p. 1 of 9

Carol Van Strum
7493 East Five Rivers Road
Tidewater, Oregon 97390
Telephone: (503) 528-7151 Telefax: (503) 528-7105

May 14, 1993

To: Dioxin Nerds

Re: Dioxins in 2,4-D: March 2, 1993 Stephen Funk memo to Jill Bloom, Special Review Branch (EPA) (attached)

Please read and supply brainstorms!

The attached memo has major implications for both the Agent Orange epidemiologic studies as well as for Vietnam veterans still being re-exposed to 2,4-D. Agent Orange was a 50/50 mixture of the n-butyl esters of 2,4-D and 2,4,5-T. The attached memo is the latest EPA word on dioxins in 2,4-D. It reports 2,3,7,8-TCDD and 1,2,3,7,8-PCDD levels in two and three (respectively) of eight samples of technical grade (i.e., purified, not product grade) 2,4-D herbicide, at levels above the EPA "limit of quantitation (loq)" of .1 ppb and .5 ppb respectively. It's important to note that the "loq" is not a limit of detection, but a "limit of quantitation required by the Agency and a reflection of the level of toxicological concern."

All other dioxin and furans analyzed for were also found, but at levels below the "loq".

These data are woefully incomplete. We can't tell which combinations were present in any one sample, or whether all analytes were in all samples. We don't know how many samples contained 2,3,7,8-TCDD at less than 100 ppt. We don't know how many manufacturers were required to conduct the analyses, whether these results are from composite samples, or indeed whether they are compiled from all the submissions or from only one or several. (Each manufacturer was required to conduct analyses of seven samples; the results reported here are for a total of only eight samples.) About the most we can say is that of eight supposedly randomly selected samples of 2,4-D, two contained as high as 130 ppt 2,3,7,8-TCDD; three contained as high as 2600 ppt 1,2,3,7,8-PCDD, and some or all contained varying levels of HxCDD, HpCDD, and all 9 furans analyzed.

This is enough to raise some red flags on 2,4-D. Getting the actual data out of EPA is likely to be a battle, because the manufacturers have uniformly claimed "Confidential Business Information" status on the entire data submission. Making a big stink about what we do have may be the quickest way to force the data out in the open.

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The red flag for the Agent Orange issue is readily apparent. The studies conducted on Vietnam vets discounted 2,4-D exposure entirely, on the assumption that 2,4-D contained no dioxins and therefore was not relevant to the studies. (See attached April 17, 1987 letter from John J. Weaver, LTCOL, USAF to U.S. Rep. Don Bonker, especially page 2).

What this means is that "control'" veterans whose occupation or experience involved exposure to 2,4-D (e.g., as pesticide applicators, spray plane pilots, farming, road work, forestry, logging, or even residential use of Weed 'n Feed) were classified in the Agent Orange studies as unexposed, thus vastly diluting the results by narrowing the ratio between effects in exposed vs. "unexposed" veterans. Even the limited data reported in the memo -- showing 25% of the 2,4-D contaminated with 100 to 130 ppt 2,3,7,8-TCDD -- would be enough to invalidate the Agent Orange studies. (Adding the other dioxins and furans would further compound the issue.)

Calling for a recalculation of the Agent Orange studies on this basis might force some of the actual data out, if some manufacturers try to defend their own products by producing negative data. It's even possible that a particularly nasty legislator or judge could force EPA and the manufacturers to produce the data. Similar data has been held not to be trade secret or confidential business information on the theory that it creates a commercial disadvantage rather than advantage. (This could likely be accomplished through the Freedom of Information Act, but having spent more than eight years in court to get EPA data from two of its biggest dioxin efforts -- the Alsea Study and the National Dioxin Study -- I don't have any hope of getting anything through the courts until it's ancient history.)

Another angle might be legislation banning 2,4-D to reduce re-exposure of Vietnam veterans already entitled by statute to disability compensation for Agent Orange exposure if they develop particular disabilities. They are now being continuously re-exposed to dioxins through widespread, heavy use of 2,4-D along state, federal, and county highways nationwide, on private and state timberlands, in agriculture, on powerline rights-of-way, and on parks, golf courses, ball fields, school and college grounds, etc. (One of the first experimental uses was on the White House lawn.) I strongly suspect that if all the data behind this memo were available, there would be enough for Congress to force an immediate suspension of 2,4-D registrations. (The scandal alone -- see brief history below -- might be enough to prompt that.)

BRIEF BACKGROUND

[References for this discussion are available upon request.]

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In October, 1980, the Canadian government reported finding several dioxins in commercial 2,4-D formulations (di-, tri-, and tetra-chlorodibenzo-p-dioxins, not including 2,3,7,8-TCDD). No dioxins were found in technical 2,4-D samples. This information was transmitted via Dow Chemical Co. to EPA and to Barclay Shepard of the Veterans Administration.

On Dec. 10, 1980, EPA issued a "data call-in" to 2,4-D manufacturers via the 2,4-D Industry Task Force, asking for analyses of technical 2,4-D acids, and reiterating an earlier (August 1980) requirement of numerous acute and chronic toxicity studies on 2,4-D (including cancer, reproduction, and teratogenicity studies).

In January, 1981, EPA announced it had already begun dioxin testing of samples "collected from the complete range of 2,4-D manufacturers" and that the analyses were being conducted at EPA's Beltsville, Maryland, laboratories. Also in January, 1981, EPA's Research Triangle Park lab reported finding 2,7-DCDD and 1,3,6,8-TCDD in two out of three 2,4-D sample extracts, and strongly recommended more efficient cleanup "for conclusive confirmation, specific isomer assignments and accurate quantification of TCDDs." The lab report also reported finding 1,3,6,8-TCDD in Dow's 2,4-D process (waste) water in 1979.

EPA's "data call-in" for 2,4-D has dragged on for 13 years since it was issued in 1980. In 1987, 2,4-D was included in a data call-in for dioxin/furan analyses of all pesticides with the potential for dioxin contamination. (According to an EPA source, this included all pesticides made from or containing any chlorophenol compounds.) The attached March 2, 1993 memo from Stephen Funk to Jill Bloom summarizes some of the results on 2,4-D. According to Jill Bloom, the rat carcinogenicity studies required by the data call-in were and still are not forthcoming from the manufacturers; she said that because of this lapse, EPA could have suspended all 2,4-D registrations, but instead found that "the public health would be better protected" by allowing continued uses while requiring manufacturers to place "exposure reduction measures" statements on the labels. These exposure reduction measures are aimed solely at reducing exposures to applicators.

The required exposure reduction measures provide no extra protection for Vietnam veterans.

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GREENPEACE USA
TOXICS CAMPAIGN

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MAR 2 1993

MEMORANDUM

Subject: 2,4-D, 2,4-DB, and 2,4-DP and Their Salts and Esters: Survey of Dibenzo-p-Dioxin and Dibenzofuran Determinations. DP Barcode D188268. CBRS No. 11419.

From: Stephen Funk, Ph.D., Chemist
Special Review Section I
Chemistry Branch II - Reregistration Support
Health Effects Division (H7509C)

Through: Andrew Rathman, Section Head
Special Review Section I
Chemistry Branch II - Reregistration Support
Health Effects Division (H7509C)

To: Jill Bloom
Special Review Branch
Special Review and Reregistration Division (H7508)

In June 1987 a data call-in was issued for information on the polyhalogenated dibenzo-p-dioxin and dibenzofuran contents of certain pesticides. The call-in consisted of two parts. One part requested detailed manufacturing information for those pesticides whose structure or mode of synthesis indicated a potential for dioxin/dibenzofuran contamination. The other part required the actual analysis of certain technical pesticides for 15 chlorinated dibenzo-p-dioxins and dibenzofurans. The latter group of pesticides are manufactured by processes documented to produce dioxin/dibenzofuran contaminants. Included in the list of pesticides that required analysis were 2,4-D, 2,4-DB, 2,4-DP, and the esters and salts of these herbicides.

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Several dioxin/dibenzofuran data submissions for 2,4-D and related pesticides were reviewed. Each manufacturer of the registered technical pesticide was requested to randomly select seven samples of the pesticide and to analyze by a gc/ms method capable of quantitation to specified concentration levels, or limits of quantitation (loq), for each dioxin and dibenzofuran of toxicological interest. The resulting submissions were reviewed for compliance with the analytical chemistry requirements of the data call-in and for scientific validity.

Table 1 summarizes the findings for 2,4-D. Only 2,3,7,8-tetrachlorodibenzo-p-dioxin and 1,2,3,7,8-pentachlorodibenzo-p-dioxin were found at or above the EPA loq's. Two of eight technical 2,4-D's contained 2,3,7,8-TCDD slightly above the 0.1 ppb loq. Three of eight technical 2,4-D's contained 1,2,3,7,8-PCDD at concentrations greater than the 0.5 ppb loq. None of the remaining thirteen chlorinated dibenzo-p-dioxins and dibenzofurans were found at or above the EPA loq's in the technical 2,4-D. Data on the 2,4-DB and 2,4-DP acids and derivatives of all three acids are too limited at this time to be useful to the 2,4-D panel.

Table 1: Summary of Results for Chlorinated Dibenzo-p-Dioxins and Dibenzofurans in Technical 2,4-D Herbicides

Analyte	EPA loq[1] (ppb)	2,4-D		
		Total Number of Technicals	Number of Technicals Greater Than loq	Observed Maximum Concentration (ppb)
2,3,7,8-TCDD	0.1	8	2	0.13[2]
1,2,3,7,8-PCDD	0.5	8	3	2.6[3]
1,2,3,4,7,8-HxCDD	2.5	8	0	0.81
1,2,3,6,7,8-HxCDD	2.5	8	0	0.77
1,2,3,7,8,9-HxCDD	2.5	8	0	0.66
1,2,3,4,6,7,8-HpCDD	100	8	0	1.6
2,3,7,8-TCDF	1	8	0	0.27
1,2,3,7,8-PCDF	5	8	0	0.62
2,3,4,7,8-PCDF	5	7	0	0.73
1,2,3,4,7,8-HxCDF	25	8	0	1.6
1,2,3,6,7,8-HxCDF	25	8	0	1.2
1,2,3,7,8,9-HxCDF	25	8	0	1.4
2,3,4,6,7,8-HxCDF	25	8	0	1.1
1,2,3,4,6,7,8-HpCDF	1000	8	0	8.3
1,2,3,4,7,8,9-HpCDF	1000	8	0	1.2

[1] Limit of quantitation required by the Agency and a reflection of the level of toxicological concern.
[2] Average 0.07 ppb, where 50% of demonstrated loq used for analytes not found.
[3] Average 0.63 ppb, where 50% of demonstrated loq used for analytes not found.

TO: Carol van Strum
FROM: Tom Webster
DATE: 11 May 1993
RE: 2,4-D

Dear Carol,

I have made some TEQ calculations on the 2,4-D data. The enclosed table shows the TEQ estimate based on the observed maximum concentrations: 2.7 ppb. We can't tell from the data whether the maximums for each isomer came from the same or different samples.

The true average concentration cannot be calculated from the data in the memo. A lower bound on the average is around 0.39 ppb, calculated as:

average 2378-TCDD	+ average 1,2,3,7,8-PeCDD * (TEF)	
(0.07 ppb)	+ (0.63 ppb)*(0.5)	= 0.39 ppb

The estimate does not include any contribution from the other isomers. Although the authors are not completely clear, I assume that the average concentrations listed for these two isomers in the table notes are the averages over all eight samples. (Note that it is unclear how they have dealt with 'non detects.' Sometimes calculations will use half of the detection level.)

It's interesting that the 12378-PeCDD isomer dominates the total TEQ. Has this been found before?

I haven't run across 'logs' before in my section of the dioxin biz. It does not appear to refect the analytic chemistry, since concentrations are reported which are far below some of the logs. Instead, it appears to be some regulatory (reporting?) requirement with an imperfect connection to the TEF values. The logs are higher for less toxic isomers, but (with the exception of the hepta isomers) not proportional to the TEFs. Of course, a 'rational' regulation might be based on the total TEQ. Note that the analysis leaves out the octa isomers, isomers which now have TEF values.

Perhaps Cate J. might know where the logs come from.

I think you have a case. Good luck. Tom.

19642

PCDD and PCDF in Technical 2,4-D Herbicides

	TEF	Observed Maximum Conc. (ppb)	TEQ (ppb)	Amount in one pound (ug)
2378-TCDD	1	0.13	0.130	0.059
12378-PeCDD	0.5	2.60	1.300	
123478-HxCDD	0.1	0.81	0.081	
123678-HxCDD	0.1	0.77	0.077	
123789-HxCDD	0.1	0.88	0.088	
1234678-HpCDD	0.01	1.80	0.018	
OCDD	0.001			
2378-TCDF	0.1	0.27	0.027	
12378-PeCDF	0.05	0.62	0.031	
23478-PeCDF	0.5	0.73	0.365	
123478-HxCDF	0.1	1.60	0.160	
123678-HxCDF	0.1	1.20	0.120	
123789-HxCDF	0.1	1.40	0.140	
234678-HxCDF	0.1	1.10	0.110	
1234678-HpCDF	0.01	8.30	0.083	
1234789-HpCDF	0.01	1.20	0.012	
OCDF	0.001			
SUM			2.74	1.25

SOURCES:
TEFs: USEPA (1992). Estimating Exposure to Dioxin-like Compounds. EPA/600/6-88/005B. Table 1-1.
Concentrations: USEPA (1993). Memo from Stephen Funk to Jill Bloom. March 2. Table 1.

NOTE: ppb=ug/kg; 1 kg=2.2 lb.

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DEPARTMENT OF THE AIR FORCE
WASHINGTON, D.C. 20330-1000

OFFICE OF THE SECRETARY

17 APR 1987

The Honorable Don Bonker
House of Representatives
Washington, D.C. 20515

Dear Mr. Bonker:

This is in reply to your most recent inquiry in behalf of Mr. Joe Cole concerning the Air Force's Ranch Hand Study. The issue raised about the inclusion of individuals who have had previous herbicide exposure obviously requires further clarification to avoid any misconceptions.

Authorities in the Office of the Surgeon General, USAF, advise that in developing the Ranch Hand protocol, Air Force medical researchers went to great lengths to ensure a valid comparison could be made between the Ranch Handers (individuals who were actually involved in spraying Herbicide Orange in Southeast Asia (SEA)) and the control group for comparisons. Each control group member is an Air Force veteran who served in SEA with C-130 aircraft but who had nothing to do with aerial spray operations. Each Ranch Hander and his controls are matched by date of birth, race, rank and job, e.g., pilot to pilot, loadmaster to loadmaster, Captain to Captain, Sergeant to Sergeant, etc. The dates of birth are normally matched within six months.

Physical exams were given to 2,269 Ranch Handers and controls in 1982, and 2,309 Ranch Handers and controls in 1985. Initially, a decision was made to randomly select 8-9 controls for each Ranch Hander and to provide one control randomly selected for each Ranch Hander with the same extensive physical exam received by the Ranch Handers. Since a higher dropout rate was anticipated for the control group, a large comparison group (9,982 total) was identified. While morbidity data is not maintained on the controls who were not included in the physical exam portion of the study, mortality data is maintained, and is included in the annual mortality report.

For your information, we have attached a detailed breakdown of the exposure data you requested. As part of the initial evaluation each Ranch Hander and the control was asked to fill out an extensive questionnaire, including an estimate of his/her total lifetime exposure to herbicides in days. The exposures were divided into leisure (e.g., home garden use), civilian occupation, and military service. The data which has been summarized for you in the attachment will be used by the epidemiologist during the evaluation of disease incident rates. While data on a number of critical medical endpoints have been collected on both groups, to date there are no overall statistically significant differences between the two groups. This is not surprising considering the relatively young age of the participants.

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The attached data represents a cumulative total of lifetime exposure days reported by the 1,173 Ranch Handers and 1,585 controls who have completed the questionnaire. At this point of the study, no attempt has been made to verify the actual exposure, other than the military experience for the Ranch Hand group. (Note: The Air Force is cooperating in a special study conducted by the Centers for Disease Control (CDC) which is attempting to estimate the total dioxin body burden by blood assay of 190 Ranch Handers). Some 15 percent of the control group felt they had been exposed to herbicides in SEA, but our experience indicates exposures to aircrew/support personnel other than Ranch Handers were grossly over-estimated by the control group.

Since the data is listed by percentile, the figures are not directly additive. The 100 percent figure represents the highest exposure reported by any one individual in that group, i.e., at least one Ranch Hander reported 720 days of exposure to herbicides in a leisure setting. On the other hand, 85 percent of the Ranch Handers estimated no exposure to herbicides in a leisure or civilian occupational setting. Ninety percent of the Ranch Handers said they had total exposures of 469 days or less. By comparing this figure to the 85 percent figure, it is possible to say that 5 percent of the Ranch Handers had exposures of greater than 368 but less than 469 days. As a point of interest, Mr. Owens, reported 2,130 days of total herbicide exposure. A total of 28 controls reported more than 5 years (1,825 days) of herbicide exposure. It should be noted this exposure is more than reported for any herbicide. Herbicide Orange was a 50/50 ratio of 2,4,5-T, not 2,4-D. Very few controls have actually been exposed to 2,4,5-T. In fact, 90 percent or more of all herbicides used or manufactured in the United States since the Viet Nam conflict were the dioxin free 2,4-D, not the contaminated 2,4,5-T.

In assessing the likely biasing effect of controls having been exposed to dioxin through contact with 2,4,5-T, the total person years of exposure in the control group from leisure and occupational contact was reduced by 90 percent to account for the widespread use of 2,4-D since Viet Nam. Reported military exposures by controls are considered grossly overestimated since personnel records indicate that controls were stationed in the Philippines, Japan, or Okinawa during the Viet Nam conflict, and when they did travel to Viet Nam, they were not visiting herbicide-sprayed areas. Actual military exposure to 2,4,5-T in the control group is, therefore, taken to be zero. These reductions yield a total of 18 person years of 2,4,5-T exposure per 1,000 controls. Worse case conditions, e.g., 18 person years of 2,4,5-T exposure per 1,000 controls, would only reduce the power of the study by 1.8 percent. This level of misclassification is commonly found in any epidemiological study and is scientifically acceptable.

The Air Force Health Study Protocol fully discusses study biases and their likely magnitudes. The baseline report acknowledges a potential selection bias due to the possibility that noncompliant controls are either less healthy or more healthy than noncompliant Ranch Handers. Misclassification bias of the kind calculated here is common to all observational epidemiological studies. The Air Force Health Study is considered to be one of the best conducted in this regard.

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With the possible exception of the long-term epidemiological follow-up on the atomic bomb survivors in Hiroshima and Nagasaki, no other epidemiolocal study has ever received the peer scrutiny the Ranch Hand Study has. Some of the world's leading epidemiologists have reviewed the protocol, and will continue their oversight as the study continues. The Air Force is extremely proud of the Ranch Hand Study and would welcome the opportunity to have one of its epidemiologists brief you or members of your staff on the study if you have any further questions.

We appreciate your personal interest in Mr. Cole and trust this information provides the additional clarification you requested.

Sincerely,

Signed

JOHN J. WEAVER, LTCOL, USAF
Congressional Inquiry Division
Office of Legislative Liaison

Attachment

19646

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

OREGON OPERATIONS OFFICE
811 S.W. 6TH AVE.
PORTLAND, OREGON 97204

Reply to
Attn of: ooo

June 4, 1993

MEMORANDUM

SUBJECT: Preventative safety steps taken by the Oregon Department of Agriculture (OSDA) in the use of the herbicide 2,4-D on private forest land in Tillamook and Lincoln Counties.

FROM: Dan Heister, FIFRA Project Officer Dan Heister
USEPA, Region X, Oregon Operations Office

TO: Senator Bob Packwood
Attn. Hance Haney
Oregon Field Office
101 S.W. Main Street
Suite 240
Portland, OR 97204

In response to Mr. Tim Sill's (Senator Packwoods' constituent) concerns regarding the aerial application of 2,4-D on privately owned forest land in Lincoln and Tillamook Counties OSDA has taken the following steps: 1) Worked closely with the Oregon Department of Forestry and the involved aerial applicators to be appraised in advance of the specific sites, the weather conditions, and the time of each application; 2) Dedicated one OSDA inspector (Richard Angyal, 378-3776) for the purpose of consultation and coordination with the involved State Forest Practice Officers and applicators regarding label interpretation; 3) Offered on site OSDA observation assistance; and 4) Responded to any complaints from the public related to the misapplication of herbicide during any of these applications. Under the law, OSDA as the designated state lead agency is only required to do step #4. In summary OSDA is aware of the public concern related to these applications and has done its utmost to see that each application followed the letter of the law.

At the Federal level the USEPA still has 2,4-D under its Special Review Process (mandated by the 1988 amendments to the Federal Insecticide, Fungicide, and Rodenticide Act) and is

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considering new data related to the herbicide's possible impact on human health and the environment. Ms. Jill Bloom (EPA HQ, 703-308-8019) is the Review Manager for 2,4-D and I contacted her regarding the status of the product and the implications of the National Cancer Institute's (NCI) report on 2,4-D as a possible carcinogen. Enclosed please find a note from Ms. Bloom addressing both the NCI study, and apparent inconsistencies in Mr. Sill's article which cites the study. Also included in the attachment is a summary of the NCI study.

It is worth noting that while Mr. Sills concerns regarding the perceived risks of 2,4-D use are shared with many other members of the public, the product is still registered with EPA as a "General Use" herbicide. As such 2,4-D is legal for use in the conditions described above (provided label instructions are followed). The spraying of these areas has now concluded for the season and as of the date of this memo no formal public complaints have been received by OSDA involving any of these applications.

If you have any questions or if I may be of any further assistance please call me at 326-6869.

cc
Floyd Winsett, USEPA R10

Attachment

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~~19058~~

Norma —

THANKS FOR ALL YOUR HELP!

BEST IN ALL,

Tim

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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

FACSIMILE REQUEST AND COVER SHEET

Please type or print in black ink only

SEND FAX TO:

NAME: Dan Heister

OF: Region X

FAX PHONE NUMBER: (503) 326-3399

OFFICE PHONE NUMBER: (503) 326-6869

FROM:

NAME:

OFFICE:

OFFICE PHONE NUMBER

OFFICE ROOM NUMBER:

MAIL CODE:

PHONE (703) 308-8019
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JILL BLOOM
REVIEW MANAGER
SPECIAL REVIEW BRANCH
SPECIAL REVIEW AND REREGISTRATION DIVISION (H7508C)
OFFICE OF PESTICIDE PROGRAMS
401 M STREET, S.W.
WASHINGTON, D.C. 20460

DATE: June 3, 1993

NUMBER OF PAGES (Including this cover): 11

PLEASE NOTE: EPA, SPECIAL REVIEW BRANCH FAX NUMBER IS (703) 308-8041

PLEASE INDICATE ANY SPECIAL INSTRUCTIONS:

19649

JUN - 3 1993

NOTE TO DAN HEISTER

I have looked over the materials you sent concerning the use of 2,4-D in Oregon (Senator Packwood's cover letter to Mr. Brooks, a handwritten note, Tom Sill's April 28 article in the *Headlight Herald*). You summarized the Senator's concern as "why hasn't EPA cancelled or restricted 2,4-D in light of studies that show a link between 2,4-D and cancer?".

I believe that Mr. Sill's article presents an inaccurate and unbalanced picture on 2,4-D, and while the Senator's concerns are not without basis, correcting the misimpressions left by the article may put things in better perspective. I will address the Senator's (paraphrased) question by correcting those misimpressions, referring to the application of FIFRA standards for regulatory action on pesticides to the case of 2,4-D, and detailing the Agency's recent efforts to reduce exposure to 2,4-D.

Of particular concern in the *Headlight Herald* article are statements attributed to Mary O'Brien of the University of Montana and Shelia Zahm of the National Cancer Institute (NCI). Dr. O'Brien is quoted as saying that 2,4-D has not been subjected to cancer testing and that the EPA panel convened to evaluate 2,4-D cancer data decided that there was insufficient information to link the two. She additionally cites an October 1992 study published by NCI that relates 2,4-D exposure to increased risk of non-Hodgkin's lymphoma (NHL) in applicators from many countries and in seeing-eye dogs belonging to people who use 2,4-D on their lawns. Dr. Zahm is quoted as offering specific critiques of the Agency's 2,4-D carcinogenicity assessment process.

The following comments attributed to Dr. O'Brien are inaccurate and/or misleading:

* The carcinogenicity of 2,4-D has been tested in laboratory animals according to approved EPA protocols, but those studies are now being repeated at higher doses. After extensive analysis, EPA determined that the earlier studies were not performed at high enough doses, through no fault of the Agency or the registrant, but because of the difficulty in anticipating the "Maximum Tolerated Dose." The results of the new studies will be available in March 1995.

* The "EPA panel" convened on April 1 and 2 was an external advisory group composed of experts nominated by government, industry, user, and environmental advocacy groups. The panel did not decide there was insufficient information to confirm the cancer link. The panel preliminarily

said that the epidemiologic data were weakly suggestive of the link in humans, the laboratory animal data showed the link was improbable in the species tested, and that no mechanism for cancer causation could be identified. The panel's report should be available within a month.

