symptoms
83%	58%
Pseudoneurasthenia syndromes in patients with arteriosclerosis of central nervous system	Developed to severe type with signs of dementia cerebri
16%	18%
Without any psychiatric symptoms or signs	Without any psychiatric symptoms or signs
3%	24%

external and internal hydrocephalus; polyneuropathy has remained unchanged throughout the 10 yr.

The neurological picture of the illness is complemented with results of repeated psychiatric examinations (Table 4). Psychiatric disorders also progress on the basis of cerebral atherosclerosis, predominantly in patients over 50 yr of age. However, a severe organic psychosyndrome with dementia is also present in a 30-yr-old patient. The depressive and anxiety components of neurasthenic disorders have completely disappeared, and the number of patients who show no signs of mental disorders has increased.

Chloracne, which in the beginning of the illness was the most constant sign of intoxication, has healed in one-fifth of the patients; one-half of the patients has only isolated cysts and comedones. Fifteen percent, however, still have florid manifestation of chloracne with large cysts, abscesses, and comedones. The pathological changes often affect the genital region, thus seriously curtailing sexual activity. Severe forms of chloracne, though healed, have left gross defects in the form of scars which have permanently disfigured the patients.

DISCUSSION

There is no doubt that TCDD intoxication is one of the most severe occupational and non-occupational poisonings. There are two reasons for this: (1) TCDD is highly toxic; and (2) the noxa interferes with many metabolic

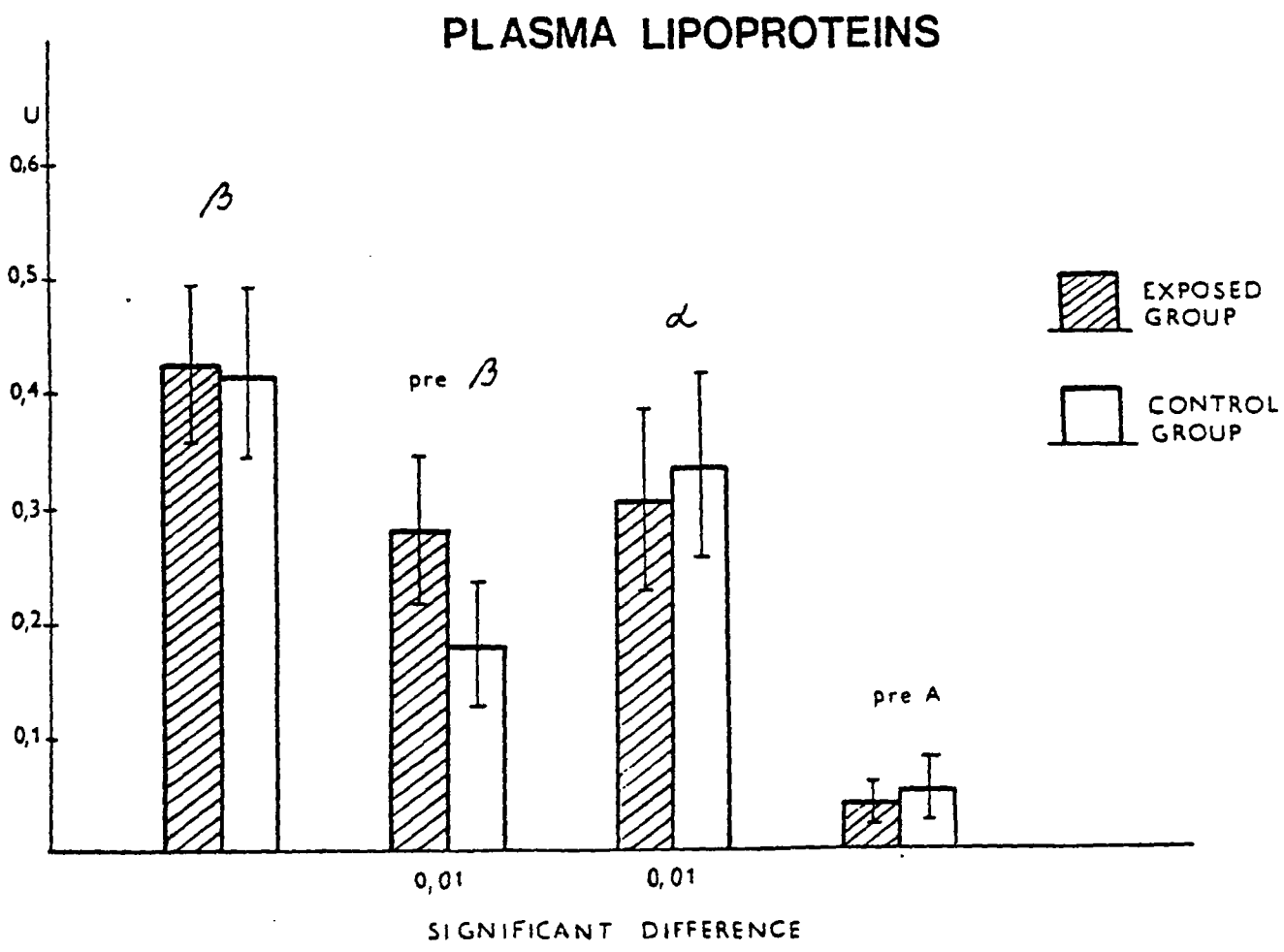

Fig. 3. Value of plasma lipoproteins in correlation with control group.

processes which still remain disturbed at a time when TCDD, in view of its short biological half-life of 21 days, should be eliminated from the organism. There is a considerable species-specificity in the sensitivity of laboratory animals to this toxic substance, and the impact on individual organs differs in different species. In monkeys, as in humans, a permanent sign is skin lesions, while hepatic impairment is in the background.

The long-term and relatively complex observation of our patient sample with chronic TCDD intoxication permits us to express a hypothesis on the nature and prognosis of this illness in man. There is no doubt that TCDD was present in the air of the workshop, and because of the constantly changing technology, its concentration in air was inconstant. TCDD caused intoxication which in turn, nonuniformly affected a number of important organs and systems. The course of the illness was more severe in individuals when the illness started during exposure than when the first symptoms appeared several months after cessation of this study.

Even though most of the patients did not experience all symptoms and signs of intoxication, and some patients showed only symptoms and signs in different combinations, we assume that in this type of intoxication all the systems and organs mentioned in this study were simultaneously affected, although some only slightly. This assumption is supported by several facts. Fluorescence of liver tissues in UV light, which is a sign of pathological porphyrin metabolism, was present in all cases of necropsy and biopsy, i.e., in persons in whom long-term monitoring of porphyrin excretion in urine and delta-aminolevulinic acid values were constantly within normal limits. Probably a slight subclinical lesion was present. Further evidence was furnished in repeated neurological examinations. Polyneuropathy of the lower extremities was manifest in some patients only in the third or fourth year of illness; we have definite clinical and electromyographic evidence that the first examinations conducted when the illness commenced were entirely normal. The manifestation of these lesions was promoted by unspecific stress (e.g., greater physical exertion, intercurrent inflammation of upper respiratory pathways, stress situations, etc.), none of which could, by itself, produce a similar illness. Similarly, slight hepatic lesions and diabetes mellitus—manifest or latent—appeared in some patients 1 or 2 yr *after* intoxication, and were related with some unspecific stress, or sometimes they occurred independently. The alteration of many metabolic processes and functional disturbances of several organs indicate a high probability that TCDD affects general enzymatic processes that are present and necessary for the activity of more systems.

Other than the direct toxic effect of TCDD on nervous tissues, we also assume that indirect intervention may exist, i.e., impaired metabolic processes in lipid and hydrocarbon metabolism. The incidence of polyneuropathy was more frequent in patients with manifest or latent diabetes. Changes were also marked in the central nervous system on the basis of atherosclerosis of cerebral arteries, the development of which might be enhanced by hypercholesterolemia, hyperlipemia, hyperphospholipemia, and higher pre-beta fraction (VLDL) in the lipoprotein spectrum.

Unfortunately, we could not arrange the autopsy of all deceased patients in a qualified, university surgery where detailed attention could have been given to atherosclerosis. The patient who was the first to die, and who had demonstrated the most severe clinical and laboratory signs of intoxication, was thoroughly examined in this respect and autopsy revealed very severe, entirely untypical atherosclerosis. Detailed information is given in our study of 1974.[7]

The mass occurrence of psychic disturbances, predominantly anxiety and depression, was in the first years of illness mainly due to exogenous influences: fear of death; disfigurement; invalidity; marital problems; and in young individuals, the difficulty of entering intimate, close relationships because of the disfigurement resulting from chloracne. Gradual adjustment to the illness, its improvement (especially on the visible skin area), and return to normal work and social life all contributed to decrease psychic disturbances, thus facilitating better adaptation to life.

It does not appear that chronic intoxication in our patients unfavorably affected the quality of offspring. All of the 18 children born to intoxicated individuals were free of the developmental anomalies; their postnatal development has also been normal. Two spontaneous abortions in 10 (10%) pregnant wives of our patients is less than the number of worldwide spontaneous abortions relative to the number of pregnancies (15-20%).[2]

In recent years the possible carcinogenicity of TCDD has been widely discussed.[1] Even though two of our patients died of bronchogenic lung carcinoma after 2 and 3 yr of the intoxication, no definite conclusions can be drawn in view of the small number of persons in the group.

This illness is characterized by its non-uniformity, both in its developments and its effects on individual organs. Deterioration was always sudden, followed by less gradual improvement. This is a rather cheerless balance of an illness, where the mechanism of origin and cause of unusual development we know virtually nothing. Being aware of this poor understanding, we were very careful in our therapy and concentrated on the prevention of further possible stressful situations that could have aggrevated the illness. We attempted to remove all neurotoxic, hepatotoxic, and dermatotoxic substances from the work and living areas. Each patient received a list of drugs known for their hepato- or neurotoxicity, and those drugs suspected of producing porphyria cutanea tarda, which he was instructed to avoid. Rarely did we apply medicines to alleviate symptoms which were particularly distressing. The treatment of chloracne is discussed elsewhere by the dermatologist, Jirásek.[8,9]

In our paper we wished to indicate the importance of having a thorough understanding and knowledge of undesired by-products resulting from synthesis or manufacture of various products, being alert to changes in technology and to systematically protect the health of workers.

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Tetrachloroazobenzene in 3,4-Dichloroaniline and Its Herbicidal Derivatives: Propanil, Diuron, Linuron, and Neburon

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ABSTRACT. The presence of 3,3',4,4'-tetrachloroazobenzene (TCAB) was determined by high performance liquid chromatography in 3, 4-dichloroaniline and herbicides made therefrom. The concentrations of TCAB in 3, 4-dichloroanilines and in different herbicides from a variety of manufacturers ranged from 9 to 1400 μg/g (ppm). The chloracnegenic potential of these products, as determined by rabbit ear test, suggests that it is in the same range of 2, 3, 7, 8-tetrachlorodibenzodioxin, a known potent chloracnegenic agent.

RECENTLY, some outbreaks of chloracne in groups of chemical workers have been attributed to 3,3',4,4'-tetrachloroazobenzene (TCAB) and 3,3',4,4'-tetrachloroazoxybenzene (TCAOB) as contaminants in 3,4-dichloroaniline and its herbicidal derivatives.[1,2] These contaminants are by-products of the commercial synthetic process.[3] In addition, several workers have reported that the herbicides degrade in soil to produce TCAB and TCAOB.[4] Chlorinated azobenzenes are structurally similar (isosteric) to the chlorinated dibenzodioxins and dibenzofurans, which also cause chloracne. Poland has reported that chlorinated dibenzofurans, dibenzodioxins,

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Safety Services Department

A STUDY TO ASSESS THE OCCUPATIONAL EXPOSURE TO 2,4-D HERBICIDES

Date: January 1981

Report: SSD-81-1

H+S

Health & Safety Division

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7.0 OBSERVATIONS AND CONCLUSIONS

As a result of this study the following conclusions can be made.

7.1 The major route of worker exposure to 2,4-D herbicides is through dermal absorption. Comparison of the breathing air and urinary data indicates at least 35 times more 2,4-D is absorbed through the skin than is inhaled with the breathing air.

7.2 The average breathing air concentrations were 0.01 mg/m^3 which is 0.1% of the current TLV of 10 mg/m^3 for 2,4-D exposures. The maximum air concentration for a single day was 0.1 mg/m^3 which is 1% of the current TLV.

7.3 The average worker excreted 2.1 mg/day of 2,4-D in urine. This is 2% of the maximum daily allowed exposure via inhalation. The maximum urinary elimination encountered was 43 mg/day. This maximum falls within the range of moderate exposure to 2,4-D.

7.4 Mist-blower operation provided the greatest air exposure to workers at 55.2 $\mu g/m^3$. The right of way spray operations average 13 $\mu g/m^3$ 2,4-D and the roadside operations provided the lowest worker air exposures to 2,4-D at 6.4 $\mu g/m^3$.

7.5 Improved work procedures, protective equipment and training provided to the workers reduced the maximum average weekly urine 2,4-D concentrations by a factor of 3 times over those measured in 1979. This reduction may also reflect increased worker awareness to possible hazards of these herbicides.

8.0 RECOMMENDATIONS

8.1 Work procedures and protective equipment used by herbicide applicators should be reviewed keeping in mind that the major worker exposure pathway is through skin absorption. Inhalation exposure to 2,4-D has been shown to be minimal.

8.2 Further reductions in 2,4-D intake can be achieved by washing of exposed skin areas and changing of clothing which has been exposed to 2,4-D residues as soon as practically possible after exposures.

8.3 There is a great variability in urine elimination rates throughout the day. Better exposure values can be obtained if 24 hour urine samples are collected rather than spot samples through the day. The 24 hour samples can be better related to the urinary model for total exposure calculations.

8.4 The 1981 herbicide monitoring program can be restricted to urine monitoring as air exposures have been shown to be negligible. Urine monitoring should be continued to check work control methods and to continue our data base.

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THE HEALTH EFFECTS OF HERBICIDE 2,4,5-T

A Report by the American Council on Science and Health

The American Council on Science and Health is an independent educational association promoting scientifically balanced evaluations of chemicals, the environment and human health.

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Individual copies of this report are available at a cost of $10.00. Prices for ten or more copies are available on request.

This report on 2,4,5 - T was researched and written by Mary Katherine Hayes, M.S., Research Associate for the American Council on Science and Health (ACSH).

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INTRODUCTION

This paper by the American Council on Science and Health was prepared as a result of the controversy concerning the suspension and possible cancellation of registration of the herbicide, 2,4,5-trichlorophenoxyacetic acid. Use of the herbicide is currently being questioned and indeed may cease permanently after scheduled hearings by the Environmental Protection Agency (EPA), which began March 14, 1980.

Registered in 1948, the herbicide, 2,4,5-T, is not a newcomer to weed control. But studies within the last ten years involving both human and animal exposure to the herbicide have raised questions regarding potential health hazards accompanying its use. In 1978, the EPA issued a Rebuttable Presumption Against Registration (RPAR) (EPA 1978) and Continued Registration of herbicides containing 2,4,5-T, initiating the process to question the need for continued registration.

However, on February 28, 1979, the EPA exercised its option by citing an "imminent health hazard" and called for an immediate Emergency Suspension of 2,4,5-T (EPA 1979c) on rights of way, forests, and pastures. Exempt from this suspension order were rangeland and rice paddy applications.

Proponents of the ban argue that the herbicide is very toxic to humans. They illustrate their point with a variety of studies that attribute an increase in miscarriages, birth defects, and certain forms of cancer to exposure to 2,4,5-T.

Opponents of the ban defend the use of the herbicide. Interested parties in this camp feel that the scientific evidence does not substantiate the claims made by critics of the chemical. They therefore feel that the EPA's proposed cancellation is unfounded.

At the heart of the matter lies the chemical 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Regarded as one of the most potent toxins known to man, TCDD is a consistent contaminant of 2,4,5-T.

The American Council on Science and Health seeks to present a balanced and unbiased assessment of this current public health issue. In preparation of this paper, the Council has diligently studied the history and past and present uses of this herbicide both in the U.S. and abroad. Furthermore, it has scrutinized available data

on the effects on human and animal health. In addition, it has reviewed information about 2,4,5-T in the popular press and from interested parties on both sides of the issue.

The American Council on Science and Health appreciates the problems encountered in making a definitive decision regarding the use of 2,4,5-T. A thorough analysis of the 2,4,5-T dilemma is complicated by a paucity of human evidence, the need to extrapolate from animal data and a lack of sophisticated detection equipment. The Council recognizes valid arguments submitted by both parties involved in this dispute. The Council presents its paper as its own opinion and interpretation of the information studied and hopes that it addresses all pertinent arguments in this important public health matter.

POSITION STATEMENT

Based on its review of the scientific evidence, the American Council on Science and Health (ACSH) concludes that there is insufficient evidence to support a ban on 2,4,5-T. No scientific reports presented to date have shown any convincing relationship between the traditional use of 2,4,5-T and adverse health effects in humans.

The toxicity of 2,4,5-T and its contaminant, 2,3,7,8-TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin), has been demonstrated under laboratory conditions at doses far higher that those to which humans are exposed. Estimates of human health risk derived from animal experiments are unreliable. Furthermore, those risks which have been calculated for 2,4,5-T and 2,3,7,8-TCDD are extremely small.

ACSH recommends that the current uses of 2,4,5-T in rice fields and rangeland be continued and the suspended uses in forests, railways and highways, and landscaping be reinstated.

ACSH recognizes the problems posed by 2,4,5-T's unavoidable contaminant, 2,3,7,8-TCDD, and urges that every effort be made to further reduce contamination during the manufacturing process. ACSH recommends that applications of 2,4,5-T, particularly aerial spraying, be strictly monitored to minimize unnecessary environmental and human exposure. ACSH believes that stringent safeguards for the manufacture and application of 2,4,5-T will effectively reduce any potential adverse effect of 2,3,7,8-TCDD while allowing for the continued use of the herbicide.

Chronology of Events Involving 2,4,5-T

1945 - developed as an herbicide

1948 - registered with USDA as a pesticide

1949 - accident at Nitro, West Virginia, 2,4,5-T plant

1957 - 2,3,7,8-TCDD impurity in 2,4,5-T made known

1962 - Vietnam defoliant spraying commenced

1966 - USDA and FDA order residue tolerances be established for most pesticide chemicals in or on food crops

1967 - deadline for obtaining tolerances for residues of most pesticide chemicals including 2,4,5-T on food and feed products and by-products

1969 - 2,4,5-T and 2,4-D were reported to produce birth defects in animals

1970 - USDA requested further teratogenic studies

1970 - Department of Defense cancels use of 2,4,5-T in defoliation procedures in Vietnam

1970 - USDA cancelled all use of granular 2,4,5-T formulations for use around the home, recreational areas and similar sites and all food crops intended for human consumption

1970 - USDA suspends use of 2,4,5-T in lakes, ponds, ditch banks, and all liquid formulations for use around the home, recreational areas, and similar sites

1970 - Congress directed DOD to contract with National Academy of Sciences for study of ecological and physiological effects of use of herbicides in Vietnam

1970 - use of 2,4,5-T banned in Italy; it is also banned in Sweden and the Netherlands

1971 - accident at racecourse in St. Louis, Missouri, involving exposure to TCDD resulting in animal death and human illness; 2,4,5-T not involved

1971 - FIFRA Advisory Committee recommends continued use of 2,4,5-T on forest, range, rice, rights of way; stipulates TCDD (dioxin) content be reduced to

0.1 ppm, 2,4,5-T be applied no more than once a year, and applied in a manner that will not contaminate humans

1971 - EPA prohibits use of 2,4,5-T on most food crops

1972 - Amendments to Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) enacted requiring registration of all pesticides and their use plus certification of applicators--Administering Agency for FIFRA is EPA

1972 - Dow Chemical obtains an injunction against EPA enjoining further action against 2,4,5-T

1973 - The study "Primary Carcinoma of the Liver in Vietnam" released in medical journal Chirurgie by Dr. Ton That Tung

1973 - U.S. Court of Appeals overturns injunction; cancellation proceedings continue

1973 - Notice of Intent to hold Hearings on all uses of 2,4,5-T. Public hearing scheduled for April, 1974, following completion of intensive monitoring for TCDD in part per trillion (ppt) range

1974 - National Academy of Science Report - "Effects of Herbicides in South Vietnam - Part A Summary and Conclusions" issued

1974 - information hearings expanded to include all insecticides and herbicides using 2,4,5-Trichlorophenol in their manufacture

1974 - EPA withdraws from cancellation and information gathering proceedings because of its inability to accurately monitor food for TCDD residues

1974 - EPA establishes Dioxin Implementation Plan to identify good analytical methods for detecting TCDD in ppt range

1976 - explosion at ICMESA Chemical Plant in Seveso, Italy, releasing an estimated 1.7 kg. (3.74 lb.) TCDD in an area with population of 100,000

1977 - decision to continue use of 2,4,5-T in New Zealand issued by government

1978 - Ministries of Agriculture, Fisheries and Food (MAFF) of United Kingdom - Advisory committee announce that herbicides containing 2,4,5-T were safe, "if used in the recommended way for the

recommended purposes -- approval given for their continued use on U.S.

1978 - Agent Orange Victims, International formed by U.S. Vietnam veteran

1978 - EPA publishes Rebuttal Presumption Against Registration (RPAR) and Continued Registration of 2,4,5-T, citing research that indicates 2,4,5-T and TCDD cause tumors, birth defects, and fetal deaths. RPAR allows continued use pending final decision

1978 - airing of ABC-TV's 20/20 News Magazine two-part program detailing 2,4,5-T and Agent Orange

1979 - suspension hearings commenced on April 19, 1979

1979 - hearings stopped on May 15, 1979, after all registrants withdrew from the hearings

1979 - "Politics of Poison," a documentary on 2,4,5-T shown on NBC San Francisco affiliate KRON-TV

1979 - Dispute Resolution Conference on 2,4,5-T held sponsored by the American Farm Bureau Federation

1979 - availability of EPA Position Document on 2,4,5-T

1979 - hearings before House Sub-committee on Oversight and Investigations on Involuntary Exposure to Toxic Herbicides and Pesticide Products

1979 - Pendulum and the Toxic Cloud by Thomas Whiteside published, dealing with the Seveso, Italy, dioxin accident

1979 - Notice of Intent to Cancel Suspended Uses of 2,4,5-T by the EPA

1979 - Alsea II report submitted to the EPA which provided grounds for initial suspension action by the EPA

1979 - EPA issues Emergency Suspension Order for 2,4,5-T on rights of way, pastures, forests, home gardens, aquatic weeds, ditch banks, and ornamental turf; exempt from this suspension were rangeland and rice paddy applications

1979 - FIFRA Scientific Advisory Panel reviews non-suspended uses of 2,4,5-T and issues opinion

1979 - PBS airs "A Plague on Our Children" as part of its NOVA series dealing in part with 2,4,5-T

1979 - EPA issues Final Determination Concerning the RPAR for certain uses of Pesticide Products and Notice of Intent to hold a hearing

1980 - Dow Chemical filing against U.S. Government claims negligence in misuse of Agent Orange and failure to inform servicemen of potential dangers of exposure to Agent Orange

1980 - Cancellation hearings of 2,4,5-T began March 14, 1980

1980 - Operation Ranch Hand - in depth study of Vietnam veterans scheduled begins

Forty years ago, while researching the properties of naturally occurring plant growth hormones, scientists discovered the phenoxy herbicides (Peterson 1967). Considered as synthetic plant growth regulators, the phenoxy compounds were developed to mimic the properties of a naturally occurring plant growth regulator, indoleacetic acid. Concurrent research in the United States and Great Britain revealed the capabilities of certain phenoxyacetic acids, including 2,4-dichlorophenoxyacetic acid (2,4-D), as active herbicides, selectively killing many broadleaf weeds in cereal grain, grasslands, and coniferous forests (Bovey and Young 1978), (Nutman, Thornton and Quastel 1945), (Blackman 1945). The military furthered their investigation by studying phenoxy herbicide use as a vegetation control weapon in 1944-1945.

By 1946, 2,4-D was used extensively to control weeds in turf, small grains, and corn. However, its efficacy did not extend to brush control. Research for an effective substitute began. Use of 2,4,5-trichlorophenoxyacetic acid began after its registration by the Amchem Products Company, Ambler, Pennsylvania, on March 2, 1948. In the years that followed, 2,4,5-T made its mark as the material of choice for effective brush control on rights of way, rangeland, forestry, and certain weeds in rice, wheat, corn, and sugarcane (CAST 1978).

Although many phenoxy compounds have herbicidal capabilities, most are not commercially available because of prohibitive cost or narrow effectiveness range. Phenoxy herbicides presently in use today in the U.S. include 2,4-D, 2,4,5-T, MCPA, Silvex, 24-DB, MCPB, dichlorprop, mecoprop, 2,4-DEP (Weed Society of America 1974), and dichlorprop-methyl (Federal Register April 7, 1980).