* The "NCI report...first published in October 1992," is a review of studies on pesticides and NHL. I have attached a copy for your reference (Zahm, S.H. and Blair, A. 1992. Pesticides and non-Hodgkin's lymphoma. Cancer Res. 52:5485S-5488S). The summary attributed to Dr. O'Brien appears to be liberally adapted from the abstract and contents of this paper. One interesting inaccuracy is the summary of the dog study--the dogs were not seeing-eye dogs, and dogs don't get NHL, but they do get an analogous disease--canine malignant lymphoma.

  More substantively, the Agency did not bypass "real scrutiny" of the study because there were more negative cases than positive." Those studies summarized in the *Cancer Research* article that provided the most specific information on 2,4-D were reviewed by the external advisory panel on their individual merits. Like all epidemiologic studies, these studies are open to interpretation because the subjects are humans whose exposures to agents other than 2,4-D cannot be limited and are difficult to eliminate as possible causes or confounders. That is why a finding of an association in one or several studies is not necessarily a "smoking gun."

Dr. Zahm presented the results of her research before the external advisory panel, as did several of her peers at NCI. Two other highly respected, non-industry researchers did the same. These individuals were invited by the Agency because of the importance of their research. By law, advisory panel meetings must be open to the public, and the industry representatives who addressed the panel did so in public comment periods. All speakers identified their affiliations, and I don't believe that the panel was unduly influenced by comments from industry. A good number of National environmental advocacy groups were invited to submit and present public comment, but all declined. My guess is that they lack the resources to cover this issue.

None of the panelists are university extension agents, and all disclosed and were clear of potential conflicts of interest with 2,4-D manufacturing interests. Mr. Sill also quotes Dr. Zahm as saying that the Agency takes the results of registrant testing of pesticides on faith, and does not acknowledge any of the safeguards we maintain for verifying that the tests are run correctly and reported accurately. Additionally, in EPA's view, the nongenotoxicity of 2,4-D does not weaken the carcinogenicity database. While the Agency has not required immunotoxicity testing for 2,4-D, that requirement could be imposed when state-of-the-art testing guidelines are complete.

Contrary to the views attributed to Dr. Zahm, the Agency is *currently* assessing the cancer risks of 2,4-D; the advisory panel report is the first step. Next, the Agency will use its standard cancer classification system to describe the "weight of evidence" of carcinogenicity for 2,4-D, and will then determine whether to initiate a Special Review. "Special Review" is an intensive review of the risks and benefits of a pesticides use to determine if changes to the pesticide's registration must be effected to bring risks down relative to benefits. Unless there is a reason to believe that a pesticide poses an "imminent hazard," this risk/benefit analysis must by law precede the cancellation or restrictions designed to address unreasonable risk. In the case of 2,4-D, we are attempting to get a finding on whether or not 2,4-D causes cancer (whether or not there is a *hazard*). If a hazard exists, we must quantify the *risks* (and benefits) before taking the kind of action suggested by the Senator's concerns. The statute offers little latitude in this type of case.

The Agency did find an opportunity to compel the registrants of 2,4-D to implement some *voluntary* restrictions last year, when we discovered that the required rodent carcinogenicity tests were behind schedule and could not be submitted by the due date. The statutory penalty for data lateness is the initiation of suspension action, possibly resulting in the suspension of 2,4-D registrations pending the submission of the data in question. The Agency believed that the public would be better served by the implementation of widespread exposure reduction measures than by the temporary suspension of 2,4-D registrations. The exposure reduction program includes a broad range of label changes and the education of the public and the user community about those changes. I have attached an accounting of the exposure reduction measures that will be written into 2,4-D product labels. They are *not* aimed primarily at reducing exposure to neighboring property and habitants, where the potential for exposure (and risk) to neighbors and bystanders is more of an unknown than the potential for applicators, but some of the measures will have direct or indirect effects on neighboring lands and people. The Agency used the findings of the NCI epidemiology studies to work out the particulars of the exposure reduction program with the registrants. I'd like to stress that those studies suggest risks for individuals who applied 2,4-D over many years and in situations where the potential for exposure is very high. The studies also suggest that simple measures, such as not reusing clothing worn during application without laundering first, greatly lower risk.

I hope this helps. Is that handwritten note the attached correspondence Senator Packwood's office refers to? Call if I can be of further assistance.

Jill Bloom

Jill Bloom, Review Manager
Special Review Branch
Special Review and
Reregistration Division (H7508W)
Office of Pesticide Programs
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Attachments

United States
Environmental Protection
Agency

Press Office (A-107)
Washington DC 20460

EPA

Environmental News

FOR IMMEDIATE RELEASE
TUESDAY, APRIL 29, 1980 O'Neill (202) 755-0344

EPA ASKS FOR MORE INFORMATION ON HERBICIDE 2,4-D

Barbara Blum, Deputy Administrator of the U.S. Environmental Protection Agency, announced today that the Agency is requesting additional information from manufacturers to determine whether 2,4-D, a widely used herbicide, is safe for humans and the environment.

"We have made this decision following a review of health effects studies of 2,4-D," Blum said. "The review showed that significant information gaps exist on the effects of 2,4-D, preventing a definite conclusion on the safety of the herbicide.

"We will ask the manufacturers of the weed killer to commence the studies to provide the missing evidence."

Blum said that if the manufacturers fail to notify EPA within 90 days that they will provide the necessary information, EPA will use a stringent new provision of the pesticides law, Section 3(c)(2)(B), which allows the agency to stop all uses of the pesticide.

If the manufacturers comply, Blum said, EPA will allow 2,4-D to continue to be used while studies are underway. However, should any of the new studies demonstrate a major health or environmental problem, she said EPA would then take appropriate regulatory action without waiting for completion of all the studies.

The name 2,4-D refers to the phenoxy herbicide 2,4-dichlorophenoxyacetic acid and related salt and ester forms. There are approximately 1500 2,4-D products which are used to kill undesirable plants in home lawns, forests, right-of-way, drainage ditch banks, rangeland, pastures, aquatic areas, cereal crops, sugar cane and commercial turf.

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Basic manufacturers of 2,4-D include Dow Chemical Co., Midland, Michigan; Monsanto Chemical Co., St. Louis; Diamond Shamrock Corp., Dallas; PBI Gordon Corp., Kansas City, Kansas; Thompson-Hayward Chemical Co., Kansas City, Kansas; AmChem Products, Inc., Ambler, Pa.

"EPA conducted its review of health-effects studies on 2,4-D because of increasing citizen concern about the high level of exposure to 2,4-D around the country and because of its chemical similarity to the dioxin-contaminated herbicides, 2,4,5-T and Silvex." Blum said.

There also has been concern because 2,4-D was a component--along with 2,4,5-T--in Agent Orange, the defoliant used by the military in Vietnam. Although never approved by EPA for civilian use in the United States, its use in Vietnam has resulted in numerous claims of adverse health effects to American military personnel. These claims are now under investigation by the Veterans Administration.

EPA, about a year ago, imposed an emergency ban on many major uses of 2,4,5-T and Silvex. More recently, the agency opened hearings to determine whether all uses of these chemicals should be banned on grounds that they can cause cancer, birth defects and miscarriages.

EPA's review, of 2,4-D studies showed that the evidence of adverse health effects weighs far more heavily against 2,4,5-T than against 2,4-D.

"For one thing," said Blum, "there is no evidence at this time that 2,4-D contains any form of dioxin, the contaminant in 2,4,5-T associated with cancerous tumors and birth defects."

Blum stated that "toxicity studies of 2,4-D have either showed that significant adverse effects were unlikely at expected human exposure levels, or they were inconclusive, or they were not conducted in a manner acceptable by today's scientific standards."

At this point, she said, the agency, while taking no action restricting use of the chemical, will require the manufacturers of 2,4-D to provide additional information in the areas of oncogenicity (tumor-inducing), reproductive effects (particularly effects to the fetus), and metabolism in animals. She said EPA also plans to conduct certain reproductive studies on 2,4-D in its own laboratories, while awaiting the industry results.

In addition, EPA will consult with its Scientific Advisory Panel during its May 28-30 meeting to determine if there are additional studies necessary to determine the safety of 2,4-D. Following the findings of the Scientific Advisory Panel, the agency will formally specify to the manufacturers what studies are needed.

Details of the agency's review of the health effects information on 2,4-D are in the attached fact sheet.

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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 procuces 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.

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 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.

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.

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 in the Market Basket Survey. However, during the 1965 to 1977 period, a variety of other food products were analyzed under other surveys in 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

UNITED STATES DEPARTMENT OF AGRICULTURE
FOREST SERVICE
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REPLY TO: 2140 Integrated Pest Management

SUBJECT: Pesticide-Use Advisory Memorandum No. 266

TO: Regional Foresters, Station Directors, and Area Directors

Enclosed is a copy of a memorandum from Dr. Philip C. Kearney, Chief, Pesticide Degradation Laboratory, documenting a telephone conversation concerning a recent Canadian report of dioxins found in 2,4-D. As Dr. Kearney indicates this disclosure may receive considerable press coverage and we are, therefore, alerting you to this finding.

We understand that EPA is accelerating the collection of samples from all 2,4-D products manufactured and used in the United States for analysis for dioxins. The analyses will be conducted by Dr. Warren Bontoyan, Branch Chief, EPA Chemical and Biological Investigation. A fact sheet abstracted from a paper by M. L. Leng, "Comparative Toxicology of Various Chlorinated Dioxins Related to Chemical Structure," CIPAC Proc. Symp. Paper I, 1979, edited by Dr. Bontoyan is also enclosed.

EINAR L. ROGET
Chairman, Washington Office
Integrated Pest Management Work Group

Enclosures

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United States Department of Agriculture
Science and Education Administration
Agricultural Research Northeastern Region Beltsville Agricultural Research Center
Beltsville Maryland 20705

October 16, 1980

SUBJECT: Dioxins in 2,4-D

TO: Terry B. Kinney, Jr., Administrator, AR

On Thursday, October 16, 1980, I received a telephone call from Dr. Etcyl Blair, Vice President and Director of Health and Environmental Sciences, Dow Chemical Company, Midland, Michigan (517-636-5509), concerning a report they have from a Dr. Cochrane in the Canadian Government. Dr. Cochrane has been analyzing samples of 2,4-D for dioxins and has detected a TCDD isomer. This is not the highly toxic 2,3,7,8 isomer, and Dow suspects it is either the 1,3,6,8 or 1,3,7,9 isomer. This finding has been confirmed, and the concentration range is 100-300 ppb. Dr. Cochrane will present this finding at a dioxin meeting in Rome next week. Dr. Sam Epstein is also attending this meeting. Ed Johnson in EPA has been alerted to this finding by Dow.

Dr. Blair told me that this TCDD isomer did not show up in U.S. samples, but only in samples produced in Canada. Dow shut down the Canadian plant some time ago for economic reasons not related to this incident. This TCDD isomer is considerably less toxic than the 2,3,7,8 isomer. Its acute toxicity is in the range of mg/kg. It is also less acneogenic. I am alerting you at this time since there is liable to be considerable press coverage on this disclosure. It also impacts on the Veterans Administration Committee and certain activities in the Department. I have contacted Barclay Shepard in VA.

As requested, I will put this memo on the telecopier this afternoon. I will try to convene a meeting with Drs. Shaw, Hilton, Fertig, and Klingman to discuss a unified response.

Philip C. Kearney

PHILIP C. KEARNEY
Chief, Pesticide Degradation Laboratory
Agricultural Environmental Quality Institute

cc:
W. C. Shaw
D. Graham

FOREST SERVICE
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Fact Sheet on TCDD's*

Origin

Low levels of chlorinated dibenzo-p-dioxins arise as byproducts in the manufacture of chlorophenols under alkaline conditions at elevated temperatures and pressures. Trace amounts of the highly toxic 2,3,7,8-TCDD are formed during the manufacture of 2,4,5-trichlorophenol. This TCDD is carried through into products such as 2,4,5-T and hexachlorophene. Condensation of 2,4,6-trichlorophenol produces the expected 1,3,6,8-TCDD as well as the isomeric 1,3,7,9-TCDD. The toxicity of TCDD isomers is strongly dependent on the position and number of chlorine substituents.

Acute Oral Toxicity

A comparison of the acute oral LD50 (µg/kg body weight) shows that the 2,3,7,8-TCDD is many thousand times more toxic than the mixed 1,3,6,8-; 1,3,7,8-TCDD isomer.

Dioxin	Rat	Guinea Pig	Mouse
1,3,6,8 } mixed 1,3,7,9 }	>100,000	-	-
2,3,7,8	22 (M) 45 (F)	0.6-2	280

Enzyme Induction

The ability of TCDD's to induce enzyme production is also correlated to structure. The 2,3,7,8-TCDD is a potent inducer of δ-aminolevulinic acid synthetase (ALA) and aryl hydrocarbon hydroxylase (AHH). By comparison, the mixed 1,3,6,8-; 1,3,7,9-TCDD isomer is a weak to negligible inducer.

Chloracne

The 2,3,7,8-TCDD is a powerful producer of chloracne. A concentration of 0.04 ppm 2,3,7,8-TCDD produced a positive response in the rabbit ear test. By comparison, a concentration of 5,000 ppm was needed to produce a positive response with a mixture of this 1,3,6,8- and 1,3,7,9-TCDD.

Summary

Although the data is sparse, the limited results currently available suggest that the mixed 1,3,6,8-; 1,3,7,9-TCDD is at least 10,000 times less of a human or environmental hazard than the 2,3,7,8-TCDD.

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*This fact sheet is abstracted from a paper by M. L. Leng, Comparative Toxicology of Various Chlorinated Dioxins Related to Chemical Structure. CIPAC Proc. Symp. Paper 1, pp 141-169, 1979. Ed. W. Bontoyan, CIPAC Limited, Hertfordshire, England.

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UNITED STATES DEPARTMENT OF AGRICULTURE
FOREST SERVICE

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REPLY TO: 2140 Integrated Pest Management NOV 17 1980

SUBJECT: Pesticide-Use Advisory Memorandum No. 271

TO: Regional Foresters, Station Directors, and Area Directors

As a followup to Pesticide-Use Advisory Memorandum No. 266 (October 30), enclosed are two additional items on dioxins in 2,4-D. They include:

1. An October 23 press release from Eugene Whelan, Agricultural Minister, Agriculture Canada.

2. "Analysis of Technical and Formulated Products of 2,4-Dichlorophenoxy Acetic Acid for the Presence of Chlorinated Dibenzo-p-dioxins," by W. P. Cochrane, et al., as presented at a meeting in Rome.

You are encouraged to make this information available to all personnel who may be questioned about 2,4-D, its use by the Forest Service, and the presence of dioxins in this herbicide.

James L. Stewart

for EINAR L. ROGET
Chairman, Washington Office
Integrated Pest Management Work Group

Enclosures (2)

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SUBJECT: 2,4-D Tests Ottawa, October 23, 1980

Agricultural Minister, Eugene Whelan today announced that tests conducted by Ag Canada have identified previously unannounced contaminants in some samples of the herbicide 2,4-D.

Scientists in Agriculture Canada, 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 Ag 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 contaminant 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 cooperation with us in pesticide regulations

"The decision on how our new findings will effect the prescribed 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 broadleaf 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% of total herbicide use

"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 highly sophisticated testing equipment did not exist. The investment my department has made in high priced lab 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 Ag 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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ANALYSIS OF TECHNICAL AND FORMULATED PRODUCTS OF 2,4-DICHLOROPHENOXY ACETIC ACID FOR THE PRESENCE OF CHLORINATED DIBENZO-P-DIOXINS

W.P. Cochrane, J. Singh, W. Miles, B. Wakeford, J. Scott

Laboratory Services Division, Food Production and Inspection Branch, Canada Agriculture, Ottawa, Ontario Canada, K1A 0C5

ABSTRACT

Sixteen samples of 2,4-D ester and amine, both technical and formulated products, representing current Canadian supplies, were analysed for the presence of different chlorinated dibenzo-p-dioxins. The method of analysis involved extraction, partitioning, multiple column chromatography with final quantitation being performed by gas chromatography/mass spectrometry using a packed column. Isomer identification was achieved on a capillary column while dioxin identity was confirmed using high resolution mass spectrometry. The methodology provided for recoveries in excess of 85% with the limit of detection being 1 ppb. Eight out of nine esters and four our of seven amine samples were found to contain di-, tri- and tetra-chlorodibenzo-p-dioxins. Ester formulations showed significantly higher levels of contamination than the amine formulations. The tetra-chlorodioxin observed was the 1,3,6,8-isomer as verified by the synthesis of an authentic analytical standard.

In addition ten 2,4-D technical acid samples from 4 different sources did not contain any mono-, di-, tri- or tetra-chlorodioxins above the 1 ppb detection limit, although low levels of polychlorinated biphenyl ethers were observed.

KEYWORDS

Gas chromatography-mass spectrometry, chlorinated dioxins, 2,4-D formulations, TCDD isomers.

INTRODUCTION

There are 75 possible isomers in the class of compounds known as the polychlorodibenzo-p-dioxins (PCDDs). PCDDs together with the polychlorinated dibenzo-furans (PCDFs) and polychlorinated diphenyl ethers (PCDDEs) have been found as microcontaminants in commercial chlorophenols (Nilsson and Renberg, 1974; Jensen and Renberg, 1972; Firestone and co-workers, 1972; Rappe, Gava and Buser, 1978b) and in pesticides which use chlorophenols in the manufacturing process. While the hexa-hepta- and octa-chlorodibenzo-p-dioxin isomers have been reported by various workers (Woolson, Thomas and Ensor, 1972; Villanueva and co-workers, 1973;

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Johnson and co-workers, 1973) in trichlorophenols, tetrachlorophenols and pentachlorophenol (PCP) at levels ranging from the low ppb (i.e. HxCCD) to 1000 ppm (OCCD), the highly toxic 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) has not been found in commercial PCP (U.S. EPA, 1978) since the appropriate precursors are not present (Johnson and co-workers, 1973). However, trace amounts of 2,3,7,8-TCDD have been found in 2,4,5-TCP (Firestone and co-workers, 1972; Elvidge, 1971) at levels ranging from 90 ppb to 6.2 ppm, in addition to ppm levels of 2,7-dichlorodibenzo-p-dioxin, 1,3,6,8-TCDD and pentachlorodioxins. Also, 2,3,7,8-TCDD can be carried through into products made from 2,4,5-TCP, such as 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (Elvidge, 1971), hexachlorophene and mixed 2,4-D/2,4,5-T formulations (1:1 mixture of butyl esters known as Agent Orange on Herbicide Orange). Herbicide Orange was found to contain 0.1-47 ppm 2,3,7,8-TCDD together with smaller amounts of other less toxic PCDDs and PCDFs (Rappe, 1978; Rappe and co-workers, 1978a). Similarly, condensation of 2,4,6-trichlorophenate during its manufacture under alkaline conditions produces the expected 1,3,6,8-TCDD, as well as the isomeric 1,3,7,9-TCDD by Smiles rearrangement (Leng, 1979). Recent reviews have summarized the current situation with respect to dioxin analysis of PCP, 2,4,5-T and the polychlorinated biphenyls (Firestone, 1977; Rappe and co-workers, 1979). In the area of the lower chlorinated phenols and phenoxyacetic acids, no PCDDs were detected in 2,4- and 2,6-dichlorophenols (Firestone and co-workers, 1972). Woolson found HxCCD in 1 sample of 2,4-D at a level between 0.5 and 10 ppm. Only tetra-, hexa-, hepta- and octachlorodioxin results were reported and none were observed in 23 other 2,4-D samples, as well as, three 2,4-DB and two 2,4-DP samples. Similarly, no di- to hexa-CDD isomers were found in older Scandinavian formulations of 2,4-D although one 2,4-D sample did contain 0.06 ppm tetra-CDF (Norstrom and co-workers, 1979). However, the analysis of 2 Herbicide Orange samples showed the presence of 1,3,6,8-TCDD (in addition to the expected 2,3,7,8-isomer) and 1,3,7-tri-CCD which were postulated as being formed from condensation products of 2,4-di and 2,4,6-trichlorophenols (Rappe and co-workers, 1978a).

As part of a continuing program concerning the identification and quantitation of microcontaminants in pesticide formulations, this paper reports the results of dioxin analysis of 2,4-D amine, esters and acids.

EXPERIMENTAL

Sample Preparation

2,4-D ester. Transfer 2.0 g sample onto a silica gel column (50 g of Merck Keiselgel 60 activated overnight at 125°C. Elute with 150 mL of 30% CH_2Cl_2/hexane, discard first 30 mL and collect remainder in a 250 mL RB flask. Concentrate to 1-2 mL and proceed to alumina column clean-up.

2,4-D acid. Dissolve 10.0 g sample in 400 mL of 1:1 acetonitrile/water with 10% methanol added. Partition three times with 100 mL hexane. Combine the organic layers and wash twice with 50% methanol/water. Dry and concentrate the extract to 1-2 mL and proceed to the alumina column clean-up.

2,4-D amine. Dissolve 2.0 g sample in 100 mL water and partition three times with 25 mL hexane. Use iso-propanol to break any emulsions. Combine organic layers, wash twice with 20 mL water, dry and concentrate to 1-2 mL and proceed to the alumina column clean-up.

Alumina column clean-up. Transfer sample extracts onto alumina column (15 g Woelm Basic Alumina Activity I). Elute with 100 mL hexane and 100 mL 2% CH_2Cl_2/hexane, discard. Collect the next 100 mL 5% CH_2Cl_2/hexane and 100 mL 10% CH_2Cl_2/hexane. 19669

Concentrate to 1-2 mL and transfer to a 5 mL graduated centrifuge tube. Evaporate to dryness under a gentle stream of nitrogen. Dissolve residue in appropriate volume of hexane.

GC-MS analysis

A 25 m fused silica capillary column coated with SP 2100 (Hewlett Packard No. 19091-60025) was coupled to a Finnigan 4000 quadrupole mass spectrometer equipped with the INCOS data system. Analysis were performed isothermally at 225°C using the splitless injection of samples at a 20 p.s.i. column pressure. PCDDs were monitored using specific masses - m/e 218 and 220 for isomers of monochloro-, 252 and 254 for dichloro; 286 and 288 for tri-chloro- and 320 and 322 for tetrachlorodioxins. Specific isomers were identified by comparing their column retention with reference compounds and confirmed by high resolution mass spectrometry analysis via elemental composition and fragmentation patterns. The lower limit of detection was 1 ppb.

For high-resolution GC/MS analysis, the gas chromatograph was equipped with a 6 ft. x 1/4 in. glass column packed with either 3% SE-30 ultra-phase on Chrom 750 (80-100 mesh) or 3% OV-17 on Chrom 750 which was coupled to a Kratos MS-50 mass spectrometer by means of a single stage glass jet separator. Single ion monitoring was carried out at m/e 321.8936 at a resolution of 20,000 (10% valley) for tetrachlorodioxins. Source temperature 250°C, separator 300°C, emission current 500 uA, accelerating voltage 8.0 Kv, detection limit 20 x 10^{-12} g. Full scan data was acquired at 10,000 resolution using the INCOS data system. The major peaks of the isotopic chlorine cluster were all within $\pm$ 10 ppm of the correct mass value.

RESULTS AND DISCUSSION

The levels of PCDDs found in the 2,4-D esters and amine samples analysed are shown in Table 1, and represent current Canadian supplies of these products. Since these formulations contained varying amounts of active ingredient the quantitation of the PCDDs was based on the guaranteed 2,4-D acid equivalent for easier comparison of results. The six 2,4-D iso-octyl esters showed levels of 2,7- or 2,8-dichlorodioxin ranging from 104 ppb to 4.2 ppm. These di-CDD isomers are the expected dimerization products of the intermediate 2,4-dichlorophenol used in the 2,4-D manufacturing process (Leng, 1979). Levels of tri-CDD varied from 346 ppb to 2.0 ppm while the presence of tetra-CDD ranged from 226 ppb to 1.7 ppm. The tetra-CDD present in the 2,4-D samples displayed a 0.80 retention time relative to the 2,3,7,8-TCDD isomer on the 3% SE-30 packed column. It was identified as the 1,3,6,8-isomer via capillary column and high resolution fragmentation comparisons with an authentic standard. On capillary column two peaks were resolved, i.e. 1,3,6,8- and 1,3,7,9-TCDD, the normal and Smiles-rearranged dimerization products of 2,4,6-trichlorophenol.

The tri-CDD in all samples appeared earlier than the 1,2,4-isomer, used as an initial standard, and resulted in baseline separation between the two on capillary column. Since the 2,7- (or 2,8)-diCDD and 1,3,6,8-/1,3,7,9-tetra CDDs had been identified, it was found that the cross condensation product of 2,4-dichlorophenol with 2,4,6-trichlorophenol gave a single tri-CDD peak with the same retention time as that found in the sample on both packed and capillary columns. Therefore, this tri-CDD is probably the 1,3,7- or 1,3,8-isomer as expected from the above condensation reaction. A comparison of the high resolution mass spectra of the synthesised tri-CDD and that found in the samples were identical. The mass spectral difference between the 3:0 (i.e. 1,2,4-isomer) and the 2:1 (i.e. 1,3,7-isomer) ring chlorine substitution becomes very apparent in the m/e 50-150 range (Buser

TABLE 1 Levels of PCDDs in 2,4-D Technical Materials and Formulations

Sample	Type	Percent 2,4-D Acid Equivalent	PCDDS (ppb) Di-	Tri-	1,3,6,8-Tetra
1	Iso-octyl ester	65.4	**[a]	346	226
2	"	65.4	2722	2079	717
3	"	50	4200	1632	1752
4	"	65.1	104	639	315
5	"	60	1238	1825	852
6	"	70	109	929	486
7	Mixed butyl ester	Technical	102	684	317
8	"	50	-	-	-
9	"	Technical	200	160	210
10	Dimethylamine salt	50	-	38	54
11	"	50	-	584	278
12	"	50	5	54	20
13	"	50	-	-	-
14	"	60	33	533	208
15	"	50	-	-	-
16	"	50	-	-	-

a/ Level not reported due to co-eluting interferences.

and Rappe, 1978). Recoveries of di-, tri- and tetra-CDDs from spiked samples was greater than 85% when added in the 1-1000 ppb range.

While all 2,4-D iso-octyl ester samples contained PCDD contaminants, only two of the three 2,4-D mixed butyl esters and four of the seven 2,4-D amines showed the presence of chlorodioxins (Table 1). Also the esters products showed significantly higher levels of contamination than the amine formulations. In addition, ten 2,4-D technical acid samples from 4 different manufacturing sources were analysed for mono-, di-, tri- and tetra-CDDs down to the 1 ppb level and hexa-CDD at the 10 ppb level and none were found. However, the presence of low levels of dichloro-, trichloro- and tetrachloro-diphenyl ether isomers were observed in all cases.

The results reported in this study differ from those found for Scandinavian formulations of 2,4-D (Norstrom and co-workers, 1979). Although significant variations exist between individual samples, other contributing factors may be cross-contamination, the source of starting material and/or the process used in the manufacture of the 2,4-D esters and amines.

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

Dec. 10, 1980

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

LETTER TO 2,4-D MANUFACTURERS

2,4-D Industry Task Force
c/o John D. Connor, Counsel
Sellers, Conner & Cuneo
1575 Eye Street, NW
Washington, D.C. 20005

Dear Sirs:

This letter responds to several questions and corollary issues raised at the Industry Task Force Meeting held on November 14, which I attended with Patricia Cohn and Dudley Thompson.

The Task Force expressed an interest in coordinating with the Canadian government on 2,4-D testing. We are consulting with representatives of Agriculture Canada and Health and Welfare Canada to coordinate Canadian and U.S. review efforts on 2,4-D. This coordination will enable us to conduct an efficient review effort and will also ensure a consistent approach to the testing requirements. If you wish to have a Canadian liaison work with the Task Force, in a role comparable to mine, I would be happy to contact the Canadian ministries on your behalf and arrange for their representation.

The Task Force raised concerns about the analytical testing required on 2,4-D technical acid products which might be used as the test substance. Specifically, you raised questions concerning available laboratories and the analytical methodology for dioxin testing.

Agriculture Canada is in agreement that we work with you to identify 5 or 6 laboratories which can conduct the necessary testing of technical 2,4-D acids. Since the analytical methods developed by the Agriculture Canada Laboratory have not been validated, this group of laboratories could carry out the required procedures to validate the methodology and have it accepted by Association of Officials Analytical Chemists (AOAC).

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I suggest that we use samples of each 2,4-D technical acid set aside by your companies as the substances to be tested. This would provide you with the analytical specifications for each product and provide input to the decision on which product should be used as the test substance for the required studies. We will, of course, make all the necessary arrangements in advance to maintain confidentiality of the testing results.

Not reviewed *

We propose that the Agriculture Canada Laboratory take the lead in this project, with EPA's laboratories at Beltsville and Research Triangle Park participating. My understanding is that you wish to use the Dow Laboratory and the laboratory at either the University of Nebraska or Wright State University. Any of these laboratories is acceptable to the Agency.

After you have selected the laboratories you will use and the necessary administrative arrangements are completed, we will arrange a meeting with representatives from each laboratory to discuss the analytical methods and specifications for the substances under consideration.

We agree with the approach to use one 2,4-D acid technical product as the test substance for all the required studies on the 2,4-D acid. When the analytical results on the technical products are available, our scientists will be available to consult with you in choosing a test substance.

As we stated in the Task Force meeting, the Agency will shortly put out a notice to modify the requirement for acute oral and dermal toxicity tests on all 2,4-D products. We will defer the testing requirements on end-use products until we have grouped these products. However, we will still require acute oral and dermal toxicity studies on each manufacturing-use product, in accordance with the schedule in the August 29 ORDER AND NOTICE.

We have received a request dated October 30, from John D. Connor, Jr., on behalf of the Task Force for a waiver of the time schedule for submission of studies to allow the Task Force to complete the necessary analyses of 2,4-D compounds.

The schedule in the August 29 NOTICE allows a reasonable amount of time to complete and submit the studies if they are initiated in a timely fashion. We realize that this will not be possible for all studies. Therefore, we have developed a priority listing for studies which we feel must begin now. We will consider revising the time schedule for the studies listed below on a study by study basis, if we receive an adequate rationale explaining why additional time is needed and proposing a new date for submission of the studies. We will defer the schedule for submission of those studies which are not on this first list.

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As Mr. Connor noted in his request, we must have an adequate chemical analysis of each 2,4-D product used as a test substance. We also recognize that there is some negotiation and coordination involved in getting the studies under way. The negotiations to obtain commitments for laboratory space and to develop protocols should continue while the analytical work is being completed. We will not grant time extensions based on the fact that these negotiations were deferred pending the outcome of the analytical work.

We have consulted with Canadian representatives to make a careful comparison of our data requirements on 2,4-D with the requirements they intend to impose. Based on this, we have jointly developed the priority list of testing requirements on 2,4-D. While most of the U.S. and Canadian testing requirements are consistent, there are several studies which are being required by Agriculture Canada which EPA is not requiring. These studies are indicated in the list with an asterisk. We are not adding these studies to our requirements, but we are deferring initiation of some of our required studies so that these can get under way.

The priority listing of studies presented below includes a schedule for submission of those studies which are required by the Agency. The dates are taken from the August 29 NOTICE. As noted above, we will consider requests for time extensions. However, we encourage you to begin now to reserve laboratory space and to develop protocols. The tests which we feel should be initiated as soon as possible are:

Tests	Test Substance	Submission Date
Acute Toxicity		
Acute Oral Toxicity	Each manufacturing use 2,4-D product	5/1/81
Acute Dermal Toxicity	Each manufacturing use 2,4-D product	5/1/81
Acute Inhalation Toxicity*	Dimethylamine salt of 2,4-D	5/1/81
Subchronic Toxicity		
Subchronic Oral Neurotoxicity	2,4-D acid in rat dimethylamine salt of 2,4-D in rat and dog (we will not require testing in the chicken at time)	9/1/81

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Chronic Toxicity		
Teratogenicity	Butoxypropyl ester	8/81
Teratogenicity	alkanolamine ester dimethylamine ester* 2,4-Dichlorophenol	
Oncogenicity in rat	2,4-D acid	12/83
Reproduction	2,4-D acid	9/82
Metabolism	2,4-D acid isooctyl ester PGBE dimethylamine	5/81
Ag. Canada Exposure studies*		

*Studies required by Agriculture Canada and Health and Welfare Canada, but not by EPA.

If you have any questions concerning this priority listing or general comments which you care to make feel free to contact me on (703) 557-8195, or Pat Cohn on (703) 557-7973.

Sincerely yours,

Kevin Keaney, Chief
Chemical Review Branch II
Special Pesticide Review Division

Phone

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE January 16, 1981

SUBJECT Analyses for DI and Tetra Chlorinated Dibenzo-p-dioxins in 2,4-D

FROM Robert Harless
HERL, ETD, ACB (MD-69)

TO Mike Dellarco, Dioxin Project Manager
Special Pesticide Review Division (TS-791)
Office of Toxic Substances
401 M St., SW
U.S. EPA
Washington, DC 20460

THRU: Robert G. Lewis
Analytical Chemistry Branch (MD-69)
ETD/HERL-RTP, NC 27711

Three sample extracts of 2,4-D were received from EPA, Beltsville, MD, January 5, 1981. An ACB ID number (151) was assigned to this shipment. The extracts were subjected to a previously described HRGC-HRMS method of analyses for dichlorodibenzo-p-dioxins (DCDDs) and tetrachlorodibenzo-p-dioxins (TCDDs). A Varian 311A mass spectrometer equipped with a 30 meter OV-101 WCOT glass capillary column was utilized for these analyses. The analytical results are shown in Table 1.

The criteria shown below were utilized for confirmation of 2,7-DCDD and 1,3,6,8-TCDD.

ANALYTICAL CRITERIA USED FOR CONFIRMATION ANALYSIS

A. HRGC-HRMS retention time of DCDD and TCDD.

B. Simultaneous HRMS-MIS responses for M^+ and M^+2 of DCDD and TCDD.

C. Co-injection of sample and standards (2,7-DCDD and 1,3,6,8-TCDD).

D. HRGC-HRMS peak matching analysis in real time to confirm the elemental composition of DCDD and TCDD molecular ions, 251.9745 and 319.8965.

DISCUSSION

HRGC-HRMS MIS Analysis

A compound was detected in each of the three extracts that satisfied the analytical criteria for 2,7-DCDD. The concentrations shown in Table 1 are based on the concentration of 2,7-DCDD standard supplied by EPA Beltsville, MD. No problems were encountered in the DCDD determinatons.

The analyses for TCDDs were performed at higher sensitivity. A compound that satisfied the analytical criteria for 1,3,6,8-TCDD was detected in 70462 and 011123. The 1,3,6,8-TCDD concentrations shown in Table 1 are based on the concentration of validated DMP 2,3,7,8-TCDD standard. 2,3,7,8-TCDD was not detected in the three samples at the stated detection limit. High concentrations of other chlorinated contamination were also detected.

HRGC-HRMS Peak Matching Analyses

500 µl of each extract was concentrated to 40 µl for determination of exact masses. The exact mass, 251.9745, corresponding to DCDD was confirmed in each extract. In addition to 2,7-DCDD, the presence of isomers in lower concentrations were also confirmed.

The exact mass, 319.8965, corresponding to TCDD was detected in each of the three extracts. In addition to 1,3,6,8-TCDD, several isomers in low concentrations were also detected in 011123 and 70462. TCDD isomers were also detected in 70459 but in lower concentrations.

Extremely high concentrations of chlorinated contamination were also present in these extracts. The major masses which interfere with

TCDD analyses were determined to be 319.9165, 319,9016, 321,9113 and 321.9091. Conclusive identifications have not been assigned.

I suggest (emphasize) that these samples be subjected to a more efficient clean-up procedure for conclusive confirmation, specific isomer assignments and accurate quantification of TCDDs. The capillary column used in these analyses was severely damaged and late eluting TCDDs would not have been detected in the contamination.

SUMMARY

DCDDs and TCDDs were detected in samples of 2,4-D. The presence of 1,3,6,8-TCDD in 2,4-D is not surprising. This laboratory reported the presence of 1,3,6,8-TCDD in a 2,4-D process water to EPA Region 5, in early 1979.

Attachment

cc: Ron Thomas
N. K. Wilson
D. E. Gardner

January 1981

EPA Regulation Of 2,4-D

In April 1980, the EPA completed a review of critical health effects studies on 2,4-D. No 2,3,7,8-tetrachlorodibenzo(para)dioxin (2,3,7,8-TCDD) has been found in 2,4-D as it has in 2,4,5-T. In the course of this review, a number of gaps in the data on 2,4-D were identified, resulting in a decision by the Agency to require additional studies from registrants (manufacturers) of the herbicide. Those toxicity studies considered scientifically acceptable showed that significant adverse effects were unlikely at human exposure levels which might be expected from current 2,4-D use patterns. New studies were needed on oncogenicity, teratogenicity and reproduction. In September 1980, registrants were notified of these requirements (see enclosed copy of the data call-in notification).

EPA is coordinating its health effects review activities on 2,4-D with Agriculture Canada. In late October 1980, the Canadian government made public the results of tests conducted on 2,4-D samples manufactured in Canada. Employing sophisticated analytical methods, Canadian scientists confirmed the absence of 2,3,7,8-TCDD, but found other, reportedly less toxic dioxins, ranging in concentration from 5 ppb to approximately 8,000 ppb, in some of their samples.

Consequently, EPA began a series of tests to detect the presence of dioxins in samples of 2,4-D produced in the United States, employing the same analytical methods as used by Canadian scientists. Testing of samples collected from the complete range of 2,4-D manufacturers is being conducted at the Agency's Beltsville, Maryland, laboratories. EPA is also collecting information on manufacturing processes which may help to explain how dioxins can form during the manufacture of 2,4-D.

To date, the Agency has tested 30 samples including both technical 2,4-D acid and ester products, and products containing amine salts of 2,4-D. In preliminary findings, employing tests sensitive to dioxin concentrations as low as 1 ppb, 27 of the samples were found free of any dioxin. Three samples contain the 2,7-dichlorodioxin in concentrations below 100 ppb. Thus, preliminary results of EPA sampling have confirmed a significant difference between 2,4-D products sold in the U.S. and in Canada, possibly due to differences between U.S. and Canadian manufacturing processes.

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EPA is continuing to assess the safety of 2,4-D by additional sampling of U.S. produced 2,4-D to determine whether manufacturing processes consistently produce 2,4-D in the range of U.S. products already tested. The Agency is also conducting a detailed review of health effects data on the dioxins identified in 2,4-D products.

In addition, new acute and chronic toxicity data supplied in response to EPA's 1980 data call-in notice, described above, will contribute health effects information needed for the comprehensive review of 2,4-D which is part of developing a registration standard for this chemical (see enclosed fact sheet on registration standards). Although development of a registration standard for 2,4-D is the Agency's long-term goal, EPA will review toxicity studies and dioxin analyses as they are submitted to determine whether a change in our regulatory position is warranted.

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Tetrachloroazobenzene in 3,4-Dichloroaniline and Its Herbicidal Derivatives: Propanil, Diuron, Linuron, and Neburon

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Atlanta, Georgia

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,

Pg. 31 -- PLAINTIFF MEMORANDUM

19682

DOW

OnStream

Vol. No. 11 Michigan Division Internal News • Dow Chemical U.S.A. • Midland, MI 48640 December 7, 1982

Division to mothball chlorobenzene production

As soon as negotiations are complete, Dow intends to suspend the manufacture of chlorobenzene and mothball the plant.

Dow currently is negotiating with Standard Chlorine to supply Dow's internal chlorobenzene needs as well as our marketing obligations. Dow intends to fulfill all its marketing commitments.

"It's hoped that this will be accomplished by January 1, 1983," said Ray Gaska, major manager for Inorganic Chemicals Production, Energy and Utilities. "This action is being taken due to the poor overall economic conditions in our country, and a severe slump in the chlorobenzenes business. It also will enable us to deploy our resources into more profitable business areas."

The Michigan Division is the only Dow location that manufactures chlorobenzene, and currently employs 75 people. These employees will be reassigned within Dow once the mothballing process is completed.

Gaska said this announcement, made yesterday, has no effect on the Diphenyl Oxide manufacturing facilities and business, both of which will continue to function as usual.

.....

For more details, watch "Business Brief" during the lunch hours Wednesday and Thursday. Featured on the program is Ray Gaska.

Employees asked to reduce vacation carry-over

Salaried division employees are being encouraged to reduce by half the number of vacation days they carried over in 1981.

The reason, according to Carl Bauer, major manager of Employee Relations, is that funds are accrued each year to account for vacation time that is earned and not used. This is considered a liability for the company because if an employee were to quit, he/she would be paid for this vacation earned and not taken.

"While this added use of vacation won't result in a cash saving for the company, a reduction of days carried over will reduce the amount of money which the company has to set aside," Bauer said. "If all employees use four days more vacation than last year, this could mean an improved profit of about $1 million for the Michigan Division."

That $1 million represents an average of each salaried employee using four days more vacation than last year.

Dow rebuts cancer allegations

(A story appeared in the local newspapers last week alleging unusually high rates of cancer deaths from soft and connective tissue sarcomas among white females in Midland County. The following is a response written by Joseph LeBeau, Dow U.S.A. director of Health and Environmental Sciences.)

Last week, an employee of Michigan's Department of Natural Resources, acting on his own initiative, released largely unpublished data obtained from the U.S. Environmental Protection Agency which he states indicate an unusually high rate of a rare form of cancer deaths (soft and connective tissue) among white females in Midland County (Michigan). (The new data comes from an EPA report titled "U.S. Cancer Mortality Rates and Trends 1950-1978," now in press). And he suggested as a possible underlying cause operations of The Dow Chemical Company's Michigan Division plant.

Inasmuch as we do not yet have the EPA data in hand (we are seeking it), our comments at this point can only be tentative and preliminary. But we would like to note the following:

--We are concerned by this report and have assigned our top health and environmental scientists to study the question. We agree that further evaluation of this issue by State

(over)

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Dow rebuts cancer allegations cont'd. . . .

Health officials is in order. And we will cooperate fully in that effort.

--But we urge caution and care in interpreting the data:

• The numbers involved -- one female death due to this very rare cancer about every two years over 28 years for a total of 13 and one male death about every three years for a total of nine -- are quite small. This is not to say we are not concerned. But conclusions drawn too soon from such a small sample could well prove misleading.

• The pattern among females and males does not seem consistent. Among women, there was one death in the 1950's, five in the '60's and seven in the '70's. But among men, there were two deaths in the '50's, four in the '60's and only three in the '70's. If exposure to an environmental agent of industrial origin were the root cause, one would expect a higher incidence among men than among women. And one would expect considerably more than three deaths among men in the '70's. Yet just the reverse seems to be the case.

• In the past, diagnosis, coding and abstracting of death certificates was far from an exact science, although there has been improvement over the years. Re-examination of the certificates in question could very well lead to different conclusions. And since the numbers involved are so small, any change could make a big difference.

• Furthermore, the hard data we do have does not support the suggestion that there is a problem associated with all cancer (1) According to "U.S. Cancer Mortality by County: 1950-1969," published by the U.S. Department of Health, Education and Welfare, total cancer is significantly less among the population of Midland County. And (2), a recently completed mortality study of Dow men employed in our Midland plant covering the years 1954-1978 shows that deaths from cancer were only 95 percent of that expected. In other words, the Dow cohort has fared better than the national population as a whole. Moreover, the Dow cohort performed better than did a similar industry-oriented (but non-chemical) community-based study group elsewhere in Michigan. Deaths due to cancer were seven percent lower. (For a more complete discussion of this study, see "The Point Is...," No. 57, October 29, 1982 -- a Dow publication.)

This episode illustrates once again the critical importance of orderly science grounded in sound research followed by peer review. Sidestepping this well-founded procedure at any point can only waste resources, as the parties involved pursue red herrings. More important, in the case of health questions, it can cause needless stress, anxiety and suffering.

— Personnel changes —

WEN CHENG has been promoted to research associate in the Organic Chemicals section of Chemicals Research, where he is involved with the terephthaloyl chloride pilot plant.

JOE DARLING has been promoted to senior quality control analyst at the Bay City Plants.

JAMES W. EDMONDS has been promoted to group leader in Chemicals Research Lab of the Michigan AS&T Labs. Jim is responsible for product and process research for aromatic monomers, zeolite catalyst technology, DPO, phenyl phenols, and Dowtherm heat transfer fluids.

DAVE GESSFORD of the Chemicals Research Laboratory has been promoted to senior research engineer in Ludington. Dave has been a part of the new calcium chloride dryer team from early in the construction phase through the recent successful start-up.

HELEN SMITH has been promoted to senior administrative office assistant in Salary Payroll.

BERNARD P. SWIERCZ has been promoted to foreman in Capital Construction Projects, assuming new first line supervisory duties of a mechanical construction operation.

LARRY WILSON has been promoted to project leader in the Designed Polymers & Chemicals Research Lab. His current research interests involve the development of polyamidoamines as a new water soluble polymer family.

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Midland Daily Ne

Vol. 126, No. 26 28 Pages Wednesday, June 1, 1983, Midland, Michigan

Dow to spend $2.5 million on diox

By LORIE SHANE
Daily News staff writer

Dow Chemical Co. today announced a six-point program of health and environmental studies aimed at addressing public anxiety about dioxin.

President Paul F. Oreffice said Dow will spend more than $2.5 million to conduct a soils study in the Midland plant, community and other locations; continue a search for dioxin sources inside the Midland plant; offer the Michigan Department of Public Health funding for a case control study of soft-tissue cancer in Midland County; establish a grant to fund research at the University of Michigan to develop technology to further reduce the amount of dioxin in Dow's waste water discharge; expand Dow's analytical capabilities; and fund an independent review of whether trace amounts of dioxin in the environment pose a health hazard to humans.

Oreffice said Dow has not changed its past conclusions that the levels of dioxin found in Midland are not a significant threat to human health. He also said Dow is still convinced that dioxin can be formed by combustion.

However, he said, "What has changed is that with all the publicity dioxin has received, the general public cannot be expected to take our word for it without corroboration."

Oreffice added he is aware that concerns and criticisms involving Dow do exist and "it bothers me a heck of a lot."

Asked why it has taken a high level of public concern to motivate Dow to mount this initiative, Oreffice said, "We have done this and more for all of these years...it isn't like it isn't a continuing thing. We have proven a lot of these things to our satisfaction. These are not being accepted."

INCLUDED IN THE plan are:

- A $250,000 proposed joint soils study with federal and state government agencies. The study would involve sampling in Midland and other locations, not yet selected. The study will be followed by analyses, independent laborotary validation and joint anouncement of results.

Dow has conducted its own limited soils study, which it said showed the levels of dioxin here are comparable to other cities. This new study, anticipated to last six months, would involve more samples and would provide a new data base for other studies.

- A search for dioxin sources inside the plant, which will be an examination of water, air and landfills.

"We will literally leave no stone unturned," Oreffice said.

The $1 million investigation would include all of Dow's operations, according to David Buzzelli, manager of agricultural chemicals and environmental services for the Michigan Division.

"I can't get any more specific," Buzzelli said. "Really, it's detective work."

Dow now has the ability to measure dioxin at parts per quadrillion levels, Buzzelli said.

The company will use outside auditors to monitor this investigation.

- A $250,000 case control study, which the state health department has said should be done to explore whether there is a link between dioxin and soft-tissue cancer mortality in Midland County. Dow, which says it believes no link exists, would not be directly involved in the actual study, but will support the MDPH efforts, Oreffice said.

Dr. James Saunders, a Dow physician, said that he believes levels of dioxin from 10 to 100 ppb are safe for the general population.

Although there is
dard for safe levels of
for Disease Control
dioxin contaminati
Beach, Mo., case be
level of 1 ppb.

- Another health
which Oreffice
approached an inde
scientific organizati
clined to identify,
address the question
amounts of dioxin in
pose a health hazard

If it accepts, Saund
nization would revie
ture on the health im
amount of money Do
not been determined.

- A $250,000 Dow
pendent research at
Michigan to develop

News

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dioxin studies

Although there is no national standard for safe levels of dioxin, the Center for Disease Control recommended that dioxin contamination in the Times Beach, Mo., case be cleaned up to the level of 1 ppb.

• Another health related study, in which Oreffice said Dow has approached an independent national scientific organization, which he declined to identify, inviting them to address the question of whether trace amounts of dioxin in the environment pose a health hazard to humans.

If it accepts, Saunders said, the organization would review existing literature on the health impact of dioxin. The amount of money Dow would spend has not been determined.

• A $250,000 Dow grant to fund independent research at the University of Michigan to develop technology aimed at reducing dioxin in Dow's waste water discharge. Dioxin has been found in the discharge by the Environmental Protection Agency at parts per quadrillion. Buzzelli said municipal effluent will also be a focus of the study.

• Finally, additional training of scientists and more laborotary equipment, which will double Dow's capability to analyze dioxins. The expansion already is under way, at an anticipated cost of $750,000.

"The main thing that we hope to learn is that all of our science is correct," Oreffice said. "We will accept whatever the results of these studies are."

Asked if Dow would consider itself liable for people's health problems if studies showed dioxin is a health threat, Oreffice replied, "I'll leave that to the lawyers."

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Lincoln County Watershed Watch
P.O. Box 343
Seal Rock, Oregon 97376
Telephone: (503) 547-4294

May 19, 1993

REQUEST FOR LINCOLN COUNTY DIOXIN TESTING ORDINANCE

Lincoln County Watershed Watch asks the Lincoln County Commission for an emergency ordinance requiring dioxin analyses of all 2,4-D products used in broadcast applications within Lincoln County. This request is based on the following information, which is keyed to tab numbers in the attached information packet:

1. The U.S. Environmental Protection Agency recently disclosed that some, if not all 2,4-D contains dioxins and related compounds, including the most toxic dioxin, 2,3,7,8-TCDD.