2,4-D predominates in the U.S. today, due to its low cost and high effectiveness. Other phenoxy herbicides are employed only in instances where they exceed the capability of 2,4-D.

In 1975, the United States used 59 million pounds of 2,4-D, 6.7 million pounds of 2,4,5-T, and two million pounds of Silvex (Stanford Research Institute 1976). MCPA, 2,4-DB, dichlorprop and mecoprop find important but limited use for specialized applications (Klingman and Ashton 1975). 2,4-DEP, a chemical related to 2,4-D, acts principally through soil transport (Crafts 1975), but it is not used with the same frequency as 2,4-D.

One hundred companies hold federal registrations and formulate 424 products containing 2,4,5-T. Eleven companies have applied for federal registration of 21 products containing 2,4,5-T previously registered only in certain states (EPA 1974).

In 1969, 11,626,000 pounds of 2,4,5-T acid, esters, and salts were produced in the United States alone. In 1970, the quantity rose to 12,335,000 pounds. Between 1971 and 1974, 738,907 pounds of 2,4,5-T were imported into the U.S. averaging a total of 148,000 pounds per year (EPA 1974).

The phenoxy herbicides gain entrance to the target site by penetrating the plant foliage, roots and soft stem tissue. When applied as a drench in diesel oil, they can soak through the dry bark of trees and enter living tissues (Crafts 1964). Accumulating in the actively growing parts of roots and stems (Crafts 1964), they cause the leaves and buds to twist and curl and new growth of stems and leaves are malformed. Sensitive young plants may die in a few days. Hardy shrubs and trees may succumb only after weeks or months or may survive without injury (Bovey 1977).

A phenoxy herbicide enters a plant in an imperfect and uncontrolled way. Once inside the plant, it interferes with the regulation of growth processes normally governed by the plant's own naturally occurring growth hormones (Ashton and Crafts 1973). The phenoxy herbicides interfere with cell division (mitosis) and cell enlargement, food utilization and various other processes necessary to stabilize life.

Scientists do not know the precise mode of action of either synthetic or natural plant growth regulators. They do know that phenoxy herbicides are far more toxic to green plants than to animals. Plant growth regulating compounds act on plant cell compounds such as cellulose and lignocellulose which are not present in animals.

Land management personnel utilize phenoxy herbicides in various situations. The following discussion lists kinds of uses and the preferred herbicides for the job.

Timber Management - Foresters have included the phenoxy herbicides among their timber management tools since the early sixties (Bentley 1967).

Forests cover a third of the U.S. (approximately 750 million acres), and two thirds of this land is usable for commercial timber purposes. The remaining, approximately 250 million acres, either produces too little timber for commercial classification or has been utilized for other functions, namely wildlife, water yield, grazing, or recreation (CAST 1978).

According to Walker (1973), competing undesirable vegetation causes about 300 million acres of commercial timber land to operate at less than two thirds of its timber production capacity. Over one hundred million acres of historically high yield areas, now support no significant timber growth because competing vegetation robs trees of vital space, sunlight, and nutrients. Phenoxy herbicides applied here literally shift the advantage to the desired trees, increasing productive land for forest purposes and allowing re-establishment of mature forests.

Traditional forestry methods emphasize hand cutting for thinning and culling of forest stands (Newton 1973), a procedure proven satisfactory as well as economically sound. But nationwide manual attendance of such large forest areas is economically and physically unfeasible.

Kimmins and Fraker (1973) have cited 280 references to herbicide uses in forestry, and Johnson and Lawrence (1977) have listed more than 80 references in a more recent review. In California, herbicides are extensively used to control weeds in Douglas Fir forests, Ponderosa Pine mixed conifer forests, and Red Fir forests.

Personnel used herbicides in two ways in forests: site preparation for stand establishment and conifer release.

The site preparation method involves treatment of land before planting desired conifer seedlings. Fires, logging, and other natural or intentional situations often leave a forest area overgrown with herbaceous and

woody "undesired" growth which must be controlled for successful seedling establishment. This area is first prepared by clearing the site and crushing or burning the waste. A broad spectrum herbicide is applied during the next spring to prevent new growth. After the conifer seedlings are planted, foresters then employ a selective herbicide for continued suppression of rapidly growing plants. This application takes place within one to two years after the desired plantings during the late spring season, a peak time for rapid growth and resprouting of broadleaf competitors.

Some areas may be treated with herbicides prior to the initial burning and planting. With either of these treatments, conifer seedlings establish themselves within six to twelve months. Occasionally land management personnel may find it necessary to re-treat areas because undesired growth has returned (Bentley 1967), (Schubert and Adams 1971), (Gratkowski 1975).

In California, low volatility ester formations of 2,4-D and 2,4,5-T, alone or together, are used for brushfield control, while amitrole, atrazine, dalapon, dicamba, and simazine regulate herbaceous plant or grass growth in site preparation (California Department of Foods and Agriculture 1978).

The conifer release method of herbicide control protects conifer seedlings from competing vegetation which robs young conifers of sunlight, nutrients and moisture.

To accomplish this, aerial application of phenoxy herbicides takes place in early spring or late summer when conifer buds have not broken or hardened, avoiding any damage or injury to new growth (California Department of Foods and Agriculture 1978).

Repeated treatment may be necessary depending on the species of brush or hardwood involved. Because conifers are relatively tolerant of 2,4,5-T, it is the herbicide of choice for broadleaf control. When the control of certain grasses and herbaceous growth is necessary for conifer release, the herbicides atrazine and simazine are used. Conifers are tolerant of these compounds unless their root systems come in contact with them.

In addition to suppressing new growth, conifer release management may also involve control of mature hardwoods, such as oak. On an overstocked plantation or forest, conifers may be thinned out through direct injection of the herbicide into the base of a tree or direct applica-

interferons suggest that it has a tantalizing degree of activity against a broad spectrum of viral diseases and tumours. But activity is not enough, or consistent enough, in most diseases to give a final verdict without more trials. Also, as genetically-manipulated bacteria start to yield sufficient amounts of the ten or so subtypes of alpha-interferon, the permutations of subtypes and diseases becomes huge.

Meanwhile, large-scale trials of beta-interferon (from fibroblasts) lag slightly behind. The largest has yet to start. Financed and organized by the National Institutes of Health (NIH), the trial will use 90,000 million units of beta-interferon, enough for several hundred patients. The interferon is being supplied by Flow Laboratories Inc., which won the $2 million contract a year ago. First deliveries were due a few weeks ago, but NIH appear to be in no hurry. This is lucky for Flow Laboratories, whose own production has not been going smoothly. Fortunately, they have a subcontract with the West Germany company of Dr Rentschler Arzneimittel GmbH which has continued to amass beta-interferon made by its own, less advanced, techniques.

The next big contract, also for NIH, will be for gamma-interferon (from cells of the immune system). Far less is known, at least publicly, about this type of interferon, but Biogen and Genentech are rumoured to be on the verge of cloning the relevant genes.

Other commercial interests centre on monoclonal antibodies against the interferons. Several new monoclonals against either alpha or beta-interferons were announced in Rotterdam, but only the original monoclonal (see *Nature* 285, 446; 1980) is as yet commercially available. The sellers are the British company Celltech Limited, so far its only product. It will be surprising if the Celltech catalogue does not double soon. **Peter Newmark**

Dioxin hazards

Secrecy at Coalite

Secrecy about the medical consequences to workers exposed to dioxin continues at the British company Coalite and Chemical Products Limited. Documents now to hand show that Coalite will not agree to the further medical investigation of workpeople if the physicians concerned insist that the results are eventually published.

Coalite's shyness is not unprecedented. Last year, the company withheld information on an epidemiological survey of workers exposed to dioxin (2,3,7,8-tetrachlorodibenzodioxin) at its Bolsover (Derbyshire) plant in 1968–71 (see *Nature*, 6 March 1980). The exposure followed an explosion in a vessel used for the manufacture of 2,4,5-trichlorophenol and the workers affected by dioxin developed the skin disease chloracne.

The fresh trouble which has arisen at Coalite results from the need for more detailed investigations of individual workers to make up for the deficiencies of the epidemiological survey of 1977–78. That involved only 41 of the 90 workers known to have been exposed, but revealed (almost a decade after the event) some abnormalities of blood chemistry and immune function — but none of the expected chromosomal abnormalities in circulating lymphocytes.

The news that Coalite was unwilling to disclose information about this survey served to alert the statutory Employment Medical Advisory Service of the Health and Safety Executive to the existence of such data, which was disclosed on a confidential basis after three weeks. The service has also persuaded Coalite that its medical adviser, Dr George May, should publish some of the results.

The employment service has in the meantime been uncomplimentary about the survey which, it says, is deficient in its failure to follow up past employees and in the inadequate matching of the control populations. The survey covered 41 workers known to have been exposed to dioxin, 54 who might have been exposed and 31 intended as a control group but drawn for convenience from senior office, laboratory and works staff, most of whom were being investigated for blood lipids at the time.

The 1977–78 survey showed blood-lipid disorders, with elevated concentrations of serum cholesterol and triglycerides, and depressed levels of high-density lipoprotein. The enzyme γ-glutamyl transpeptidase, diagnostic of liver function, was abnormally high in the exposed group. On the other hand, levels of two immunoglobulins (IgD and IgM) were depressed in the exposed group, suggesting impairment of immune as well as liver function.

The significance of these findings is far from clear, with the consensus among physicians in the field that further investigations are needed. They argue that the persistence of the phenomena uncovered by the earlier study should be confirmed — but also that further surveys should be more carefully controlled.

Dr George May, Coalite's company doctor, confirms that those workers included in the original survey have since been offered a second medical examination, but that "not everybody availed themselves of the opportunity". In the event, 29 of the original sample of 41 workers were re-examined, but measurements of immunoglobulin were not made.

There are no plans, however, for further investigations of the Coalite workers, according to Dr George Sorrie, deputy director of the Employment Medical Advisory Service, who says that his service has not been presented with any "realistic and useful" proposals for a long-term assessment of the health of the Coalite workers. The reassessment of the state of health of dioxin-exposed workers at Coalite is thus far from complete. One clinician describes the re-examination of the 29 workers as a "totally useless piece of work" which cannot be expected to yield any meaningful results.

Coalite's managing director, Mr Charles Needham, has been approached by several clinicians prepared to carry out further investigations. Coalite's reluctance to agree to publication of the results from any future comprehensive medical screen of its workers has, however, forced at least one clinician to abandon his proposal.

Mr Needham, described by his secretary as solely responsible for press relations, has not been available for comment. One consequence of criticisms of the 1977-78 survey, and of Coalite's continued insistence on secrecy, is that the financial sponsor of the survey (an independent non-governmental source) will be unwilling to provide further support.

As the law stands, Coalite may have the last word. Hitherto, the company has been able to exploit an ambiguity in the 1974 Health and Safety at Work Act when deciding whether or not to release medical information on its workforce (see *Nature* 6 March 1980, p.2). The routine powers of the Health and Safety Executive to demand medical records of workers likely to have been affected by a product lapse when manufacture stops. Although Section 27 of the act allows the executive to disclose whatever information it requires (see *Nature* 1 May 1980, p.4), epidemiologists at the executive consider that a test case is required to clarify the law. **Alastair Hay**

Dioxin a sarcoma risk

Reassessing clinical data is not the only reason for monitoring the health of workers exposed to dioxin. Recent letters in *The Lancet* (P. A. Honchor and W. E. Halperin, I, 268, 31 January 1980; and R. R. Cook, I, 618, 14 March 1980) highlight another reason.

The authors of the letters point out that in four industry-sponsored mortality studies of dioxin-exposed workers in the United States, 105 deaths were recorded. In four of these cases, death was caused by soft tissue sarcomas. These are rare forms of cancer and for most the aetiologies are unknown.

Soft tissue sarcomas have also been identified in another cohort of workers considered to have been exposed to dioxin. According to two Swedish epidemiologists, Dr Lennart Hardell and Anita Sandstrom of the Centre of Oncology at the University of Umea, exposure to the dioxin contaminated herbicide 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) or chlorinated phenols 6 to 20 years previously could be responsible for the sixfold greater incidence of soft tissue sarcomas recorded in a survey of Swedish forestry workers (*British Journal of Cancer* 39, 711; 1979). **Alastair Hay**

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U.S. DEPARTMENT OF AGRICULTURE • SCIENCE AND EDUCATION ADMINISTRATION • NORTHEASTERN REGION

WORKERS' EXPOSURE TO 2,4-D STUDIED

ATLANTA, Ga., April 2--How much 2,4-D enters the body of an average 175-pound worker who applies this herbicide 30 days a year for 30 years? The estimate is less than 1 gram.

The conclusion is based on a study that measured the amount of 2,4-D (2,4-dichlorophenoxy acetic acid) in the urine of workers involved in ground or aerial applications, according to Ralph G. Nash, a U.S. Department of Agriculture chemist who is a specialist in analyzing pesticide residues.

Evidence suggests that the amount of 2,4-D excreted is equal to the amount absorbed, Nash told an audience at the American Chemical Society's National Meeting here today. He cited studies by J. B. Kohli and colleagues (reported in Xenobiotica, 1974) and M. W. Sauerhoff (reported in Toxicology 1980) which indicate that this herbicide is not metabolized in the human body, but rather passes through unchanged after a large dose is ingested. Studies on a similar herbicide--2,4,5-T--substantiate this finding, he added.

"The present study gives us an estimate of exposure for a segment of the population in closest contact with 2,4-D," says Nash of USDA's Science and Education Administration (SEA). "And our figures can generally be interpreted as the upper limit of exposure for more toxic pesticides. Because users of 2,4-D consider the herbicide to have a low order of toxicity, they are less likely to wear protective clothing than when applying more toxic pesticides," he noted. Some pesticides, however, may be more rapidly absorbed, and more toxic, he cautioned.

The study was conducted in spring 1980 among two groups of workers who applied 2,4-D to wheat fields in two areas of the country. Ground applicators in North Dakota applied the herbicide only once and provided daily urine samples

- MORE -

for six days afterwards--enough time for complete excretion. A different sampling procedure was used with the second group to optimize the validity of the findings. Aerial applicators in Washington State applied the herbicide intermittently for 2 weeks and provided urine samples every other day for 12 days. Both groups used routine dress and procedures when applying 2,4-D. Absorption was presumably through the skin, inhalation, and possibly some ingestion.

The North Dakota samples were analyzed in Nash's laboratory at SEA's Agricultural Research Center in Beltsville, Md., while the Washington State samples were analyzed at SEA's Agricultural Research Laboratory in Yakima, Wash. Working with Nash were pesticide specialists P.C. Kearney and S.N. Fertig from Beltsville; and J.C. Maitlen and C.R. Sell, from the Yakima Laboratory.

Results showed that absorption is directly related to the type of job, the amount of herbicide applied and the length of time it is handled. Those who mixed and loaded (and, in North Dakota, applied) 2,4-D had the highest total absorption--0.02 milligrams per kilogram of body weight (or 1.6 milligrams for a 175-pound person). The least exposed group--pilots--absorbed less than one-third that amount.

The information from this study and other similar studies will be evaluated by the U.S. Department of Agriculture, other Federal agencies, and the Environmental Protection Agency (EPA) which, last spring, requested additional safety data from 2,4-D manufacturers. Absorption data will be compared with toxicity data--how much is harmful or safe--when the chemical is reevaluated.

2,4-D, which is the active ingredient in many products from six major companies and several smaller manufacturers, was registered about 1946 and has been used widely and safely for more than 35 years. It is used extensively to kill

Science and Education Administration
Agricultural Research Center
Beltsville, Maryland 20705
April 1981 P-16

Contact:
Judy McBride
(301) 344-3541

weeds in crops, rangelands, and noncropland areas. Some groups have expressed concern about the reported finding in Canada of minute quantities of dioxins in certain formulations of 2,4-D. It should be noted, however, that while 2,4-D has been reported to contain small amounts of relatively nontoxic dioxin compounds the highly toxic 2,3,7,8-TCDD has never been found in this herbicide.

The study with aerial applicators will be continued during 1981 to further assess methods of reducing the level of exposure reported in these studies.

# # # #

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THE DOW CHEMICAL COMPANY QUALITY ASSURANCE OFFICE
QACACI SPECIFICATION CONFIRMATION COPY

DATE PRINTED: 2-JUN-81 PAGE: 1
PRODUCT: 28749 QAC: 290 REVIEWED: 29 MAY 81 REPLACES: 28749 16 MAR 81

NAME: ESTERON (R) 245 HERBICIDE

DESC: AMBER, OILY, EMULSIFIABLE LIQUID.
APPL GOVT/IND STDS: EPA REG. NO. 464-205
: EPA EST. NO. 464-MI-1
: FED SPEC O-H-210C, TYPE II, CL2
MSD: 303

PROD'N PTS U.S. :MM DEPT: 31

	PROD'N	DATA	TERM'L	RAW MAT'L	SALES	TEST METHOD
DATES :	:	:	:	:	:	
LATEST:	29 MAY 81	:	:	:	2 SEP 80	
PRIOR :	2 SEP 80	:	:	:	9 JAN 76	

------TEST ITEMS------

:2,4,5-TRICHLOROPHENOXY ACETIC (2,4,5-T)					
:ACID, PROPYLENE GLYCOL BUTYL ETHER ESTERS,					
:MIN. UNIT:%					
:69.2	:---	:---	:---	:P	:28749B
:2,4,5-T ACID EQUIV., MIN. UNIT:%					
:45.0	:---	:---	:---	:P	:28749B
:2,4,5-T ACID EQUIV. UNIT:LBS/GAL					
:3.97-4.1	:---	:---	:---	:4	:28749B
:INERT INGREDIENTS UNIT:%					
:30.8	:---	:---	:---	:P	:28749B
:2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN UNIT:PPM					
:<0.1 BASED ON	:---	:---	:---	:P	:28749B
:2,4,5-T ACID					
:2,4,5-T ACID EQUIV. UNIT:LBS/GAL					
:3.97-4.1	:---	:---	:---	:4	:---
:EMULSION CREAM RATE @ 1 HR.					
:	:---	:---	:---	:*	:AG 15B-2
: 100 PPM HARD WATER UNIT:ML					
:0.6 MAX.	:---	:---	:---	:*	:---
: 500 PPM HARD WATER UNIT:ML					
:0.6	:---	:---	:---	:*	:---

------COMPOSITION (NOMINAL)------

:M					
:	:---	:---	:---	:*	:---
:2,4,5-T, PROPYLENE GLYCOL BUTYL ETHER (PG					
:BE) ESTERS UNIT:%					
:69.0	:---	:---	:---	:*	:027613-72-5
:2,3,6-TRICHLOROPHENOXYACETIC ACID, PG BE					
:ESTERS UNIT:%					
:1.4	:---	:---	:---	:*	:REQUESTED
:2,4-DICHLOROPHENOXYACETIC ACID, PG BE ESTERS UNIT:%					
:0.7	:---	:---	:---	:*	:001320-18-9
:2-METHOXY 4,5-DICHLOROPHENOXYACETIC ACID,					

(R) INDICATES A TRADEMARK OF THE DOW CHEMICAL COMPANY

*** * * * DOW CONFIDENTIAL * * * *** 28749

THE DOW CHEMICAL COMPANY QUALITY ASSURANCE OFFICE

QACACI SPECIFICATION CONFIRMATION COPY

PRODUCT: 28749 (CONTINUED) PAGE: 2

NAME: ESTERON (R) 245 HERBICIDE

PROD'N	DATA	TERM'L	RAW MAT'L	SALES	TEST METHOD
------COMPOSITION (NOMINAL)------ (CONTINUED)					
:PG BE ESTERS UNIT:%					
:1.0	:---	:---	:---	:-->	:REQUESTED
:4-METHOXY 2,5-DICHLOROPHENOXYACETIC ACID,					
:PG BE ESTERS UNIT:%					
:1.0	:---	:---	:---	:-->	:REQUESTED
:5-METHOXY 2,4-DICHLOROPHENOXYACETIC ACID,					
:PG BE ESTERS UNIT:%					
:1.0	:---	:---	:---	:-->	:REQUESTED
:POLYGLYCOL 59-13 (TRIDECYLALCOHOL + E.O.) UNIT:%					
:0.9	:---	:---	:---	:-->	:024938-91-8
:EMCOL (SPONTO) AC 31-2 UNIT:%					
:2.6	:---	:---	:---	:-->	:TNO
:KEROSENE UNIT:%					
:27.0	:---	:---	:---	:-->	:008008-20-6
------MISCELLANEOUS------					
:SPECIFIC GRAVITY 68/68 F					
:1.075 APPROX.	:---	:---	:---	:---	:---
:BOILING POINT (IBP) UNIT:C					
:---	:---	:---	:---	:-->	:---
:VAPOR PRESSURE @ 25 C UNIT:MM/HG					
:---	:CC	:---	:---	:-->	:---
:FLASH POINT UNIT:F					
:---	:180	:---	:---	:-->	:TOC:ASTM D-1310
------RAW MATERIALS------					
:2,4,5-T ACID BUTOXY PROPYL ESTER					
:---	:---	:---	:87621-R2	:-->	:027613-72-5
:POLYGLYCOL 59-13					
:---	:---	:---	:81722-R2	:-->	:024938-91-8
:SPONTO AC 31-2					
:---	:---	:---	:80943-R1	:-->	:TNO
:KEROSENE					
:---	:---	:---	:42783-R2	:---	:008008-20-6

PI: 1754381 BULK SAMPLE
PI: 1092519 1 GAL CAN
PI: 1103514 5 GAL PAIL
PI: 1101518 30 GAL DRUM
PI: 1107515 55 GAL DRUM
PI: 2135226 5 GAL PAIL (SPANISH LABEL)
PI: 1093517 55 GAL DRUM (SPANISH LABEL)

PROD'N NOTE

(1) REVISION 29 MAY 81 TO CHANGE TEST LIMIT FOR EMULSION CREAM RATE. NO CHANGE NECESSARY IN SALES SPECIFICATION AT THIS TIME.

(2) NO FURTHER PRODUCTION EXPECTED OF THIS PRODUCT. QUANTITIES ON 8429

(R) INDICATES A TRADEMARK OF THE DOW CHEMICAL COMPANY

DOW 1680096

DOW 1680096

THE DOW CHEMICAL COMPANY QUALITY ASSURANCE OFFICE
QACACI SPECIFICATION CONFIRMATION COPY

PRODUCT: 28749 (CONTINUED) PAGE: 3
NAME: ESTERON (R) 245 HERBICIDE
PROD'N NOTE (CONTINUED)

HAND TO BE SOLD UNTIL SUPPLY DEPLETION.
(3) FORMULATION IS M-3506.

APPROVERS: W.L. GOLD APPROVAL OF CHANGES INDICATED ABOVE:
J.M. FRASER

APPROVERS OF INDIVIDUAL SPECS:
PRODN: W.L. GOLD QAC 28 MAY 81
PRODN: W.R. KRACHT METHODS 22 APR 80
PRODN: G.R. VEURINK PROD. 22 APR 81
PRODN: L. KLOCKE PROD. 22 APR 81
PRODN: J.R. GLEDHILL ACPD 23 APR 81
PRODN: J.S. WOODS QAC/QAA 28 MAY 81
PRODN: E.J. KING R&D 18 MAY 81
PRODN: J.W. DRENCKPOHL AG QA 26 MAY 81
PRODN: C.D. WOODS PSC 22 MAY 81
PRODN: R.W. MORGAN AG REG. 22 MAY 81
PRODN: J.M. FRASER QAO 29 MAY 81
SALES: W.L. GOLD QAC 29 AUG 80
SALES: C.D. WOODS PSC 18 JUN 80
SALES: D.W. FREDERICK PSM 2 MAY 80
SALES: J.W. DRENCKPOHL AG QA 26 JUN 80
SALES: J.S. WOODS QAC/QAA 29 AUG 80
SALES: J.M. FRASER QA DEPT. 2 SEP 80

APPROVALS	:DIV-DEPT	: DATE	APPROVALS	:DIV-DEPT	: DATE

(R) INDICATES A TRADEMARK OF THE DOW CHEMICAL COMPANY
* * * DOW CONFIDENTIAL * * * LAST PAGE

8430

0007488

1588097

MANUFACTURING SPECIFICATION

DISTRIBUTION FOR APPROVAL Please sign on Blue Page 3

~~R. L. GANTZ~~	9008
~~J. DICENCKPOHL~~	9008
~~[illegible]~~	489
~~J. R. Stobbill~~	474
~~R. [illegible]~~	574

Please review the attached specification and send to the next person listed.

1. Review specification as listed.
2. Note approval with signature, location and date.
3. If not approved, note necessary changes and initial.