2. The EPA previously found 2,3,7,8-TCDD in environmental and human tissue samples from Lincoln County and other parts of the Oregon Coast Range. EPA attributed the 2,3,7,8-TCDD found in small birds and mammals, other wildlife, domestic water supplies, deer and elk meat, and tissue from a baby born without a brain to forest and roadside spraying of herbicide 2,4,5-T. Sediment levels of 2,3,7,8-TCDD from a tributary of the Alsea River were the highest ever recorded in the Pacific Northwest.

3. EPA calculated that fish levels of 2,3,7,8-TCDD would equal sediment levels, but did not follow up with actual fish studies in the Alsea drainage. Fish, particularly trout and other salmonid species, are exquisitely sensitive to TCDD, which bioconcentrates up to 159,000 times water levels in fish tissues and causes toxic effects and death at the lowest doses ever tested. EPA scientists have warned that concentrations as low as one part per trillion TCDD in fish could be a reproductive hazard to human consumers.

4. In some forest areas, EPA has found high soil levels of 2,3,7,8-TCDD from forest spraying decades after the last herbicide application. Nevertheless, neither EPA nor any other government agency has followed up its findings in Lincoln County, to determine whether the high levels found in the Alsea watershed are reflected throughout the county.

5. A 1980 preliminary U.S. Centers for Disease Control study suggested a link between aerial 2,4-D spraying and a 13-fold excess of neural tube birth defects in Lincoln County.

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6. EPA never attributed environmental dioxin contamination to 2,4-D, because it was thought that 2,4-D contained no 2,3,7,8-TCDD. EPA required 2,4-D manufacturers to test their products for dioxins in 1980, but did not disclose any results of that testing until March, 1993. EPA's summary of those results does not reveal which manufacturers' products contain dioxins, or how many samples contained some, if not all, dioxins. EPA will not release that information because manufacturers have uniformly claimed trade secrecy status on their dioxin analyses.

7. In light of these dioxin results, EPA has required 2,4-D manufacturers to add "Exposure Reduction Measures" to their 2,4-D labels. However, these label measures are aimed primarily at reducing applicator exposure, and will not significantly reduce dioxin exposure to others or the environment. EPA has not required 2,4-D manufacturers to disclose the dioxin content of their products on the labels.

The disclosure that any 2,4-D contains dioxins, including the most toxic 2,3,7,8-TCDD, raises strong concerns about adding any dioxin to the levels already accumulated in Lincoln County sediments, soil, fish, wildlife, and humans.

Therefore, in order to protect the public health and natural resources of our area, Lincoln County Watershed Watch requests the Lincoln County Commissioners immediately to require full dioxin analyses, to be funded by the manufacturer or purchaser, of every batch of 2,4-D destined for any broadcast application in Lincoln County, with full public disclosure of analytical data and results before such applications are begun. Broadcast application means aerial, roadside, or high-volume ground application.

Lincoln County Watershed Watch also asks the Commissioners to request from EPA the complete list of all pesticides for which EPA has required manufacturers to submit dioxin analyses, in order to determine whether any product used by Lincoln County (e.g., Garlon used by the Road Department) or others for broadcast applications in Lincoln County may be adding to the dioxin levels already accumulated in county sediments, soil, fish, wildlife, and humans.

Respectfully submitted,

Daniel Blackwell
Carol Van Strum

Lincoln County Watershed Watch

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TAB 1

1993 U.S. EPA, Dioxins in 2,4-D

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GREENPEACE USA
TOXICS CAMPAIGN

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MAR 2 1993

MEMORANDUM

Subject: 2,4-D, 2,4-DB, and 2,4-DP and Their Salts and Esters: Survey of Dibenzo-p-Dioxin and Dibenzofuran Determinations. DP Barcode D188268. CBRS No. 11419.

From: Stephen Funk, Ph.D., Chemist
Special Review Section I
Chemistry Branch II - Reregistration Support
Health Effects Division (H7509C)

Through: Andrew Rathman, Section Head
Special Review Section I
Chemistry Branch II - Reregistration Support
Health Effects Division (H7509C)

To: Jill Bloom
Special Review Branch
Special Review and Reregistration Division (H7508)

In June 1987 a data call-in was issued for information on the polyhalogenated dibenzo-p-dioxin and dibenzofuran contents of certain pesticides. The call-in consisted of two parts. One part requested detailed manufacturing information for those pesticides whose structure or mode of synthesis indicated a potential for dioxin/dibenzofuran contamination. The other part required the actual analysis of certain technical pesticides for 15 chlorinated dibenzo-p-dioxins and dibenzofurans. The latter group of pesticides are manufactured by processes documented to produce dioxin/dibenzofuran contaminants. Included in the list of pesticides that required analysis were 2,4-D, 2,4-DB, 2,4-DP, and the esters and salts of these herbicides.

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Printed with Soy/Canola Ink on Recycled Paper

Several dioxin/dibenzofuran data submissions for 2,4-D and related pesticides were reviewed. Each manufacturer of the registered technical pesticide was requested to randomly select seven samples of the pesticide and to analyze by a gc/ms method capable of quantitation to specified concentration levels, or limits of quantitation (loq), for each dioxin and dibenzofuran of toxicological interest. The resulting submissions were reviewed for compliance with the analytical chemistry requirements of the data call-in and for scientific validity.

Table 1 summarizes the findings for 2,4-D. Only 2,3,7,8-tetrachlorodibenzo-p-dioxin and 1,2,3,7,8-pentachlorodibenzo-p-dioxin were found at or above the EPA loq's. Two of eight technical 2,4-D's contained 2,3,7,8-TCDD slightly above the 0.1 ppb loq. Three of eight technical 2,4-D's contained 1,2,3,7,8-PCDD at concentrations greater than the 0.5 ppb loq. None of the remaining thirteen chlorinated dibenzo-p-dioxins and dibenzofurans were found at or above the EPA loq's in the technical 2,4-D. Data on the 2,4-DB and 2,4-DP acids and derivatives of all three acids are too limited at this time to be useful to the 2,4-D panel.

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Table 1: Summary of Results for Chlorinated Dibenzo-p-Dioxins and Dibenzofurans in Technical 2,4-D Herbicides

Analyte	EPA loq[1] (ppb)	2,4-D		
		Total Number of Technicals	Number of Technicals Greater Than loq	Observed Maximum Concentration (ppb)
2,3,7,8-TCDD	0.1	8	2	0.13[2]
1,2,3,7,8-PCDD	0.5	8	3	2.6[3]
1,2,3,4,7,8-HxCDD	2.5	8	0	0.81
1,2,3,6,7,8-HxCDD	2.5	8	0	0.77
1,2,3,7,8,9-HxCDD	2.5	8	0	0.65
1,2,3,4,6,7,8-HpCDD	100	8	0	1.5
2,3,7,8-TCDF	1	8	0	0.27
1,2,3,7,8-PCDF	5	8	0	0.62
2,3,4,7,8-PCDF	5	7	0	0.73
1,2,3,4,7,8-HxCDF	25	8	0	1.6
1,2,3,6,7,8-HxCDF	25	8	0	1.2
1,2,3,7,8,9-HxCDF	25	8	0	1.4
2,3,4,6,7,8-HxCDF	25	8	0	1.1
1,2,3,4,6,7,8-HpCDF	1000	8	0	8.3
1,2,3,4,7,8,9-HpCDF	1000	8	0	1.2

[1] Limit of quantitation required by the Agency and a reflection of the level of toxicological concern.
[2] Average 0.07 ppb, where 50% of demonstrated loq used for analytes not found.
[3] Average 0.63 ppb, where 50% of demonstrated loq used for analytes not found.

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TAB 2

Oregon Dioxin Data

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1978

FOREST SERVICE-USDA
PACIFIC NORTHWEST REGION
FINAL ENVIRONMENTAL STATEMENT
VEGETATION MANAGEMENT WITH HERBICIDES
USDA-FS-R6-FES(Adm)75-18 (Revised)
Prepared in Accordance with
Section 102(2)(C) of Public Law 91-190
The National Environmental Policy Act of 1969

Responsible Official for National Forest Lands:

R. E. Worthington
Regional Forester
Pacific Northwest Region
Forest Service-USDA
P. O. Box 3623
Portland, OR 97208

Summary

I. Draft ( ) Final (X)

II. Forest Service

III. Administrative (X) Legislative ( )

IV. DESCRIPTION OF PROPOSED ACTION

Approximately 150,000 out of 24,333,612 acres of National Forest lands within the Pacific Northwest Region of the U. S. Forest Service are proposed for vegetation management with herbicides for the Fiscal Year 1978. The areas are located on National Forest lands in Washington, Oregon, and Del Norte and Siskiyou counties in California.

The preferred alternative is to use all the methods available to the Region for vegetation management. These methods include using all the registered herbicides available at this time, mechanical clearing, manual clearing, biological control, and prescribed burning.

In addition to the preferred alternative, four other alternatives are discussed and evaluated. These alternatives vary the combination of vegetation management methods and funding levels to accomplish vegetation control. Environmental impacts of the preferred and other alternatives are described for both immediate and cumulative effects.

The proposed action has been reviewed in light of the guidelines set forth in the Interim Directions issued to implement the National Forest Management Act (P.L. 94-588), and is determined to be consistent with those guidelines.

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TABLE 7.

F O R E S T

(Retyped to improve clarity of reproduction from Table 7 attached to October 19,1977 letter from D. Coville.)

Type of Sample	Date Collected/ Sprayed	Site Number	2,4,5-T Application Rate (lb/A)	2,4,5-T Lot No.7	TCDD Level in 2,4,5-T	Accession Number	Sample Weight	Rec. Corr. For PCB?	Percent Recovery	TCDD Det. Limit(PPT)[1]	TCDD Level
Oregon Meadow Mouse		Hebo Unit A				4-26-326	5.0	No[2]	102	66.0	ND
Hermit Thrush		"				332	5.0	Yes	32	20.0	ND
Bewicks Wren		"				329	3.0	No[2]	41	31.2	83
Hairy Woodpecker		"				336	20.0	No[3]	55	3.0	ND
~~Downy Woodpecker~~		Hebo Unit 3	~~3~~	Amchem	<0.1 ppm	-	~~10.0~~	~~No~~[1]	~~43~~	~~14.6~~	~~NB~~
Rainbow Trout 5		"	"	6310	"						
Deer Mouse		"	"	"	"	328	5.0	Yes	65	9.6	ND
Bewicks Wren 3		"	"	"	"	330	10.0	No[3]	43	14.6	ND
Dendrocopos Pubescens		"	"	"	"						
Hairy Woodpecker		"	"	"	"	240	20.0	Yes	40	25	ND
Hermit Thrush		"	"	"	"	253	10.0	Yes	28	19	ND
Deer Mice		"	"	"	"	260	10.0	Yes	40	44.0	ND
Winier Wrens		"	"	"	"	261	5.0	Yes	40	21	ND
Rainbow Trout		"	"	"	"						
Downy Woodpecker		"	"	"	"	334	10.0	Yes	82	9.4	ND
Deer Mouse		"	"	"	"	328	5.0	Yes	65	9.6	ND
Bewicks Wren		"	"	"	"	330	10.0	No[1]	43	14.6	ND
Dendrocopos Pubescens		"	"	"	"	333	10.0	Yes	29	35.8	ND
Song Sparrow		Waldport Unit A				327	8.0	No[3]	68	4.8	ND
Stellers Jay		Waldport Unit 16	3	Amchem	<0.1 ppm	-	-	-	-	-	-
Fox Sparrow		"	"	6310	"	-	-	-	-	-	-
Mountain Beaver		"	"	"	"	325	20.0	No[2]	13	17.2	ND
~~Spotted-Skunks~~		"	"	"	"	-	-	-	-	-	-
Cutthroat Trout		"	"	"	"	245	20.0	No[3]	34	3.8	ND
Coho Salmon		"	"	"	"	246	4.0	Yes	36	60.2	ND
Rainbow Trout		"	"	"	"	247	10.0	No[2]	5	550	ND
Chestnut-Backed Chickadee		"	"	"	"	252	10.0	No[2]	4	92	ND
Deer Mice		"	"	"	"	263	10.0	No[3]	67	5.6	ND
Deer Mice		"	"	"	"	265	10.0	No[3]	94	7.7	ND
Deer Mice		"	"	"	"	268	10.0	Yes	16	37	ND
Brush Rabbit		"	"	"	"	-	-	-	-	-	-
Spotted Skunk		"	"	"	"	-	-	-	-	-	-
~~Spotted-Skunk-~~		Walport Unit 20	3	Amchem	<0.1 ppm	-	-	-	-	-	-
~~Spotted-Skunks-2~~		"	"	6310	"	-	-	-	-	-	-
Fox Sparrow		"	"	"	"	248	10.0	No[2]	3	773	ND
Short-Tailed Weasel		"	"	"	"	250	20.0	Yes	17	20.2	ND
Stellers Jay		"	"	"	"	251	20.0	Yes	48	7.5	12.1
Wren		"	"	"	"	254	5.0	Yes	6	254	ND
Deer Mice		"	"	"	"	262	10.0	Yes	46	8.9	14.3
Deer Mice		"	"	"	"	264	10.0	Yes	52	68.7	ND
Deer Mice		"	"	"	"	266	10.0	No[3]	17	47.4	ND
Deer Mouse		"	"	"	"	267	10.0	No[3]	34	11.0	14.4
Mountain Beaver		"	"	"	"	268	10.0	Yes	16	35.6	ND
Thryomanes Bawickii		"	"	"	"	337	4.0	Yes	37	32.2	133.3
Rough Skinned Newt		Chetco Unit 112	1.5	Amchem		318	10.0	Yes	37	10.2	ND
Rainbow Trout		"	"	IBK		317	10.0	No[3]	21	15.4	ND
Pacific Giant Salamander		"	"	"		320	20.0	No[2]	43	3.6	ND
Deer Mice 6		Brookings Unit	"	"							
Spotted Skunk		122									
Varied Thrush 4		"				335	20.0	No[3]	31	13.8	ND
Mountain Quail		"				-					
Scrub Jays 2		"				-					
Rainbow Trout 10		"				316	20.0	Yes	18	11	ND
Ruby Crowned Kinglet		"									
~~Microtus-longicaudus~~ Pipilo		"				331	10.0	No[3]	34	21.6	136.1
Porcupine		"									
Porcupine Skin		"				~~323~~	~~20.0~~	~~Yes~~	~~59~~	~~290~~	~~NB~~
Freshwater Leech		"									
Salamander		"									
Long-Tailed Meadow Mouse		"									
Piryon Mouse		"									
Fox Sparrow		"									
News 2		"									
~~Pipilo-Erythrophthalous~~		"				~~331~~	~~10.0~~				
Stellers Jay		"									
Mountain Beaver		Brookings Unit									
Varied Thrust 3		125				323	20.0	Yes	58	2.9	ND
Golden Crowned Sparrows 2		"				-					
Water Dogs 3		"				-					

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TABLE 7.- cont.

FOREST

e of Sample	Date Collected/ Sprayed	Site Number	2,4,5-T Application Rate (lb/A)	2,4,5-T Lot No.7	TCDD Level in 2,4,5-T	Accession Number	Sample Weight	Rec. Corr. For PCB?	Percent Recovery	TCDD Det. Limit(PPT)[1]	TCDD Level(PPT)
Deer Mice 8		Brookings Unit									
Mountain Quail		125									
Fox Sparrow		"									
Scrub Jay		"				321	20.0	Yes	17	12.8	ND
Snails 2		"									
Stellers Jay 2		"				322	20.0	No[1]	46	5.1	ND
Golden Crowned Kinglet		"									
Dusky Footed Wood Rat 2		"				324	20.0	No[1]	45	4.6	ND
Rufons Sided Towhee		"									
Rainbow Trout 5		"				319	20.0	No[1]	25	10.8	ND
Racoons 2		"									
Song Sparrow		6361	3	Amchem	<0.1 ppm	225	15.0	Yes	27	14.5	ND[5]
Song Sparrows 2		"		6310	"	226	20.0	Yes	25	6.6	30.4
Bewicks Wren		"		"	"	227	5.0	Yes	27	27.0	143.0
White-Footed Mice 2		"		"	"	228	20.0	No[3]	59	4.8	ND[5]
Winter Wren		"		"	"	229	5.0	Yes	24	47.3	ND[5]
Banana Slug		"		"	"	230	5.0	Yes	10	45.2	ND[5]

[1] TCDD detection limits and levels are corrected for recovery values.

[2] Recovery value was not corrected for PCB interference. PCB level too high for accurate correction.

[3] Recovery correction for the presence of PCB was unnecessary.

[4] Recovery value was not corrected for PCB interference due to broken sample tube.

[5] ND means that TCDD was Not Detected in the sample.

[6] Instrument malfunction prevented PCB correction.

[7] Herbicides beginning with "MM" are Dow Chemical products; those beginning with "A3" are Chipman ViscoRap products; the remainder are Amchem products.

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Table III. Analysis of Water and Sediment for TCDD (Alsea, Oregon Study - Phase I).

Sample No.	Sample Type	Ngs Spike	Conc (ppt)	Det limit	% Recovery	Isotope Ratio	Data Report
UN 1	WATER	2.5	.067	.02	75		2-IVB
UN-1	WATER	2.5	.027	.005	65		3-IV
UN 2	WATER	2.5	.76	.04	85		2-IVB
UN 3	WATER	2.5	.092	.01	90		2-IVB
UN-3	WATER	2.5	.023	.009	45		3-IV
UN 4	WATER	2.5	.067	.03	80		2-IVB
UN 5	WATER	2.5	.041	.03	50		2-IVB
UN-5	WATER	2.5	ND	.008	55		3-IV
UN 6	WATER	2.5	.061	.03	50		2-IVB
UN 7	WATER	2.5	.31	.02	50		2-IVB
UN 8	WATER	2.5	ND	.03	75		2-IVB
UN 9	WATER	2.5	ND	.04	60		2-IVB
UN 10	WATER	2.5	.040	.03	65		2-IVB
UN-10	WATER	2.5	ND	.007	55		3-IV
UN 11	WATER	2.5	ND	.04	60		2-IVB
UN 12	WATER	2.5	.070	.02	75		2-IVB
UN 13	SEDIMENT	2.5	ND	3	60		2-IVB
UN-14	SEDIMENT	2.5	13	5	60		3-I
UN-14	SEDIMENT	2.5	ND	.9	45		3-IV
UN-15	SEDIMENT	2.5	30	14	55		3-I
UN-15	SEDIMENT	2.5	2.0	1.4	30		3-IV
UN-15	SEDIMENT		1.9	.2		.78	3-V
UN-16	SEDIMENT	2.5	5.9	3	105		3-I
UN-16	SEDIMENT		ND	1.5		-	3-V
UN-16	SEDIMENT		ND	.7		-	3-V
UN-17	SEDIMENT	2.5	19	9	80		3-I
UN-17	SEDIMENT		2.3	.5		.83	3-V
UN-18	SEDIMENT	2.5	ND	11	60		3-I
UN-19	WATER	2.5	.061	.03	70		3-II
UN-20	WATER	2.5	ND	.02	120		3-II
UN-21	WATER	2.5	ND	.04	70		3-II
UN-22	WATER	2.5	.083	.02	90		3-II
UN-23	WATER	2.5	.065	.03	60		3-II
UN-23	WATER	2.5	.0081	.005	60		3-IV
UN-24	WATER	2.5	ND	.05	80		3-II
UN-25	WATER	2.5	.11	.04	60		3-II
UN-25	WATER	2.5	.011	.009	50		3-IV
UN-26	WATER	2.5	.081	.06	45		3-II
UN-26	WATER	2.5	ND	.004	55		3-IV
UN-27	WATER	2.5	ND	.07	45		3-II
UN-28	WATER	2.5	ND	.07	40		3-II
UN-29	WATER	2.5	ND	.08	40		3-II
UN-30	WATER	2.5	.17	.03	70		3-II
UN-31	WATER	2.5	ND	.08	45		3-II
UN-32	SEDIMENT	2.5	ND	9	70		3-I
UN-32	SEDIMENT	2.5	ND	.4	65		3-IV
UN-33	SEDIMENT	2.5	ND	4	85		3-I
UN-34	SEDIMENT	2.5	ND	4	90		3-I

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UN-35	SEDIMENT	2.5	ND	14	35		3-I
UN-36	SEDIMENT	2.5	22	5	35		3-I
UN-37	SEDIMENT	2.5	ND	13	70		3-I
UN-38	SEDIMENT	2.5	ND	9	75		3-I
UN-39	SEDIMENT	2.5	38	4	35		3-I
UN-39	SEDIMENT		11.1	.7		.80	3-V
UN-40	SEDIMENT	2.5	21	3	55		3-I
UN-41	SEDIMENT	2.5	34	16	35		3-I
UN-41	SEDIMENT		11.7	1.6		.63	3-V
UN-42	SEDIMENT	2.5	20	12	25		3-I
UN-42	SEDIMENT		4.4	.5		.83	3-V
UN-43	SEDIMENT	2.5	ND	1.8	20		3-III
UN-44	SEDIMENT	2.5	1.3	.4	60		3-III
UN-45	SEDIMENT	2.5	ND	12	60		3-III
UN-46	SEDIMENT	2.5	ND	.9	45		3-III
UN-47	SEDIMENT	2.5	3.6	1.2	50		3-III
UN-47	SEDIMENT		3.6	.4		.86	3-V
UN-48	SEDIMENT	2.5	4.4	1.4	40		3-III
UN-48	SEDIMENT		5.8	.6		.78	3-V
UN-49	SEDIMENT	2.5	ND	.9	60		3-III
UN-50	SEDIMENT	2.5	ND	.8	60		3-III
UN 51	WATER	2.5	ND	.03	65		9
UN 52	WATER	2.5	ND	.06	80		9
UN 53	WATER	2.5	ND	.07	55		9
UN 54	WATER	2.5	.08	.03	100		9
UN 55	WATER	2.5	ND	.10	75		9
UN 56	SEDIMENT	2.5	64	17	45		9
		2.5	40	8	55		9
UN 57	SEDIMENT	2.5	24	13	55		9
UN 58	SEDIMENT	2.5	7	3	70		9
UN 59	SEDIMENT	2.5	32	4	50		9
		2.5	60	12	35		9
UN 60	SEDIMENT	2.5	7	4	35		9
UN 61	SEDIMENT	2.5	7	2	50		9
UN 62	SEDIMENT	2.5	5	2	45		9
UN 63	SEDIMENT	2.5	ND	2	55		9
UN 64	SEDIMENT	2.5	9	4	80		9
UN 65	SEDIMENT	2.5	58	5	75		9

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Table VII. Analysis of TCDD in Biological and Environmental Samples ("Alsea, Oregon Phase II Project").