When distribution has been completed:

Return to: John Woodell ACP+ES QA
Ag. Chem. Prod'n.
834 Building

October 16, 1981

— NEW —

ESTERON 245 ~~T~~E HERBICIDE
245CE

+ advance to "commercial" status is in circulation; JWD/PLS

Dioxin spec removed from Sales & Pr mgt

12-17-81

John

When the product code has been available I will change the spec number from ML-mm-SC-66 to the correct spec number. I added calc of dioxin to the method. Also let me know about the name. — Bill —

NEED NEW METHOD —

MNO 12332

DOW 2133685

8432

0000427

MEDICAL DOW INFORMATION

MATERIAL: ESTERON™ 245 BE HERBICIDE — MATERIAL NO: M-4498
SYNONYMS: Dow Rangeland Brush Killer T, M-4498 — SOLUBILITY:
COMPOSITION: see below — PHYSICAL STATE: amber liquid

TOXICOLOGY — ANTICIPATED HUMAN RESPONSE — BASED ON: 1. ANIMAL DATA ☐ 2. HUMAN DATA ☐ 3. STRUC 4. LITERA

EYES: Slight transient irritation and/or corneal injury.

SKIN: Prolonged contact: slight irritation.
Repeated contact: moderate irritation, drying, even a burn.
Not likely to be absorbed in toxic amounts.

ORAL: Moderate to low single dose toxicity.

RESP: Dow guide for naphtha 350 mg/m^3 vapor, 10 mg/m^3 aerosol.
COMPOSITION: 59.1% 2,4,5-T, Butoxyethyl ester
32.05% aromatic or aromatic/aliphatic blended oil (petroleum naphth diesel
5.85% emulsifiers GAFAC RE-610 and GAFAC PE-510

BY:	DATE:	REFERENCE:
Pat Keeler	12-30-81	based on ingredients and similar products

SUGGESTED — TREATMENT AND HUMAN EXPERIENCE

EYES: May cause irritation. Injury is unlikely. Stain for evidence of corneal injury.

SKIN: May cause irritation. Not likely to be absorbed in acutely toxic amounts.
Effects may be cumulative.

RESP: Anesthetic or narcotic effect may occur.

ORAL: May cause reaction similar to petroleum or petroleum-like solvent. Danger of chem pneumonia must be weighed against toxicity when considering emptying the stomach. If lavage is performed suggest endotracheal and/or esophagoscopic control.

SYSTEMIC: Anesthetic or narcotic effect may occur. May increase myocardial irritabilit Avoid epinephrine or similar acting drugs if at all possible. No specific antidot Treatment based on the sound judgment of physician and the individual reactions of the patient.

BY:	DATE:	REFERENCE:
H.C. Scharnweber, MD	12-30-81	

SUGGESTED FIRST AID PROCEDURES

EYES: Irrigation immediately with water for 5 minutes is good safety practice.

SKIN: Contact will probably cause no more than irritation. Wash off in flowing water or shower. Wash clothing before reuse.

INHALATION: Remove to fresh air if effects occur. If respiration stops give mouth-to-mouth resuscitation.

INGESTION: Do not induce vomiting. Call a physician and/or transport to emergency facility.

BY:	DATE:	REFERENCE:
H.C. Scharnweber, MD	12-30-81	

FORM C-5670 PRINTED IN U.S.A. 8-7-77

MN078664

DOW 2120497

8434 0008370

MEDICAL DOW INFORMATION

MATERIAL: ESTERON 245 BRUSH AND WEED KILLER — MATERIAL NO: M-3506

SYNONYMS: M-3506 — SOLUBILITY: Emulsifiable in

COMPOSITION: SEE BACK * — PHYSICAL STATE: Liquid

TOXICOLOGY — ANTICIPATED HUMAN RESPONSE — BASED ON: 1. ANIMAL DATA ☐ 3. STRUC ? HUMAN DATA ☐ 4. LITER

EYES: Slight to moderate pain, slight transient conjunctival inflammation and iritis.

SKIN: Prolonged contact, intact skin, unconfined: slight erythema. Repeated skin contact slight to moderate erythema and edema. Skin absorption capacity not evaluated (Based on minimal tox study).

ORAL: Moderate to low acute oral lethality (LD50 rats approx. 1 g/kg body weight. (Based on minimal tox study).

RESP: One hour exposure of 20 rats to an aerosol of M-3506 resulted in no adverse effects.

MN0786644

BY:	DATE:	REFERENCE:
Pat Keeler	6-24-80 *Revised	

SUGGESTED — TREATMENT AND HUMAN EXPERIENCE

EYES: Stain for evidence of corneal abrasion or injury.

SKIN:

RESP:

ORAL: May cause reaction similar to petroleum or petroleum-like solvent. Product moderately toxic. Danger of chemical pneumonia must be weighed against toxicity. If lavage is performed suggest endotracheal and/or esophagoscopic control.

SYSTEMIC: Human effects not established. Probably could cause serious illness with spontaneous recovery. Based on minimal data.

DOW 2120498

BY:	DATE:	REFERENCE:
J M Lanham	10-30-78	

SUGGESTED FIRST AID PROCEDURES

EYES: Irrigate with flowing water immediately and continuously for fifteen minutes. Refer to medical personnel.

SKIN: Wash off in flowing water. Decontaminate clothing and accessories before reuse. Good personal hygiene.

INHALATION: Remove to fresh air if effects occur. Consult medical personnel.

0008371

INGESTION: Do not induce vomiting. Call a physician and/or transport to emergency facility.

8435

MATERIAL: ESTERON @ 245 CONCENTRATE BRUSH AND WEED KILLER
MATERIAL NO: M-3557
SYNONYMS: M-3557
SOLUBILITY: Emulsifies in H
COMPOSITION: An emulsifiable formulation 2, 4, 5 Trichlorobenzetic acid PGBE Ester
PHYSICAL STATE: Liquid

TOXICOLOGY — ANTICIPATED HUMAN RESPONSE — BASED ON: 1. ANIMAL DATA ☐ 2. HUMAN DATA ☐ 3. STRU 4. LITER

EYES: May be a mild irritant but should cause no more than slight transient corneal effects.

SKIN: May cause mild to moderate irritation on repeated contact. Not absorbed in toxic amounts.

ORAL: Moderate single does oral toxicity. LD50 (rat) in the range of 700 to 1000 mg/kg.

RESP: TLV: No guide for control established. Considered to be low in hazard by inha Solvent low in volatility.

MN078664

BY:	DATE:	REFERENCE:
Pat Keeler	7/4/77	

SUGGESTED — TREATMENT AND HUMAN EXPERIENCE

EYES: May cause mild irritation. May cause corneal injury or burn. Stain for eviden of corneal injury. If cornea is burned, instill antibiotic steroid preparation frequently. Consult ophthalmologist.

SKIN: May cause mild irritation. Wash clothing before reuse.

RESP: No tox data. Human effects not established.

ORAL: May cause reaction similar to petroleum or petroleum-like solvent. May cause chemical pneumonia if aspirated into lungs. Not likely to be absorbed in acutely toxic amounts. If lavage is performed, suggest endotracheal and/or esophagscopic control.

SYSTEMIC: Anesthetic or narcotic effect may occur. May cause kidney damage. May cause liver damage. No specific antidote. Treatment based on sound judgment of physician and individual reactions of the patient.

BY:	DATE:	REFERENCE:
W. A. Fishbeck	10-30-78	

SUGGESTED FIRST AID PROCEDURES

EYES: Irrigate with flowing water immediately and continuously for fifteen minutes. Refer to medical personnel.

SKIN: Contact will probably cause no more than irritation. Wash off in flowing water of shower.

INHALATION: Remove to fresh air if effects occur. Consult medical personnel.

DOW 2120496

INGESTION: Do not induce vomiting. Call a physician and/or transport to emergency facility.

8436 0008369

BY:	DATE:	REFERENCE:
W. A. Fishbeck	10-30-78	

234

REPORT OF THE COUNCIL ON SCIENTIFIC AFFAIRS

American Medical Association

Report: A
(I-81)

Subject: Health Effects of "Agent Orange" and Dioxine Contaminants

Presented by: William D. Dolan, M.D., Chairman

Referred to: Reference Committee E (John J. Gaughan, M.D., Chairman)

The American Medical Association's Council on Scientific Affairs, in response to a request from the Medical Student Section, has reviewed the medical evidence regarding the toxicity and long-term health effects of Agent Orange and its associated contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). This Executive Summary, which was prepared by the Council on Scientific Affairs Advisory Panel on Toxic Substances,* summarizes the findings in its Technical Report on the subject, which is available on request.

BACKGROUND

During the latter stages of the US' involvement in Vietnam, herbicidal mixtures of 2,4,-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), otherwise identified by the military as Agent Orange, were sprayed over certain areas of Vietnam for the express purpose of defoliating the jungle and destroying one of the enemy's means of concealment. Similar spray programs have been used in the US as a means of forestry management. For the past 30 years, mixtures of 2,4-D and 2,4,5-T have been used extensively by the homeowner and farmer for ridding lawns and agricultural acreage of unwanted broadleaf vegetation. Large numbers of persons have been exposed to varying amounts of 2,4,-D and/or 2,4,5-T, as well as the contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), in the normal course of employment.

Also over these years, there has been a number of industrial incidents wherein workers, as well as civilian populations, have been subjected to accidental exposure to these compounds. There are now

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* John R. Beljan, MD; Nelson S. Irey, MD; Wendell W. Kilgore, PhD; Kazuo Kimura, MD, PhD; Raymond R. Suskind, MD; Jaroslav J. Vostal, MD, PhD; R.H. Wheater, MS, Secretary

pending a number of litigious actions and government regulatory responses that are based upon alleged adverse health effects from such exposures.

The most serious of these allegations by Vietnam veterans and persons who were involved in accidental industrial exposures assert that Agent Orange, or compounds of a like nature, may have caused malignant tumors, sterility, spontaneous abortions, birth defects, disfiguring skin diseases and other illnesses. In spite of the voluminous data on the biological effects of the phenoxy-type pesticides and the associated chlorinated dioxins, there is still very little substantive evidence for the many claims that have been made against these compounds. Data from experimental animals do indicate that TCDD is a toxic material; however, while suggestive, the animal data are not necessarily applicable to man. Still, a number of those exposures to TCDD of industrial and general populations that have occurred have been sufficiently well documented to offer some insight into the effect of TCDD on man.

Agent Orange, or Herbicide Orange, was a label given by the US military forces to a 50:50 mixture of the n-butyl esters of 2,4-D and 2,4,5-T together with a minor amount (1%) of the free acid of 2,4,5-T and varying amounts of the contaminant TCDD. Agents Green, Pink and Purple also were used as defoliants by the military forces from 1962 thru 1964, a time when very few American troops were committed to the field. Another formulation, Herbicide Orange II, was similar to Agent Orange except that the isooctyl ester of 2,4,5-T was substituted for the n-butyl ester of 2,4,5-T. In addition to Agent Orange, other spray defoliants used in Vietnam included Herbicide White, whose active ingredient was picloram (or the triisopropanolamine salt of 4-amino-3,5,6-trichloropicolinic acid). This substance is very persistent in the environment and highly carcinogenic in rats and mice. Lesser amounts of Herbicide Blue, which contained sodium cacodylate* (26%) and cacodylic acid (5%), were used. Though the long-term effects in humans of either or both of these compounds is uncertain, picloram and cacodylic acid should be considered along with the above agents that were encountered in Vietnam.

TCDD may form as a by-product of the synthesis of 2,4,5-trichlorophenol (TCP), a precursor of 2,4,5-T, when 1,2,4,5-tetrachlorobenzene is subjected to alkaline hydrolysis at elevated temperature and pressure. If the reaction temperature is allowed to go above 180° C, the sodium-2-hydroethoxide (formed from the ethylene glycol solvent and caustic soda) decomposes exothermically and promotes the dimerization of sodium trichlorophenate to TCDD. The presence of TCDD as a contaminant of 2,4,5-trichlorophenol was discovered in 1957, when workmen involved in the manufacture of TCP developed chloracne.

* Sodium cacodylate is the sodium salt of cacodylic acid (hydroxydimethylarsine oxide)

About 20 years ago, commercially available 2,4,5-T contained anywhere from 1 to 70 ppm of TCDD. When the industry became aware of the contaminant's existence and toxicity, production operations were monitored and altered to reduce the level. Current manufacturing operations are able to control the amount of TCDD in commercial 2,4,5-T formulations to less than 0.01 ppm (with occasional batches as high as 0.05 ppm), a level believed to be non-hazardous to humans and other organisms. Data relating to an acceptable maximum level are presently under regulatory review by FIFRA (Federal Insecticide, Fungicide and Rodenticide Act); the recommended maximum concentration is now placed at 0.1 ppm.

Commercial formulations of 2,4,5-T and 2,4-D were used safely in agriculture for over 30 years with no recognizable evidence of carcinogenicity or birth defects in humans. Those adverse effects that did occur from massive doses of either pure 2,4-D or pure 2,4,5-T were manifested soon after the exposure, and the victims recovered with no signs of long-term damage. When the first symptoms were to present months or years after the last exposure to these compounds, it was evident another causal agent had to be responsible. That agent was later suspected to be TCDD. Though closely related chemically to 2,4,5-T, 2,4-D is not generally contaminated with TCDD.

BIOLOGICAL EFFECTS

Two of the more pronounced biological effects of some of the chlorinated dioxins are their tendency to cause chloracne (especially, in the rabbit, nude mouse, monkey and man) and the accumulation of fluid (ascites) in the pericardium and peritoneal cavity of chicks.

Chloracne in man is typified by comedones in a malar distribution; the pre- and postauricular portions are often accompanied by hirsutism and sometimes by melanosis and a secondary inflammation. The disease was first described in 1899; its cause was discovered in 1918 to be due to contact with certain chlorinated hydrocarbons. Chloracne has now become one of the more common forms of occupational dermatitis. Other acute toxic reactions to dioxin include liver and renal damage, porphyria cutanea tarda, hyperpigmentation, hirsutism, polyneuropathies (eg, sensory impairments and weakness in lower extremities) and neurasthenic or depressive syndromes. Thus far, long-term effects, except for persistent chloracne, have not been seen.

Chloracne is not caused by 2,4,5-T and 2,4-D per se; if the condition occurs upon exposure to either or both of these compounds, it is most likely that the contaminant TCDD is responsible. Chloracne usually appears within 2 to 3 weeks after the first exposure. Mild chloracne clears up within several months after cessation of exposure; severe chloracne, on the other hand, has been known to persist for as long as 30 years following the last exposure. Persons most responsive are those who are prone to develop acne vulgaris. If one's exposure to TCDD is severe enough, cysts form and, on occasion, inflammation and scarring will occur. If there is no medical history of chloracne, then the likelihood of a significant exposure to, or adverse health effects

from, TCDD is remote. Hence, chloracne is the clinical marker of TCDD exposure.

Chronic exposures to TCDD lead to degeneration of the liver and thymus in experimental animals: one sensitive index of exposure is atrophy of the thymus. Porphyria, altered levels in serum enzymes and weight loss are also observed. Major organs to be affected are the liver, blood forming organs and the reticuloendothelial system. Progressive weight loss, the first clinical sign of toxicity in the monkey, may be accompanied by alopecia, facial edema and a dry, scaly dermatitis over the rest of the body.

The metabolism of TCDD in man is unknown, and for the present there is only limited information available on the metabolic pathways and metabolites that may occur in other mammals. TCDD is distributed equally among the fat and liver of mammals, to a lesser extent in the kidneys, and is eliminated via the feces. Samples of fat from beef cattle and samples of milk from cows that had grazed on 2,4,5-T-treated pasture or rangeland, in addition to human milk from an area where 2,4,5-T herbicides were used repeatedly over a period of 20 years, had small to undetectable (not more than 10 ppt) amounts of TCDD.

No clearly defined mutagenic effect has been observed in vitro with TCDD. TCDD does induce genetic changes by the Ames test with S typhimurium and E coli but not with repair-defective strains; there is no evidence (from dominant lethal and cytogenetic evaluations in rodents) that such changes occur in whole animals.

Of perhaps more relevance to man are the in vitro studies on mammalian cells--ie, HeLa; Balb-3T3, normal mouse fibroblasts; SV101, virus (SV40)-transformed 3T3 mouse fibroblasts; human foreskin fibroblasts; and normal human lymphocytes. No significant growth inhibition in the cell cultures nor discernible ultrastructural changes have been observed by electron microscopy.

The teratogenicity and fetotoxicity of TCDD were discovered in 1969, in the course of a study on the biological activity of 2,4,5-T. The sample being used was later found to be contaminated with TCDD. The incidence of cleft palate was greater in two particular mouse strains (C57BL/6 and AKR), while the C57BL/6 mouse and the rat developed a higher incidence of cystic kidney. All doses given the rat led to gastrointestinal hemorrhage in the fetus. The increased ratio of fetal liver to body weight in the mouse suggested that TCDD was fetotoxic in this particular species.

A majority of studies using high doses of 2,4,5-T with 0.1 ppm of TCDD or less showed cleft palate in mice, but no other species, and embryotoxicity in the mouse, rat, hamster, sheep, monkey and rabbit. There is no scientific evidence that 2,4-D, 2,4,5-T or TCDD has caused reproductive difficulties or hazards in the human. No conclusive evidence is yet available that phenoxy herbicides or TCDD are mutagenic or teratogenic in man.

8411

TCDD can induce cancer or serve as a cancer promoter in some strains of rats and mice. In contrast to some other chemical carcinogens, the carcinogenicity is always accompanied by considerable systemic toxicity.

From an environmental view, TCDD breaks down rapidly on leaves of plants, in water and on the surface of soil, especially through the action of sunlight. In soil it generally has a half-life of about 230 days; some soil microorganisms can degrade it, especially if other chlorinated hydrocarbons are present.

EXPERIENCE IN MAN

One of the most extensive human experiences with the adverse effects of TCDD in man involves the residents of Seveso, Italy. In July of 1976, TCDD was accidentally released from the ICMESA* trichlorophenol synthesis plant when a safety disk in a steam-heated reactor vessel ruptured. The plume of reactor contents, including TCDD, rose 160 feet above the factory and fell in a cone-shaped pattern about a mile long and a half-mile wide. This is the largest single population to have been exposed to the compound. Over 37,000 persons were potentially exposed to varying doses.

Two years after the incident occurred, the acute and mid-term health effects were assessed; the mild chloracne, which occurred mainly in a small group of children, healed quickly. Subclinical peripheral nerve impairment was reported; there was also some liver involvement, but without apparent functional disorder. Neither immunoresponse nor susceptibility to infectious diseases was altered.

The most recent progress report on the long-term epidemiologic survey of the residents of the Seveso area emphasizes the preliminary nature of their findings and reiterates the conclusions of prior investigators. Except for the skin, no organs or body functions were impaired. No derangement of gestation, no fetal lethality and loss, no gross malformations, no growth retardation at term and no cytogenetic abnormalities have yet occurred.

The first of several accidental releases of TCDD and other dioxins, attending the manufacture of 2,4,5-trichlorophenol (TCP) or 2,4,5-T occurred in 1949 in the US. At least 11 other industrial accidents or exposure incidents have occurred since then, both here and abroad. To date, an estimated 579 workers are known to have been exposed, including 156 employees in the ICMESA plant at Seveso.

CURRENT STUDIES

There are now a number of studies underway by agencies of the US government and industry, which may resolve questions on the kinds and

* Industrie Chimiche Meda Societa Anonima

extent of human damage from exposure to low levels of TCDD:

Thru its Department of Environmental and Drug-Induced Pathology, the Armed Forces Institute of Pathology (AFIP) is examining biopsy and autopsy tissue of all Vietnam veterans. To date, only 152 cases have been assessed: the dominant diseases are epidermal inclusion cysts and chronic, non-specific dermatitis. If any malignancies were to have been induced by TCDD, they should be appearing by now, yet there have been no unusual morphological features nor clustering of tumors by diagnosis or site as to implicate Agent Orange.

A soft-tissue sarcoma study also has been proposed that will be conducted jointly by the Armed Forces Institute of Pathology and the National Cancer Institute.

The Air Force, through Project Ranch Hand, will administer and examine the 1,200 personnel who were involved in the actual handling and spraying of Agent Orange. They, and the control population of 20,000, are to be followed over the next 20 years.

The University of California, Los Angeles, was awarded a contract by the Veterans Administration for the design of an epidemiologic study of Vietnam veterans.

Approximately 45,000 Vietnam veterans who expressed concern about the hazards of Agent Orange have been examined by the VA; data on 25,000 of these men have been placed in a special Agent Orange Registry, which may serve later to identify them and to provide medical information as well as indications of health trends over the long term.

The Chloracne Task Force was established to sift out those cases of dermatitis that either resemble or are truly chloracne. Cases of the former type will be re-examined by dermatologists who have an expert knowledge of the disease. Thus far, there are only 700 cases of "skin conditions" out of the total of 3,500 filed claims for damage from Agent Orange.

RECOMMENDATIONS

The Council on Scientific Affairs recommends that:

(1) The above studies on exposed, or allegedly exposed, persons continue to be supported and, if feasible, enlarged to include the cooperative engagement of all internationally known exposure data, as recommended by the International Agency for Research on Cancer (IARC).

(2) All physicians be alerted through AMA publications to the classical signs of chloracne and the possible signs and adverse effects of TCDD exposure. They should be encouraged to enlist in the present efforts to identify and treat those persons who have had serious exposures to TCDD, and to cooperate in the collection of vital information that is needed for the ongoing human epidemiologic studies.

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be assessed on lots found to be deficient in quality or quantity. The money collected would be paid to the pesticide users, when known.

Vincent Giglio, director of the department's Division of Inspection, March 3 distributed a letter to pesticide control officials from other states seeking comment on the proposal and inquiring about practices followed by other states.

For further information, contact Giglio at the Florida Department of Agriculture and Consumer Services, Room 232, Mayo Building, Tallahassee, Fla. 32301.

Health Hazards

REDUCED SPERM COUNTS FOUND BY NIOSH IN PRODUCTION WORKERS AT KENTUCKY PLANT

Workers in a Kentucky plant who were exposed to toluene diamine (TDA) and dinitrotoluene (DNT) during the production of TDA were found by the National Institute for Occupational Safety and Health to have reduced sperm counts.

The findings were made after the discovery of abnormal sperm morphology in one worker in the TDA unit at Olin Chemical Corp., Brandenburg, Ky., according to the institute.

Some 30 workers participated in the study, including nine workers currently exposed to both substances, 12 who were exposed in the past, and nine with no history of exposure, the institute reported.

The currently exposed workers had "significantly reduced sperm counts" compared with the non-exposed group, the institute said.

Wives of the exposed workers indicated that spontaneous abortions had become more frequent after their husbands were first exposed, the institute commented. It cautioned, however, that "this finding had only borderline statistical significance, and may have been affected by factors such as age and inaccuracy of recall."

Implications Indeterminate

The findings "can neither be considered conclusive nor can they be dismissed as insignificant," the institute commented. Because the population size was small, a "large number" of additional subjects must be studied to corroborate the findings, it asserted.

NIOSH said it plans to locate other plants using TDA to determine if the problems that were identified exist elsewhere, and to recommend that the National Toxicology Program conduct additional animal studies to assess further the reproductive toxicity of the substances.

Benzene

NO EFFECT ON REPRODUCTIVE PERFORMANCE FOUND IN STUDIES CONDUCTED FOR INDUSTRY

Benzene has no effect on the reproductive performance of laboratory animals, according to a study recently completed for the Chemical Manufacturers Association and the American Petroleum Institute.

The study, conducted by Bio/dynamics Inc., East Millstone, N.J., subjected mature male and female rats to benzene at 1 to 300 parts per million for six hours a day, five days a week, during a 10-week period prior to mating with untreated animals.

Female rats continued to be exposed during the mating and gestation periods and days five to 21 of the lactation period. No statistically significant adverse effects on reproduction or offspring were observed in any of the tests, according to CMA.

Testicular changes were observed in two out of 20 male rats at the highest dose level, but this did not appear to affect reproductive performance. Nor was it clear if these changes were related to benzene exposure, the group said.

The study results were submitted to the Environmental Protection Agency, the National Cancer Institute, the Occupational Safety and Health Administration, the National Institute for Occupational Safety and Health, the National Institute of Environmental Health Sciences, the Food and Drug Administration, and the Consumer Product Safety Commission.

Dioxins

SECOND DOW SARCOMA CASE FOUND; COMPANY SUGGESTS SMOKING AS FACTOR

Dow Chemical U.S.A. March 11 reported that it found a second case of soft tissue sarcoma among Dow workers exposed in the past to dioxins.

The company stated, however, that the conditions to which the employee may have been exposed "do not exist in the workplace today." The worker also was a cigarette smoker, "which may have a bearing on this incident," Dow said.

According to Dow, the employee began work in the production area of a trichlorophenol plant in the company's Michigan Division in 1951. An outbreak of chloracne appeared in that process area in late 1963 and 1964, apparently due to contamination by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the company reported.

The worker cited by the company developed chloracne, and was diagnosed by his personal physician in late 1979 or early 1980 as having a malignant fibrous histiocytoma, Dow said.

Production of trichlorophenol by Dow in the U.S. ceased in 1979, the company said. It added that its overseas production facilities have been modified over the years so that exposure to the contaminant TCDD "virtually has been eliminated."

Smoking Seen Factor

Dow noted that another trichlorophenol-production worker was found in an earlier company study to have died from fibrosarcoma. This worker, and two Monsanto workers who also had been exposed to dioxin and had died from soft tissue sarcoma, were noted by researchers with the National Institute for Occupational Safety and Health, who said that the deaths represented a higher than expected mortality rate (Current Report, p. Feb. 27, p. 1517).

A review of the two Dow and two Monsanto cases revealed some "common characteristics," Dow maintained:

- All four workers were cigarette smokers.
- Three of the employees had substantial exposure to trichlorophenol, and all four probably had substantial exposure to TCDD.
- Two of the workers developed chloracne, and another had facial dermatitis not diagnosed as chloracne.
- Although the report on the fourth employee does not indicate if he had chloracne, it mentions that a number of other employees in his work area at that time did have the condition.

No definitive cause/effect relationship can be drawn, but the data suggest that persons who exhibit chloracne as a result of substantial TCDD exposure, and who were smokers, may be at increased risk of developing soft-tissue sarcomas, according to Dow.

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Cancer Rate Said Less

Dow reported the second case of malignant fibrous histiocytoma to the Environmental Protection Agency March 6, to provide "technical compliance" with the Toxic Substances Control Act. The information "does not, in our judgment, scientifically demonstrate a substantial risk at this time," according to a memorandum signed by Etcyl H. Blair, Dow vice-president and director of health and environmental sciences.

None of the four studies evaluated in aggregate by NIOSH researchers found "any increased overall mortality, nor significantly increased mortality due to cancer," Dow maintained. When combined, the studies "reveal an apparent increase of soft-tissue sarcomas (albeit histiologically distinct)," but the "overall cancer was substantially less than that expected in the general population," the company said.

Noting that NIOSH has further dioxin studies under way, Dow said it was making the latest data available so that the information could be included in the studies.

Pesticides

EPA PUBLISHES TOLERANCES, PERMITS, GRANTS 13 SPECIFIC PESTICIDE EXEMPTIONS

The Environmental Protection Agency March 6-18 acted on 29 pesticide petitions and received two petitions and two notices of crisis exemptions.

Tolerance Amendments

The agency March 17 set maximum levels of acephate and its metabolite methamidophos on mint hay at 15 parts per million (ppm) (46 FR 17020).

For further information contact Clinton Fletcher, Registration Division, Office of Pesticide Programs, EPA, 1921 Jefferson Davis Highway, Arlington, Va. 22202.

Tolerances for *O,O*-dimethyl S- [(4-oxo-1,2,3-benzotriazin-3(4H)methyl] phosphorodithioate on birdsfoot trefoil and birdsfoot trefoil hay also were established March 17, at 2 and 5 ppm respectively (46 FR 17021). Contact: Fletcher.

A proposed tolerance of 0.5 ppm for chlorthiophos on tomatoes imported from Mexico was published March 16 (46 FR 16917). Send comments by March 26 to Jay Ellenberger at the above address.

EPA March 18 proposed to set tolerances for amiben on pigeon peas and pigeon pea forage at 0.1 ppm (46 FR 17229). Comments to Fletcher by April 17.

On March 18 the agency also proposed that boiled linseed oil be exempted from tolerance requirements when used in a formulation of S-ethyl hexahydro-1H-azepine-1-carbothioate applied to growing rice before edible parts form (46 FR 17230). Comments to: John Shaughnessy, at the above address, by April 17.

Tolerance Petitions

Monsanto Co. filed two petitions with the agency. One requested an increase in a proposed tolerance for glyphosate and its metabolite aminomethylphosphonic acid on cottonseed from 6 ppm to 15 ppm, and the second proposed to set tolerances for S-2,3,3-trichloroallyl diisopropylthiocarbamate on sunflower seed, mustard seed, safflower seed, flax seed and buckwheat seed at 0.02 ppm.

Temporary Tolerances

EPA issued a temporary tolerance for norflurazon and its desmethyl metabolite on soybeans at 0.10 part per million (ppm) with an expiration date of April 20, 1982.

Temporary tolerances were renewed for glyphosate and its metabolite aminomethylphosphonic acid on forage legumes at 0.4 ppm, and the liver and kidney of cattle, goats, hogs, horses, poultry, and sheep at 0.1 ppm. The tolerances expire Jan. 29, 1982.

Specific and Crisis Exemptions

Exemptions for the use of pesticides in emergencies were issued to:

- Animal and Plant Health Inspection Service, to use naled to eradicate the oriental fruit fly in California.
- Arkansas, to use Machete and Propanil to control grasses and weeds in dry-seeded rice fields.
- California, to use Botran and orthophenylphenol on kiwi fruit to control *Alternaria alternata and Botrytis cinerea.*
- California, to use Carzol on strawberries to control the two-spotted spider mite.
- Fish and Wildlife Service, to use sodium-cyanide-loaded M-44 devices to control coyotes and red foxes preying on the whooping crane.
- Florida, to use heptachlor to control the West Indian sugarcane rootstalk borer weevil on ornamental plants and nonbearing citrus nursery stock.
- Florida, to use permethrin to control the vegetable leafminer on celery, lettuce, and tomatoes and to control tomato pinworms on tomatoes.
- Georgia, to use fenvalerate on cabbage to control the cabbageworm.
- Idaho, Oregon, and Washington, to use benomyl in fall seeded wheat acreage to control *Cercosporella* foot rot.
- Washington, to use Nemacur 3 EC on raspberries to control the lesion nematode.
- Washington, to use napropamide to control annual grasses in mint fields.

The Texas Department of Agriculture notified EPA that it had used a crisis exemption to apply Paraquat CL to mung beans and other dry beans as a harvest aid. Vermont also used a crisis exemption, for zinc phosphide to control the red squirrel in sugar maple orchards.

Experimental Use Permits

Permits to use pesticides in experiments were issued to:

- Monsanto Co., for 8,000 pounds of glyphosate and alachlor on corn and soybeans to evaluate control of weeds.
- Uniroyal Chemical, for 296 pounds of UBI-S734 on cotton, peanuts, potatoes, soybeans, sugar beets, and sunflowers to evaluate control of weeds.
- Dow Chemical Co., for 1,000 pounds of chlorpyrifos on wheat to evaluate control of aphids, brown wheat mites, grasshoppers, army worms, and cutworms.
- Agway, Inc., for alkanolamine salt of dinoseb on field and sweet corn to evaluate use as a plant growth regulator.
- Sandoz Inc., for 30,000 pounds of norflurazone on soybeans to evaluate control of grass and broadleaf weeds.

EPA extended two permits issued to Abbott Laboratories, each for eight pounds of gibberellic acid and 6-benzyladenine on apples to evaluate typiness and shape improvement.

The agency also amended a Nor-Am Agricultural Products Inc. permit for use of propyl [3-(dimethyl-amino) propyl] carbamate monohydrochloride on turf grass to evaluate control of pythium blight by including acreage in Nebraska and New York.

Registration

EPA approved an application submitted by Chempar Chemical Co. Inc. to register conditionally MAKI Rat and Mouse Meal Bait containing 3-[3-(4-Bromo-1,1'-biphen-

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Chloracne and its potential clinical implications

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It is essential to recognize that chloracne is always a symptom of systemic poisoning and not just a cutaneous affection (Goldmann, 1973). Although most cases of mild or moderate chloracne appear fit and well such a statement may seem contradictory (May, 1973), but it is not. Since chloracne appears to be the most sensitive indicator of poisoning in the human subject (Moore, 1978), in most cases the systemic levels of chloracneigen are insufficient to cause target organ damage either clinically, or as assessed by laboratory investigation. There are two factors which probably make up this equation; the relationship between dose and route of absorption on the one hand, and chloracne and systemic effects on the other. Much work remains to be done in this field but one thing is certain—animal experiments demonstrate conclusively that the effects of an arbitrary amount of any chloracneigenic toxin are less severe as a single dose than if given in divided doses over a longer period. The effects of the route of absorption will be discussed later.

Definition

Chloracne may be defined as an acneiform eruption due to poisoning by halogenated aromatic compounds having a specific molecular shape (Poland & Glover, 1977). Since bromination renders such a compound more acneigenic than chlorination (Echobichon, Hansell & Safe, 1977), halogen acne may be a more specific term, but the word chloracne is now far too well established to be abandoned.

Chloracneigens

Only the following substances can unequivocally be proven to have caused chloracne in man, and some in experimental animals also:

(a) Chlornaphthalenes (CNs).
(b) Polychlorinated biphenyls (PCBs).

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(c) Polychlorinated dibenzofurans (PCDFs).
(d) Polychlorinated dibenzo-dioxins (PCDDs).
(e) Tetrachloroazobenzene (TCAB).
(f) Tetrachloroazoxybenzene (TCAOB).

Bromination of certain naphthalenes, biphenyls and dibenzofurans has been achieved and their acneigenicity confirmed in experimental animals (Kimbrough, Burse & Liddle, 1977a), but so far only brominated biphenyls, mainly as 2, 4, 5, 2′,4′,5′ hexabromobiphenyl has caused chloracne in human subjects from systemic poisoning (Selikoff, 1979), when cattle feed was accidentally contaminated with hexabromobiphenyl manufactured as a flame retardant in Michigan USA in 1973 (Landrigan *et al.*, 1979).

No less than four of the chloracneigens on this list are found mainly as contaminants formed accidentally during the manufacture of other materials. Thus, the dioxins occur in chlorinated phenols, the chlordibenzofurans in chlorobiphenyls and also chlorophenols (Taylor, 1979), whilst 3, 3′, 4, 4′ tetrachlorazo and azoxybenzenes are formed duringthe manufacture of 3, 4 dichloroaniline and various end products and chemical processes involving its use or formation (Taylor, 1977).

It is essential to understand that the degree of halogenation does not necessarily determine toxicity; the position of the halogen atoms on the outside of the molecule (isomerism) is vital (McConnell *et al.*, 1978a), and therefore a full knowledge of the nature and quantity of the various isomers in any single chloracneigen is essential before any prediction of its possible toxicity can be made. Great advances in analytical chemistry by conventional and more recent radio immunoassays have made this possible (Albro *et al.*, 1979).

Cutaneous manifestations

The distribution of chloracne lesions is of considerable diagnostic importance. The most sensitive areas of the human skin are below and to the outer side of the eye (the so-called malar crescent) and behind the ear. They frequently may be affected when the rest of the skin is perfectly normal. Furthermore, they are the areas most likely to show residual lesions years after more extensive chloracne has faded. Next in frequency come the cheeks, forehead and neck but the nose is almost invariably spared. This should cause us to reflect deeply when we consider the sebaceous gland development of this region, for the pathological basis of chloracne is squamous metaplasia of sebaceous glands into keratin-forming cysts. The genitalia, both penis and scrotum, but particularly the latter, are sensitive regions. With increasing toxicity the spread of the lesions affects the shoulders, chest and back, and eventually buttocks and abdomen. The hands, forearms, feet, legs and thighs are rarely involved and usually only in the worst cases. One curious 'quirk' of distribution is axillary lesions (Jirasek *et al.*, 1974) which have only commonly been seen in those patients where ingestion and/or inhalation have been known to be either the only, or a major route of absorption, as in Japan in 1968 (Yusho poisoning), or at Seveso in Italy in 1976 where axillary lesions were seen only in those few children who were actually enveloped in the toxic cloud.

The basic lesion of chloracne is the comedone, and, in the mildest examples, these may

Figure 1. Chloracne: typical comedones.

be the only lesions present (Fig. 1). If so, they are likely to involve only the very sensitive areas, i.e. malar crescents and behind the ears, and a few as a dozen lesions on each side may be diagnostic. One must, however, be most careful in older age groups to distinguish the so-called senile comedones, so often seen in the malar areas or, in younger patients, acne vulgaris which may exactly mimic chloracne. The distinction in fact may be clinically impossible, but a consideration of various other factors should decide the issue. Thus, apart from the distribution, unusual age of onset, clustering of similar cases in a factory, involvement of a specific occupation or even a township, the presence of known chloracneigens or of chemicals with a similar molecular shape, as well as the absence of other external causes of acne such as pitch, tar and mineral oils, considered together make the diagnosis fairly straightforward. Where doubt still remains, histology is usually conclusive.

In all but the mildest cases small, pale yellow cysts, from pinhead to lentil size, mingling with the comedones (Fig. 2) make up the characteristic picture of typical chloracne (Crow, 1970). As the severity of the disease increases, not only do the lesions become more numerous, but, in the worst cases, comedones some no larger than pinpoints may involve every follicle giving the appearance of greyish sheets. These lesions are to be distinguished from the equally profuse but pale follicular hyperkeratoses yet to be described.

In the most severe cases inflammatory lesions begin to appear, and with them larger cysts and even cold abscesses (Fig. 3). As ever wider areas become involved the picture may well come to resemble that of severe cystic acne but with much less inflammation than in the latter disease. Such gross lesions are most often seen on the back of the neck, trunk and buttocks (Fig. 4). Widespread changes resembling solar elastosis have been described with chloracne from 2,4,5 trichlorophenol manufacture (Jirasek *et al.*, 1973) and the author has

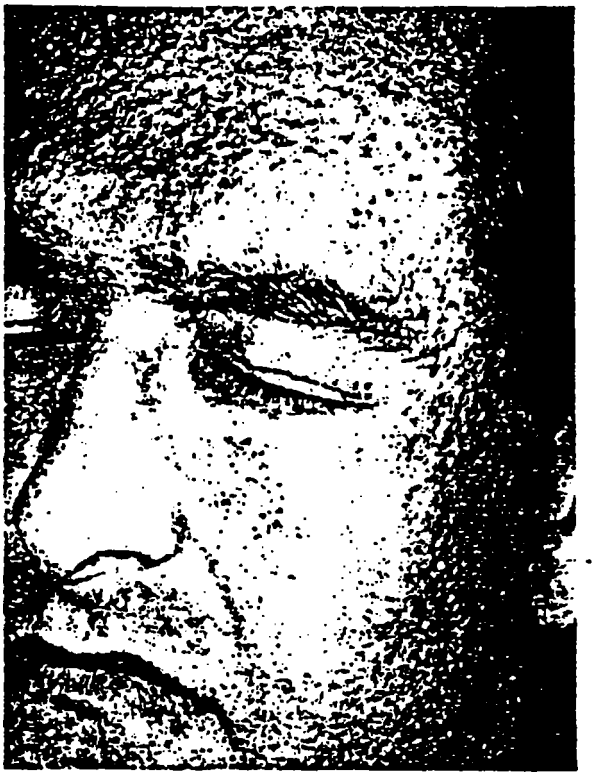

Figure 2. Chloracne: comedones and small cysts.

seen such changes still present in some of over 116 cases examined in 1979 in West Virginia, U.S.A., 20–30 years after their initial severe chloracne, and some years after all contact with 245T had ceased. A similar case which was also examined, was due presumably to hexachlordioxins from pentachlorophenol manufacture. The histology was that of chloracne.

Scarring, absent in the mildest cases, varies from a fine pitting, like atrophoderma vermiculata, to extensive lesions of the sort following severe cystic acne. In the worst cases, lesions may still be present after 30 years but usually only in the malar region and behind the ears. Very mild cases may clear a few months after contact ceases, as at Seveso (Puccinelli, 1977), and after 2–3 years all but a hard core of 20% or so are likely to have resolved.

Pigmentation

Pigmentation is largely confined to the face but may in the worst cases extend more widely, and has been known to be generalized and so severe as to cast doubt upon the patient's racial origin. Japanese victims of a mass poisoning in 1968 called Yusho due to the use of a rice-based cooking oil (Kuratsune *et al.*, 1972) accidentally contaminated with large amounts of tetrachlorobiphenyl, itself heavily contaminated with chlordibenzofurans (Rappe *et al.*, 1977),

Figure 3. Chloracne: cysts and inflammatory lesions.

exhibited a curious pigmentation affecting the nails, lips, gingival and buccal mucosae, and the conjunctivae in about 70%. Such pigmentation affecting the nails and conjunctivae has been described also in industrial PCB poisoning (Fishbein *et al.*, 1979), but only in 2–3%. This difference may be a dose effect, racial or both. Yusho is the only recorded instance of human poisoning where external contact and inhalation can positively be excluded, and a direct comparison made with toxicological animal feeding/intubation experiments.

Hypertrichosis

Hypertrichosis, a rare finding, is mainly confined to the temples and may be secondary to the hepatic porphyria caused by TCDD, but it has undoubtedly been present also in patients whose uroporphyrins have been measured and remained consistently normal (Jirasek *et al.*, 1974).

Phrynoderma

Follicular hyperkeratosis, to be distinguished from comedones may, in rare cases with usually severe accompanying chloracne, be widespread and even generalized (Crow, 1978).

Figure 4. Chloracne: resembling gross cystic acne.

On the other hand, despite its usual rarity, no less than 70% of the Japanese Yusho victims developed a similar fine follicular hyperkeratosis on the upper trunk, neck and, most unusual of all, on the flexural areas (Goto & Higuchi, 1969). It is interesting to speculate whether this is due wholly or in part to the exclusively gastro-intestinal route of poisoning in these cases. Cutaneous findings in still-born infants and neonates born to Yusho mothers poisoned with PCBs and PCDFs have been of great interest. Instead of chloracne, the entire skin was hyperpigmented and covered with greyish scales (Higuchi, 1976a). Several months after birth the skin became normal. The histology showed an atrophic epidermis with hyperkeratosis and dilatation of follicles which were filled with keratin. These findings are clinically and histologically similar to those which occurred in cattle poisoned with penta and hexachlornaphthalenes in 1947 (Olafson, 1947), and with hexabromobiphenyl in Michigan, U.S.A., in 1973. Similar changes were again found in horses poisoned with TCDD in Missouri in 1971 (Kimbrough *et al.*, 1977b).

Ophthalmic changes

Conjunctivitis has often been noted in severe poisoning with chloracneigens, but has only

been seen in an extreme form in Japanese Yusho victims whose meibomian glands were converted into squamous cysts filled with a cheesy keratinous material (Higuchi, 1976b).

It is of some interest that in ingestion experiments, similar lesions are induced in Rhesus monkeys by chlordibenzodioxins, chlordibenzofurans and 3,4,3′,4′ tetrachlorobiphenyl (McConnell *et al.*, 1978b). They appear to have been an even more sensitive indicator of poisoning in the Rhesus monkey than chloracne in the Yusho patients. Where poisoning has been mainly by external contact, however, chloracne is much more common than meibomian gland changes, thus almost certainly indicating the importance of the route of absorption in determining the clinical spectrum.

Erythema

The erythematous changes which may occasionally be associated with the onset of chloracne (Jirasek *et al.*, 1974) May, 1973) have been the subject of confusion in the literature. Because such erythema is confined exclusively to exposed areas it has wrongly been ascribed to photosensitivity.

Telegina & Bikulatuva (1970) describing an outbreak of severe chloracne and systemic poisoning during the manufacture of 2,4,5 trichlorophenol, established that their cases had a reduced sensitivity to U.V.L.

A few cases of erythema preceding the severe chloracne resulting from massive internal exposure to probable chlornaphthalenes are genuine, but apart from these the other recorded cases have all occurred during chlorophenol manufacture. Such erythema has never been recorded from PCBs, even in the massive Yusho poisoning, nor from TCAB or TCAOB.

Exposure to chloracneigens in chlorophenol manufacture implies exposure also to sodium salts of chlorophenols (Suskind, 1978; Joint NIEHS/IARC Working Group Report, 1978) as well as to the dioxins and dibenzofurans. The corrosiveness of adequate amounts of the sodium salts on damp skin is unquestioned and there was every reason to believe that erythema was likely to have been caused by sodium chlorophenate burns. It was the Seveso accident, however, which provided abundant evidence to support this theory.

Seveso

The Icmesa factory at Seveso was designed in such a way that the vent pipe from the reactor vessel's bursting disc was extended through the factory roof into the open air.

On 10 July 1976, at around 12 noon, the full reactor began an exothermic reaction (Reggiani, 1980), terminating in an explosion which thereupon discharged its contents in a vertical jet into the air. The cloud of finely dispersed reactor contents, mainly the potentially corrosive sodium 2,4,5 trichchlorophenate, drifted slowly down wind on a slight South-East breeze. The day was the hottest day of that summer so far and those who were caught in the cloud with sweaty skins or who handled objects covered with the discharge suffered chemical burns.

Seventy-six per cent of 447 cases of adults and children examined within days of the explosion had erythema on the exposed areas of skin. In many cases it was severe enough to

cause blistering. Needless to say, the small children who were contaminated suffered most. By far the most severe burns were suffered by eight children actually caught in the chemical cloud.

An examination of several of the most severely burned children in Milan at the end of July revealed chemical burns which were quite typical, affecting face, neck, forearms, and arms below clothing, as well as legs and the lower part of the thighs. In the burned areas were many curious, circumscribed, discoid, raised lesions, mainly confined to the hands, forearms and legs. That these were simply a part of the chemical burns and nothing more esoteric was confirmed as they subsided with the rest of the lesions. A follicular hyperkeratosis affecting virtually every follicle in the burned areas heralded the first sign of chloracne. As the burns faded leaving hyperpigmentation, so the chloracne developed. With the occasional exception of the axillae, it affected very few covered areas. There were in all, eight severe and eleven moderately burned children with a curious form of chloracne which, in the more severe cases, formed diffuse thick hyperkeratotic sheets due to every single follicle having formed a small keratinous cyst. Four months later this diffuse crusting was already separating leaving small atrophoderma vermiculata-like scarring scattered with comedones.

There were 168 other cases of chloracne, all mild to minimal in extent. Unlike the children, less than 5% of the adults who had received caustic burns developed chloracne and even then of a very minor degree. It seems likely that the major contact at Seveso was external since there were cases where the chloracne was exactly limited to odd shaped areas of pigmented skin where burns had previously been present, the intervening skin being unaffected (Crow, 1976). Some ingestion and/or inhalation could not of course be excluded. There has at no time been any clear evidence of systemic poisoning in any of the Seveso cases despite extensive and continuing investigation, again consistent with a largely external contact.

Some properties of all chloracneigens

The acneigenic potential of all chloracneigens can be equated with their overall toxicity. This is supported both by animal experiments determining the LD50 and an ingenious experimental method making use of a characteristic of all chloracneigenic toxins—their ability to induce various microsomal drug metabolizing enzymes of which liver cells are a particularly rich source. The most useful of these has been arylhydrocarbon hydroxylase (A.H.H.) (Poland & Kende, 1976), which is responsible for the initial rupture of the aromatic nucleus and therefore the first step in the metabolism of these compounds. The most powerful known inducer of A.H.H. is 2,3,7,8 tetrachlorodibenzo-p-dioxin, and by animal experiments it can be proved not only to be the most toxic small molecule known to man but also the most powerful to all chloracneigens. Thus we have a simple method of determining the relative toxicity and therefore acneigenicity of any given chemical and its isomers. This same technique has, therefore, enabled the structure-activity relationships of many possible chloracneigenic isomers to be determined (Poland & Glover, 1977). All such isomers, whilst varying greatly in their overall toxicity, share the characteristic of attacking the same target organs of various animal species (Moore *et al.*, 1979). The biological basis of chloracne, in particular its pre-

dilection for certain areas of skin, is unknown. Investigation is hampered by the lack of an analytical method sufficiently sensitive to study the material in comedones and cysts.

Apart from the human subject, chloracne, or something very like it clinically and histologically, has been produced in only three experimental animals; the rhesus monkey (on the face with loss of hair and disruption of meibomian glands as in the human subject), the hairless mouse and, most important of all, the inner surface of the rabbit ear (Adams *et al.*, 1941). It is not possible to produce chloracne on any other part of the rabbit's skin. Indeed, even systemic absorption of chloracneigens by the rabbit produces chloracne only on the inner surfaces of the ears (Rowe, 1978). Thus, there is a clear parallel to the curious sensitivity of the malar crescents and ears in the human subject. The rabbit ear appears to be the most sensitive biological surface known, reacting to as little as 1 μg of the most potent known chloracneigen.

Histology

Where exposure has been severe the histological changes may begin within five days. Initially there is stimulation of the epithelium of the outer root sheath and sebaceous gland ducts (Hambrick, 1957). It seems likely that the subsequent disappearance of the sebaceous glands is due to squamous metaplasia of sebaceous forming cells. Thus the sebaceous gland is inevitably replaced by a keratinous cyst, which always has an attachment to the epidermis. The exit is tiny in some lesions whilst others are little more than a shallow trough. Inflammatory changes are minimal in the majority of lesions.