Sample No.	Sample Type	Ngs Spike	Conc (ppt)	Det limit	% Recovery	Isotope Ratio	Data Report
UN 159	SEDIMENT	2.05	ND	19	30		10-IV
UN 160	SEDIMENT	2.05	120	15	40		10-IV
UN 160	SEDIMENT		-	8		-	10-V
UN 161	SEDIMENT	2.05	105	16	80		10-IV
UN 161	SEDIMENT		-	41		.21	10-V
UN 162	SEDIMENT	2.0	30	13	50		10-IV
UN 162	SEDIMENT		-	12		1.63	10-V
UN 163	SEDIMENT		-	680		2.00	10-V
UN 164	SEDIMENT	2.0	210	24	50		10-IV
UN 164	SEDIMENT		-	48		1.96	10-V
UN 165	SEDIMENT		-	10		-	10-V
UN 166	SLUDGE	4.0	220	140	75		10-IV
UN BLANK	SOLVENT	2.0	ND	4	50		10-IV
UN BLANK	SOLVENT	2.0	ND	1	70		10-IV
UN 166	SLUDGE		-	8		.96	10-V
UN 167	SLUDGE		-	8		.90	10-V
UN 168	SLUDGE		160	12		.78	10-V
UN 169	SLUDGE		5800	56		.78	10-V
UN 170	SLUDGE		470	10		.80	10-V
UN 171	SLUDGE		283	48		.79	10-V
UN 172	WATER		-	.25		2.16	10-V
UN 173	WATER		.38	.2		.84	10-V
UN 185	WATER FILTER	2.0	ND	5	50		10-II
UN 185	WATER FILTER		-	5		.39	10-VI
UN 186	CAT LIVER	1.85	ND	15	50		10-II
UN 187A	PRODUCTS OF CONCEPTION	2.05	ND	19	50		10-II
UN 187A	PRODUCTS OF CONCEPTION	Extracted only.		Analyzed elsewhere.			12-I
UN 188A	PRODUCTS OF CONCEPTION	2.0	3	2	50		10-II
UN BLANK	SOLVENT	10.0	ND	12	50		10-II
UN BLANK	CHARCOAL	10.0	ND	12	20		10-II
UN 188A	PRODUCTS OF CONCEPTION		-	1		-	10-VI
UN 188A	PRODUCTS OF CONCEPTION	Extracted only.		Analyzed elsewhere.			12-I
UN 191	MOUSE	2.5	ND	4	55		10-I
UN 192	SHREW	2.5	ND	3	55		10-I
UN 193	MOUSE	2.5	ND	18	6		10-I
UN 193	MOUSE	Extracted only.		Analyzed elsewhere.			12-II
UN 194	MOUSE	2.5	ND	2	50		10-I
UN 195	MOUSE	2.5	ND	3	50		10-I
UN 196	MOUSE	2.45	ND	3	55		10-I
UN 197	SHREW	Extracted only.		Analyzed elsewhere.			12-II
UN 197	SHREW	2.5	ND	8	30		10-I
UN 198	SHREW	2.45	ND	7	50		10-I
UN 199	SHREW	2.5	ND	4	65		10-I

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UN 199	SHREW		ND	1		-	10-VI
UN 199	SHREW		ND	1		.98	10-VI
UN 200	BIRD	2.5	ND	5	50		10-I
UN 201	MOUSE	2.5	ND	2	60		10-I
UN 202	BIRD	2.5	ND	3	50		10-I
UN 202	BIRD	Extracted only.		Analyzed elsewhere.			12-I
UN 203	MOUSE	2.5	ND	3	30		10-I
BLANK 001	SOLVENT						12-II
BLANK 002	SOLVENT						12-II
BLANK 003	SOLVENT						12-II
UN 203	MOUSE	Extracted only.		Analyzed elsewhere.			12-II
UN 204	NEWTS	2.5	3	2	50		10-I
BLANK	SOLVENT	2.45	ND	5	50		10-I
BLANK	SOLVENT	2.4	ND	4	50		10-I
BLANK	SOLVENT	2.5	ND	3	55		10-I
UN 204	NEWTS		ND	1		-	10-VI
UN 204	NEWTS	Extracted only.		Analyzed elsewhere.			12-I

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DRAFT

1/23

Acession #: 9

Title of Project: DMP Deer and Elk Study

Status of Project: in progress

Location of Sampling: Oregon and Washington

Herbicide Use: forest

Sample Media: deer and elk adipose tissue

Range of Limit of Detection: RTP: 0.8 - 6.0 ppt
WSU: 8.0 - 34.0 ppt

Average Limit of Detection: RTP: 2.7 ppt
WSU: 14.8 ppt

# of Samples Collected: deer: 6
elk : 9

# of Samples Analyzed: 15

# of Samples Suspected Positive: : deer: 3 of 6, 50.0%
elk: 7 of 9, 77.8%

Comments:

It is important to note that four samples were analyzed below 50% recovery of the 37Cl TCDD standard and therefore require re-extraction and re-analysis according to standard DMP procedures. These samples are # OR-D-1, WA-D-4, WA-D-8, and WA-E-7. Nevertheless, the data indicate the presence of 2,3,7,8 TCDD residues in both deer and elk.

Also it is important to note that RTP reported the presence of other minor isomers in addition to the major 2,3,7,8 TCDD isomer (based on the DMP analytical criteria).

The result of this study indicates that additional sampling may be useful in providing more information about the extent of dioxin contamination associated with the use of 2,4,5-T and silvex in this geographic area.

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Preliminary Data

DRAFT 1/23

Adipose Sample Description	Toxicant Analysis Center Sample #	ppt[c] Native TCDD Added to Sample	RTP #	Research Triangle Park TCDD Detected (ppt)[c]	RTP TCDD Detection Limit (ppt)[c]	RTP 37CL[d] % Recovery	WSU #[f]	Wright State University TCDD Detected (ppt)[c]	WSU TCDD Detection Limit (ppt)[c]	WSU 37CL % Recovery
deer	OR-D-5		124[e]	12	2	89	1[g]	31	21	46
deer	WA-D-1		125	ND	2	50	2	ND	21	46
deer	OR-D-1		126	ND	4	34	3[g]	ND	34	29
deer	Control	7	127	9	2	78	4	14	13	51
deer	WA-D-4		128	ND	3	36	NA			
deer	OR-D-6		129[e]	7	2	84	5	14	13	59
deer	WA-D-8		130	7	4	31	6[g]	ND	24	33
Method Blank[a]		0	131	ND	3	50	7	ND	8	105
elk	WA-E-2		132[e]	9	2	67	NA			
elk	OR-E-11		133	ND	2	71	8	ND	8	97
elk	WA-E-6		134[e]	54	0.8	100	9	68	10	79
deer	Control	21	135[e]	34	6	50	10[g]	41	8	150
elk	OR-E-7		136	24	3	50	11	29	8	102
elk	OR-E-9		137[e]	5	3	100+	12[g]	ND	8	98
elk	WA-E-5		138	12	3	57	13[g]	ND	19	43
elk	OR-E-8		139[e]	4	1	87	14[g]	ND	10	84
Standard Solution[b]		14	140	23	2	100+	15	17	11	76
elk	WA-E-4		141[e]	21	2	76	16[g]	21	11	70
elk	WA-E-7		142	ND	4	36	17[g]	ND	25	32

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(a) Method 1 , extraction procedure using solvent only.

(b) Standard Solution: a standard solution containing 2,3,7,8-tetrachloro-dibenzo-p-dioxin

(c) ppt: parts per trillion

(d) corrected for recovery loss

(e) two other isomers in addition to 2,3,7,8-tetrachloro-dibenzo-p-dioxin the major isomer, were observed

(f) WSU analyses reported here are the average of two runs

(g) evidence of PCB contamination in sample

ND: Not Detected

NA: Not analyzed by WSU due to limited amount of sample

NB: Sample wt. for all samples was 5g.; 37CL TCDD addition to each sample is 5 nanograms (ng) except Control Sample RTP-135/WSU-10 which contained 1.33 ng.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HEALTH EFFECTS RESEARCH LABORATORY
RESEARCH TRIANGLE PARK
NORTH CAROLINA 27711

DATE: December 17, 1979

SUBJECT: Results of Capillary Column GC/HRMS Analyses Performed on Extracts of Deer and Elk Adipose Tissue for 2,3,7,8-TCDD Residues

FROM: Robert Harless
HERL, ETD, ACB (MD-69)

TO: Mike Dellarco, Dioxin Project Manager
Special Pesticide Review Division (TS-791)
Office of Toxic Substances
401 M Street, SW
US EPA
Washington, DC 20460

THRU: Dr. R. G. Lewis, Chief
Analytical Chemistry Branch (MD-69)
HERL, ETD

Per your request, these samples were not analyzed until the most high priority samples, "Vertac", etc. were analyzed.

This shipment of sample extracts was received from the EPA Pesticide Monitoring Laboratory, Bay-St. Louis, Mississippi, 9-6-79, and was assigned the identification number ACB-108. The sample extracts were subjected to a previously described capillary column GC/HRMS multiple ion monitoring method of analysis for 2,3,7,8-TCDD residues utilizing a Varian 311A mass spectrometer interfaced with an SE-30 WCOT glass capillary column.

The criteria utilized for confirmation of 2,3,7,8-TCDD were:

1. Capillary column GC/HRMS retention time of 2,3,7,8-TCDD.
2. Co-injection of sample fortified with ^{37}Cl-TCDD and 2,3,7,8-TCDD standard.
3. Molecular ion chlorine isotope ratio (m/e 320 and m/e 322).
4. Capillary column GC/HRMS simultaneous multiple ion monitoring response (m/e 320, m/e 322, and m/e 328) for TCDD.
5. M/e 320 and m/e 322 MS response greater than 2.5 mm noise level.

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The capillary column GC/HRMS retention time of 2,3,7,8-TCDD was 15 minutes ± 15 seconds. The MS mass resolution (8,500) was sufficient to resolve TCDD from contamination. The masses monitored during these analyses were:

1. m/e 318.9793 PFK reference
2. m/e 319.8965 TCDD
3. m/e 321.8935 TCDD
4. m/e 327.8847 ^{37}Cl-TCDD

Results

The results are shown in Table 1. The recovery of ^{37}Cl-TCDD was below 50% for specific sample extracts. Therefore, the results should not be reported. These specific samples should be subjected to analytical clean-up and GC/HRMS analysis again to confirm the reported results. TCDD isomers (3) were detected in RTP-124, 129, 132, 134, 135, 137, 139, and 141. The isomer having exact GC/HRMS retention time as 2,3,7,8-TCDD was the major isomer detected (high concentration). No problems were encountered in these analyses.

Summary

2,3,7,8-TCDD and two (2) TCDD isomers were detected in deer and elk adipose tissue samples.

CC: Dr. William Durham, Director
Environmental Toxicology Division (MD-66)

Dr. Nancy Wilson, Chief
Chemical Characterization Section (MD-69)

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TABLE 1 ACB #108

ANALYTICAL RESULTS FOR 2,3,7,8-TCDD RESIDUES

Sample ID	Sample Weight (g)	^{37}Cl-TCDD Fortification Level (ng)	^{37}Cl-TCDD % Recovery	TCDD Detection Limit (ppt)*	TCDD Detected (ppt) *	Comments
RTP-124	5	5	89	2	12	Deer Adipose
RTP-125	5	5	50	2	ND	" "
RTP-126	5	5	34	4	ND	" "
RTP-127	5	5	78	2	9	" "
RTP-128	5	5	36	3	ND	" "
RTP-129	5	5	84	2	9	" "
RTP-130	5	5	31	4	7	" "
RTP-131	5	5	50	3	ND	" "
RTP-132	4	4	67	2	9	Elk Adipose
RTP-133	5	5	71	2	ND	" "
RTP-134	5	5	100	0.8	54	" "
RTP-135	5	1.33	50	6	34	" "
RTP-136	5	5	50	3	24	" "
RTP-137	5	5	100+	3	5	" "
RTP-138	5	5	57	3	12	" "
RTP-139	5	5	87	1	4	" "
RTP-140	5	5	100+	2	23	" "
RTP-141	5	5	76	2	21	" "
RTP-142	5	5	36	4	ND	" "

ND = not detected ppt = parts per trillion * = corrected for recovery losses

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Wright State University

Dayton, Ohio 45431

November 29, 1979

Mr. W. T. Hollaway
U.S. Environmental Protection Agency
Office of Toxic Substances
Special Pesticide Review Div. (TS-791)
Crystal Mall #2
1921 Jefferson Davis Highway, Rm. 728
Arlington, Virginia 22202

DEC - 8. 1979

Dear Mr. Hollaway:

Attached is a table showing the results of analyses of the remaining samples in the batch of 17 which we have been analyzing. Results for the first nine samples were reported in our recent Quarterly Report. We are proceeding as rapidly as possible with the MS-30 modifications to permit isomer-specific TCDD determinations, and will provide you with a status report on those developments in the near future.

Sincerely,

Thomas O. Tiernan, Ph.D.
Professor of Chemistry and
Director of the Brehm Laboratory

TOT/aam
Attachment

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TABLE 1

RESULTS OF GC-HIGH RESOLUTION MS ANALYSES OF SAMPLE EXTRACTS PROVIDED BY EPA FOR TETRACHLORODIBENZO-p-DIOXIN (TCDD) BY WRIGHT STATE UNIVERSITY

EPA Sample No.	Run 1 Native TCDD Detected (parts-per-trillion) m/e 320	m/e 322	Average	Run 2 Native TCDD Detected (parts-per-trillion) m/e 320	m/e 322	Average	Average Native TCDD (ppt)	Average M.D.C. (ppt)	Average % Recovery	Notes
WSU-10	31	43	37	48	43	45	41	8	150	a.,b.
WSU-11	25	23	24	35	32	34	29	8	102	--
WSU-12	0	0	0	0	0	0	0	8	98	a.
WSU-13	0	0	0	0	0	0	0	19	43	a.
WSU-14	0	0	0	0	0	0	0	10	84	a.
WSU-15	15	20	18	14	16	15	17	11	76	--
WSU-16	18	26	22	17	20	19	21	11	70	a.
WSU-17	0	0	0	0	0	0	0	25	32	a.

a. PCB contamination of sample is evident.

b. This sample was supposedly spiked with only 1.33 ng total ^{37}Cl-TCDD. The indicated recovery however indicates a possible error in spiking.

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TABLE 1

INFORMATION ON SEDIMENT SAMPLES TAKEN FROM
FIVE RIVERS, OREGON AREA IN AUGUST, 1984

Region X Sample No.	ECL[1] No.	EMCL/RTP[2] No.	Sample Location	Sample Type	Sample Weight	% Moisture in sample
ALA6	D-907	D-979	Initial stream location	6 inch core	10 g	13.4
ALB6	D-908	D-980	Opposite side of stream	6 inch core	10 g	36.3
		D-986	Duplicate			
ALC6	D-909	D-981	Approx. 25' downstream	6 inch core	10 g	24.1
ALA1	D-910	D-982	Approx. 45' further downstr.	Surface	10 g	17.2
ALB1	D-911	D-983	Approx. 40' further downstr.	Surface	10 g	22.6
ALC1	D-913	D-985	Approx. 30' further downstr.	Surface	10 g	32.5

1. EPA's Envrionmental Chemistry Laboratory in Bay St. Louis, Mississippi
2. EPA's Environmental Monitoring and Support Laboratory in Research Triangle Park, NC

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TABLE 2

ANALYTICAL RESULTS ON SEDIMENT SAMPLES TAKEN FROM
FIVE RIVERS, OREGON AREA IN AUGUST, 1984

	ECL[1] Analyses				RTP[2] Analsyes		
Region X Sample No.	2,4,5-T	% Recovery[4]	2,3,7,8-TCDD ppt, wet wt.[5]	2,3,7,8-TCDD ppt, dry wt.[6]	% Recovery[4]	2,3,7,8-TCDD ppt, wet wt.[5]	2,3,7,8-TCDD ppt, dry wt.[6]
ALA6	ND	65	ND (3)	ND (3)	98	2 (1)	2 (1)
ALB6	ND	76	50 (3)	78 (5)	92 86	23 (3) 33 (3)[7]	36 (5) 52 (5)[7]
ALC6	ND	60	4.5 (2)	6(3)	80	4 (1)	5 (1)
ALA1	ND	62	ND (3)	ND (4)	98	3 (1)	4 (1)
ALB1	ND	57	ND (2)	ND (3)	98	ND (1)	ND (1)
ALC1	ND	61	4.5 (2)	6 (3)	98	4 (1)	6 (1)

1. EPA's Environmental Chemistry Laboratory, Bay St. Louis, Mississippi
2. EPA's Environmental Monitoring and Support Laboratory in Research Triangle Park, NC
3. ND = not detected; minimum level of detection = 2 ppb.
4. % recovery of 5 ng of ^{13}C-labelled 2,3,7,8-TCDD. This quantity is a measure of method efficiency.
5. ND = not detected; minimum level of detection in ppt is included in parentheses.
6. ppt, dry wt. = [ppt, wet wt. / (100 - % moisture)] X 100
7. Separate extraction and analysis of the same sample.

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TAB 3

EPA: Dioxin effects and bioconcentration in fish, 1987

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE 4 February 1987

SUBJECT 2,3,7,8-TCDD in Aquatic Environments

FROM Philip M. Cook, Ph.D. PMC
Chief, Hazardous Waste Research Branch, ERL-Duluth

TO Jim Cummings
Office of the Assistant Administrator
for Solid Waste and Emergency Response

This memorandum is provided in response to your request for an update on the state of knowledge concerning 2,3,7,8-TCDD in aquatic environments. A considerable amount of new information is being generated and much will be reported during 1987. Most of the information I can provide results from our own research. I believe you have already received reprints for research results already published.

I reported bioconcentration factor (BCF) determinations for 2,3,7,8-TCDD, 1,2,3,4-TCDD, 1,3,6,8-TCDD and 1,3,7,9-TCDD at the Society for Environmental Toxicology and Chemistry meeting last November. A journal publication is in preparation. The EPA Water Quality Criteria Document presently uses a value of 5000 for the 2,3,7,8-TCDD BCF. We determined a value of 66,000 for carp and 97,000 and 159,000 for fathead minnows at two different exposure concentrations. Our BCF data for the four TCDD isomers is summarized in the attached table. We concluded from this study that ---

1. BCFs for different TCDD isomers vary greatly as expected from field monitoring data.

2. TCDD isomers other than 2,3,7,8-TCDD have lower BCFs than predicted on the basis of structure or log Kow due to more rapid rates of elimination.

3. Differences in rates of metabolism probably explain differences in TCDD rates of elimination and thus BCFs.

4. The gill uptake efficiencies for the four TCDD isomers studied appear to be similar despite structural differences and different uptake rate measurements attributed to large differences in elimination rates.

5. Approximately 90% of the TCDD in the fish exposure water was associated with particulate and dissolved organic matter. Thus, BCFs calculated on the basis of organic carbon free TCDD in the water would be ten times greater.

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6. The Water Quality Criteria Document BCF value for 2,3,7,8-TCDD is very low because previously reported BCF determinations were made on the basis of very short exposure periods, inadequate depuration data, static exposure conditions, overestimates of water exposure concentrations, and other factors which lower the estimate of equilibrium fish concentrations with respect to actual water concentrations.

7. 2,3,7,8-TCDD is so toxic to fish that BCF determinations have not yet been made over long exposure periods without toxic effects and mortality occurring. No-effect levels are likely to be less than 10 ppq total 2,3,7,8-TCDD in water and possibly less than 1 ppq if only "dissolved" 2,3,7,8-TCDD is considered in the bioaccumulatable and toxic component.

8. 2,3,7,8-TCDD was lethal to carp at an accumulated dose of 2 ug/Kg. Rainbow trout appear to be a little more sensitive. This toxicity is comparable to the 1 ug/Kg LD50 found for the guinea pig, the most sensitive mammalian species known. Fathead minnows appear to be at least five times less sensitive than carp or rainbow trout.

It is likely that fish bioaccumulation of PCDDs and PCDFs is greatly influenced by food chain links to contaminated sediments and contact time of fish with sediment. Field monitoring data generally supports this premise. For example, fish collected from field surveys when analyzed for all TCDD isomers generally only have detectable amounts of 2,3,7,8-TCDD despite the presence of greater amounts of other TCDD isomers in contaminated sediments. Many of the TCDD isomers have relatively low bioaccumulation potential as seen from our BCF measurements for 1,2,3,4-TCDD and 1,3,7,9-TCDD and thus are not likely to be detected. 1,3,6,8-TCDD, however, would be expected in the fish in detectable levels if uptake from water was the major route for bioaccumulation. The lack of 1,3,6,8-TCDD in the fish is consistent with a kinetic effect involving decreasing amounts of 1,3,6,8-TCDD with respect to 2,3,7,8-TCDD in each step along the food chain to a fish and the absence of significant uptake from water.

For higher chlorinated PCDD and PCDF congeners differences in elimination rates from fish and their food chain organisms create similar preferential bioaccumulation of 2,3,7,8-substituted planar molecules which are likely to be metabolized at a slower rate. In addition, as molecular weight and size increase with increasing degree of chlorination, it is apparent that the rate uptake from water across the gills decreases. Absorption efficiency from ingested material is also probably less for higher chlorinated congeners.

The net result of the above considerations is that many PCDDs and PCDFs found in sediments are not detectable in fish. The attached table on "Congener Dependent Bioavailability of PCDDs and PCDFs"

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demonstrates how this same effect occurs for laboratory exposure of fish to municipal incinerator fly ash. The effect is more extreme when the "food chain chromatography" effect is present and longer exposure times are involved (much longer time required to reach steady state) as with the fish exposed to sediment in a reservoir. The compounds included in the table are all members of the "biosignificant fraction of PCDDs and PCDFs in that they do appear to bioaccumulate, are all 2,3,7,8-substituted and thus all have significant toxic potential. We developed a simple expression called the "bioavailability index" (BI) for comparing relative bioaccumulation tendencies for different chemicals associated with different solid wastes on sediments. The BI is simply the ratio of chemicals accumulated per gram of fish lipid to the amount present per gram of organic carbon in the solid material the fish are exposed to. The BI can be normalized to a value of 1.0 for 2,3,7,8-TCDD in order to make comparison of the other PCDD and PCDF congeners BIs easier. Although the magnitudes of the fly ash and sediment BIs cannot be directly compared due to great differences in the fish exposures, the normalized BIs for both fly ash and sediment show the same trends. For both PCDDs and PCDFs the normalized BIs decrease as the degree of chlorination increases. There also appears to be a tendency for 2,3,7,8-TCDF to be less bioaccumulable than 2,3,7,8-TCDD. The penta-CDD and -CDF results for the sediment seem divergent and will be rechecked before this data is published in this form. We will soon have much more of this kind of data when results are obtained for Lake Ontario sediments and paper mill sludges.

EPA is frequently faced with the question of what fish TCDD contamination levels will result from known or projected environmental contamination levels. The use of a BCF value, no matter how accurate, for predicting fish residues has a major limitation in that environmental TCDD water concentrations can never be detected even with the most sensitive techniques. Even if water measurements could be made, it would be difficult to determine what fraction of TCDD in water is not associated with dissolved or particulate organic carbon so that a laboratory derived BCF could be applied. An alternative approach is to use expected equilibrium partitioning relationships for sediment and fish to predict maximum levels of fish contamination and rely on site-specific sediment to fish TCDD ratios to determine more realistic "approach to steady-state" relationships likely to exist between sediments and fish. This should be done on the basis of partitioning between organic carbon in sediment and lipid in fish. In theory there should be a simple 1:1 equilibrium relationship between sediment organic carbon and lipid concentrations for very hydrophobic organic compounds such as 2,3,7,8-TCDD which are very slowly metabolized and eliminated from the organism. There are data for compounds such as PCBs which indicate approximately a four-fold preference of these compounds for lipids over organic carbon in sediment. Our 2,3,7,8-TCDD BI value of .27 for sediment is 4X less than the theoretical partitioning value of 1.0 and 16X less than the lipid preference value of 4.0 at least in part because steady-state conditions were not reached when the fish were exposed to the sediment.

In many environmental situations expected steady-state relationships between fish bioaccumulation levels and sediment contamination levels will

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not be reached. Kinetic models and appropriate rate constants are needed to accurately predict fish bioaccumulation levels. When an aquatic ecosystem has a constant input of TCDD so that surface sediment concentrations are relatively constant, fish concentrations will approach a steady-state level dependent on rates of uptake from water, food and contact with sediment. For Lake Ontario we are investigating sediment to fish TCDD ratios under present conditions so that remedial actions for Superfund sites and other sources of TCDD can be evaluated with respect to changes in fish residues which will result in the future. That is, if sediment TCDD levels are decreased or increased in the future through man's activities, we should be able to predict eventual changes in fish contamination levels when a new "approach to steady-state" system results. In Lake Ontario our preliminary data indicates that fish lipids have only about 5% of the TCDD concentration found in the organic carbon fraction of the surface sediments. An extensive survey of sediment and fish TCDD levels throughout Lake Ontario is scheduled for this summer.

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Dioxin levels high in some Lakes fish

Detroit News

By Dudley K. Pierson
News Lansing Bureau, MAY 13 '84

LANSING -- Sport fish from some areas of the Great Lakes and tributaries should not be eaten regularly because they contain unsatisfactory levels of the cancer-causing chemical dioxin, reports the U.S. Environmental Protection Agency (EPA).

The warning came yesterday as the EPA released results of a $2 million study that tested carp and other fish for the most toxic form of dioxin.

The chemical was found in 29 of 50 areas where carp were sampled throughout the Great Lakes Basin. Most of the locations are in waters already thought to be polluted with industrial chemicals. But these are the first general warnings based on dioxin levels.

CARP, A bottom-feeding fish high in fat where toxic chemicals tend to be stored, is used by the EPA as a barometer for toxics in more desireable sport fish.

"There may be a significant enough magnitude (of dioxin) to warrant concern," said Peter Wise, the EPA's director of the Great Lakes National Program Office. He said the EPA needs to do more monitoring of sport fish.

The single highest level of dioxin was found at Midland, the home of Dow Chemical Co., where Tittabawassee River carp containing 525 parts per trillion of dioxin were taken.

Please see Dioxin /9A

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High levels found in some Great Lakes fish

From page 1A

Detroit News MAY 13 '86

[illegible] officials said they assumed "that human health concerns could begin to be raised at concentrations of about 1 part per trillion."

CARP CONTAINING 24.1 parts per trillion were found in the Rouge River in Detroit and carp containing from 2.7 to 14 parts per trillion were found in the Detroit River Trenton Channel beside Grosse Ile. In the Detroit River near Belle Isle, carp samples contained 9 parts per trillion.

To calculate the dioxin levels in sport fish, the EPA used a rule of thumb that sport fish probably contain from 1/5 to 1/8 the amount of dioxin found in bottom feeders such as carp.

Outstate EPA researchers were concerned about dioxin levels in fish taken from the Flint River, Saginaw Bay, and the Grand River at Grand Ledge.

In general the study showed that Lake Ontario contained the highest levels of dioxin-contaminated carp, followed by lakes Huron and Michigan, then Erie and Superior.

THE STUDY, begun in 1983, as part of a national dioxin investigation that will be released to Congress this summer, said EPA Regional Administrator Valdas Adamkus. He said it is not intended to show which fish are safe to eat, but to provide a "snapshot" of a relatively few number of fish spread over a wide geographic area.