Clinical signs and symptoms in non-cutaneous systems

Because of cutaneous absorption (which has been estimated as half the applied epidermal dose for TCDD—Schwetz *et al.*, 1973), possible ingestion and/or inhalation, all cases of chloracne must be submitted to careful clinical and laboratory investigations designed to detect the following abnormalities.

Weight

Weight loss is certainly one of the most sensitive indicators of poisoning in experimental animals, especially the rhesus monkey (McNulty, 1979) but in most human poisonings, wasting has not been carefully monitored or, where it has, it has been found only in more severe cases (Jirasek *et al.*, 1974).

Hepatic change

Liver damage has always been heralded as one of the most classic signs of systemic poisoning from chloracneigens, but the facts do not support this. Liver damage undoubtedly does occur (Goldman, 1973; Jirasek *et al.*, 1974) in some severely poisoned cases, but apparently not in others (Joint NIEHS IARC Working Group Report, 1978). This is presumably a factor

of dose and route of absorption. It is important not to assume that liver enlargement necessarily means detectable liver damage. The increase in size and weight may be due, as in the rat for example, to a great increase in smooth endoplasmic reticulum (SER) (Higuchi, 1976c) which is thought to be an indication of increased enzyme induction.

Lipoprotein

Lipoprotein abnormalities are most important because of a possible (though as yet unconfirmed) association with cardiovascular disease. The only consistent abnormality in animals and human subjects is a raised triglyceride level. Cholesterol is variable but usually normal as are HDL/cholesterol levels where these have been done. It is interesting that recent work with TCDD in guinea-pigs has revealed raised triglycerides and unchanged cholesterol and HDL. The cause of the raised triglycerides is much debated but two mechanisms may be involved, separately or together. The evidence for increased hepatic enzyme activity might support the suggestion of increased triglyceride synthesis. Alternatively, there may be a decrease in removal of plasma triglyceride due to decrease in plasma lipoprotein lipase activity as revealed in Yusho patients (Higuchi, 1976d).

Neurological (central)

The reported symptoms of CNS involvement, being entirely subjective, are most difficult to evaluate, but a combination of headache, fatigue, irritability, insomnia, impotence and loss of libido have occurred so often as to be unquestionably genuine symptoms. However, it cannot be stressed too strongly that they were reported only in cases of very severe poisoning (Suskind, 1978; Jirasek *et al.*, 1974; Goldmann, 1973) before the terms chloracne, TCDD, etc., became household words all over the world after the Seveso accident in 1976. Furthermore, these symptoms arose during the worst of the poisoning and not after a symptomless interval of several years.

Neurological (peripheral)

Peripheral sensory nerves, particularly in the legs, may be affected in severe cases, almost always associated with halogenated dioxin poisoning. The neuritis may cause lower limb pains of disabling severity, together with patchy numbness. This neuropathy may be confirmed by biopsy which shows demyelination or, more easily, by measurement of conduction velocity which is found to be lowered. The neuropathy is remarkable in that it frequently arises relatively late in the poisoning syndrome and may appear 2 or even 3 years after the onset of toxicity and when other signs and symptoms may have begun to subside (Jirasek *et al.*, 1974). Motor nerves are rarely affected and then only after sensory involvement.

Pulmonary

Pulmonary changes are frequent, and persistent bronchitis with effort dyspnoea is well

documented, but the recent discovery that there is a lowering of the vital capacity is particularly interesting for in PCB poisoning it may be the only sign of toxicity (Warshaw *et al.*, 1979).

Porphyrins

Porphyria of the hepatic type is a most interesting finding, described only twice so far in human poisoning, each time from TCDD in 245T manufacture (Bleiberg *et al.*, 1964; Jirasek *et al.*, 1974). Patients exhibited, in exposed areas, hyperpigmentation, hypertrichosis, traumatic and actinic bullae, milia and scars. TCDD will also produce porphyria in experimental animals (Rose *et al.*, 1976) whereas the very closely related 2,3,7,8 tetrachlorodibenzofuran appears not to do so (Oishi, Morita & Fukuda, 1978). PCBs have produced porphyria in animals and also an excess of porphyrins in the liver tissue of Yusho victims. Urinary uroporphyrin levels are only moderately raised in most cases. The enormous induction by powerful chloracneigens of delta-aminolaevulinic acid synthetase in liver microsomes made it seem likely that this was the cause of the porphyria. Recent work with TCDD, however, has shown that it inhibits the enzyme uroporphyrinogen decarboxylase which is the almost certain cause of the hepatic porphyria (Jones & Sweeney, 1977). Rapid poisoning seems to be ineffective, long term moderate doses being apparently necessary to produce overt porphyric changes.

Sweating

Hyperhidrosis, mainly of the palms and soles, has been reported by Jirasek *et al.* (1974) and Goto & Higuchi (1969), but it is hard to be sure that it may not have been overlooked elsewhere.

Gastro-intestinal

The same is true of nausea, vomiting and diarrhoea which seem to be confined to acute poisoning and may therefore be due to associated chlorophenols for example. On the other hand, these symptoms occurred in 20% of Yusho victims.

Muscolo-skeletal

Rarer still is bursitis, usually of the olecranon or prepatellar bursae, and oedema of all four limbs (Kuratsune *et al.*, 1972; Baader & Bauer, 1951).

Immunological

Immunological deficiencies have been indicated in animals of various species but the work is confusing and of doubtful significance as yet. In humans a decrease in circulating T cells has been demonstrated in poisoning from hexabromobiphenyl (Bekesi *et al.*, 1978).

Teratogenicity and foetotoxicity

Teratogenicity has been demonstrated in rats and mice but the far more sensitive effect of chloracneigens as foetotoxic is clearly a limiting factor. Neither of these two effects has yet been demonstrated in the only two episodes of poisoning with chloracneigens in which women were involved equally with men, i.e. Seveso and Yusho.

Miscellaneous

The actual cause of death from chloracneigens is unknown (McConnell *et al.*, 1978b), but even when the minimum lethal dose is greatly increased, the time to death, e.g. 14–21 days, remains unchanged. Rapid deaths ascribed to chloracneigens must, therefore, be seriously questioned and other causes sought.

As in animal toxicology, so with the human subject is it even more difficult when severe poisoning is present to distinguish lesions which are purely secondary to severe illness from those which are specifically due to the toxin responsible. The symptoms and signs described so far have occurred in a sufficient number of poisonings from different chloracneigens to be certainly specific. Other findings which have been recorded, such as cardiac, renal, pancreatic and other changes, must await further confirmation.

Carcinogenicity

Numerous studies for mutagenicity have been somewhat equivocal but careful lifetime feeding studies on rats (Kociba *et al.*, 1978) and mice (Holmes *et al.*, 1978) with TCDD and the two most toxic hexachlordioxin isomers have revealed that malignant tumours can be induced, but only by doses large enough to produce a state of chronic toxicity, low doses having no effect. Skin painting (Holmes *et al.*, 1978) suggested that dioxins may be complete carcinogens, i.e. initiators and promoters, but other experimental evidence throws doubt on this. PCBs fed to rodents throughout their lives produce liver tumours, the true malignancy of which is not fully established. Against this background what are the human data?

Seventy men with chloracne and very severely poisoned with TCDD during 245T manufacture and carefully followed up for 25 years, have shown an increase in stomach cancer in one age group only. Seventy-nine cases of chloracne from TCDD following the explosion of a 245T reactor in 1968 had, 10 years later, shown no excessive evidence of malignant neoplasms. Yusho victims have shown an increased mortality from malignant neoplasms (four of eleven autopsied), but this is not considered to be statistically significant and the survey must continue (Urabe, Koda & Asaki, 1979). A follow up of 121 men, all with severe chloracne and very severe poisoning from TCDD again after the explosion of a 245T reactor, has, 29 years later, shown an incidence of nine cancer deaths against an expected figure of 9·04 for that area (Zack & Suskind, 1980).

The evidence, as far as it goes, seems to suggest that severe and lifelong toxicity in rodents may produce excess malignancies, but so far concrete evidence of similar lesions in humans is not forthcoming. There is no reliable evidence so far of any increase in cardio-vascular

disease in these cases. The raised triglycerides in the apparent absence of lowered HDL suggests that all such data will have to be most carefully evaluated.

Routes of absorption

Although there is no experimental evidence indicating whether or not variation of the route of absorption of a chloracneigen alters the distinctive features of poisoning, there is circumstantial evidence which allows some speculation. It is undoubtedly in industry where the cutaneous route of absorption has been maximal and ingestion and/or inhalation relatively less, so the tendency has always been for chloracne to be more severe than systemic changes—if the latter could indeed be detected at all. Typical examples are: the Coalite explosion in 1968 involving TCDD (May, 1973) where there was little evidence of systemic changes in seventy-nine cases of chloracne, some quite severe; a personal experience of forty cases of chloracne from penta/hexachlornaphthalene from 1957–63; twenty-nine cases from hexachlordioxins and 26 from 3,4,3',4'tetrachloroazobenzene in 1978, all without obvious evidence of systemic disorders.

Further evidence of the opportunities for external contact in industry are afforded by the examples of children at home developing chloracne from transient contact with clothes which the worker has worn all day at work (Kimmig & Shulz, 1957; Crow, 1970; May, 1973; Taylor *et al.*, 1977). Conversely, the only incident where absorption was known to be solely by ingestion led to 18% of over 1,000 cases (Kuratsune *et al.*, 1972) developing signs of systemic poisoning (which could be confirmed by the highly characteristic pattern of PCBs in the blood of victims) without chloracne being present. Furthermore, chloracne when it developed did so in many cases several months after other signs and symptoms of poisoning had already appeared. This one outbreak, quite unique in the total absence of skin contact, is an exception which does not disprove the otherwise almost universal rule that chloracne, in man, is the most sensitive indicator of poisoning by chloracneigens simply because cutaneous contamination is rarely absent and, indeed, everything usually points to the skin as the major route. Nevertheless, there is the clearest indication that those who contact chloracneigens either in industry or elsewhere, must be investigated regularly, both during their exposure and, if possible, for the rest of their lives.

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Dave B.

JOB NO. SHEET OF FILE BY TYPE

MN0506620

Esteron 2,4,5-T (E-245T

ESTERON 245 BRUSH + WEED KILLER

2,4,5-T acid equivalents (lbs/gal) = 4

Esteron Brushkiller (EBK)

ESTERON BRUSH KILLER

2,4-D acid equivalents (lbs/gal) = 2

2,4,5-T " " " = 2

4

DOW 1 732543

Kuron

KURON BRUSH + WEED KILLER

SILVEX acid equivalents (lbs/gal) = 4

(Chevron Mix (CHEVMIX)

BUTOXY PROPYL ESTERS MIX NO 1

Silvex Mix 240 BPE (% Ester 67.5) AE 41.2% (-1.5+2.0)

Silvex (% Ester) 32.5) AE 20.6% (-1.5+2.0)

R = 9.95 #/gal x .6182 = 6.1 ← AE (#/gal.)

Specifications obsolete Dec. 12, 1979

8464

NOT IN FILE

Vean 2,4,5-T

52.7% amine salt

VEAN 245 WEED + BRUSH KILLER AE = 40.8%

Specifications obsolete Jan 7, 1980 AE = 4 (lbs/gal)

NOT IN FILE

Solvent Mix 67.5% 240 BPL. % Solids

AE 41.2 % (-1.5 + 2.0)

Silicone % Solids 22.5

AE 20.6 (-1.5 # 2.0)

AE (#/gal) _____

Veon 245

4 #/gal

3.97# - 4.1

57.2% Ammonium salt

AE (245) 40.8%

Dow 173254

8465

238

8466

238

2,4-D ACID, TECHNICAL ESTERS DERIVED FROM 2,4-D ACID AND TECHNICAL AMINE CONCENTRATE WILL BE CONSIDERED ACCEPTABLE FOR INTED FUTURE (1981 USE SEASON) IN ABSENCE OF EXCLAMATION AND SUPPORTING ANALYSIS. THIS REQUIREMENT HAS BEEN MADE NECESSARY BY CONFIRMATION BY DEP'T SCIENTISTS OF DIOXIN CONTAMINATION IN 2,4-D AS SUPPLIED TO THE COM MARKET. ALL INFO AVAILABLE TO ME INDICATES THAT IT IS HIGHLY UNLIKELY THAT 2,4-D ACID WILL BE FREE OF POLYCHLORINATED DIBENZO-P-DIOXINS. SIMILARLY ALL INFO AVAILABLE TO ME SUGGESTS THAT 2,4-D ESTERS MANUFACTURED VIA A DIRECT ESTER SYNTHESIS PROCESS HAVE A HIGH PROBABILITY OF BEING CONTAMINATED AT SUBSTANTIVE LEVELS WITH THESE DIOXINS. THUS I AM OBLIGED TO LIMIT FURTHER ENTRY TO MARKET OF TECHNICAL ESTERS PRODUCED VIA THIS PROCESS. APPLICANTS ARE REMINDED THAT BY VIRTUE OF SECTION 9 OF REGULATIONS THEY MAY BE REQUIRED TO PROVIDE SUCH INFO FURTHER AND OTHER THAN THAT REQUIRED BY SECTION 4, "THAT I MAY REQUIRE TO DETERMINE SAFETY, MERIT AND VALUE OF THE PRODUCT. SUBJECT TO SECTION 20 OF THE REGS. ANY REGISTRATION OF 2,4-D WILL EXPIRE ON DEC 31/81 AND ANY CERTIFICATES OF REGISTRATION FOR 2,4-D WILL PROVIDE THAT REGISTRATION EXPIRES ON THAT DATE.

8467

RECEIVED
JAN 2 5 1981
REGISTRATION
000397R

U.S. DEPARTMENT OF AGRICULTURE OTTAWA K1A 0C5

MRR 1980051

...by S. McGowan (Reg Regulatory Affairs Canadian Dept. of Agriculture) for prod information. If you require further confirmation, please call.
From: [illegible]

A. Flynn, 3030 Midland
B. Beasley, 3030 Midland
C. Russo, 3030 Midland
D. Flannery, 3030 Mid
E. Robertson, 3005
R. Russell, 3008

SECTION 3(A) OF FIFRA REGULATIONS IN FUTURE WHENEVER EFFECTIVE DATES REQUIRE REGISTRATION OF 2,4-D. PURSUANT TO SECTION 7 (F) (1) APPLICATION FOR REGISTRATION SHOULD INCLUDE DETAILED PRODUCT SPECIFICATIONS. APPLICANTS SHOULD REFER TO TRADE MEMO T-1-223 RE ADMINISTRATIVE GUIDELINE WITH PARTICULAR REF TO DETAILS OF MANUFACTURING PROCESS. ANY PRODUCT DECLARED BY APPLICANT TO BE FREE OF POLYCHLORINATED DIBENZO-P-DIOXINS (PCDD) DEMONSTRATED BY VALID ANALYSIS SENSITIVE TO 1 PPB WILL BE CONSIDERED ACCEPTABLE FOR REGISTRATION. IN ABSENCE OF SUCH DECLARATION AND APPROPRIATE SUPPORTING ANALYTICAL INFO. TECHNICAL ESTERS PRODUCED VIA A DIRECT ESTER SYNTHESIS PROCESS WILL NOT BE CONSIDERED ACCEPTABLE.

istration." An OMB review of EPA's proposed RCRA rules in May, 1980, found that they represent "an irresponsible system for public-private creation, processing and transmission of information."

EPA and OMB have been jousting ever since over OMB's authority to delay, revise or reject regulations because of inadequate estimates of the economic burdens imposed on industry. EPA contends that OMB's authority extends to only a review of the cost and utility of forms, with burden defined as only the time needed to fill out the forms.

OMB regards EPA's interpretations of the laws as "bizarre," "narrow" and "questionable" and recommends that these legal interpretations be "overturned." In addition, OMB recommends that a thorough regulatory-economic analysis of the entire RCRA program be started and suggests that "the structure of the regulations must be radically simplified to remove hundreds of inconsistencies that have been identified." □

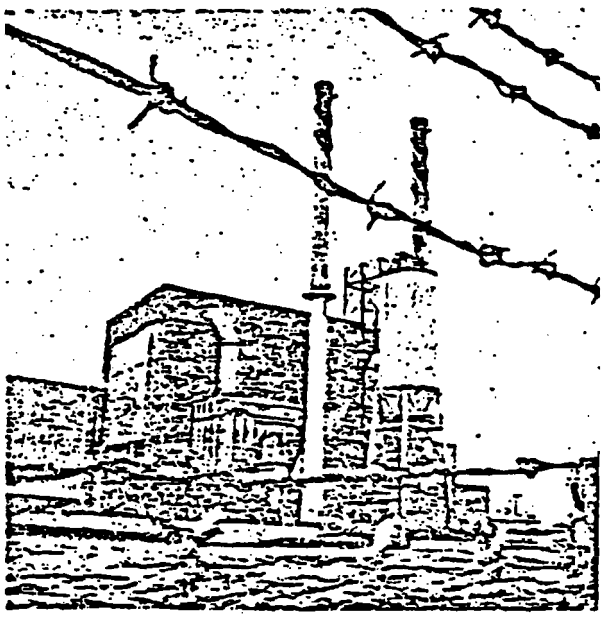
Potential regulatory targets

Regulations under development	*Projected costs*	*Sectors affected*
Prevention of significant deterioration	Several billion over 10 years	Electric utilities
Radioactive waste disposal	$800 million	Nuclear power industry
Best available technology effluent guidelines	$1.7 billion	Electric utilities, steel, paper
Organic chemicals in drinking water	$1 billion over 3 years	Public water systems
Sewage sludge disposal	Unknown	water systems
Superfund regulations	Unknown	Chemicals, petroleum
Final regulations		
Review of ambient air quality standards for NO_2	*Information and capital costs $16 billion annually*	*Electric utilities*
Review of air quality standards for SO_2	*$16 billion annually*	*Electric utilities*
Prevention of significant deterioration	*$6 billion for enforcement*	*Electric utilities, many others*
Air, water compliance schedules for steel industry	*$1.4 billion deferred between 1981-1984*	*Steel*
Consolidated permit program	*$100 million reporting cost*	*Many*
Hazardous waste disposal regulations	*$15 billion over 10 years*	*Many*

Dioxin haunts EPA refuse plans

The furor created in New York by the discovery of dioxin at a refuse recycling plant on Long Island last summer has died down to a dull hum of confusion and resignation among federal environmental officials that they've started down a long, expensive path toward resolving a problem that most believe is not a problem.

"We've done it to ourselves again," says a high-ranking Environmental Protection Agency official. "It's a nonissue that has become an issue that is going to be extremely expensive to lay to rest."



Toxics in the stack idled Hempstead, N.Y., plant.

Investigations done since trace concentrations of the most toxic man-made chemical known—2,3,7,8-tetrachlorodibenzo-p-dioxin—were discovered in stack emissions at the 2,000-ton-per-day Hempstead, N.Y., plant have raised the question of whether most large-scale combustion processes produce minute quantities of the chlorinated compound. Indications are that they do, but in concentrations in the parts per billion and trillion range.

At those levels, health risks are considered minimal, especially when compared to the environmental and economic benefits of resource recovery systems. Nevertheless, the $120-million Hempstead boiler problems and later at the insistence of state and municipal officials because of the discovery of dioxin.

The political situation surrounding the start up problems at the plant and the discovery and announcement of dioxin in the stack gases make Hempstead an extreme example.

It's the only plant affected by the dioxin issue so far. And there are questions about whether the discovery of 3 to 9 parts per trillion of dioxin in the stack

ground level around the plant—is th only reason the problem-plagued re source recovery plant is down.

But the controversy that started o Long Island now threatens to spread t other resource recovery plants and coul eventually encompass everything fror sewage sludge incinerators to coal-fire powerplants.

Unravelling the complex issues—c nonissues—and heading off problem before they arise will be a delicate task fc a number of reasons:

- Dioxin at any concentration is harm ful. There is no proven lower threshold : which the chemical ceases to caus adverse health effects in laboratory ani mals.
- Exhaustive tests done by Dov Chemical Co. indicate that dioxin is cre ated in a number of manufacturing pro cesses and in most combustion system Dow's test results, produced as part of i defense of a suit brought by environmer tal groups trying to stop Dow's produc tion of a herbicide, have neither bee refuted nor duplicated. Literature surve of European incinerator tests, howeve indicate that dioxin may be formed i virtually all refuse furnaces.
- Testing for the most toxic of the 2 isomers of dioxin is very expensive. A analysis done for EPA in December, 198 put the cost of testing a single industri combustion source at $170,000 t $700,000. Finding out if dioxin is form

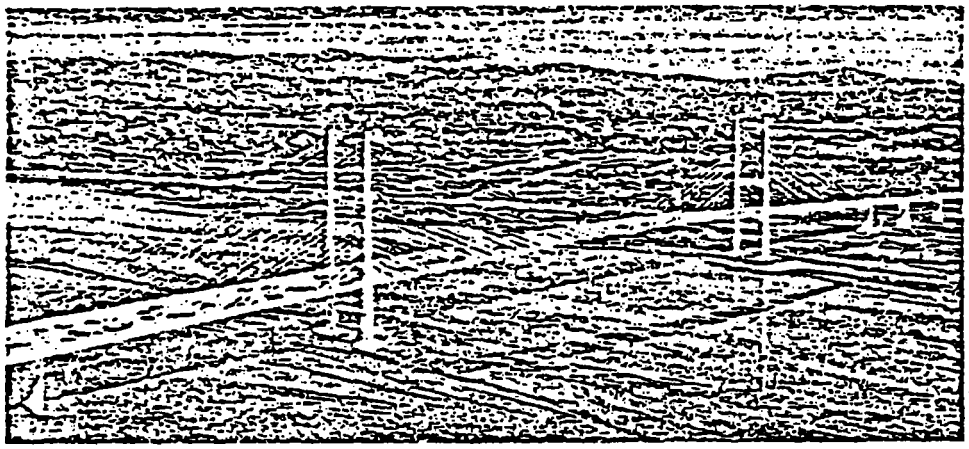
through tests at specific sites—EPA is currently completing analyses of samples taken from an Ames, Iowa, coal and refuse-fired incinerator and a much larger refuse incinerator in Chicago—opens the door for community and political problems such as were created at Hempstead.

• There is currently no regulatory framework for determining the relative risk of creating minute concentrations of toxic pollutants in incinerators and the risk to groundwater supplies of leachate from improperly designed landfill operations.

According to the EPA official, the agency has created its own regulatory mess on the dioxin issue, first raised in connection with Agent Orange, a defoliant used in Vietnam, and again after an explosion at a herbicide manufacturing plant at Seveso, Italy, that contaminated a large area with dioxin. "EPA got hot on dioxin and went after the processes that create it," says the official.

Specifically, the agency went after Dow, attempting and failing to refute the chemical manufacturer's analytical studies of dioxin. "In the process, we ended up finding dioxin at Hempstead and elsewhere. All indications are that Dow is right. If you look for dioxin, you'll find it," he says.

Another EPA official maintains that good incinerator combustion and particulate controls can reduce dioxin emissions to negligible levels. "The whole issue of micropollutants is not an issue. But we can't just say it now. We've got to prove it and that will take three years and anywhere from $10 million to $18 million," he says, adding, "There are couple of us who ought to be shot for raising the issue in the first place." Yah! Yah! □



Cable stayed bridge will offer competing concrete and steel superstructure designs.

Design let for record span

British Columbia's Ministry of Transportation and Highways has retained consultants to prepare detailed alternate designs of a bridge that will have the world's longest cable-stayed span. The agency expects to call for bids on the structure, now estimated at $64 million (U.S.), early next year. The total project, including approaches, will cost about $110 million.

The four-lane, high-level crossing is to span one channel of the Fraser River ear Vancouver, reaching from the eastern shore to Annacis Island. A low-level bridge will cross the other channel.

An earlier feasibility and preliminary engineering study prepared by CBA Engineering Ltd., Vancouver, for the major structure proposes a main span of 440 m (1,444 ft), rising 184 ft above the water. One engineer involved with the ment might shorten the main span slightly or extend it to about 1,520 ft. In either case, it would capture the record. The longest stayed girder main span now is 1,325 ft, part of a Loire River crossing in France completed in 1975.

The ministry has commissioned competing concrete and steel deck superstructure designs. The former assignment went to a combine of two Vancouver firms, Bush, Bohlman & Partners and Reid, Crowther & Partners Ltd. They have retained as an adviser the Vancouver office of DRC Consultants, Inc., New York City. Design of the steel alternative went to CBA along with Buckland & Taylor, also of Vancouver. Foundation design will be carried out by Golder and Associates, based in the same city.

The crossing, totaling about 9,000 ft with its approaches, is slated for comple-

China vows compensation for canceled projects

Japanese lost $1.57 billion

Chinese Deputy Premier Gu Mu told former Japanese Foreign Minister Saburo Okita that his country is willing to compensate Japanese corporations that lost money when China unilaterally canceled several multimillion-dollar construction projects, press reports from Beijing say.

According to Japanese reports, Gu Mu apologized to Okita for the troubles China's "readjustment of the national economy" had caused and said China is willing to make up for Japan's financial losses "in accordance with international commercial practices."

Okita, as the Japanese government's trade representative, flew to Beijing last week to learn of China's plans regarding a series of cancelations and postponements of steel and petrochemical plants whose contracted value for Japanese firms reportedly totaled almost $1.57 billion.

Chinese trade officials plan to visit Tokyo soon to discuss how to handle the situation, which Japanese industry worries might lead to a near-freezing of trade relations between the two countries.

Japanese contractors were keeping a cautious attitude. "It is a matter of common sense that China pay compensation in accordance with international custom," says one industry source. "Our concern is to what degree and with what priority. We will ask the Chinese to make up for our loss 100%."

Major Japanese projects canceled by China include a $420-million hot-strip mill complex, a $640-million cold-strip mill and petrochemical complexes worth $32 million, $260 million and $500 million. □

U.S. readies Oman as troop staging site

8470

Oman is shaping up as the likeliest site for initial staging of U.S. troops and air units to police the Persian Gulf area. Administration officials refuse to comment on such a prospect but recent events make it increasingly credible.

The Sultan of Oman told President Reagan last week of his "concern," says one source, about a steady buildup of Soviet naval forces in the Indian Ocean, centered on South Yemen. Simultaneously, some 250 Army and Air Force troops prepared to embark for Oman to set up a military communications center oriented to the needs of rapid-deployment U.S. air

240

8471

JAN 19 1982

STATE OF CALIFORNIA — EDMUND G. BROWN JR., Governor

DEPARTMENT OF FOOD AND AGRICULTURE

1220 N Street, Room A151
Sacramento 95814

January 12, 1982

R. W. Colby, Ph.D.
DOW CHEMICAL U.S.A.
Route 1, Box 1313
Davis, California 95616

Dear Dr. Colby

Subject: Special Local Need Registrations
ESTERON BRUSH KILLER, CA-780065
ESTERON 245 HERBICIDE, CA-780066

This letter is to notify you that the subject first-party special local need registrations have been inactivated at your request.

If you have any further questions, please contact me.

Sincerely

M D Black

M. D. Black
Registration Specialist
Pesticide Registration and
Agricultural Productivity
(916) 322-5130

cc Ferial Bishop, EPA
Agricultural Commissioners

8472

DEVELOPMENTAL PRODUCT TRANSFER TO COMMERCIAL STATUS

INITIATOR

1. INITIATED BY: R. L. Gantz | DIVISION: Ag Products | LOCATION: Midland | DATE: 8/25/81

PROPOSED DESIGNATION: ESTERON®245 BE Herbicide | CURRENT DESIGNATION: Dow Rangeland Brush Killer I (XRM-4498)

GENERIC PRODUCT DESCRIPTION: 2,4,5-T butoxyethyl ester, emulsifiable concentrate containing 4.0 lb. ae/gal.

DOW 214430 MN 300822

X — DEVELOPMENT COMPLETED

— — MARKET OLD PRODUCT

X - Plan to sell in 1982 Subregistered under Union Carbide registration

PROD. RESPON.

2. ADDED INVESTMENT REQUIRED TO PURCHASE OLD ITEM: — | DATE REQUIRED: — | DATE FOR PRODUCTION: —

ITEMS TO BE DISCONTINUED: —

None (Pending)

PATENT STATUS REVIEWED

R. L. Gantz Ag, 9008, Midland R. L. Gantz 8/26/81

---------- same

APPROVAL

J. W. Ehrmantraut J W Ehrmantraut 8/31/81 (Produced by U.C. for Dow)

C. R. Wood C R Wood 9/9/81 R. F. Flannery R F Flannery 9-9-81

Comments:

Dow makes the technical ester for this product which is also formulated and sold by Union Carbide as "WEEDONE 2,4,5-T". Dow needs to sell this subregistered product in order to liquidate a large inventory of the technical butoxyethyl ester of 2,4,5-T. (Approved Advance to Sales is attached for reference.)

DISTRIBUTION

PROD. SAFETY COMPLIANCE/ LABELING

8473

0008546

JWE.

bcc: J. Gledhill/J. Tic

DOW CHEMICAL U.S.A.

MICHIGAN DIVISION
March 19, 1982

MIDLAND, MICHIGAN 48640

818/CONN

A. E. Schober
H&E Sciences
1803 Building

cc: C. H. Goodman, 2030

ESTERON 2,4,5 BE-TCDD ANALYSIS

Currently our inventory of BEE 2,4,5-T technical ester is made up of one bulk tank which contains about 635,000 pounds of product and 16,500 pounds of product packaged in 55 gallon drums. The bulk tank was sampled on March 2, 1982, and was analyzed and found to contain 2 ppb of 2,3,7,8 TCDD. The analytical research method used is an unvalidated research method with a detection limit of 1 ppb. I have attached the raw analytical data which includes the chromatograms.

All of the product in 55 gallon drums is from one production lot and will be sampled and analyzed next week. I will communicate the results as soon as they are available.

DOW 2111319?

D. T. Buzzelli
Ag Chemicals Production
Environmental Services

r

Attachment

cc A/O file

8475

LIFE IS FRAGILE · HANDLE WITH CARE

STANDARD

$\frac{9}{3.8} \times 100 \times \frac{1}{10} = 2.4$

Samples concentrated 10 times

STANDARDS

$\frac{8}{3.5} \times 100 \times \frac{1}{10} = 2.3$

STANDARDS

DOW 2193198

THE DOW CHEMICAL COMPANY QUALITY ASSURANCE 28751
PRODUCTION SPECIFICATION

PRODUCT CODE: 28751 GAC: 290 EFFECTIVE:

NAME: ESTERON (R) 245 BE HERBICIDE

DESC: AMBER, OILY, EMULSIFIABLE LIQUID.
APPL GOVT/IND STDS: EPA REG. NO. 264-89-464
EPA EST. NO. 464-MI-1

MN0123332

PRODN PTS U.S. :MN DEPT: 31

TEST ITEM	UNIT	LIMITS	TEST METHODS
2,4,5-TRICHLOROPHENOXY ACETIC (2,4,5-T) BUTOXY ETHYL ACID, ESTERS, MIN.	%	~~MIN.~~ 60.9	~~PENDING~~ 28751
2,4,5-T ACID EQUIV., MIN.	%	~~MIN.~~ 43.8	28751
2,4,5-T ACID EQUIV.	LBS/GAL	3.97-4.1	28751
INERT INGREDIENTS	%	~~MAX.~~ 39.1	28751
2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN	PPM	<0.1 BASED ON 2,4,5-T ACID	
*SPECIFIC GRAVITY @ 20	LBS/GAL	~~1.089~~ 1.089 (APPROX.)	ASTM D891
*EMULSION CREAM RATE @ 1 HR.			AG 156-2
* 100 PPM HARD WATER	ML	1.0 MAX.	
* 500 PPM HARD WATER	ML	0.8	
------COMPOSITION (NOMINAL)------			
*M			
*2,4,5-T,BUTOXYETHYL ESTERS	%	~~MIN.~~ 60.9	027613-72-5
*ASSOCIATED COMPONENTS FROM 2,4,5-T BUTOXYETHYLESTER, TOTAL, MAX.	%	1.8	REQUESTED
*GAFAC PE 410	%	2.3	TNO
*GAFAC PE 510	%	3.5	REQUESTED
~~*AROMATIC SP~~ AROMATIC/ALIPHATIC BLENDED OIL	%	31.3	
------MISCELLANEOUS------			
~~*SPECIFIC GRAVITY 60/60 F 1.075 APPROX.~~			
------RAW MATERIALS------		-RM SPEC-	CAS# --
*2,4,5-T ACID BUTOXY ETHYL ESTER			002545-59-7
*GAFAC PE 410			TNO
*GAFAC PE 510			TNO
*KEROSENE		42731-51	008008-20-6
*NAPHTHA, HEAVY AROMATIC SOLVENT		56204-91	068333-88-0

PRODN NOTE:
FORMULATION IS XRT 4498.

(R) INDICATES A TRADEMARK OF THE DOW CHEMICAL COMPANY
* * * D A T A C O N F I D E N T I A L * * * ANOTHER PAGE FOLLOWS

DOM 2133681

PRODUCT CODE: 28751
(CONTINUED)

MN0123332

PRODUCTION SPEC APPROVERS:

APPROVALS	DIV-DEPT	DATE	APPROVALS	DIV-DEPT	DATE
J M Tudor	NCRES 489	3-23-82			
M J Lynch	CPRES 489	3-23-82			
J F Fedders	ACP Admin	3.23.82			
Bob Seeburger	mktg	4-27-82			

PRODUCTS NOT MEETING THIS SPECIFICATION MUST NOT BE SHIPPED
UNLESS AUTHORIZED BY SALES AND PRODUCTION MANAGEMENT
(R) INDICATES A TRADEMARK OF THE DOW CHEMICAL COMPANY
* * * D O W C O N F I D E N T I A L * * * LAST PAGE

DOW 2133682

8473 0008424

DOW CHEMICAL U.S.A.

March 24, 1982

MIDLAND, MICHIGAN 48640

Mr. T. E. Adamczyk, Head
Technical Support Section
Fungicide-Herbicide Branch
U.S. Environmental Protection Agency
401 M Street, S.W., Room 239
Washington, D. C. 20460

Subject: ESTERON 245BE
EPA Reg. No. 464-574
Your letter of March 16, 1982

Dear Mr. Adamczyk:

Enclosed are five copies of finished labeling for subject product. The Dow Chemical Company agrees that we will submit and/or cite all data required for registration/reregistration of this product under FIFRA Section 3(c)(5) when the Agency requires all registrants of similar products to submit such data.

Also enclosed is a revised Confidential Statement of Formula declaring maximum TCDD contamination of less than 0.008 ppm (acid equivalent) for the technical ester. As described in the attached letter of D. T. Buzzelli, the majority of the technical ester (EPA Reg. No. 464-491) is in one bulk tank. The attached chromatagram and raw lab book data demonstrate the TCDD content of this quantity to be 2 parts per billion. This is the technical ester we intend to formulate and package at this time. Since it is in bulk storage and represents several "batches" of production produced according to the manufacturing process already submitted, analyses of individual batches is not possible. The single sample analysis is therefore representative.

The 16,500 pounds of technical ester stored in 55 gallon drums is from one production lot and is currently being analyzed. This material will not be used until the analysis is completed to ensure that it contains less than 0.008ppm TCDD. The analysis of this production lot will be submitted as soon as it is completed. We trust that final conditional registration can be granted immediately and not be held up while this analysis is being completed.

The Dow Chemical Company verifies that the amount of ESTERON 245BE to be formulated, approximating 114,000 gallons, will be from existing stocks of technical ester produced by the manufacturing process already submitted. We further understand that any future production of ESTERON 245BE or its active ingredient by a different manufacturing process would require an amended registration.

Thank you for the excellent cooperation in expediting this registration.

Sincerely,

Arthur E. Schober

Arthur E. Schober
Product Registration Manager
Agricultural Products Department

nbe
Attach:

bcc: C. Goodman - 2030
D. Buzzelli - 834
E. Conyers
R. Laning
E. Ross

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DOW 2115845 MN071991

Disregard! See letter of 3-16-82
RES 3-8-82

Mr. Arthur E. Schober
The Dow Chemical Company
P.O. Box 1706
Midland, MI 48640

Dear Mr. Schober:

Subject: Esteron 245 BE
EPA File Symbol 464-LTU
Resubmission: February 3, 1982

We have completed review of the materials submitted on the above date. The data concerning the TCDD levels in this product are incomplete.

It is our understanding, from discussions with individuals in our Office of General Counsel, and based on a February 25th conversation with Mr. Akerman, that this application applies to existing stocks of 2,4,5-T butoxyethanol ester. Please confirm this for the record. In order to reasonably assess this proposal we need to know the size of existing stocks and the dates of manufacture. For the TCDD contaminant levels reported, you must submit raw analytical data and chromatograms for at least 5 batches representative of commercial production. If the existing stocks were produced at various intervals, samples must adequately cover the different batches.

Is the manufacturing process described in this submission that intended for future production?

The formula statement submitted November 9, 1981 states a maximum TCDD content of 0.1 ppm. The manufacturing process for this ester as submitted specifies a typical analysis of 0.02 ppm. Since the level of TCDD contaminant is an issue in the present negotiations between yourselves and the Agency over continued registerability of 2,4,5-T pesticides you must furnish a full and accurate description of the TCDD contaminant in this ester.

Sincerely,

Richard F Mountfort

Richard F. Mountfort
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (TS-767)

8484

0008346

DOW CHEMICAL U.S.A.

March 2, 1982

MIDLAND, MICHIGAN 48640

DOW 2115846 MN071991

bcc: E. S. Conyers
C. H. Goodman - 2030
E. R. Laning
G. L. Ytzen
E. R. Ross

Mr. James K. Akerman
Chief-Herbicide-Fungicide Branch
Environmental Protection Agency
401 M Street, S.W., Rm. 237
Washington, D. C. 20460

Subject: ESTERON* 245BE
EPA File Symbol 464-LTU

Dear Mr. Akerman:

On November 9, 1981, Dow applied for registration of subject formulation. The purpose of this registration is only to enable Dow to dispose of our inventory of technical ester, which was produced earlier for another formulator. This ester was manufactured by the process submitted February 3, 1982.

The inventory of the technical 2,4,5-T butoxyethyl ester has a 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) content of less than 0.008 ppm. As you know, 2,4,5-T and silvex negotiations are presently in progress between EPA and Dow which may result in agreement concerning permissible levels of TCDD in higher or lower levels. Therefore, the level stated for this inventory should not be construed as a precedent for other inventories which may be a subject of the negotiations.

We also assume that since no other concerns have been raised by EPA about this application, the label wording as submitted is acceptable. Accordingly, to assure meeting a very tight production schedule we have ordered containers to be printed on that basis.

We trust this clarification will enable acceptance of this application.

Sincerely,

Arthur E. Schober

Arthur E. Schober
Product Registration Manager
Agricultural Products Department

nbe

cc: Edward C. Gray, Esquire
Acting Associate General Counsel
Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

8485

DOW CHEMICAL U.S.A.

February 3, 1982 P. O. BOX: 1706 MIDLAND, MICHIGAN 48640

Mr. Richard Mountfort
Product Manager (23)
Registration Division (TS-767C)
U.S. Environmental Protection Agency
401 M Street S.W.
Washington, D. C. 20460

Subject: ESTERON 245BE
EPA File Symbol 464-LTU
Your Letter of January 13, 1982

Dear Mr. Mountfort:

Attached are the data requested to enable completion of the processing of this application.

1. A description of the manufacturing process, including composition and purity of starting and intermediate materials. A theoretical discussion of impurities which may be present is also included.

2. Physical and chemical properties.

3. Analytical methods for active ingredient and impurities in the technical product including validation reports and raw data.

4. Analytical method for active ingredient in the formulation.

We trust that these data will enable the registration to be issued. While negotiations are underway between ourselves and the Agency regarding 2,4,5-T, we hope that registration can proceed under FIFRA Section 3(c)(7)(A).

If additional data of a nature similar to this request are deemed necessary for this registration under the "cite all" method, we respectfully request that a "conditional registration" be granted. This would enable us to participate in this use season which begins in March.

I will call in a few days to learn the status of the application. We appreciate the excellent cooperation we have received.

Sincerely,

Arthur E. Schober
Product Registration Manager
Agricultural Products Department

bcc: C. Goodman - 2030
E. R. Laning - 9008
G. L. Ytzen - 9008
Sherri Arnold - 2030(Attachment)
Duane Fairbairn - Sarnia "
Eva Ross - 9008 "

nbe
Attach:

8486

DOW CHEMICAL U.S.A.

November 9, 1981

MIDLAND, MICHIGAN 48640

DOW 2115869

MN071991

Mr. Richard Mountfort
Product Manager (23)
Registration Division (TS-767C)
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

SUBJECT: ESTERON 245 BE
APPLICATION FOR NEW REGISTRATION

Dear Mr. Mountfort:

Enclosed is an application for registration of ESTERON 245 BE, a formulation containing the butoxyethyl ester of 2,4,5-T. The label copy is identical to that of our ESTERON 245 (EPA Reg. No. 464-205) which contains the propylene glycol butyl ether esters of 2,4,5-T.

ESTERON 245 BE is essentially identical to a presently registered product (EPA Reg. No. 264-89). We therefore request that this application proceed under Section 3(c)(7)(A) of FIFRA as amended. The Dow Chemical agrees that it will submit and/or cite all data required for registration/re-registration of this product under FIFRA Section 3(c)(5) when the Agency requires all registrants of similar products to submit such data.

In the event that it is necessary to obtain concurrence from an EPA attorney that this application may be processed, we suggest either Mr. Edward Gray or Mr. Timothy Backetrom be contacted.

Sincerely,

Arthur E. Schober

A. E. Schober
Product Development Manager
Development and Registration
Agricultural Products Department

nbe
Enc.

bcc: E. R. Laning
C. D. Woods - 2030 (label)
C. H. Goodman - 9001 (label)
G. L. Ytzen
2,4,5-T BE Action File
Start New File, ESTERON 245 BE

8487

REVISED 8/16/79

CERTIFICATION STATEMENT

EPA File Symbol/ Reg. No. 464- Date of application to which this statement applies 11-9-81

Product Name ESTERON 245 BE

Applicant's Name and Address Dow Chemical Company
P. O. Box 1706
Midland, MI 48640

MN071991

DOW 211-5872

I certify that I have notified in writing the companies (except those with whom I have reached written agreement) who have submitted data upon which I have relied to support my application and offered to:

1. Pay compensation for those data in accordance with Sections 3(c)(1)(D) and 3(c)(2)(D) of the Federal Insecticide, Fungicide and Rodenticide Act, as amended; and

2. Commence negotiations to determine which data are subject to the compensation requirements of FIFRA, and the amount and terms of compensation, if any, due.

The companies I have notified are:

[x] All companies listed on the Pesticide Data Submitters List for all active ingredients contained in my product (see 40 CFR 162.9-5). (Check this box only if you are using the "cite-all" method of support.)

[ ] All companies listed on the Pesticide Data Submitters List for all active ingredients contained in my product which are not derived from registered and purchased products (see 40 CFR 162.9-8(f)). (Check this box only if you are using the "combined" method of support.)

[ ] Those companies who have conducted the studies which I have submitted (or cited if conducted with an identical product)(see 40 CFR 162.9-8(e)). (Check this box if you are using either the "alternate" method of support or the "combined" method of support.)

Signature and Title A. E. Schober Product Registration Manager

Typed name A. E. Schober Date signed Nov. 9, 1981

8488

0008350

AIR APPLICATION FOR BRUSH CONTROL

Consult the Agricultural Experiment Station, your local Extension Service Weed or Range specialists for best time to treat and need for re-treatment in your area. Do not use from early boot to milk stage where grass seed production is desired.

Mesquite: Use 1 pint ESTERON 245BE plus 1/2 to 1 gallon of oil in enough water to make 4 gallons of total spray per acre. Apply 40 to 90 days after first leaves appear.

Sand Shinnery Oak: Use 1/2 to 1 quart of ESTERON 245BE plus 1 gallon of oil in enough water to make 4 gallons of total spray per acre.

Post and Blackjack Oaks: Use 2 quarts of ESTERON 245BE plus 1 gallon of oil in enough water to make 4 to 6 gallons of total spray per acre.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

STORAGE: Keep container tightly closed when not in use. This product can be stored in an unheated building. If exposed to subfreezing temperatures, the product should be warmed to at least 40°F and mixed thoroughly before using.

PESTICIDE DISPOSAL: Pesticide, spray mixture or rinsate that cannot be used according to label instructions must be disposed of according to Federal, State, or local procedures under the Resource Conservation and Recovery Act.

CONTAINER DISPOSAL: Do not reuse containers. Dispose of them in a sanitary landfill or by other State and local procedures.

USE PRECAUTIONS

Note: Do not graze dairy animals on treated areas within 6 weeks after application. Do not graze meat animals on treated areas within 2 weeks of slaughter.

AVOID CONTACT WITH 2,4,5-T SUSCEPTIBLE CROPS AND OTHER DESIRABLE BROADLEAF PLANTS—ESTERON 245BE Herbicide is injurious to most broadleaf plants. Therefore, do not apply directly to or otherwise permit even minute amounts to contact cotton, grapes, tobacco, fruit trees, vegetables, flowers, ornamentals or other desirable plants susceptible to 2,4,5-T. Do not use in or near a greenhouse.

DO NOT APPLY IN THE VICINITY OF COTTON, GRAPES, TOBACCO, TOMATOES OR OTHER DESIRABLE 2,4,5-T SUSCEPTIBLE CROPS OR ORNAMENTAL PLANTS.

DO NOT SPRAY WHEN WIND IS BLOWING TOWARDS SUSCEPTIBLE CROPS OR ORNAMENTAL PLANTS.

AVOID SPRAY DRIFT—Applications should be made only when there is no hazard from spray drift since very small quantities of spray, which may not be visible, may severely injure susceptible crops during both growing and dormant periods. Use coarse sprays to minimize drift since, under adverse weather conditions, fine spray droplets may drift a mile or more. The spray thickening agent, NALCO-TROL[1], may be used with this product to aid in reducing spray drift. If used follow all use recommendations and precautions on the product label.

[1]NALCO-TROL—Trademark of NALCO Chemical Company

GROUND EQUIPMENT—With ground equipment, spray drift can be lessened by keeping the spray boom as low as possible; by applying 20 gallons or more of spray per acre; by using no more than 20 pounds spraying pressure with large droplet producing nozzle tips; by spraying when wind velocity is 8 miles per hour or less. Do not apply with hollow cone-type insecticide or other nozzles that produce a fine-droplet spray.

SPECIMEN LABEL
(BACK)

DOH 2122309

0008388

8490

DOW 2122495

MN012332

0008359 8491

AIR APPLICATION FOR BRUSH CONTROL

Consult the Agricultural Experiment Station, your local Extension Service agent or Ranger concerning the best time to treat and read the instructions in your area. Do not use more early than is safe stage where grass seed production is desired.

10 pounds: Use 1 pint ESTERON 245BE plus 1/2 to 1 gallon of oil in enough water to make 4 gallons of total spray per acre. Apply 40 to 50 days after first harvest or prior.

Sand Sagebrush Only: Use 1/2 to 1 quart of ESTERON 245BE plus 1 gallon of oil in enough water to make 4 gallons of total spray per acre.

Pine and Black Jack Oaks: Use 2 quarts of ESTERON 245BE plus 1 gallon of oil in enough water to make 4 to 8 gallons of total spray per acre.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

STORAGE: Keep container tightly closed when not in use. This product can be stored in an unheated building. If exposed to subfreezing temperatures, the product should be warmed to at least 40°F and mixed thoroughly before using.

PESTICIDE DISPOSAL: Pesticide, spray mixtures or rinsates that cannot be used according to label instructions must be disposed of according to Federal, State, or local procedures under the Resource Conservation and Recovery Act.

CONTAINER DISPOSAL: Do not reuse containers. Dispose of them in a sanitary landfill or by other State and local procedures.

USE PRECAUTIONS

Note: Do not graze dairy animals on treated areas within 5 weeks after application. Do not graze meat animals on treated areas within 2 weeks of slaughter.

AVOID CONTACT WITH 2,4,5-T SUSCEPTIBLE CROPS AND OTHER DESIRABLE BROADLEAF PLANTS – ESTERON 245BE Herbicide is injurious to most broadleaf plants. Therefore, do not apply directly to or otherwise permit even minute amounts to contact cotton, grapes, tobacco, bean trees, vegetables, flowering ornamentals or other desirable plants, because as 2,4,5-T. Do not use in or near a greenhouse.

DO NOT APPLY IN THE VICINITY OF COTTON, GRAPES, TOBACCO, TOMATOES OR OTHER DESIRABLE 2,4,5-T SUSCEPTIBLE CROPS OR ORNAMENTAL PLANTS

DO NOT SPRAY WHEN WIND IS BLOWING TOWARDS SUSCEPTIBLE CROPS OR ORNAMENTAL PLANTS

AVOID SPRAY DRIFT – Application should be made only when there is no hazard from spray drift since very small quantities of spray, which may not be visible, may severely injure susceptible crops during both growing and dormant periods. Use coarse sprays to minimize drift and to smaller droplets, under certain conditions. Spray drifting may drift a mile or more. The spray discharging agent "HALCO TROL", may be used with this product to aid in reducing spray drift. If used follow all use recommendations and precautions on the product label.