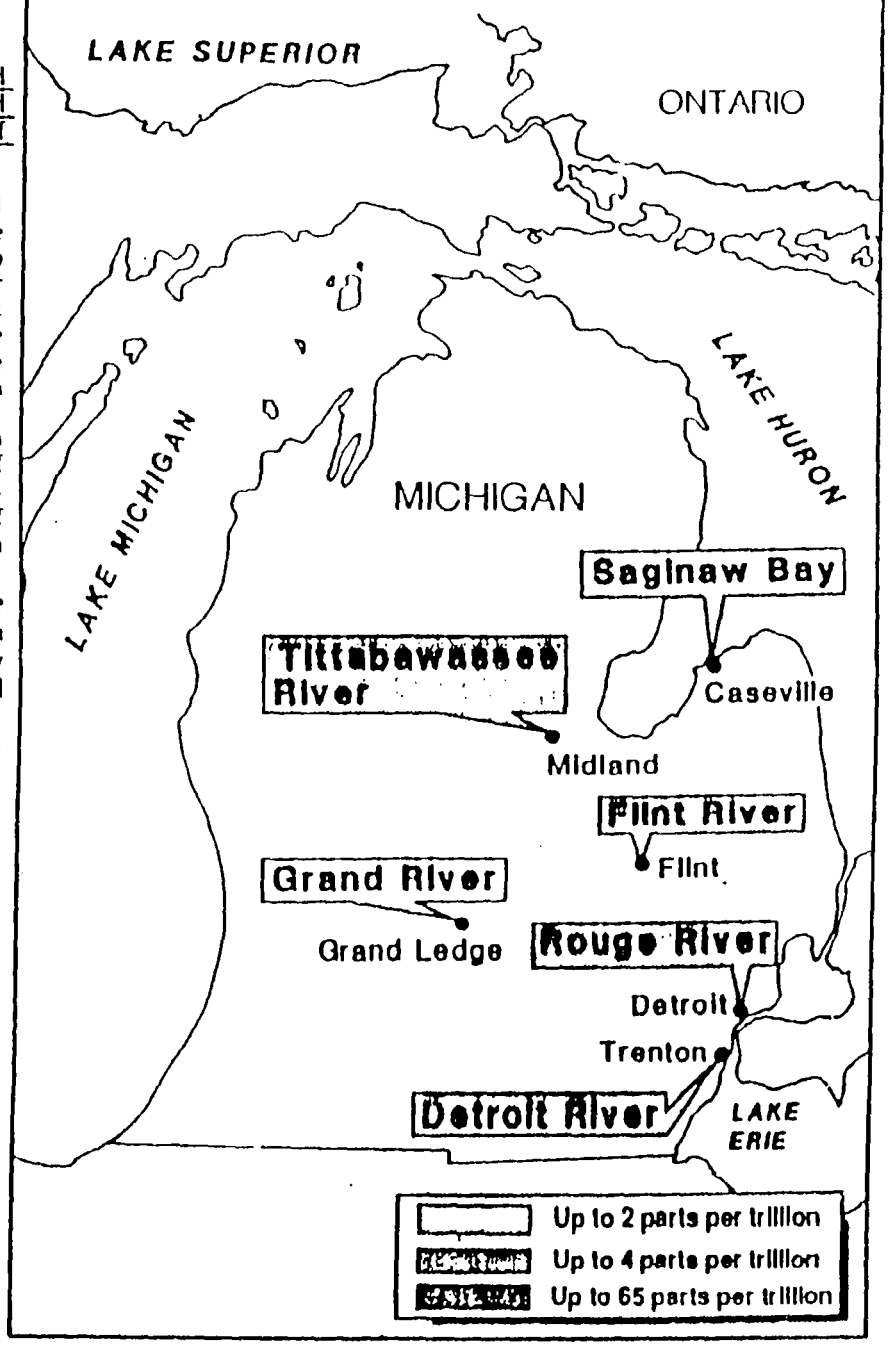
However, the snapshot included a limited number of samples of skinned lake trout fillets caught in Lakes Michigan, Huron, Ontario, St. Clair and Erie. Several of these contained levels of dioxins high enough for the EPA to warn against eating them regularly.

Walleye from Anchor Bay in Lake St. Clair, for instance, contained dioxin from 2.3 parts per trillion to 5.8 parts per trillion. Lake trout from Lake Huron near Alpena had from 5 parts per trillion to 9.8 parts per trillion.

In most of the areas where the EPA found dioxin-contaminated carp, fish advisories are already in effect warning anglers which fish are safe to eat. These advisories had been issued based on findings of PCBs, DDT and other toxic chemicals.

DIOXIN, CONSIDERED to be one of the most toxic chemical substances known, can cause cancers, [illegible] EPA

[illegible] dioxin in carp, [illegible] areas of [illegible] can contain more than 1 part per trillion of dioxin — enough to make them a health risk to people who eat them.



NEWSMAP

sources, industrial wastewater discharges.

Wise, of the Great Lakes National Program Office said toxic chemical contaminants in Great Lakes fish are "generally" higher than in other waters. That's due to heavy industrial and agricultural activities within the Great Lakes Basin, he said.

"In a lot of national studies we find Great Lakes fish are very high and that's because they (the lakes) have a lot of fat, old fish," he said.

He added that levels of other chemicals in Great Lakes fish appear to be decreasing and that indicates the amount of dioxin might also be declining.

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Tittabawassee carp tops dioxin list in EPA study

State health officials, though, insist river sport fish are safe

BY WAYNE SCHMIDT SAGNEWS
News Lansing Bureau
and DAVE ELLIS
News Staff Writer MAY 13 1984

A Tittabawassee River carp was the most contaminated in a U.S. Environmental Protection Agency study of dioxin in Great Lakes fish, but state health officials say sport fish in the river are safe.

The study, released Monday, showed dioxin contamination of fish is more extensive than previously documented in the Great Lakes.

State health officials, however, contend contamination levels in lake trout are for the most part at acceptable levels.

They also say the new findings are neither unexpected nor alarming.

The EPA study, part of a $2 million, multi-year effort, concluded that dioxin contamination of lake trout spans the Great Lakes.

"It means that dioxin contamination is pretty widely distributed throughout the Great Lakes," said David DeVault, coordinator of EPA's Great Lakes monitoring program.

The greatest amounts of dioxin in lake trout were found in Lake Ontario, which had up to four times the levels found in fish from Great Lakes bordering Michigan, according to the EPA study.

Dioxin is an industrial byproduct in the manufacture of some herbicides. It is suspected of causing cancer in humans.

As a result of the study, EPA officials recommended that Great Lakes states again review fish-eating advisories involving dioxin and other contaminants.

Michigan health officials contend that fish are safe to consume as long as dioxin contamination is lower than 10 parts per trillion.

Ten parts per trillion is equivalent to about 10 inches in 16 million miles.

The only fish found to be above 10 parts per trillion in Michigan waters were in the Saginaw Bay and inland streams, including the Tittabawassee, Flint, Grand, Rouge and Detroit rivers.

Carp fillets from the Tittabawassee ranged from 12 to 525 parts per trillion, said Richard A. Powers, chief of the DNR's toxic chemical evaluation section.

That was the most dioxin the federal study found in any fish, Powers said.

Powers said game fish from the river showed fewer than 10 parts per trillion of dioxin.

A whole carp from Saginaw Bay at Caseville showed 18 parts per trillion, while a carp fillet contained 13.2 parts per trillion.

• Is dioxin danger overblown? Ballot Box, The Back Page.

A whole walleye from the same site contained 6.8 parts per trillion and a fillet harbored .7 parts per trillion of the contaminant.

The federal study was intended to chart the worst-case scenario for contamination.

For example, the study sampled large, fatty trout in Great Lakes and bottom-feeding fish such as carp in inland waters. Those fish are most likely to accumulate and store dioxin contamination in their fatty tissue.

Popular game fish such as walleye and perch, however, typically have a small fraction of the levels found in bottom-feeding fish, said Peter Wise, director of EPA's Great Lakes National Program Office.

The EPA study is expected to reignite a controversy over what

Please see FISH, Page A-2

SAGINAW, MICHIGAN NEWS, MAY 13, 1986

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FISH

MAY 17 '85

Continued from Page A-1

levels of contamination are safe for human consumption. The agency in the past has criticized the way Michigan arrived at its safety limit.

It has again issued a call for new studies by states surrounding the Great Lakes.

According to the federal study, dioxin contamination was discovered in carp and other bottom-feeding fish from 11 rivers, two inland lakes and the Saginaw Bay in Michigan. Walleye from Lake St. Clair and large lake trout in lakes Superior, Michigan and Huron also showed measurable levels of dioxin.

Additional warnings against eating some fish may be necessary in light of the new EPA results, said John Hesse, a scientist with the state health department.

Other Michigan waters where bottom-feeding fish showed dioxin levels present but below health department limits were St. Joseph River, Berrien County; Kalamazoo River, Allegan; Muskegon River, Bridgeton; White Lake, Montague; St. Clair River, Algonac; Clinton River, Mount Clemens; Muskegon Lake, Muskegon; Pine River, Alma; and Detroit River, Belle Isle.

Unacceptable risks of cancer in humans may be caused by regularly eating fish with only one part per trillion, EPA's DeVault said.

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TAB 4

EPA National Dioxin Study (1987)

Tonto National Forest, Arizona
Mark Twain National Forest, Missouri

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United States
Environmental Protection
Agency

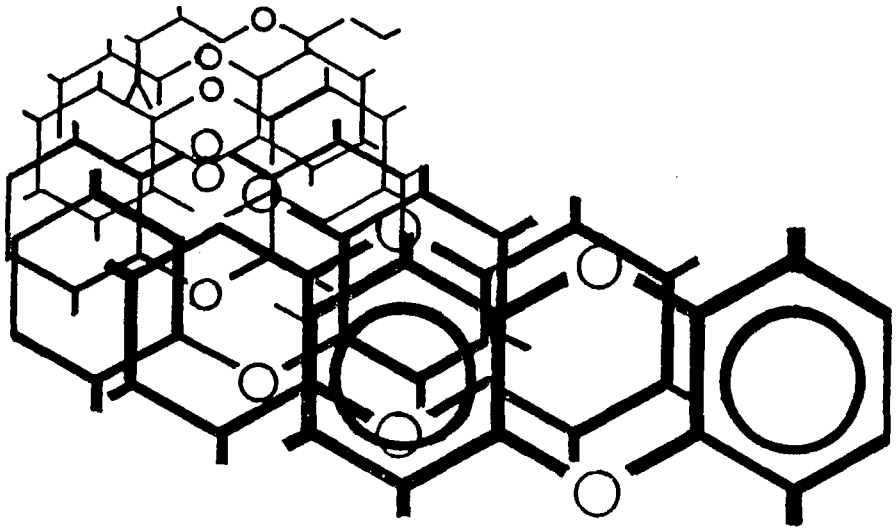
Office of Solid Waste
and Emergency Response

August 1987
EPA/530-SW-87-025

Solid Waste

EPA

National Dioxin Study



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1983. Thirty-five samples and 1 sediment sample were randomly collected; 2,3,7,8-TCDD was detected in 9 soil samples at levels between 0.3 and 0.4 ppt. No 2,3,7,8-TCDD was detected in the sediment sample.

No additional action is planned.

Region VI Pointe Coupee Parish, Louisiana

This site, used for growing sugarcane prior to 1985 and soybeans in 1985, was treated with silvex in 1983.

Twenty-five soil samples were randomly collected from two fields, 2.6 acres and 2.7 acres in area. Twenty samples contained 2,3,7,8-TCDD at levels ranging from 1.0 to 2.5 ppt.

No additional action is planned.

Region VI Rio Grande Plain Experimental Ranch, Kinney Co., Texas

This site is an experimental ranch used for research on brush control and livestock production. In 1981, parts of three experimental pastures (five acres each) were aerially sprayed with 2,4,5-T. Parts of each were left untreated as controls.

Thirty-eight soil samples were randomly collected from the three pastures among the treated and untreated areas. Twelve samples contained 2,3,7,8-TCDD--5 samples from treated areas and 7 samples from untreated areas--at levels between 0.2 and 3 ppt. No 2,3,7,8-TCDD was detected in a rattlesnake or in six vegetation samples collected from the sprayed pastures.

No additional action is planned.

Region VII Mark Twain National Forest, Missouri

The herbicide 2,4,5-T was applied in 1977 to 3 sites totaling approximately 95 acres within the forest, to facilitate the relief of shortleaf pines from competing hardwoods. A tractor drawn, high-volume ground spray tanker unit was used to apply the herbicide.

A total of 50 soil samples were collected from 2 sub-areas at one of the 3 treated sites. These areas were located at the bottom of slopes, where herbicide runoff would tend to accumulate. Twenty-one of 50 soil samples contained 2,3,7,8-TCDD at levels between 0.3 and 120 ppt.

No additional action is planned at this time. The contamination is within a forest area, not used for grazing.

Region IX Tonto National Forest, Arizona

Between 1965 and 1969, 2,4,5-T, 2,4-D, and silvex were sprayed over more than 2,500 acres in the Globe Ranger District. This spraying project was designed to improve rangeland and to increase water runoff, resulting in increased water yields for downstream users.

Soil samples were collected from three helicopter landing areas used as herbicide mixing-loading areas and from five other

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locations within the sprayed area. Whole animals and animal tissues were also collected within the sprayed areas. Twenty-four of 77 soil samples had 2,3,7,8-TCDD at levels of 2 to 564 ppt. Soil contamination was found at two of the three mixing-loading areas. (The mixing-loading area where no 2,3,7,8-TCDD was found was later determined not to have been used for that purpose.) 2,3,7,8-TCDD was detected a short distance beyond the boundaries of the actual mixing/loading locations, but no 2,3,7,8-TCDD was detected at the other five locations. No 2,3,7,8-TCDD was detected in any of the animal samples.

Forty-five additional samples, which included soil and fish, were collected from 3 additional and 1 previously sampled mixing/loading area. Twenty-one soil samples contained 2,3,7,8-TCDD at levels from 0.4 to 6623 ppt. Four samples had levels greater than 1,000 ppt. No 2,3,7,8-TCDD was detected in the fish collected.

The U.S. Forest Service has restricted access to the contaminated heli-pads. EPA Region IX is reviewing alternative treatment technologies, focusing on in situ treatment. The Forest Service has indicated willingness to sponsor a pilot project.

Region IX Santa Ana River, California

The Santa Ana River Basin includes agricultural, industrial, and residential areas.

Twenty-eight sediment samples were collected from stations along the Santa Ana River and a few of its tributaries. These locations have been routinely monitored for conventional and priority pollutants. Fish samples were collected at eight of the sediment stations where water flow was sufficient to support fish. One sediment sample had 2,3,7,8-TCDD at 0.6 ppt; one of the seven whole fish had 2,3,7,8-TCDD at 4.6 ppt.

Region X Santiam Forest, Gates, Oregon

A 75-acre area of this forest site was aerially sprayed with a herbicide containing 2,4-D and 2,4,5-T in 1976 and 1977.

Twelve sediment samples were collected from a stream that runs through the sprayed area, from an area where this stream empties into the North Santiam River, and from an area of the North Santiam River near the confluence with the stream. Thirty-five soil samples were collected from a wetlands area south of the sprayed area, a heliport used by helicopters that sprayed the area, and the heliport drainage area. One fish sample was collected from the North Santiam River sampling area. 2,3,7,8-TCDD was detected in 3 of 12 sediment samples at levels of 0.2 and 0.4 ppt. No 2,3,7,8-TCDD was detected in the 35 soil samples analyzed or the 1 fish sample.

3.2.4 Findings

- Contamination was found at a variety of the pesticide use sites where 2,4,5-T, silvex, and 2,4,5-TCP based pesti-

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TAB 5

U.S. Centers for Disease Control, 1980
Preliminary Study of Birth Defects in Oregon

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TAB 6

pages	
1-2	EPA 1980 Press Statement on 2,4-D
3-5	EPA 1981 letter to private citizen on 2,4-D

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Dave

RECEIVED 7/27/80

JUL 21 1980

MEMORANDUM

SUBJECT: Epidemiologic Investigation of Birth Defects in Oregon

FROM: Martin P. Halper, Director
Survey and Analysis Division (TS-793)

TO: Edwin Johnson
Deputy Assistant Administrator
for Office of Pesticides Programs

THRU: Marilyn C. Bracken
Deputy Assistant Administrator
for Office of Program Integration and Information
(TS-793)

The Survey and Analysis Division (SAD) recently received the attached proposal from the Center for Disease Control (CDC). The Center is proposing that OPTS support an epidemiologic retrospective matched case control investigation in western Oregon. The object of this endeavor would be to determine whether parental exposure to aerial herbicide application is associated with the birth of infants having central nervous system (CNS) defects.

This proposal was the result of a preliminary assessment of the situation by CDC personnel after they were contacted by Oregon physicians and other concerned citizens in the area. CDC's review of data amassed through their National Birth Defects Monitoring Program indicated that there were increases in rates of certain CNS birth defects between 1970 and 1979. Specifically, 8 cases of anencephaly were observed with 4 expected; 16 cases of hydrocephaly were observed with 10 expected.

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Accordingly, SAD is forwarding a copy of the CDC proposal for review and comments. We would appreciate receiving all comments by July 29 so that we may respond to CDC in a timely fashion.

Attachment

cc: Dave Menotti, OGC
Jim Reisa, OTS

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
ATLANTA, GEORGIA 30333
TELEPHONE: (404) 633-3311

404-452-4036
June 18, 1980

Susan Strassman-Sundy
Survey & Analysis Division
(TS-793)
U.S., E.P.A.
401 M Street, S.W.
Washington, D.C. 20460

Dear Ms. Strassman-Sundy:

As follow-up to our telephone conversation regarding a proposed study of herbicide exposure and birth defects, I am sending the report we prepared for the Oregon Pesticide Analytic Research Center (PARC) and the State Health Department.

We feel the proposed study, if PARC and the Oregon Health Department decide to formally invite CDC to help conduct it, is very much the type of cooperative effort that would be covered by the pending interagency agreement between SAD/EPA and the Chronic Diseases Division, CDC. Our problem as mentioned in our conversation, is that we currently do not have the manpower or the funds to conduct such a large study. Because of our mutual interest in herbicide exposure and health effects, the proposal should be of interest to the E.P.A. If EPA finds the proposal of interest and current funding is available, we should explore our mutual interest as soon as possible in anticipation of the request for assistance from the PARC board and the Oregon Health Dept.

Sincerely yours,

Larry Edmonds

Larry Edmonds, M.S.P.H.
Epidemiologist
Birth Defects Branch
Bureau of Epidemiology

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REPORT TO THE PESTICIDE ANALYTIC RESEARCH CENTER (PARC)

THROUGH JAMES GOOGINS, M.D. STATE EPIDEMIOLOGIST

OREGON HEALTH DEPARTMENT

June 10, 1980

Larry D. Edmonds

Birth Defects Branch
Chronic Disease Division
Center for Disease Control
Atlanta, Ga. 30333

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During the Fall of 1979, a group of physicians and other concerned citizens from Lincoln County, Oregon reported their belief that an excessive number of babies in that county were being born with birth defects. They linked these data with herbicide exposure (2,4-D) and called for a ban on the use of 2,4-D until more data are available. Because of these concerns, and the results of the EPA Study of abortions and 2,4,5-T in Alsea, Oregon, the Birth Defects Branch reviewed the data available through the National Birth Defects Monitoring Program. That review indicated that there were increases in the rates of anencephaly in Benton County (8 observed cases, 4 expected), and of hydrocephaly in Lane County (16 observed cases, 10 expected) between 1970 and 1977.

The BDMP findings, along with the concerns of the Lincoln County physicians led us to discuss these data with the Oregon Health Department. John Googin, M.D, State Epidemiologist, invited CDC to meet with the Oregon Pesticide Analysis Research Center (PARC) Board on November 21, 1979. The Board was formed to evaluate possible adverse health effects of chemicals used in agriculture. The PARC Board asked the Birth Defects Branch to review available data and make a recommendation about what kind of epidemiologic study should be done to evaluate the relationship between maternal exposure to herbicide spraying and birth defects.

Study Approach

A retrospective case-control study appeared to be the most appropriate type of study for several reasons. First because birth defects are rare events, it would be difficult otherwise to obtain enough cases for a study with sufficient statistical power. Second, the ban of 2,4,5-T in 1978 eliminated the source of exposure. In addition, a retrospective study would also allow the opportunity to evaluate possible increases in malformation rates from sources other than herbicides. The definition of cases and controls would be relatively straight forward. Cases would be identified as Oregon resident births identified with central nervous system defects and controls as normal Oregon infants matched on maternal race, place and date of birth. All cases would be identified, even those from urban areas, because the preliminary BDMP data found high CNS defect rates in counties predominantly urban as well as those predominantly rural. A reliable, unbiased estimate of exposure would be needed for both cases and controls. Determining this rate poses some difficulty. Because of obvious bias resulting from questioning individuals about spraying exposure and the unavailability of a retrospective biochemical test, we needed some other method of determining exposure. We undertook a pilot study to learn if it was feasible to obtain an unbiased estimate of exposure, and if it was, to learn the rate of exposure. The latter figure is necessary to determine an adequate sample size or to determine the statistical power of any smaller sample size.

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Pilot Study

The purpose of the pilot study was to estimate the rate of herbicide exposure in Benton, Polk and Lincoln Counties as a measure of exposure in western Oregon. These three counties are primarily forested and Lincoln and Benton counties are where the initial concerns about birth defects were raised. For the pilot study, a random sample of 72 births was selected from each country using vital records. An equal number of birth certificates (12) were chosen for each year, 1973-1977, and one was randomly selected from each month. The residences of the 72 births were determined, and for those with rural addresses, the owners of tracts of land within two miles of the residence of the case were sought. Identified landowners were contacted and asked to give spray history occurring from 1 month before conception of the case to 3 months after conception.

Results of Pilot

Thirty rural cases were identified. The original approach to identify exposures was not feasible. There were too many owners within 2.0 miles and the owners had no, or few written records, so they had to depend upon recollection of any spraying, when it occurred, or what was sprayed. It was obvious, from this pilot study, that we could not reliably document herbicide usage by questioning individuals or land owners.

Extension of Pilot

The only definition of herbicide exposure that appeared to be workable was for aerial herbicide spraying near a residence that is documented in some official form. With this definition in mind, we plotted all the sample births on county maps. We plotted the 30 rural births as before, and all the remaining births listed with a city address were plotted as residents within the city limits. We also used computer printouts, generated for the pilot study by the Department of Forestry, to identify any forest land that was sprayed between Jan. 1974 and Jan. 1980. Under Oregon law, all land owners (excluding the U.S. Forest Service and the Bureau of Land Management have to file a proposed spraying plan with the State Department of Forestry. The majority of the births plotted were not near U.S. Forest Service land so the state clearinghouse was a good source of information. We assumed the U.S. Forest Service would furnish data if requested.

We next reviewed the spray data to identify any aerial herbicide spraying that occurred within two miles of any sample birth. Using this admittedly crude estimate, we identified 8 births that had aerial herbicide spraying within 2 miles of their residence during the critical period around conception. There were 2 additional babies that had possible spraying within two miles of their residence. The exact location of spraying was unknown, but spraying occurred in the area. Thus, we identified a maximum of 10 "exposed" infants, for a rate of 4.6%. This "exposure" rate should be applicable to the western areas of Oregon where the vast majority of births occur.

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It is important to note that this "exposure" rate is only a rough estimate of aerial herbicide spraying within 2 miles of a residence, and not a measure of actual exposure to herbicides. It appears to be impracticable, if not impossible, to determine retrospectively what the true exposure of pregnant women was. We can only evaluate if aerial spraying occurred in the general proximity of infants with CNS defects more often than in a group of normal infants. The misclassification of women into exposed and not exposed categories would have the effect of lowering the power of the study to detect possible teratogenicity.

Sample Size Estimate

The sample size needed to detect an exposure effect depends on the rate of "exposure", the increase in risk among these exposed, and the statistical power desired. Using the estimate of 4.6% overall "exposure" from the pilot, if we want to have at least an 80% chance of finding a 2-fold increase in risk, we would need 435 cases and 435 controls. If the attack rate is 1-1/2 times greater in exposed than in unexposed, we would need 1,533 each of cases and controls.

A statistical power of 80% was the minimum figure we had hoped for. Unfortunately, we can't find enough cases in western Oregon with documented exposure status to achieve this power. Table 1 presents an estimate of the number of cases that could be located, interviewed, and the herbicide exposure documented. This number of cases (264) and an equal number of controls would produce a study with a 62% chance of detecting a 2-fold difference in attack rates, using a 1-tailed test at the 0.05 level of significance. If the attack rate is 1-1/2 times greater in cases than controls, then we have a 27% chance of finding a difference.

Proposed Epidemiologic Study

Hypothesis: The hypothesis to be tested is whether maternal exposure to aerial spraying of herbicide is associated with the birth of infants with central nervous systems (CNS) defects.

Study Design: A retrospective matched case-control study in western Oregon. Indepth personal interviews would be conducted of 264 CNS cases and 264 normal controls to evaluate various maternal and paternal risk factors.