"HALCO TROL" - Trademark of HALCO Chemical Company

GROUND EQUIPMENT – Most ground equipment, spray drift can be minimized by keeping the spray boom as low as possible, by applying 20 gallons or more of spray per acre, by using no more than 30 pounds spray pressure with large droplet producing nozzle tips, by applying when wind velocity is 5 miles per hour or less. Do not apply with medium sized type insecticides or other sprayers that produce a fine droplet spray.

DOW

Esteron 245BE herbicide

FOR THE CONTROL OF TREES, BRUSH AND BROADLEAF WEEDS

Low-Volatile Brush and Weed Herbicide for Industrial Vegetation Control, Fencerows, and Rangeland

Contains Butoxyethyl Ester of 2,4,5-T
Acid Equivalent: 4 Pounds per Gallon

ACTIVE INGREDIENT
2,4,5 Trichlorophenoxypropionic Acid,
Butoxyethyl ester 59.1%
INERT INGREDIENTS 40.9%
2,4,5 Trichlorophenoxyacetic Acid Equivalent 42.5% - 4 Pounds per Gallon
Contains petroleum distillates
E.P.A. Registration No. 464-574 E.P.A. Est. 464-MI-1

PRECAUCION AL USUARIO: Si usted no lee inglés, no use este producto hasta que la etiqueta le haya sido explicada completamente.
TRANSLATION TO THE USER: If you cannot read English, do not use this product until the label has been fully explained to you.

KEEP OUT OF REACH OF CHILDREN

CAUTION

HARMFUL IF SWALLOWED • MAY CAUSE IRRITATION
Read Complete Precautionary Statements on Side Panel

In case of an emergency endangering life or property involving this product call collect 517-636-4400

AGRICULTURAL CHEMICAL
Do Not Ship or Store with Food, Feeds, Drugs or Clothing

3.79 L / 1 gal

NOT FOR REPRODUCTION

KEEP OUT OF REACH OF CHILDREN

CAUTION

PRECAUTIONARY STATEMENTS
Hazards to Humans and Domestic Animals
HARMFUL IF SWALLOWED MAY CAUSE IRRITATION
Avoid Contact with Skin, Eyes, or Clothing • Wash Thoroughly After Handling

Statements of Practical Treatment
In case of contact, immediately flush eyes or skin with plenty of water. Get medical attention if irritation persists. If swallowed, do not induce vomiting. Call a physician.

Physical or Chemical Hazards
Do Not Cut or Weld Container

Environmental Hazards
This product is toxic to fish. Keep out of lakes, streams or ponds. Do not apply where runoff is likely to occur. Do not contaminate water by cleaning of equipment or disposal of wastes. Do not contaminate irrigation ditches or water used for irrigation or domestic purposes.

USE PRECAUTIONS (continued)

AERIAL APPLICATION – Wind, aircraft, drift can be lessened by applying a coarse spray, by using no more than 30 pounds spray pressure at the nozzles, by using straight stream nozzles directed straight back; by using a spray boom no longer than 3/4 the wing span of the aircraft; and by spraying only when wind velocity is less than 8 mph.

DO NOT APPLY BY AIRCRAFT WHEN AN AIR TEMPERATURE INVERSION EXISTS. Such a condition is characterized by haze or fog called, with no temperature losses near the ground than at higher levels. The use of a continuous smoke column at or near site of application is suggested as indicating direction and velocity of air movement, and to indicate a temperature inversion by layering of the smoke.

As high temperature vapors from this product may injure most nearby planted growing crops. Do not use in or near a greenhouse. Extended exposure of this herbicide to the soil may temporarily hinder seed germination or plant growth.

Do not use around the home, recreation areas or similar sites.

To avoid injury to shade tree plants, do not plant, handle or apply other agricultural chemicals within the spray coverage of equipment used with ESTERON 245BE except as specified on this label.

Local conditions may affect the use of herbicides. Consult your State Agricultural Experiment Station or Extension Service agent specialized for advice in selecting treatments from this label to best fit local conditions. Be sure that use of this product conforms to all applicable regulations. Apply this product only as specified on this label.

U1100-001-1 70751-360

THE DOW CHEMICAL COMPANY
MIDLAND, MICHIGAN 48640
A Trademark of The Dow Chemical Company

DIRECTIONS FOR USE

It is a violation of federal law to use this product in a manner inconsistent with its labeling.

ESTERON 245BE herbicide is recommended for industrial vegetation control, fencerows, and rangeland. Do not use in forest lands, rights-of-way, or pastures.

This herbicide controls hardwoods and woody plants including such 2,4-D resistant species as: ash, black gum, brambles, gum, hackberry, hawthorn, honeysuckle, maple, mesquite, oak, osageorange, persimmon, pignut, poison ivy, prickly pear cactus, redbay, sassafrass, sweetgum, sweetbay, wild blackberry, wild rose, and yaupon species of trees. Do not apply ESTERON 245BE where spray drift may contact nearby 2,4,5-T susceptible crops or other desirable plants or may contaminate water intended for irrigation or domestic purposes. Read and follow all Use Precautions given on this label.

PREPARING THE SPRAY

Use only diesel oil, No. 1 or No. 2 fuel oil or kerosene where oil is recommended in the spray mixture.

Oil Sprays: Add ESTERON 245BE to the required amount of oil in the spray tank or mixing tank and mix thoroughly. This mixture can be made in any tank before actual use and any agitation is not necessary. Do not prepare, or all water mixtures sprays get into the ESTERON 245BE or into the finished mixture as it may form a gel.

Water Sprays: Fill the spray tank about half full with clean water, add the required amount of ESTERON 245BE and complete filling the tank. Mix thoroughly and continue agitation while applying. Caution: See NOTE in paragraph on Oil Water Mixture Sprays.

Oil Water Mixture Sprays: When vegetation is wood, 1 gallon of ESTERON 245BE will emulsify up to 10 gallons of oil in 100 gallons of spray mixture. First, premix the ESTERON 245BE and oil in a separate container. Do not allow any water or mixture containing water to get into the ESTERON 245BE or the premix. Fill the spray tank about half full with water, then slowly add the premix with continuous agitation and complete filling the tank with water. If the premix is put in the tank without any water, the two water soluble may form a thick, "gooey" lumpy oil emulsion which will be hard to break. As the proper procedure, the oil may be added after the ESTERON 245BE is mixed in the water, but highly vigorous mechanical agitation is required and a poor emulsion may be formed. The premix method is preferred.

NOTE: ESTERON 245BE in water or oil-water sprays forms an emulsion, not a solution, and separation may take place unless sprays are agitated continuously. Mechanical agitation is not recommended.

HIGH VOLUME SPRAYS

Basal Bark Treatment: Brush and small trees can be controlled by spraying the basal parts of brush stems and tree trunks to a height of 12 to 15 inches from the ground line. Use a solution of 3 gallons of ESTERON 245BE in 100 gallons (1 part in 4 gallons) of oil. With certain resistant species, 4 gallons of ESTERON 245BE in 100 gallons (1 part in 3 gallons) of oil is effective. As only the basal portions of the trees are treated, the total amount sprayed per acre would not be expected to exceed 100 gallons. Knapsack or power equipment may be used. Best complete wetting of the undesired area is necessary, particularly at the ground line. The material spraying until run down or run off to the ground line is noticeable. Old or rough bark requires more spray than young or smooth bark. Low pressure are desirable. Apply at any time, including the winter months, but not when trees are in water and were spraying to the ground line. Other delayed response and kill may can be expected.

Dormant Brush: Treat any time after leaves or die more and when not on the ground has developed. Spray should be concentrated at the base of stems and in addition the upper parts of the stems should be treated per sprayed enough to wet them. Under approaching sprays are such as bumps, persimmon, sycamore and locust, also spray the ground area to control small root suckers that may not be readily visible. Use 1 1/2 gallons of ESTERON 245BE in 100 gallons of oil. Brush of average density and 4 to 6 feet high may take up to 150 gallons of spray mixture per acre.

Stump Treatment: When a growth is more than 6 to 8 feet tall, cut it close to the ground and spray the freshly cut stumps and sides with 3 gallons of ESTERON 245BE in 100 gallons (1 part in 4 gallons) of oil. Invest thoroughly. For more resistant species, use 4 gallons of ESTERON 245BE in 100 gallons (1 part in 3 gallons) of oil. Wet thoroughly all exposed bark, as well as cut surfaces. This means spraying until run down or run off to the ground line is noticeable. Old or rough bark requires more spray volume than young or smooth bark. Apply at any time, including winter months, except when ice, snow or water prevent spraying to the ground line. Best results are obtained on brushy and stumps less inches prices or larger. Adequate coverage normally requires from 10 to 100 gallons per acre depending on density of stumps and size.

"Frill" Treatment: For large trees, make a single hack or girdle at "frill" of overhanging and cuts completely around the tree so close to the ground as feasible. Spray the hack thoroughly using a mixture of 3 gallons of ESTERON 245BE in 100 gallons (1 1/2 pint in 3 gallons) of oil.

Spot Foliage Treatment: Use 1/4 gal of ESTERON 245BE in 3 gallons of water and spray to wet all foliage shoots, leaves and bark without runoff.

LOW VOLUME SPRAYS

Apply low volume sprays containing ESTERON 245BE when foliage is well developed and plants are actively growing. For best results are actively spreading, but moisture should be sufficient to promote later growth. Spraying during prolonged heat, dry weather or after leaves have lost their normal green color and vigor may not give satisfactory control. Apply low volume sprays by air or ground equipment only when spray drift and not be a problem - such as pastures.

Basal Treatment Using Powered Knapsack Sprayer - Mix 1 1/2 to 2 gallons of ESTERON 245BE with fuel oil or kerosene to make 25 gallons of basal spray solution. Apply with a suitable knapsack mistblower to all sides of basal brush stems including the root collar. Good coverage of the stem collar is essential for best results. Run mistblower at 1/4 to 1/2 throttle for best spray delivery and coverage. For maximum drift control use a basal nozzle attachment and do not work nozzle above the horizontal position.

NOTICE: Seller warrants that the product conforms to its chemical description and is reasonably fit for the purposes stated on the label when used in accordance with directions under normal conditions of use. Seller neither this warranty nor any other warranty, of MERCHANTABILITY or FITNESS FOR A PARTICULAR PURPOSE (express or implied) extends to the use of any product if in any to label instructions or under abnormal conditions or under conditions not reasonably foreseeable to seller, and buyer assumes the risk of any such use.

SPECIFICATION	ALL BLACK AREAS APPEAR PANTONE 347 GREEN
12106-001-1	
DA: Dow 3-1-87 Binding Ed. Corrected	TRADEMARKS: SC, J 5/11/87
	ALL WHITE AREAS APPEAR PANTONE WHITE

THE DOW CHEMICAL COMPANY QUALITY ASSURANCE OFFICE
DACAC SPECIFICATION CONFIRMATION COPY

DATE PRINTED: 11-AUG-82 PAGE: 1
PRODUCT: 28752 DAC: 290 REVISED: 27 JUL 82 REPLACES: 28752 6 APR 82

NAME: ESTERON (R) 245C HERBICIDE

DESC: AN EMULSIFIABLE HERBICIDE FORMULATION CONTAINING THE BUTYL ESTERS OF 2,4,5-TRICHLOROPHENOXYACETIC ACID.
MSD: NONE

PROD'N PTS LAT.AMER. :LC DEPT: 31

	REVISION	DATA	TERM'L	RAW MAT'L	SALES	TEST METHOD
DATES :	:	:	:	:	:	
LATEST:	27 JUL 82	:	:	:		
PRIOR :	6 APR 82	:	:	:		

------TEST ITEMS------

:2,4,5-TRICHLOROPHENOXYACETIC (2,4,5-T) ACID, BUTYL ESTER, MIN. UNIT:WT %					
:54.7	:---	:---	:---	:---	:LA-AMC-82001
:2,4,5-T ACID EQUIVALENT, MIN. UNIT:WT %					
:44.8	:---	:---	:---	:---	:LA-AMC-82001
:2,4,5-T ACID CONTENT, MIN. UNIT:G/L					
:480	:---	:---	:---	:---	:LA-AMC-82001
:2,4,5-T ACID CONTENT, MIN. UNIT:LB/GL					
:4.0	:---	:---	:---	:---	:LA-AMC-82001
:2,3,7,8 TETRACHLORO DIBENZO-P-DIOXIN, MAX. UNIT:PPM					
:0.1	:---	:---	:---	:---	:SEE NOTE 1
:EMULSION TEST, 100 PPM & 600 PPM HARDNESS WATER 1/100					
:NO CREAM IN 1 HR.	:---	:---	:---	:---	:AG 15B-2
:SPECIFIC GRAVITY 20/20 C, APPROX.					
:1.272	:---	:---	:---	:---	:ASTM D891

------COMPOSITION (NOMINAL)------

:2,4,5-T ACID BUTYL ESTER UNIT:W/W %					
:54.5	:---	:---	:---	:---	:---
:SALCA UNIT:W/W %					
:5.0	:---	:---	:---	:---	:---
:SURFONIC N-95 UNIT:W/W %					
:3.0	:---	:---	:---	:---	:---
:SULFONIC 3800 UNIT:W/W %					
:3.0	:---	:---	:---	:---	:---
:DIESEL OIL PLUS ESTER IMPURITIES UNIT:W/W %					
:36.4	:---	:---	:---	:---	:---

------RAW MATERIALS------

:2,4,5-T ACID BUTYL ESTER					
:---	:---	:---	:---	:---	:---
:SALCA					
:---	:---	:---	:---	:---	:---
:SURFONIC [illegible]					

(R) INDICATES A TRADEMARK OF THE DOW CHEMICAL COMPANY

PRODUCT: 28752 (CONTINUED) PAGE: 2
NAME: ESTERON (R) 245C HERBICIDE

PROC*N	DATA	TERM*L	RAW MAT*L	SALES	TEST METHOD
------RAW MATERIALS------ (CONTINUED)					
:---	:---	:---	:---	:---	:---
:POLYGLYCOL PP13					
:---	:---	:---	:---	:---	:---
:SURFONIC 3800					
:---	:---	:---	:---	:---	:---
:DIESEL OIL					
:---	:---	:---	:---	:---	:---

DOW 2122541

PROC*N NOTE
REVISION 27 JUL 82 TO CHANGE METHOD NUMBER AND ADD METHOD ITEMS;
CHANGES MADE BY GAA WITHOUT NEW SIGNATURES.
(1) THE LEVEL OF 2,3,7,8 TETRACHLORODIBENZO-P-DIOXIN (TCDD) IN 2,4,5-T ACID AND ITS ESTERS AS PRODUCED BY CELAMERCK, IS LESS THAN 0.1 PPM. SINCE THERE IS NO OTHER SOURCE OF TCDD IN 2,4,5,-T HERBICIDE FORMULATIONS, THE FORMULATIONS THUS CONTAIN LESS THAN 0.1 PPM OF TCDD.
(2) PACKAGING - 208 LTS STEEL DRUMS.

SALES NOTE
NO U.S. SALES SPECIFICATION; MANUFACTURED AND SOLD IN LATIN AMERICAN AREA ONLY.

APPROVERS: W.L. GOLD APPROVAL OF CHANGES INDICATED ABOVE:...
J.M. FRASER .....

APPROVERS OF INDIVIDUAL SPECS:
PRODN: W.L. GOLD GAC 15 JUL 82
PRODN: J.S. WOODS GAA 15 JUL 82
PRODN: J. GILCHRIST PROD 23 FEB 82
PRODN: J. ROLDAN REG. GAC 23 FEB 82
PRODN: C. RAMIREZ R&D 26 FEB 82
PRODN: M.L.S. DEMUJICA LA GAA 8 MAR 82
PRODN: A. CASTRO OPERATIONS 24 MAR 82
PRODN: A. RUIZ R&D 24 MAR 82
PRODN: A. ORLANDI L&A GAC 29 MAR 82
PRODN: J.W. SPENCKPOHL QA DEPT 27 JUL 82
SALES:
TERM:

(R) INDICATES A TRADEMARK OF THE DOW CHEMICAL COMPANY

0008391

8493

PRODUCT: 267-P (CONTINUED) PAGE: 5
UNIT: ESTERON (R) 245 HERBICIDE
(CONTINUED)

APPROVALS	DIV-DEPT	DATE	APPROVALS	DIV-DEPT	DATE

(R) INDICATES A TRADEMARK OF THE DOW CHEMICAL COMPANY

PRODUCT CODE: 28752 FAC: 890 EFFECTIVE: 27 JUL 82 SUPERSEDES: 8 APR 82

WEED ESTER® (R) 2450 HERBICIDE

DESC: AN EMULSIFIABLE HERBICIDE FORMULATION CONTAINING THE BUTYL ESTERS OF 2,4,5-TRICHLOROPHENOXYACETIC ACID.

PRODN PTS LAT.AMER. :LC DEPT: 31

TEST ITEM	UNIT	LIMITS	TEST METHODS
*2,4,5-TRICHLOROPHENOXYACETIC (2,4,5-T) ACID, BUTYL ESTER, MIN.	WT %	54.7	LA-AMC-82001
*2,4,5-T ACID EQUIVALENT, MIN.	WT %	44.8	LA-AMC-82001
*2,4,5-T ACID CONTENT, MIN.	G/L	480	LA-AMC-82001
*2,4,5-T ACID CONTENT, MIN.	LB/GL	4.0	LA-AMC-82001
*2,3,7,8 TETRACHLORO DIBENZO-P-DIOXIN, MAX.	PPM	0.1	SEE NOTE 1
*EMULSION TEST, 100 PPM W 500 PPM HARDNESS WATER 1/1 JAR		2.0 CREAM IN 1 HR.	AG 156-2
*SPECIFIC GRAVITY 25/25 C, APPRX.		1.072	ASTM D891
------COMPOSITION (NOMINAL)------			
*2,4,5-T ACID BUTYL ESTER	W/W %	54.6	
*SALCA	W/W %	3.0	
*SURFONIC N-95	W/W %	3.0	
*SULFONIC 3830	W/W %	3.0	
*DIESEL OIL PLUS ESTER IMPURITIES	W/W %	36.4	

------RAW MATERIALS------	-RM SPEC#	CAS# --
*2,4,5-T ACID BUTYL ESTER		
*SALCA		
*SURFONIC N-95		
*POLYGLYCOL 5913		
*SURFONIC 3830		
*DIESEL OIL		

PRODN NOTE:
REVISION 27 JUL 82 TO CHANGE METHOD NUMBER AND ADD METHOD ITEMS; CHANGES MADE BY QAA WITHOUT NEW SIGNATURES.
(1) THE LEVEL OF 2,3,7,8 TETRACHLORODIBENZO-P-DIOXIN (TCDD) IN 2,4,5-T ACID AND ITS ESTERS AS PRODUCED BY DELAMEPCK, IS LESS THAN 0.1 PPM. SINCE THERE IS NO OTHER SOURCE OF TCDD IN 2,4,5-T HERBICIDE FORMULATIONS, THE FORMULATIONS THUS CONTAIN LESS THAN 0.1 PPM OF TCDD.
(2) PACKAGING - 208 LTS STEEL DRUMS.

PRODUCTION SPEC APPROVED:
LAB. DEPT. MGR. 15 JUL 82
QUAL. ASSUR. MGR. 19 JUL 82

(R) INDICATES A TRADEMARK OF THE DOW CHEMICAL COMPANY

PRODUCT CODE: 28752
(CONTINUED)

J. GILCHRIST PROD 23 FEB 82
J. GOLDEN REG. QAC 24 FEB 82
C. RAMIREZ R&D 25 FEB 82
M.L.E. DENNUDICA LA QAA 8 MAR 82
A. CASTRO PRODUCTION S 30 MAR 82
A. RUIZ R&D 24 MAR 82
A. ORLANDI LAA QAC 29 MAR 82
J.W. OFFENKRONL QA DEPT 27 JUL 82

APPROVALS	:DIV-DEPT	DATE	:APPROVALS	:DIV-DEPT	DATE
	:	:	:	:	:
	:	:	:	:	:
	:	:	:	:	:
	:	:	:	:	:

PRODUCTS NOT MEETING THIS SPECIFICATION MUST NOT BE SHIPPED
UNLESS AUTHORIZED BY SALES AND PRODUCTION MANAGEMENT
(R) INDICATES A TRADEMARK OF THE DOW CHEMICAL COMPANY
* * * D O W C O N F I D E N T I A L * * * LAST PAGE

DOW 2122544

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THE DOW CHEMICAL COMPANY

QUALIFIED PRODUCING POINTS	
CANADA	
EUROPE	
PACIFIC	
LATIN AM.	LC
U.S.A.	

QAC 290 DEPT 31

RESTRICTED
LIMITED INTERNAL USE

PRODUCTION SPECIFICATION

FOR

ESTERON 2,4,5 C HERBICIDE

NUMBER	DATE
P 28752	8APR82
SUPERSEDES	
NUMBER	DATE

APPL. GOV'T./IND. STDS.

TEST ITEM	UNIT	LIMITS	TEST METHODS
2,4,5, T ACID CONTENT	g/l	480 MIN	LA-ALC-82017
2,3,7,8 TETRACHLORO DIBENZO-P-DIOXIN	ppm	0.1 MAX	See Note 1
SPECIFIC GRAVITY, 20/20°C, APROX.		1.072	ASTM D891
EMULSION TEST, 100 ppm AND 600 ppm HARDNESS WATER 1/100		NO CREAM IN 1 HOUR	AG 15b-2

DOW 2122547

COMPOSITION W/W (m)

2,4,5, T ACID BUTYL ESTER	w/w%	54.6 MIN	
SALCA	w/w%	3.0	
SURFONIC N-95	w/w%	3.0	
SULFONIC 3800	w/w%	3.0	
DIESEL OIL PLUS ESTER IMPURITIES	w/w%	36.4	

SALES NOTE: No US sales specification manufactured + sold in LATIN AMERICAN AREA ONLY

PROD NOTE 2. PACKAGING: 205 lts STEEL DRUMS

PROD NOTE 1: THE LEVEL OF 2,3,7,8-TETRACHLORODIBENZO -p- DIOXIN (TCDD) IN 2,4,5,T ACID AND ITS ESTERS AS PRODUCED BY THE CELAMERCK, IS LESS THAN 0.1 ppm. SINCE THERE IS NO OTHER SOURCE OF TCDD IN 2,4,5,-T HERBICIDE FORMULATIONS, THE FORMULATIONS THUS CONTAIN LESS THAN 0.1 pp OF TCDD.

→ DENOTES CHANGE

LIMITED TO DISTRIBUTION INDICAT

ITEMS MARKED WITH AN ASTERISK * ARE NOT TO BE INCLUDED IN THE SALES SPECIFICATION

APPROVED (SIGNATURE)	DIVISION OR DEPT.	DATE	COPIES	APPROVED (SIGNATURE)	DIVISION OR DEPT.	DATE	COPIE
	Production	2-5-82		G.M. Fraser	QA DEPT	8APR82	
	Reg. QAC	Feb 2/82					
	R&D North Form	Feb 4/82					
	L.A. QAA	Mar. 8/82					
	Operations	3/26/82				8497	
	R&D Area	3/17/82					
	LAA QAC	March 29/82					
	QAC/QAA	2APR82					

PRODUCTS NOT MEETING THIS SPECIFICATION MUST NOT BE SHIPPED UNLESS AUTHORIZED BY SALES AND PRODUCTION MGMT.

FORM C-16020
PRINTED R-4-73

SALES SPECIFICATIONS FOR THIS PRODUCT APPROVED FOR OUTSIDE DISTRIBUTION AVAILABLE SALES OFFICES OR FROM QUALITY STANDARDS OFFICES.