Cost: To conduct this proposed study would cost approximately $192,000 (See attached budget).

Required Time: With adequate staff the study could be completed in 9 to 18 months after approval to conduct the study has been given.

Summary: With completion of the pilot, some judgements can be made about the merits of the proposed epidemiologic study of "herbicide exposure" and birth defects. The measurement of exposure is troublesome. Lacking some better way to identify exposed mothers, we can only investigate the relationship between proximate aerial herbicide spraying and CNS birth defects. Such a study would compare these exposure rates in infants with CNS defects and normal infants.

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With the available sample of 264 cases and 264 controls, we would have a 62% chance of detecting a 2-fold relative risk. If there is a 50% increase in the attack rate among the exposed, we would have a 27% chance of detecting this difference. These power figures are not particularly encouranging. In addition, it may well be that these relative risks apply only to women with a specific level or type of exposure. Since the available measure of exposure is so coarse, the relative risks of "exposed" women based on aerial spraying data might be much lower. In that case, the statistical power would be even lower.

It is important that the limits of such an epidemiologic study are identified in the beginning. We feel that if a study is undertaken, the case-control approach is the best approach. If you decide to go ahead with such a study, the Birth Defects Branch would be willing to assist the State Health Department and the PARC Board in planning and implementing the study.

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Table I

Estimated number of central nervous system cases in Oregon in the years (1974 to 1979) for which exposure can be documented. (Estimate based on Oregon rate from the Birth Defects Monitoring Program data.)	380
Estimated number of cases in eastern Oregon. (The exposure rate here may be lower than in pilot area.)	50
Estimated number of CNS cases in western Oregon, 1974-1979.	330
Estimated number of cases in western Oregon that we will be able to locate and interview. (Estimate of 20% lost to followup based on Atlanta experience.)	264

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Budget of Proposed Case-Control Study
In Oregon

Personnel - Salary and Benefits			$12
	Person Years	**Category & grade**	**Salary & Benefits**
	2.0	Health Technician (GS-7) (case finding - 8 persons @ 12 wks)	$31,000
	2.0	Health Technicians (GS-7) interviewing - 8 persons @ 12 wks)	31,000
	1.0	Coder (GS-5)	13,000
	1.0	Public Health Advisor (GS-11)	24,000
	.2	Statistician (GS-13)	7,000
	.50	Epidemiologist (0-5)	14,000
Travel			35
Equipment & Supplies			1
Rent and Communications & Utilities			2
Printing			1
		Subtotal	160
		Plus CDC overhead @ 20%	32
		Total	$192

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BDMP data — Oregon, 1970-1978

Defect	Code	County: Lincoln No. Cases	Lincoln Rate	Benton No. Cases	Benton Rate	Polk No. Cases	Lane No. Cases	Lane Rate	Total Lincoln, Benton, Polk, Lane Counties No. Cases	Total Lincoln, Benton, Polk, Lane Counties Rate	All Oregon No. Cases	All Oregon Rate	70-77 U.S. Rate
Anencephaly	45	2	15.3	9	9.9*	--	12	4.6	23	6.2	85	4.9	4.6
Hydrocephaly	65	-	--	4	4.4	--	17	6.6*	21	5.6	39	4.0	4.4
Spina Bifida	56	1	7.7	10	11.0	--	9	3.5	20	5.4	72	4.1	6.2
Total CNS	125	4	30.6	27	29.6*	--	48	18.6	79	21.2	307	17.6	
Cleft Lip	325	-	--	5	5.5	--	23	8.9	28	7.5	102	5.8	5.2
Cleft Palate	329	1	7.7	7	7.7	--	33	12.8*	41	11.0	167	9.6	9.6
T.E. Fistula	375	-	--	1	1.1	--	11	4.3	12	3.2	46	2.6	1.6
Rectal Atresia	393	-	--	4	4.4	--	11	4.3	15	4.0	61	3.5	3.4
Renal Agenesis	450	-	--	1	1.1	--	4	1.5	5	1.3	23	1.3	1.0
Reduction Deformity	483	1	7.7	3	3.3	--	17	6.6*	21	5.6	59	3.4	3.3
Twins	626	1	7.7	3	3.3	--	27	10.4	31	8.3	155	8.9	8.1
Births in BDMP		1,307		9,123		1,051	25,860		37,341		174,659	7,903,544	
Monitored		100%		100%			89%				65%	33%	

70-77 significant increases Benton - anencephaly (observed 8, expected 3.7) p = .05
Total CNS (observed 23, expected 16.68) p = .05

Lane - hydrocephaly (observed 16, expected 9.9) p = .05
cleft lip (observed 23, expected 11.6) p = .01
reduction deformity (observed 16, expected 7.3) p = .01

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rate /10,000

United States
Environmental Protection
Agency

Press Office (A-107)
Washington DC 20460

EPA

Environmental News

FOR IMMEDIATE RELEASE
TUESDAY, APRIL 29, 1980 O'Neill (202) 755-0344

EPA ASKS FOR MORE INFORMATION ON HERBICIDE 2,4-D

Barbara Blum, Deputy Administrator of the U.S. Environmental Protection Agency, announced today that the Agency is requesting additional information from manufacturers to determine whether 2,4-D, a widely used herbicide, is safe for humans and the environment.

"We have made this decision following a review of health effects studies of 2,4-D," Blum said. "The review showed that significant information gaps exist on the effects of 2,4-D, preventing a definite conclusion on the safety of the herbicide.

"We will ask the manufacturers of the weed killer to commence the studies to provide the missing evidence."

Blum said that if the manufacturers fail to notify EPA within 90 days that they will provide the necessary information, EPA will use a stringent new provision of the pesticides law, Section 3(c)(2)(B), which allows the agency to stop all uses of the pesticide.

If the manufacturers comply, Blum said, EPA will allow 2,4-D to continue to be used while studies are underway. However, should any of the new studies demonstrate a major health or environmental problem, she said EPA would then take appropriate regulatory action without waiting for completion of all the studies.

The name 2,4-D refers to the phenoxy herbicide 2,4-dichlorophenoxyacetic acid and related salt and ester forms. There are approximately 1500 2,4-D products which are used to kill undesirable plants in home lawns, forests, right-of-way, drainage ditch banks, rangeland, pastures, aquatic areas, cereal crops, sugar cane and commercial turf.

(more)

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Basic manufacturers of 2,4-D include Dow Chemical Co., Midland, Michigan; Monsanto Chemical Co., St. Louis; Diamond Shamrock Corp., Dallas; PBI Gordon Corp., Kansas City, Kansas; Thompson-Hayward Chemical Co., Kansas City, Kansas; AmChem Products, Inc., Ambler, Pa.

"EPA conducted its review of health-effects studies on 2,4-D because of increasing citizen concern about the high level of exposure to 2,4-D around the country and because of its chemical similarity to the dioxin-contaminated herbicides, 2,4,5-T and Silvex." Blum said.

There also has been concern because 2,4-D was a component--along with 2,4,5-T--in Agent Orange, the defoliant used by the military in Vietnam. Although never approved by EPA for civilian use in the United States, its use in Vietnam has resulted in numerous claims of adverse health effects to American military personnel. These claims are now under investigation by the Veterans Administration.

EPA, about a year ago, imposed an emergency ban on many major uses of 2,4,5-T and Silvex. More recently, the agency opened hearings to determine whether all uses of these chemicals should be banned on grounds that they can cause cancer, birth defects and miscarriages.

EPA's review, of 2,4-D studies showed that the evidence of adverse health effects weighs far more heavily against 2,4,5-T than against 2,4-D.

"For one thing," said Blum, "there is no evidence at this time that 2,4-D contains any form of dioxin, the contaminant in 2,4,5-T associated with cancerous tumors and birth defects."

Blum stated that "toxicity studies of 2,4-D have either showed that significant adverse effects were unlikely at expected human exposure levels, or they were inconclusive, or they were not conducted in a manner acceptable by today's scientific standards."

At this point, she said, the agency, while taking no action restricting use of the chemical, will require the manufacturers of 2,4-D to provide additional information in the areas of oncogenicity (tumor-inducing), reproductive effects (particularly effects to the fetus), and metabolism in animals. She said EPA also plans to conduct certain reproductive studies on 2,4-D in its own laboratories, while awaiting the industry results.

In addition, EPA will consult with its Scientific Advisory Panel during its May 28-30 meeting to determine if there are additional studies necessary to determine the safety of 2,4-D. Following the findings of the Scientific Advisory Panel, the agency will formally specify to the manufacturers what studies are needed.

Details of the agency's review of the health effects information on 2,4-D are in the attached fact sheet.

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APR 1981

Ms. Judith L. Krott
P.O. Box 145
Dolgeville, New York 13329

Dear Ms. Krott:

Thank you for your letter of March 6, 1981, requesting information on Agent Orange.

As you may know, EPA is responsible for administering the provisions of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). This Act regulates the marketing of pesticides and requires, among other things, that such products be registered with EPA. Under the FIFRA, the registration of any pesticide is contingent upon the availability of data adequate to demonstrate that the product will not pose the risk of unreasonable adverse effects on man and other nontarget organisms or the environment when used in accordance with its approved labeling.

Herbicide Orange, which is a highly concentrated compound of the phenoxy herbicides, 2,4,5-T and 2,4-D, was never registered or used in the United States. It was used as a defoliant during the Vietnam conflict by the Air Force. In 1971, the Department of Defense proscribed further use of the compound because of animal tests which demonstrated that a compound with the chemical name 2,3,7,8,Tetrachlorodibenzo(para)dioxin, or TCDD, a contaminant of 2,4,5-T, caused birth defects and other reproductive problems. The 2.3 million gallons remaining in Air Force stocks were burned at sea under an EPA permit by the end of September 1977.

EPA does have authority over use in the United States of products containing 2,4,5-T and 2,4-D, which are far less concentrated than was Herbicide Orange. Domestic uses of 2,4,5-T to which women of childbearing age were thought to be most likely exposed were cancelled in 1970 following the animal tests mentioned above.

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In April 1978, the EPA initiated intensive review of risks and benefits associated with the remaining uses of 2,4,5-T through the rebuttable presumption against registration process. Subsequently, new evidence on human health risks came to light and on March 1, 1979, EPA announced emergency suspension of 2,4,5-T and silvex, a related phenoxy herbicide, for use in forestry, pasture, and rights-of-way management. The Agency's intent to cancel registration of these herbicides accompanied the suspension notice. Cancellation hearings to explore the long-term risks and benefits of 2,4,5-T and silvex began March 14, 1980. Information gathering hearings on the remaining nonsuspended uses of these herbicides (rangeland, rice, and noncrop uses) have been combined with the cancellation hearings on the suspended uses. The hearings were recently halted to provide time for the Agency and the other parties to explore the possibilities of reaching a settlement agreement. I have enclosed several documents explaining the Agency's actions on 2,4,5-T and silvex.

In April 1980, the EPA completed a review of critical health effects studies on 2,4-D. No TCDD dioxin has been found in 2,4-D as it has in 2,4,5-T. In the course of this review, a number of gaps in the data on 2,4-D were identified, resulting in a decision by the Agency to require additional studies from registrants (manufacturers) of the herbicide. Those toxicity studies considered scientifically acceptable showed that significant adverse effects were unlikely at human exposure levels which might be expected from current 2,4-D use patterns. New studies were needed on oncogenicity, teratogenicity and reproduction. In September 1980, registrants were notified of these requirements.

EPA is coordinating its health effects review activities on 2,4-D with Agriculture Canada. In late October 1980, the Canadian government made public the results of tests conducted on 2,4-D samples manufactured in Canada. Employing sophisticated analytical methods, Canadian scientists confirmed the absence of 2,3,7,8-TCDD, but found other, reportedly less toxic dioxins, ranging in concentration from 5 ppb to approximately 8,000 ppb, in some of their samples.

Consequently, EPA began a series of tests to detect the presence of dioxins in samples of 2,4-D produced in the United States, employing the same analytical methods as used by Canadian scientists. Testing of samples collected from the complete range of 2,4-D manufacturers is being conducted at the Agency's Beltsville, Maryland, laboratories. EPA is also collecting information on manufacturing processes which may help to explain how dioxins can form during the manufacture of 2,4-D.

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Currently, EPA cannot justify regulatory action which would either restrict uses of 2,4-D products or prohibit 2,4-D production in the U.S. Available data on the toxic effects of any of the dioxins found in 2,4-D samples indicate they are significantly less toxic than 2,3,7,8-TCDD. The concentrations of 2,7-dichlorodioxin found in preliminary analyses of U.S. manufacturing-use products do not appear to pose a health hazard.

Your questions concerning responsibility for the herbicide program in Vietnam, and the possible health effects which may have resulted, can best be addressed by the Department of Defense and the Veterans Administration.

The Veterans Administration (VA) is working with the Department of Defense (DOD) in an attempt to determine which soldiers might have been exposed to 2,3,7,8-TCDD from the use of contaminated chemicals in Vietnam. Through an aggressive VA outreach program these veterans are being given thorough medical examinations to determine if their health has been affected and to institute corrective action as necessary. Dr. Barclay Shepard of the VA in Washington (address enclosed) is in charge of this program and can provide you with more details.

The General Accounting Office (GAO), an Agency of the U.S. Congress, has issued reports on the exposure of U.S. troops to Herbicide Orange in Vietnam and on the known health effects of the ingredient chemicals. These reports are available from GAO (address enclosed). When ordering these reports, use both the date and reference number; November 16, 1979, FPCD-80-23 (troop exposure) and April 6, 1979, CED-79-22 (health effects). I am enclosing an extract of the report on troop exposure which you may find useful.

I hope this information and that which can be provided by the sources cited above will answer your questions.

Sincerely yours,

-S-

Edwin L. Johnson
Deputy Assistant Adminstrator
for Pesticide Programs

Enclosures

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TAB 7

U.S. EPA 1993
"Exposure Reduction Measures" for 2,4-D

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AGREEMENT on EXPOSURE REDUCTION MEASURES for 2,4-D LABELS
Summary--April 1993

The agreement will be effected through the amendment of registrations of technical and manufacturing-use products containing 2,4-D acetic acid or any derivative of the acid. In addition to requiring new exposure reduction measures on product labels, the agreement also includes provisions for the implementation of a 2,4-D user education program on exposure reduction and for revised deadlines for submitting health and safety data required by the Agency. Where more restrictive requirements currently appear on product labels (because of multiple active ingredients, existing maximum application rates, or the like), the more restrictive requirements will apply.

Products containing the following active ingredients are covered by the exposure reduction measures:

2,4-Dichlorophenoxyacetic acid (2,4-D) and its derivatives:
Sodium salt of 2,4-D or sodium 2,4-dichlorophenoxyacetate
Diethanolamine salt of 2,4-D or diethanolamine 2,4-dichlorophenoxyacetate
Dimethylamine salt of 2,4-D or dimethylamine 2,4-dichlorophenoxyacetate
Isopropylamine salt of 2,4-D or isopropylamine 2,4-dichlorophenoxyacetate
Triisopropanolamine salt of 2,4-D or triisopropanolamine 2,4-dichlorophenoxyacetate
2-Butoxyethyl ester of 2,4-D or butoxyethyl 2,4-dichlorophenoxyacetate
Isooctyl (2-ethylhexyl) ester of 2,4-D or acetic acid, (2,4-dichlorophenoxy)-, 2-ethylhexyl ester
Isopropyl ester of 2,4-D or isopropyl 2,4-dichlorophenoxyacetate

Protective Clothing

All users and mixers/loaders/applicators (M/L/As) must wear long-sleeved shirt, long pants, shoes, socks.

M/L/As of agricultural, industrial (rights-of-way, roadside maintenance, etc.) and aquatic use products must also wear chemical-resistant gloves and face shield or safety glasses. Eye protection is not required for applicators in completely enclosed cabs or cockpits.

Users of turf liquid products with "WARNING" or "DANGER" signal words must also wear eye protection.

Commercial users of all turf liquid products, except when used on golf courses, must also wear chemical-resistant gloves.

Non-commercial users and users on golf courses of turf liquid ester, Na (sodium) salt, and acid products must also wear chemical-resistant gloves.

Non-commercial users and users on golf courses users of turf liquid amine products must also wear rubber gloves.

Persons who engage in open pouring of containers of over 1 gallon (and less than 5 gallons) in capacity must also wear coveralls or chemical-resistant apron. 19746

Mechanical Transfer Systems

"Probe and pump" systems must be used for transferring the contents of containers 5 gallons or more in capacity. Probe must be decontaminated before removal from an empty container.

Maximum Application Rates

2 lbs. acid equivalent (ae) per acre per application for pasture and rangeland

4 lbs. ae per acre per application for forestry site preparation

2 lbs. ae per acre per application for turf

Maximum Application Frequency

2 broadcast applications per year per site for turf

Hygiene Statements

For agricultural, industrial, and aquatic uses:

"Wash hands, face and arms with soap and water as soon as possible after mixing, loading, or applying this product. Wash hands, face and arms with soap and water before eating, smoking, or drinking. Wash hands and arms before using toilet. After work, remove all clothing and shower using soap and water. Do not reuse clothing worn during the previous day's mixing and loading or application of this product without cleaning first. Clothing must be kept and washed separately from other household laundry. Remove saturated clothing as soon as possible and shower."

For turf uses:

For granular products, "After using this product, remove clothing and launder separately before reuse, and promptly and thoroughly wash hands and exposed skin with soap and water."

For liquid products, "After using this product, rinse gloves before removing, remove clothing and launder separately before reuse, and promptly and thoroughly wash hands and exposed skin with soap and water. Remove saturated clothing as soon as possible and shower."

Restricted Entry Interval

Agricultural uses (including sod farms) and forestry uses are covered by the provisions of the Worker Protection Standard.

For turf: "Do not allow people (other than applicator) or pets on treatment area during application. Do not enter treated areas until spray has dried or dust has settled."

Effective Dates

Any consumer 2,4-D product formulated after October 23, 1993 or sold by the registrant after April 15, 1994 for use on sites other than turf (including sod farms) will have the new exposure reduction measures on the label.

Any consumer 2,4-D product formulated after June 15, 1994 or sold by the registrant after January 1, 1995 for use on residential or other turf sites (excluding sod farms) will have the new exposure reduction measures on the label.

For more information, contact:

Jill Bloom (703) 308-8019 or
Rich Dumas (703) 308-8015
Special Review and Reregistration Division (H7508W)
U.S. Environmental Protection Agency
401 M St., S.W.
Washington, DC 20460

Men, women reverse roles in non-traditional careers
Page B1

Cover story: Wearable art at fashion show
Pacific Coast Seniors, special section

OFWC approves ocean salmon season
Page C1

Headlight Herald

Serving the people of Tillamook County since 1888

Vol. 105, No. 40 Tillamook, Oregon for the week beginning Wednesday, April 28, 1993 Five Sections, 74 pages, 50 cents **Index on Page 2**

Chemical weeding: Is the cost too high?

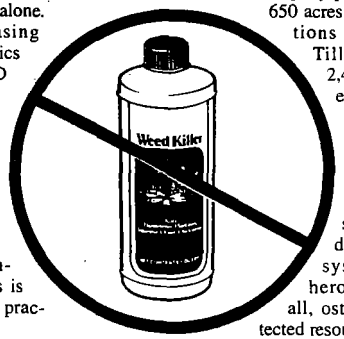
by Tim Sills, H-H staff

Aaron and David Grover have the perfect back yard; woods and field, wild animals, creeks – every day another secret spot. Theirs are two-, maybe three-hundred acres of green and burrowed mysteries – an endless tour of joy until cars and girls beguile them out of boyhood. And all of it, this place of blithe scouting, comes without chores; it belongs to an absent owner.

But any day now, Debra Grover will remove her 10 and 11-year-old sons far from their adopted hillside. With teenage daughter, Sensaira, husband, David, Sr., and an over-friendly dog, she plans to temporarily abandon her home of two years.

That's when residents of Tillamook will see a helicopter making repeated passes close by Deer Ridge subdivision – four miles west – where the Grovers and 54 other households are located. But from town it will be difficult to make out the wide, spiny boom bolted to the chopper's belly. And even harder to hear the steady wheeze of nozzles fogging Aaron and David's private playground with the state's most popular herbicide – '2,4-D'.

Not everybody residing in Deer Ridge plans to avoid the airborn delivery as consciously as the Grovers. Many will stay home, and some even venture outdoors to watch the show. The Grovers, however, are not alone.



An increasing number of skeptics believe 2,4-D may be more dangerous than users realize. The concern is especially acute in the Coast Range where chemical control of rampant alder stands is routine industry practice.

Residents of Beaver Creek, in Lincoln County, are circulating a petition to halt 2,4-D spraying there, and in Tillamook County, a handful of doubters – including the Grovers – would like Cavenham Forest Industries (formerly Crown Zellerbach), to tend its turf without the same infusion. What's goading apprehension is the unsettled verdict in the scientific argument over risk.

Cavenham owns the land surrounding Deer Ridge, as well as thousands of forested acres throughout Tillamook and Clatsop counties. The company plans to blanket 650 acres at seven locations close to Tillamook with 2,4-D before the end of April. Within or adjacent to the aerial operation are four major streams, a domestic water system and a heron rookery – all, ostensibly, "protected resources."

But the timber baron has a steady green light from government to drop the disputed solution; first from Oregon's Department of Forestry, which in turn gets clearance from the system's top chemical cop – the U.S. Environmental Protection Agency. And few, if any, authorities involved think it's a big deal.

Cavenham is hardly alone as an advocate of chemically-enhanced crops – in the woods or out. The ubiquitous 2,4-D has been amping timber production in every coniferous corner of the Pacific Northwest for nearly a half-century. Federal, state, county and private foresters unanimously consider it the preferred method for eliminating greenery that competes with newly planted firs.

Application is quick, easy and economical. Results are certain: blackberry, snowberry, salmonberry, alder, vine maple and a trunkful of other broadleaf tangles succumb to the compound, while Oregon's major money tree – Douglas fir – survives and thrives. Net dollars dependent on the practice begin at eight figures.

Beyond timber, 2,4-D beneficiaries include farmers. Tillamook County dairymen, for example, rely heavily on the chemical to deal with noxious pasture intruders, such as tansy ragwort. The stuff is also practically family to thousands of lawn-lovers, where profit is measured by near-nuke effectiveness against yard villains like thistle and dandelion.

According to John Williams of Tillamook County's Oregon State University Extension Service, use of 2,4-D is almost unlimited.

"It's such an old chemical," Williams says. "In one form or another, 2,4-D is probably used by half the people in the county. You find it in very common household products – *Weed-B-Gon*, *Crossbow*, *Weedone*. Given application in compliance with its label, it's not really a problem."

So small a problem, apparently, that many states – including Oregon – don't require records of how much is sold, used, or on what ground (Washington and California do). But conservative estimates from EPA suggest upwards of 65-million pounds of 2,4-D, and chemically-related herbicides, lacquer America annually.

While comparable numbers for Oregon are unknown, a rough idea of Tillamook County's contribution can be gauged by its two-dimensional geography: Out of 700,000-plus total acres in the county, at least 96 percent is farm or forest land. In both domains, peak production is linked to chemically-dependent crops.

Inexact data, however, has hamstrung scientists' efforts to reach consensus on the stickier issues of herbicide exposure. The long-term hazards debate, staged between reputable independent researchers and equally reputable agents of sanction, is heating up.

"2,4-D was one of the first herbicides to be registered in the U.S.," says Mary O'Brien, a Professor of Environmental Studies at University of Montana, in Missoula.

"Now, 50 years later, it still hasn't been subjected to approved EPA cancer tests."

O'Brien, who earned a Ph.D. in botany from Claremont University in southern Calif., served from 1981-'90 as staff scientist for National Coalition for Alternatives to Pesticides, in Eugene. She says EPA's knowledge of 2,4-D is based on flawed review processes. What's dropped between the cracks, claims O'Brien, is hard evidence this no-problem nectar can cause cancer.

Continued on Page A6

Mott sentenced to two consecutive life terms

Randal Paul Mott was sentenced [illegible] April 23 for the

The two life sentences will run [illegible] consecutively, and at the end of 20

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Chemical weeding

Continued from Page A1

Earlier this month, in Arlington, Va., an EPA panel decided there was insufficient information to confirm 2,4-D's alleged cancer links. One submission came from the highly-regarded National Cancer Institute, outside of Washington, D.C.

"It was an elegant study," O'Brien says of the NCI report, which was first published last October.

"They [NCI] looked at Non-Hodgkin's lymphoma – that's cancer of the blood – in categories of low, medium and high exposure to 2,4-D. But EPA's response was bean counting. Since there were more negative cases than positive, EPA did no real scrutiny of the study, which showed an average 50 percent greater incidence of Non-Hodgkin's lymphoma among 2,4-D applicators in diverse areas."

The NCI paper indicates two-to-eight-fold jumps in that specific cancer among farmers in Sweden, Canada, Kansas and Nebraska who use phenoxyacetic acid herbicides, particularly the most common in that class – 2,4-D. The study additionally established that seeing-eye dogs owned by people using 2,4-D lawn and garden products also developed unusually high rates of the lethal disease.