0008395

THE DOW CHEMICAL COMPANY QUALITY ASSURANCE 28751-R1
RAW MATERIAL SPECIFICATION INTERNAL COPY

SUPPLIER CONFIDENTIAL

SUPPLIER: DOW CHEMICAL COMPANY

SPEC NO.: 28751-R1 EFFECTIVE DATE: 5 APR 83 GAC CODE: 290

NAME: ESTERON (R) 245 BE HERBICIDE

DESCRIPTION: AMBER, OILY, EMULSIFIABLE LIQUID.
MSDS: 1580

PROD'N PTS U.S. MM

CLASS-COMMODITY CODE: PURCH SUPPLY MGR CODE:

TEST ITEM	UNIT	LIMITS	TEST METHODS
2,4,5-TRICHLOROPHENOXY ACETIC (2,4,5-T) BUTOXYETHYL ACID, ESTER, MIN.	%	60.9	28751
2,4,5-T ACID EQUIV., MIN.	%	43.8	28751
2,4,5-T ACID CONTENT	LBS/GAL	4	28751
INERT INGREDIENTS	%	39.1	28751
2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN	PPM	<0.008 BASED ON 2,4,5-T ACID	

MN012332

DOW 2122629

APPROVED SOURCE	SOURCE REFERENCE	PURCHASED AS
DOW CHEMICAL COMPANY	SALES GRADE 28751	ESTERON 245 BE

END USE	BLDG	LOCATION	USER GAC
DOW 2+2 BRUSH KILLER (P.C. 22030)	---	MM	290

APPROVER: W.L. GOLD/N.G. DELISLE DEPT: QAC 5 APR 83
APPROVER: J.W. DRENCKPOHL DEPT: QA DEPT. 5 APR 83

APPROVALS	DIV-DEPT	DATE	APPROVALS	DIV-DEPT	DATE

0008396

8498

Sample

THE DOW CHEMICAL COMPANY QUALITY ASSURANCE 28751-R1
RAW MATERIAL ~~SALES~~ SPECIFICATION

PRODUCT CODE: 28751 QAC: 290 EFFECTIVE: ~~24 MAY 82~~ 5Apr83 New

NAME: ESTERON (R) 245 BE HERBICIDE

DESC: AMBER, OILY, EMULSIFIABLE LIQUID.
APPL GOVT/IND STDS: EPA REG. NO. 264-89-464
: EPA EST. NO. 464-MI-1

PROD'N PTS U.S. :MM DEPT: 31

TEST ITEM	UNIT	LIMITS	TEST METHODS
2,4,5-TRICHLOROPHENOXY ACETIC (2,4,5-T) BUTOXYETHYL ACID, ESTERS, MIN.	%	60.9	28751
2,4,5-T ACID EQUIV., MIN.	%	43.8	28751
2,4,5-T ACID CONTENT	LBS/GAL	4	28751
INERT INGREDIENTS	%	39.1	28751
2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN	PPM	<0.008 BASED ON 2,4,5-T ACID	

DOW 2122630

MN012332

SALES SPEC APPROVERS:
W.L. GOLD QAC 28 APR 82
J.G. CONTINO PSC 13 APR 82
G. YTZEN PSM 25 MAR 82
J.W. DRENCKPOHL AG QA 25 MAR 82
J.S. WOODS QAC/QAD 28 APR 82
J.W. DRENCKPOHL QA DEPT 24 MAY 82

APPROVALS	:DIV-DEPT	DATE	APPROVALS	:DIV-DEPT	DATE
W.L.Gold/N.G.DeLisle	QAC-290	5Apr83			
T.W. Drenckpohl	QAD	5Apr83			

(R) INDICATES A TRADEMARK OF THE DOW CHEMICAL COMPANY
LAST PAGE

Source
Dow Chemical Co.

Ref.
sales grade 28751

Name
Esteron 245 BE

Formula
Dow 2+2 Brush killer (PC 22036) mm 290

0008397
8499

cont'd

THE DOW CHEMICAL COMPANY QUALITY ASSURANCE 28751
PRODUCTION SPECIFICATION

PAGE: 1

PRODUCT CODE: 28751 GAC: 290 EFFECTIVE:

NAME: ESTERON (R) 245 BE HERBICIDE

DESC: AMBER, OILY, EMULSIFIABLE LIQUID.
APPL GOVT/IND STDS: EPA REG. NO. ~~264-89-464~~ 464-574
EPA EST. NO. 464-MI-1

PROD'N PTS U.S. :MN DEPT: 31

TEST ITEM	UNIT	LIMITS	TEST METHODS
2,4,5-TRICHLOROPHENOXY ACETIC (2,4,5-T) BUTOXY-ETHYL ACID ESTERS, MIN.	%	~~60.0~~ 60.9 (NOTE 1)	PENDING
2,4,5-T ACID EQUIV., MIN.	%	~~43.0~~ 43.8	PENDING
2,4,5-T ACID EQUIV. CONTENT	LBS/~~GAL~~ GSG	3.97-4.1	MN0123332
INERT INGREDIENTS	%	~~40.0~~ 39.1	
2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD)	PPM	<0.05 <~~0.1~~ BASED ON 2,4,5-T ACID	
*SPECIFIC GRAVITY @ 20C	LBS/~~GAL~~ GSG	~~1.110~~ 1.089 (APPROX.)	ASTM D891
*EMULSION CREAM RATE @ 1 HR.			AG 158-2
* 100 PPM HARD WATER	ML	1.0 MAX.	
* 500 PPM HARD WATER	ML	0.8	
------COMPOSITION (NOMINAL)------			
*2,4,5-T BUTOXYETHYL ESTERS	%	~~60.0~~ 60.9	027613-72-5
*ASSOCIATED COMPONENTS FROM 2,4,5-T BUTOXYETHYLESTER, TOTAL, MAX.	%	1.8	REQUESTED
*GAFAC PE 610	%	2.3	TNO
*GAFAC PE 510	%	3.5	REQUESTED
~~*PROPYLENE~~			
AROMATIC/ALIPHATIC BLENDED OIL	%	38.3	
------MISCELLANEOUS------			
~~*SPECIFIC GRAVITY @ 20C~~		~~1.075 APPROX.~~	

DOM 21336B9

------RAW MATERIALS------	-RM SPEC=	CAS# --
*2,4,5-T ACID BUTOXYETHYL ESTER		002545-59-7
*GAFAC PE 610		TNO
*GAFAC PE 510		TNO
*KEROSENE	42731-R1	008008-20-6
*NAPHTHA, HEAVY AROMATIC SOLVENT	56204-R1	068333-88-0

SEE 1. (see back of attached routing sheet at left)

PROD'N NOTE: 1. Specification is for product to be manufactured from existing inventories of 2,4,5-T to BE ester; normal FORMULATION IS ~~XAM 4495~~.

(R) INDICATES A TRADEMARK OF THE DOW CHEMICAL COMPANY
• • • D O W C O N F I D E N T I A L • • • ANOTHER PAGE FOLLOWS

8501 0008425

BE ester manufact anticipat

PRODUCT CODE: 28751
(CONTINUED)

MN0123332

PRODUCTION SPEC APPROVERS:

APPROVALS	:DIV-DEPT	DATE	:APPROVALS	:DIV-DEPT	DATE
	:	:	R.L.GANTZ	:	:
	:	:	V. SCHULTZ	:	:
	:	:	Johnw Dewkett	: Agqa	:15Apr82
S/A.E.Schober	: Ag Regis.	:16Apr82	:	:LH-PSC	:4-13-82

PRODUCTS NOT MEETING THIS SPECIFICATION MUST NOT BE SHIPPED
UNLESS AUTHORIZED BY SALES AND PRODUCTION MANAGEMENT
(R) INDICATES A TRADEMARK OF THE DOW CHEMICAL COMPANY
* * * D O W C O N F I D E N T I A L * * * LAST PAGE

OK
Dlw.

Our registration shows 59.1% ester, 42.5% acid equivalent, 40.9% inerts. The only changes that I believe should be made on the "pending approval" copy are those in red plus John's note 2.

Jess Contino
4-13-82

DOW 2133684

8502

0008426

247

MANUFACTURING SPECIFICATION

DISTRIBUTION FOR APPROVAL

~~J. W. DRINKENBERG~~

SEE BACKSIDE

Please review the attached specification and send to the next person listed.

1. Review specification as listed.
2. Note approval with signature, location and date.
3. If not approved, note necessary changes and initial.

When distribution has been completed:

Return to: John Woodell. Rm
Ag. Chem. Prod'n.
834 Building

ESTERON 245BE HERBICIC

Change in Sp Gr to 1.089 reg
increase in AE % to meet
4 LB/GL product.

COPY #1 sent to PRODUCTION.

TCDD < 0.001 ppm committed to EI
to get registration - ABS.

MND 12332

UUM 2133688

8504

0008428

Note

1. [illegible] claim (59.1% solids 12.5% acid) to existing product meets pounds per gallon claim with formulation using lighter solvent system; is feasible but not desirable ~~to do~~ as product life is likely to deplete current stock.

TWD
16 Apr 82

AES
16 Apr 82

2133687

8505

0008436

QUALIFIED PRODUCING POINTS						
CANADA						
EUROPE						
PACIFIC						
LATIN AM.						
U.S.A.	YMV					
DEPT	21					

DOW

RESTRICTED
LIMITED INTERNAL USE

PRODUCTION SPECIFICATION

NUMBER	DATE
P	initial
SUPERSEDES	
NUMBER	DATE
XRM 4498	9/23/

APPL. GOV'T./IND. STDS.

ESTERON 145BE FOR ~~245BE~~ HEROICIDE — no space, continue, or skip line JWD. EPA REG. 264-89-46 (NOTE 4) ~~EPA EST. NO~~ MN0123332

DESC: 2,4,5-T BUTOXYETHYL ESTER, EMULSIFIABLE CONCENTRATE AMBER, OILY LIQUID.

TEST ITEMS	UNITS	LIMIT	TEST METH
2,4,5-TRICHLOROPHENOXY ACETIC ~~ACID~~ (2,4,5-T) ACID, BUTOXYETHYL ESTER, MIN	WT %	60.9 ~~59.1~~	~~AM-80-66~~
2,4,5-T ACID EQUIVALENT, MIN	WT %	43.8 ~~42.5~~	PERKINS (Colorf ~~AM-80-66~~
2,4,5-T ACID CONTENT	LB/~~GAL~~ USG	3.97-4.1 ~~3.97-4.1~~	PERKINS ~~AM-80-66~~
~~2,3,7,8-~~ 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN ~~(NOTE 1)~~	PPM WT	want to obtain < 0.1 BASED ON 39 ppm 2,4,5-T ACID	(Note 1)
INERT, MAX	WT %	39.1 ~~40.9~~	~~AM-80-66~~ PERKINS
SPECIFIC GRAVITY @ 20°C		~~1.127~~ approx 1.099	ASTM D
EMULSION CREAM RATE @ 1 HR • 100 PPM HARD WATER • 500 PPM HARD WATER	ML	1.0 ~~0.6~~ MAX ~~0.6~~ MAX 0.8	AG 15B-2

MDH 2133688

DENOTES CHANGE — LIMITED TO DISTRIBUTION INDICATE

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APPROVED (SIGNATURE)	DIVISION OR DEPT.	DATE	COPIES	APPROVED (SIGNATURE)	DIVISION OR DEPT.	DATE	COPIES
						8506	

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FORM C-18020
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000843

DOW THE DOW CHEMICAL COMPANY

QUALIFIED PRODUCING POINTS						
CANADA						
EUROPE						
PACIFIC						
LATIN AM.						
U.S.A.						

RESTRICTED
LIMITED INTERNAL USE

PRODUCTION SPECIFICATION

FOR

ESTERON 245 BE HERBICIDE

NUMBER	DATE
P	
SUPERSEDES	
NUMBER	DATE

APPL. GOV'T./IND. STDS.

COMPOSITION		CAS No:	
2,4,5-T Butoxy Ethyl Ester	% ~~57.1~~ 60.9	00 2545-59-7	
Associated Components from 2,4,5-T Butoxy Ethyl Ester - Total, max.	~~2.6~~ 2.0 ~~2.6~~ 1.8	------	
2,3,6-T Butoxy Ethyl Ester, max.	~~1.3~~ ~~1.0~~ 0.8	REQUESTED	
2,4-D Butoxy Ethyl, Ester, max.	0.6 0.4	001929-73-3	
2-Methoxy-4,5-Dichlorophenoxy Acetic Acid, BE Ester, max.	~~0.3~~ 0.2	REQUESTED	
4-Methoxy-2,5-Dichloro Phenoxy Acetic Acid, BE Ester, max.	~~0.3~~ 0.2	REQUESTED	
5-Methoxy-2,4-Dichloro Phenoxy Acetic Acid, BE Ester, max.	~~0.3~~ 0.2	REQUESTED	
GAFAC RE 610	% ~~2.3~~ 2.3	TNO	
GAFAC PE 510	% ~~3.5~~ 3.5	TNO	
~~Aromatic Oil~~ Aromatic/Aliphatic Blended Oil	% ~~33.3~~ balance		

not needed: other components part of spec for 245T BE ester (EPA 464-491) DWD.

MN 012332

UUM 2133689

→ DENOTES CHANGE

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						0008431	

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QUALIFIED PRODUCING POINTS						
CANADA						
EUROPE						
PACIFIC						
LATIN AM.						
U.S.A.						

THE DOW CHEMICAL COMPANY

RESTRICTED
LIMITED INTERNAL USE

PRODUCTION SPECIFICATION

FOR

ESTERON 245 BE HERCICIDE

NUMBER	DATE
P	
SUPERSEDES	
NUMBER	DATE

APPL. GOV'T./IND. STDS.

RAW MATERIALS	R.M. SPEC.	CAS.
2,4,5-T ACID BUTOXY ETHYL ESTER (NOTE 1 + 2)		002545-59
GAFAC RE 610		
GAFAC PE 510		
NAPHTHA, HEAVY AROMATIC SOLVENT	56204-R1	068333-88
DIESEL OIL 260, ESSO		

MN0123323

PRODN NOTE:

1. THE 2,4,5-T ACID USED IN PREPARATION OF THE 2,4,5-T BUTOXY ETHYL ESTER WILL CONTAIN LESS THAN 0.1 PPM WT OF 2,3,7,8- TETRA CHLORO DIBENZO-P-DIOXIN (TCD
2. AMOUNT OF 2,4,5-T BUTOXY ETHYL ESTER BASED ON MINIMUM 97 PERCENT ASSAY (69.7% MINIMUM 2,4,5-T ACID EQUIVALENT).
3. THIS SPECIFICATION IS DERIVED FROM EXPERIMENTAL HERBICIDE XRM 4498.
4. Product is sub-registered from Union Carbide.

DOW 2133690

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E. J. King	Ag Prod.	11-1-81	2	Norma. Mirtlighter	Ag Lit	Cancel	!
A.E. Schelling	Ag. Reg.	11-4-81	1	!			
R.L. Lantz	Ag Products BD	11-5-81	1				
L.D. Hess	Ag Products	11-5-81	1			8508	
[illegible]	EA	11-9-81	1				
M.J. Thrasher	PROD	11-18-81	1				
D.J. Turner	Formulation	12-11-81	1			0008432	
Hugh Seaborn	Methods	12-17-81	0				
John B. Gledhill	Ag Admin	12-21-81	0				

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MN300822

M A T E R I A L S A F E T Y D A T A S H E E T PAGE: 1

OW CHEMICAL U.S.A. MIDLAND MICHIGAN 48640 EMERGENCY PHONE: 517-636-4400

FFECTIVE DATE: 19 MAY 82 PRODUCT CODE: 28751

RODUCT NAME: ESTERON (R) 245 BE HERBICIDE MSD: 1580

NGREDIENTS (TYPICAL VALUES-NOT SPECIFICATIONS)	: % :
2,4,5-TRICHLOROPHENOXYACETIC ACID, BUTYOXYETHYL ESTER	: 59.1 :
EMULSIFIERS PLUS PETROLEUM SOLVENT	: 40.9 :

DOW211130I4

SECTION 1 PHYSICAL DATA

OILING POINT: IBP > 300F (150C) : SOL. IN WATER: EMULSIFIABLE
AP PRESS: <6 MMHG @ 20C : SP. GRAVITY: 1.129 (68/68F)
AP DENSITY (AIR=1): NOT APPLIC. : % VOLATILE BY VOL: NIL UNDER 150C

PPEARANCE AND ODOR: AMBER LIQUID.

SECTION 2 FIRE AND EXPLOSION HAZARD DATA

LASH POINT: 175F, 79C : FLAMMABLE LIMITS
ETHOD USED: TCC : LFL: NOT DETER. UFL: NOT DETER.

XTINGUISHING MEDIA: WATER FOG, FOAM, ALCOHOL FOAM, CO2, DRY CHEMICAL.

PECIAL FIRE FIGHTING EQUIPMENT AND HAZARDS: NOXIOUS FUMES UNDER FIRE CONDITIONS. USE POSITIVE-PRESSURE AIR SUPPLY.

SECTION 3 REACTIVITY DATA

TABILITY: AVOID TEMPERATURES NEAR OR ABOVE FLASH POINT.

NCOMPATIBILITY: ACID, BASE, OXIDIZING MATERIAL. CONSULT MANUFACTURER FOR SPECIFIC CASES.

AZARDOUS DECOMPOSITION PRODUCTS: NOXIOUS FUMES UNDER FIRE CONDITIONS - HYDROGEN CHLORIDE AND OTHERS.

AZARDOUS POLYMERIZATION: WILL NOT OCCUR.

8510

SECTION 4 SPILL, LEAK, AND DISPOSAL PROCEDURES

CTION TO TAKE FOR SPILLS (USE APPROPRIATE SAFETY EQUIPMENT): ABSORB SPILLS WITH INERT DRY MATERIAL SUCH AS SAND OR SAWDUST. DIKE AREA IN IN CASE OF LARGE SPILLS. DO NOT USE WATER FOR CLEANUP.

CONTINUED ON PAGE 2)

0003997

OW CHEMICAL U.S.A. MIDLAND MICHIGAN 48640 EMERGENCY PHONE: 517-636-4400

FFECTIVE DATE: 19 MAY 82 PRODUCT CODE: 28751
RODUCT (CONT'D): ESTERON (R) 245 BE HERBICIDE MSD: 1580

SECTION 4 SPILL, LEAK, AND DISPOSAL PROCEDURES (CONTINUED)

ISPOSAL METHOD: DISPOSE IN ACCORDANCE WITH LOCAL, STATE OR FEDERAL REGULATIONS.

DOW211130015

SECTION 5 HEALTH HAZARD DATA

NGESTION: MODERATE TO LOW SINGLE DOSE ORAL TOXICITY.

YE CONTACT: SLIGHT TRANSIENT CORNEAL INJURY AND IRRITATION.

KIN CONTACT: PROLONGED CONTACT: SLIGHT IRRITATION; REPEATED CONTACT: MODERATE IRRITATION, DRYING, AND EVEN A BURN.

KIN ABSORPTION: NOT LIKELY TO BE ABSORBED IN TOXIC AMOUNTS.

NHALATION: NO GUIDE FOR CONTROL OF MIXTURE ESTABLISHED. DOW INDUSTRIAL HYGIENE GUIDE 10 MG/M3 AEROSOL, 350 MG/M3 VAPOR NAPHTHA.

FFECTS OF OVEREXPOSURE: NAUSEA IF SWALLOWED, ANESTHESIA.

SECTION 6 FIRST AID

YES: IRRIGATION IMMEDIATELY WITH WATER FOR 5 MINUTES IS GOOD SAFETY PRACTICE.

KIN: CONTACT WILL PROBABLY CAUSE NO MORE THAN IRRITATION. WASH OFF IN FLOWING WATER OR SHOWER. WASH CLOTHING BEFORE REUSE.

NHALATION: REMOVE TO FRESH AIR IF EFFECTS OCCUR. IF RESPIRATION STOPS GIVE MOUTH-TO-MOUTH RESUSCITATION.

NGESTION: DO NOT INDUCE VOMITING. CALL A PHYSICIAN AND/OR TRANSPORT TO EMERGENCY FACILITY.

OTE TO PHYSICIAN:
EYES: MAY CAUSE IRRITATION. INJURY IS UNLIKELY. STAIN FOR EVIDENCE OF CORNEAL INJURY.
SKIN: MAY CAUSE IRRITATION. NOT LIKELY TO BE ABSORBED IN ACUTELY TOXIC AMOUNTS. EFFECTS MAY BE CUMULATIVE.
RESPIRATORY: ANESTHETIC OR NARCOTIC EFFECTS MAY OCCUR.
ORAL: MAY CAUSE REACTION SIMILAR TO PETROLEUM OR PETROLEUM-LIKE SOLVENT. DANGER OF CHEMICAL PNEUMONIA MUST BE WEIGHED AGAINST TOXICITY WHEN CONSIDERING EMPTYING THE STOMACH. IF LAVAGE IS PERFORMED SUGGEST ENDOTRACHEAL AND/OR ESOPHAGOSCOPIC CONTROL.
SYSTEMIC: ANESTHETIC OR NARCOTIC EFFECT MAY OCCUR. MAY INCREASE MYOCARDIAL IRRITABILITY. AVOID EPINEPHRINE OR SIMILAR ACTING DRUGS IF AT ALL POSSIBLE. NO SPECIFIC ANTIDOTE. TREATMENT BASED ON THE SOUND JUDGMENT OF PHYSICIAN AND THE INDIVIDUAL REACTIONS OF THE PATIENT.

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CONTINUED ON PAGE 3)

OW CHEMICAL U.S.A. MIDLAND MICHIGAN 48640 EMERGENCY PHONE: 517-636-4400

EFFECTIVE DATE: 19 MAY 82 PRODUCT CODE: 28751
RODUCT (CONT'D): ESTERON (R) 245 BE HERBICIDE MSD: 1580

SECTION 7 SPECIAL HANDLING INFORMATION

ENTILATION: RECOMMEND CONTROL OF NAPHTHA VAPORS OR AEROSALS TO SUGGESTED GUIDE.

ESPIRATORY PROTECTION: NONE LIKELY TO BE NEEDED IN ANTICIPATED OPERATIONS. FOR EMERGENCIES, A POSITIVE-PRESSURE BREATHING APPARATUS OR A FULL-FACE RESPIRATOR WITH AN APPROVED ORGANIC VAPOR CANISTER IS RECOMMENDED.

ROTECTIVE CLOTHING: CLEAN BODY-COVERING CLOTHING.

YE PROTECTION: SAFETY GLASSES WITHOUT SIDE SHIELDS.

DOW2113016

SECTION 8 SPECIAL PRECAUTIONS AND ADDITIONAL INFORMATION

RECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE: SEE LABEL. KEEP OUT OF REACH OF CHILDREN. AVOID CONTACT WITH SKIN AND EYES. PROVIDE WASHING FACILITIES NEAR WORK AREA. DO NOT STORE NEAR FERTILIZER, SEEDS, INSECTICIDES, AND FUNGICIDES. KEEP AWAY FROM OPEN FLAME.

DDITIONAL INFORMATION: NEW MSDS 19 MAY 82.

AST PAGE

R) INDICATES A TRADEMARK OF THE DOW CHEMICAL COMPANY

ONSULT THE DOW CHEMICAL COMPANY FOR FURTHER INFORMATION.

HE INFORMATION HEREIN IS GIVEN IN GOOD FAITH, BUT NO WARRANTY, XPRESSED OR IMPLIED, IS MADE.

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RLG (from

DOW CHEMICAL U.S.A.

MIDLAND, MICHIGAN 48640

9001 BUILDING
May 21, 1982

R. L. Eischer, 9008
R. G. Holzschu, 9008
E. R. Laning, 9008
J. A. Schultz, 9001
M. J. Skurski, 489
J. Woods, 834

cc: D. W. Osborne, 9001
J. M. Tichon, 489
G. L. Ytzen, 9008

MEETING REGARDING ESTERON* 245BE QUALITY AND OPTIONS

Meeting was held to discuss possible responses to the appearance of a crystalline sludge (as much as 3/4 inch in some gallon cans) in ESTERON* 245BE formulated and manufactured in 1982. All cans do not contain precipitate, even within the same lot.

Background:

-- Technical ester was produced in 1976-77.

-- The formulation and registration package for the material was obtained from Union Carbide.

-- 55M Gallons of product were formulated and packaged; 35M in one gallon cans and 20M in 55 gallon drums. The one gallon cans have all been shipped except for a recent lot of 3.2M gallons; 19.4M gallons of the drummed material is still at 489 Building.

Technical Considerations:

-- The crystalline precipitate has been identified as the bis (2,4,5-T) ester of ethylene glycol.

-- The liquid above the solid material in one can of lot 82041467 has an assay of 42.0% T acid (label says 42.5%).

-- In general, the precipitate appears when the material is cooled to 45°F.

-- The limited data available indicates the tech ester is continuously degrading. Without a major change in formulation, the tech ester will be totally unusable by 1984 or 85.

*Trademark of The Dow Chemical Company.

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Technical Considerations: Continued

-- Both the liquid supernatant above the precipitate and also the formulation containing redissolved solids give acceptable emulsion properties upon dilution.

-- There is no way to burn or dispose of the tech ester. It must be sold.

Options:

-- For drums: Redissolve solid; then, ship all material to Texas/Oklahoma with adequate notification to customer that material should not over-winter.

-- For 1 gal. cans: Distribute through dealers a tie-on-tag telling the user to heat the can in a bucket of water and shake before using. This would require the appropriate fire-sale rebates. There appears to be a comfortable margin here for rebates, given the difference between the standard cost in 1977 dollars and the selling price in 1982 dollars.

-- The alternative is recall of 1 gallon cans. This would involve loss of the cans, can disposal costs, shipping, and reprocessing costs. Rework technology would have to be developed. Waste solids that couldn't be burned would probably be made in the product rework.

To Do:

-- Determine if drums can be heated and rolled to redissolve solids (Skurski).

-- Depending on business considerations, consider the possibility of developing a new formulation for the 300M lbs. of tech ester remaining in storage. This could not be ready in time for any 1982 sales.

Marketing will make the recall vs. "fire-sale" rebate decision in the near future.

Jim

Jim Havel
Application Systems
Agricultural Products Department

8515

psk

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250