More importantly, NCI's probe demonstrated the incidence of Non-Hodgkin's lymphoma has shot up dramatically – over 50 percent – during the past 15 years; the same time frame for 2,4-D's proliferation among the general population via use on lawns, golf courses and roadways – not to mention forests, Oregon's most frequented recreational zone.

But the researcher who authored the NCI report says non-industry concerns were poorly represented at the EPA hearing.

"The only people from the outside who addressed the review panel were from industry," observes Shelia Zahm. "About 15 of them. It appeared to be very one-sided input."

Zahm is an NCI epidemiologist who feels that, without a major procedural overhaul, EPA won't get around to assessing 2,4-D dangers anytime soon.

"EPA doesn't do research themselves," says Zahm. "They require chemical companies to submit their own research. Sometimes EPA might run a duplicate test on what industry has done – *if* they can get the money for it. But generally they have to take it on faith that industry is doing their job."

She adds that 2,4-D was grandfathered into approval when registration and testing rules for herbicides were ordered updated in 1987. Long-standing credence in 2,4-D's clean bill of health means an accurate re-registration of the chemical could be years away.

More discouraging to Zahm is the way government looks at substances suspected of promoting cancer.

"2,4-D is not geno-toxic," she explains, "it doesn't cause cell mutation in the normal fashion, by attacking chromosomes. But most classic, well-accepted carcinogens – say, vinyl-chloride – are geno-toxic. Our work indicates 2,4-D is probably immuno-toxic. Non-Hodgkin's lymphoma is very related to immune system problems.

"Well, the catch is that immuno-toxicity is not required by EPA to be tested. Until they build that test into their proceedure, review panels won't have a hard time accepting 2,4-D."

Even then, the same panels might find it difficult to sock it to an industry as availing as herbicide manufacturers.

Zahm says her research was reviewed by academicians brought in by the EPA; toxicologists, epedemiologists, statisticians – many from agricultural universities. Such schools are consistently the recipients of research grants provided by industry. It doesn't surprise Zahm that both institutions often share minimally-conflicting environmental persuasions.

"Most university extension services are notoriously pro-pesticide," she says.

For its part, OSU denies inappropriate relationships with industry, but the college admits financial support from the same. In spite of this, last fall the school's Tillamook extension began a controversial program with dairy farmers aimed at renovating pasture with 'chemical plows.'

"The extension service is working with me on 'no till' seeding," Ed Myers says of OSU's local outreach.

The Tillamook farmer owns Coastal View Dairy, and believes his labor-intensive task of periodic soil renewal can be replaced by a time-and-money-efficient chemical proceedure that eliminates traditional disc plowing.

"We spray the field completely," Myers relates. "Kill everything. Then after the spray wears down – a couple weeks or so – we plug sprouted grass seedlings into the soil with a machine built for that. It saves a heck of a lot of time!"

The herbicide for this project, glyphosate, was developed in 1974, and is sold under the trade names, 'Roundup' and 'Accord.' It is known to encourage high nitrite levels in soil, and nitrites are among the most carcinogenic families on the planet.

According to a study completed by OSU-Tillamook's John Williams (also the specialist assisting Myers' no-till experiment), local forestland use of glyphosate has surpassed application of 2,4-D in both acreage and volume.

But at least one player in the woods has found that shelving production-friendly chemicals saves money elsewhere.

"Region Six – that's Oregon and Washington national forests – was taken to court for its use of herbicides," recalls Don Gonzalez. He oversees the Hebo Ranger District, which accounts for 92,000 acres in Tillamook County.

"Well, the opposing party won. We appealed, but the original judgement was upheld. The upshot is that throughout Region Six, herbicides are used less now than any other type of control for unwanted vegetation. Actually, we try not to use them at all."

State of Oregon doesn't see it the same.

"We feel 2,4-D is safe," says Mark Labhart. "As long as you follow the label, it's just like any chemical."

Labhart is chief forester for the Tillamook District of Tillamook State Forest, which totals over 300,000 acres. When Cavenham commences spraying next week, an observer from Labhart's office will be there to certify all is done according to application guidelines.

That guarantee, though, falls short for many area residents.

"I'm not happy about it," says David Grover.

The 32-year-old father feels cornered by favored bottom-line policies.

"You know, we moved here because it's such a natural area. I know jobs and production are important, but human values simply have to come first.

"It's not as if there aren't options. The owner could bring in a crew to clear tree space manually – then you'd get away from chemicals and at the same time employ more people.

Grover watches his sons romp through a horizon-stretched neighborhood of Cavenham forest. They come into the house laughing and dirty – happily oblivious to thoroughly adult deliberations that will likely condemn their primitive 'Disneyland.'

"We need to get all the information in before we start making decisions that come back on us," the father says. "That come back on our children."

FOREST NEIGHBORS – Members of the Grover family stand in their yard, which borders forest land to be sprayed with 2,4-D between Tillamook and Netarts. The Grovers plan to move away temporarily while the spraying is going on. Shown above, l. to r.: Debra, David Sr., Sensaira, David Jr., with Aaron in front.

(H-H photo by Tim Sills)

Town hall meetings

Continued from Page A1

To Benefit the Children of Lincoln City Montessori School
SPRING BLOSSOM

19750

National Network To Prevent Birth Defects

Box 15309, Southeast Station, Washington, D.C. 20003, 202 543-5450

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

Prepared by Erik Jansson

February 2, 1987

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

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

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

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

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

Alternatives to Pesticides

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

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

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

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

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

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

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

> "Acute effects of 2,4-D in human include headache, weakness and rapid fatigue, nausea and vomiting, diarrhea, burning eyes, sore throat with burning in the chest, and impaired senses of taste and smell. Delayed effects of acute exposure include numbness and pain in hands and feet, occasionally progressing to limb paralysis, and visual problems including diplopia. Residual effects include continued numbness and pain in limbs, chronic respiratory impairment, bleeding tendency including menstrual problems, concentration and memory problems, and hypersensitivity to non-physiologic chemicals. All of these have lasted for years and have been reported in cases of bystander exposure as well as user exposure.
>
> Nearly all of these human symptoms are undetectable in laboratory rodents. Bleeding is detectable, however, and has been demonstrated in animals given high doses of 2,4-D and in fetal rats whose mother was given very low doses. Humans would be far more susceptible to such capillary injuries resulting from depletion of tissue ascorbic acid content because the test animals can synthesize ascorbic acid (Vitamin C) while human cannot. Research has shown that ascorbic acid is used up in the detoxification of organochlorine pesticides, and other studies have demonstrated that a 2,4-D family injury found at very lose dose in rodents is depletion of ascorbic acid in spite of the fact that they are capable of replacing it by synthesis." (Belova and Sokolova, 1971)

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

CANCER AND 2,4-D

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

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

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

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

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

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

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

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

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

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

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2,4-D and Non-Hodgkin's Lymphoma

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

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

*Five controls had missing data.
†One patient and ten controls had unknown frequency of exposure.
‡First available for use in 1942.

(Hoar et al)

Phenoxy Herbicides and Cancers

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

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

[a] $p<0.01$
[b] An association was found with exposure to organic solvents, RR equals 3.1
[c] Organic solvents, RR equals 3.0
[d] Not significant. For all other RR, $p<0.001$.

(Adapted from Hardell[11])

(O'Brien)

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

Animal Studies on Cancer

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

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

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

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

Immune System and Cancers

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

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

The recent findings at the Quail Run Mobile Home Park in

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

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

MUTATION AND 2,4-D

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

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

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

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

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

** Significance at $P < 0.05$; *** $P < 0.001$
† Duncan's *t* value, which the treatment *t* value (to the right of the /) must equal or exceed to be statistically significant
‡ Value from ANOVA of sister chromatid exchanges from 2,4-D treatments
§ *F* table value for the corresponding *df*

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

Panel 2

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

TABLE 4.

Main experimental immunological diseases

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

[a]Howie and Helyer, 1966.
[b]Steinberg et al., 1980.
[c]Smith et al., 1983.
[d]Wick et al., 1970a; Welch et al., 1973.
[e]Wick et al., 1970b.
[f]Arnason et al., 1962; Jankovic and Isvaneski, 1963.
[g]Jankovic and Isvaneski, 1963.
[h]Rowe et al., 1963.

TABLE 5.

Relative dependence of infections on B and T cell function

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

Data obtained on the following lines of evidence:
[a] relative incidence in children with T or B cell immuno deficiency, or in adults with Hodgkin's disease (T cell deficiency) (Allison, 1972, 1973; Good et al., 1971).
[b] high incidence of infections in ALS-treated mice (see Chapter 6).
[c] protection by antibody (B cells) or sensitized cells (T cells) in mice irradiated or treated with high doses of cyclophosphamide (Allison, 1973).

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(Bach and Strom)

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

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

RESULTS and DISCUSSION

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

TABLE 6.

Inhibition of testicular DNA synthesis by various phenoxy acids

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Laboratory Findings About Developmental Toxicology

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

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Panel 3

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

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

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

Worker Reports With Similar Medical Problems

AU - Elina VA
AA - Ufim. Inst. Gig. Profzabol., Ufa, USSR
TI - Effect of products of organochlorine herbicide production on specific functions of the female body
[illegible] - CA/087/106184Z
SO - Gig. Tr. Sostoyanie Spetsificheskikh Funkts. Rab. Neftekhim. Khim. Prom-sti.; 1974, 187-90
LA - Russ

AB - CBAC COPYRIGHT: CHEM ABS Workers of organochlorine herbicide prodn. of the 2,4-D family, are exposed to chlorinated hydrocarbons in concns. exceeding max. admissible concns. (MAC). (94-75-7 2,4-D) Substantial impairment of menstrual and child-bearing function arise manifested as higher rate of miscarriages, premature births, toxicosis of second half of pregnancy, and the menace of miscarriages during whole pregnancy period. Sanitary-hygienic recommendations are discussed.

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

A group of 11 female field workers who had developed symptoms of acute poisoning after exposure to the herbicide 2,4-dichloro pheoxyacetic acid (2,4-D) were followed-for 2 yr. At the initial examination the patients complained of periodic headache, vertigo (7), fatigue, numbness and pain in legs and arms, irritability (5) and partial amnesia (2). All patients had cardiac pain, six patients featured palpitation and five had marked dyspnea. Within 1-1.5 mo of poisoning 9/11 patients developed oligomenorrhea (in 7 women the menstrual cycle normalized within 5-6 mo). Six patients had mono- and lymphocytosis, while all patients had statistically significant decreases in the activity of a series of oxidative enzymes of the peripheral blood leukocytes. Two patients had chronic toxic hepatitis, 9 developed encaphalopolyneuritis, myocardiodystrophy and vascular dystonia, and 8 patients had chronic conjunctivitis.

(EPA Pesticide Abstracts,
Vol. 12, No. 9, Sept. 1979)

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2. Conclusions

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

Malformation: skeletal at high dose (60 mg/kg/day or above), peripheral circulatory system distended at low dose (0.1 mg/kg/day) and after single high dose (1/2 LD_{50}), eye anomalies at 100 mg/kg/day.

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

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

Lethality: pre-implantation not reported. Post-implantation at 100 mg/kg/day and above, or after a single high dose (1/2 LD_{50}). Postnatal in progeny of rats fed 150 mg/kg/day, or in a pig fed 500 ppm.

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

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

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

Shearer, 1980

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

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

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

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

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

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

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

Farm Animal Studies and Reports

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

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

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

NEUROLOGICAL EFFECTS OF 2,4-D IN ADULTS

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

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

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

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

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

Loss of Nerve Conduction Velocity in Adults

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

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

NCV AND EXPOSURE TO PHENOXY HERBICIDE

TABLE 7.

MEAN NERVE CONDUCTION VELOCITIES OF STUDY VERSUS CONTROL GROUPS[a]

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

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

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

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

Laboratory Studies

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

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

1. There is an inhibition of cerebral electrical activity in acute and chronic 2,4-D exposures, with severe damage to higher nervous activity occuring, as measured by conditioned reflex experiments;

2. This occurs without obvious structural changes in nerve cells;

3. Spinal cord damage may be responsible for paralysis in extremities;

4. It must be assumed that human subjects may suffer milder disturbances from smaller doses in function of the nervous system.

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

LEARNING DISABILITIES AND 2,4-D

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

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

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

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

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

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

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

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

The Dioxin and Liver Enzyme Issue

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

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

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

Microneuronal Hypoplasia

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

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

OTHER HEALTH ISSUES AND FIELD SURVEYS

Heart Disease and Stroke

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

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

Field Studies

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

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

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

Dioxins

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

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

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

Panel 5

Most Americans become exposed to dioxins during their life.

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

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

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

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

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

†Geometric mean.

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

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Damage to Other Crops and the Environment

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

Damage to sunflowers and cotton are other examples.

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

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

CONCLUSION

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

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

APPENDIX VII.0 HEALTH EFFECTS OF 2,4-D

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

PRAIRIE INSTITUTE OF ENVIRONMENTAL HEALTH
2220 Lorne St., Regina, Saskatchewan.
S4P 2M7
Phone: 525-5644
525-5645

November 15, 1976.

HEALTH EFFECTS OF 2,4-D

1. As far as I am aware there are no reliable statistics relating to the health effects of 2,4-D usage in Saskatchewan, where, in 1971 it was estimated that 70% of the cultivated acreage of the province was sprayed with the herbicide in a year.

2. A small unidentified number of persons, mainly children, have been hospitalised with acute poisoning, circumstances unknown.

3. Because of the widespread use of the herbicide 2,4-D and because no mechanism existed in Saskatchewan which identified agricultural chemical poisoning, a general question was included in a questionaire used in 1969,1970 as part of a field survey of respiratory diseases and effects amongst farmers and grain elevator operators

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

IF YES

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

4. 20% of 3,300 farmers and grain elevator operators surveyed, responded yes to the question. Whilst the question was a general one, certain conclusions were drawn from it

a) farmers found 2,4-D the most troublesome chemical they used (it is also the most widely used)

b) symptoms were confined to the season (or time) of spraying and were similar amongst farmers who complained of health effects 1) nausea, loss of appetite, loss of weight, occasional vomiting during the spraying season. 2) a skin rash in a small number of persons. 3) the symptons of one year often worse than the year before leading to a significant number of farmers having to stop spraying themselves and contracting the spraying out.

5. The conclusions drawn from the questionaire are supported whenever health and safety problems are identified and discussed at farmer/rural meetings

6. The significance of these observations in relation to long term effects is unknown; it appears to me that some farmers develop a sensitivity to the effects of 2,4-D (not necessarily the same thing as an allergy) and that this sensitivity is enhanced with repeated exposure over time.

C. A. R. Dennis

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

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

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

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

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

c) (Warnock, 1980)

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

d) Summary:

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

DIOXIN AND 2,4-D (From Wright)

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

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

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

c) Dioxins can form by heating or burning of vegetation sprayed with 2,4-D. Although few controlled experiments of this kind have been done with 2,4-D, the chemistry is sufficiently understood that this point is generally accepted. In manufacturing, the temperature is kept as low as possible for exactly that reason. Also, dioxin formation has been demonstrated from burning chlorophenols (Rappe and Markland, 1978), (Nelsson et al, 1974) and vegetation sprayed with 2,4,5-T (Stehl and Lamparski, 1977).

d) It is possible that dioxins can be formed by the action of sunlight on 2,4-D (Akermark, 1978). More studies need to be done in this area, but the coupling of two molecules of dichlorophenol can yield an isomer of dioxin, especially under alkaline conditions

e) The range of toxicities of the 75 possible dioxins varies widely. The most toxic 2,3,7,8-isomer has not been found in 2,4-D. However, their chemical structure suggests that they are resistent to breakdown, and being fat soluble, may deposit in the liver, potentially acting as a cumulative poison. The dioxins tested so far in mice and guinea pigs produced similar clinicopathologic symptoms as TCDD, at difference dose levels (McConnel, 1978)

f) the 2,7-dioxin, apparently the most prevalent in the 2,4-D esters, causes defects in the heart muscle of rats at the low dose level of 1-2 mg/kg (Khera and Ruddick, 1973).

g) Summary: There is enough evidence on dioxin contamination of 2,4-D, or formation from 2,4-D, to indicate considerable caution in its use. The chemistry of the formation of dioxins under laboratory conditions is fairly well understood, but environmental studies of dioxin formation are just beginning. Any form of heating of 2,4-D, short of high temperature (greater

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

V. CONCLUSIONS

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

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

VI. RECOMMENDATIONS

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

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MINUTES OF A MEETING HELD TO DISCUSS AND EVALUATE THE TOXICITY OF 2,4-D AND 2,4,5-T COMPOUNDS

25 April 1963

Orig minutes
sent to Col Coleman
for CBR Agency files.

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SUBJECT: Minutes of a meeting held to discuss and evaluate the toxicity of 2,4-D and 2,4,5-T compounds with particular emphasis on use of these materials in military operations as herbicides.

TIME: 1000 hours

DATE: 26 April 1965

PLACE: Room 202, Bldg 3510 (330), Edgewood Arsenal, Maryland

ATTENDEES:

Brig Gen F. J. Delbert, Commanding General, CBR Agcy, E.A., Md.
Col F.L. Bauer, Chairman, Director of Med Res, CBDL, E.A., Md.
Dr. E.P. McNamara, Secretary, Dir/Med/Res, CBDL, E.A., Md.
Dr. J.T. Thurston, Office of Secretary of Defense, Wash., D.C.
Dr. J.B. Dewitt, Patuxent Wildlife Res Center, Laurel, Md.
Dr. W.C. Shaw, US Dept of Agriculture, Beltsville, Md.
Dr. W.H. Summerson, Chief Scientist, CBR Agcy, E. A., Md.
Dr. C.E. Minarik, Fort Detrick, Frederick, Md.
Dr. J.S. Leary, US Dept of Agriculture, Beltsville, Md.
Dr. W. Marshland, Army Res Office, Arlington Hall, Va.
Dr. E.J. Cotton, Am Chem Products, Inc., Ambler, Pa.
Dr. V.K. Rowe, Dow Chemical Co., Midland, Michigan
Dr. S.Silver, Scientific Director, CBDL, E.A., Md.
Dr. H.P. Averill, Toxicology Div, Dir/Med/Res, CBDL, E.A., Md.
Dr. John C. Atkinson, Statistician, Dir/Med/[illegible], CBDL, E.A.,Md.
Lt Col D.E. Rice, Hq CBR Agency, E. A., Md.
Capt E.A. Navarro, Clin Res Div, CBDL, E.A., Md.
Mr. Frank J. Vecci, Ch, Basic Tox Br, CBDL, E.A., Md.
Dr. Harold M. Macfarland, Battelle Labs, Falls Church, Va.
Mrs. Martha A. Lingen, Stenographer, Tox Div, CBDL, E.A., Md.

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The meeting was called to order by the Chairman, Col Sauer, who commented that vast areas of the tropics and semitropics are covered by dense growths of trees, shrubs, etc. Dependent upon circumstances, this vegetative ground cover has in times past been a problem to health (malaria control, scrub typhus mite control), a source of ambuscades, an obstruction of lines of fire, observation, transportation, etc.

The Chairman stated that those in attendance would be familiarized with the actual use of certain herbicides in Viet Nam during the past two years. He stated that the sought-for end of the meeting was a general statement about dose levels and hazards to health of man and domestic animals from 2,4-D and 2,4,5-T based on the medical literature and unpublished data of various research laboratories. The Committee was asked to evaluate the toxicity of a mixture known as "Purple". This mixture consists of 50% normal butyl 2,4-D, 30% normal butyl 2,4,5-T, and 20% isobutyl 2,4,5-T. The Chairman further stated that the Committee should also review this information in light of actual use of these materials as military herbicides in Viet Nam and comment as to whether health hazards were engendered by such operational use.

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General F.J. Delmore presented a
herbicides in military operations.

Dr. W.C. Shaw described the use
expenditure and contact with the mate
operators. His remarks are attached

Dr. C.E. Minerik presented image
body splash exposures in manufacturin
Viet Nam. He commented further that
posures to these compounds there were

Col F.L. Bauer presented an eval
out dose to man of herbicides as they
culations are attached as Appendix B.

Dr. B.P. McNamara presented data
various animal species. These remark
was also mentioned that the medical l
where toxic effects possibly were att

Dr. W. Northland discussed the t
possibly due to exposure to 2,4-D pu
Jones and Brown and the fourth publi
Int. Med. No. 3, 122, 1963.

Dr. H.W. MacFarland commented o
ingestion of not less than 6500 mg e
one man ingested 500 mg of 2,4-D per
perceptible effects. The specific r
page 225, 1962.

Dr. J.S. Lenry described the De
criteria for use of herbicides and p
were as follows: the criteria for t
that they must be, by regulation, no
flammable, available in large quanti
addition, operationally, the Departm
constant control in areas where the

Dr. J. B. DeWitt stated that te
and 2,4,5-T were added to the diets
stages of growth. He confirmed that
chronic and acute toxicity. The onl
crease in egg-laying of mallard duck
2,4-D and/or 2,4,5-T at a dose level
hand, the quail produced a larger th
the test period.

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Dr. V.E. Rowe stated that the available toxicity data are adequate for the prediction of toxic doses. He based this on experimental evidence, as well as on field applications. He explained that there was a nuisance factor involved in that people have complained of a harsh taste in the drinking water.

Dr. R.J. Otten stated his experiences on the use of herbicides in practical field applications. He commented that his firm has a number of contracts with industrial firms making these continuous field applications over very large areas. Even though thousands of people were involved in these operations, skin sensitization was the maximum effect produced. This was noted in probably one out of a thousand persons.

Dr. McNamara summarized the LD50 and LD1 data for oral, intratracheal, intraperitoneal, and percutaneous routes on several species of animals. Based upon all data presented, the Committee decided to adopt as acute toxicity standards the figures which are cited in the conclusion of this report.

The Committee adopted the following observation and conclusions:

OBSERVATIONS - Based upon the data reviewed and presented, the Committee recommended acceptance of these figures for acute toxicity of purple mixture. The Committee further noted that these were compiled from several animal species, that toxicity data were similar from species to species, and that the occasional cases of accidental poisoning and/or attempted suicide in man report even higher figures.

Oral and intraperitoneal routes	(LD50 - 300-1000 mg/kg (LD1 - 100-333 mg/kg
Percutaneous routes	(LD50 - 1000-6000 mg/kg (LD1 - 600-2000 mg/kg

CONCLUSIONS - The Committee stated in summary and after careful review of toxicological data related to 2,4-D and 2,4,5-T plus the knowledge as to the manner these materials have been used for defoliation in military situations in Southeast Asia, the Committee concluded that no health hazard is or was involved to man or domestic animals from the amounts or manner these materials were used in the aforementioned exercise.

Additional information pertinent to this meeting are attached as Appendices D, E, and F.

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APPENDIX

To

Minutes of a Meeting Held to Discuss and Evaluate the Toxicity of 2,4-D and 2,4,5-T Compounds

held

25 April 1963

APPENDIX A

Presentation by Dr. W.C. Shaw

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Appendix A

The Phenoxyacetate herbicides are used to control weeds in wheat, oats, barley, rice, asparagus, sugarcane, corn, and other crops. They are also used to control weeds and brush in swamplands and pastures, some croplands, undesirable hardwood trees in conifer forests, on utility rights-of-ways, industrial and military sites and military operations. These compounds are applied at rates of 1/16 to 160 pounds/acre depending on the vegetation to be controlled and method of application.

The herbicidal properties of these chemicals were reported in 1944 and their commercial manufacture began in about 1946. Since 1947 more than 300 million pounds have been produced and used to control vegetation on more than 400 million acres of land.

The annual production of the phenoxyacetate herbicides is estimated to exceed 50 million pounds and they are used on about 50 million acres of land each year.

These herbicides are registered by the U.S. Department of Agriculture and their use for weed control in food crops is permitted with a tolerance of 5 ppm on apples, asparagus, and other edible crops.

During the 15 years these herbicides have been used extensively in the U.S., the Dept of Agriculture records show that the Department has not received a single complaint of injury to humans, livestock, wildlife, or soils from the phenoxy herbicides. In addition, the major manufacturers of the phenoxy herbicides have certified that none of the workmen in their factories have shown any ill effects. Approximately 200 scientists conduct research with these compounds each year. Not a single case of injury, illness, or irritation of any kind has ever been reported.

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APPENDIX B

An Evaluation of Possible Skin Fall-Out Dose to Man

Presented by

Col F. L. Bauer

19792

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Appendix B

Body Area - a 50 kg, 157 centimeter tall (110 lbs. 62 in) human has a total body area of 1.5 meters or 16.2 sq ft. For purpose of computation, it is assumed that a maximum of 1/2 of the body area can be made available to fall-out, i.e., 8 sq. ft.

Based upon well documented studies, the fall-out ratio between VX on the ground and on a human in various positions averages 1:075. Therefore, the theoretical maximum fall-out and deposition on a human body would be 8 sq ft x 250 mg per sq ft = 2000 x 0.75 (VX correction)= 1500 mg total body.

1500 mg/50 kg = 30 mg/kg body weight

It is also known from VX experiments that 1-2 layers of clothing provide 4 to 10-fold protection against fall-out skin deposition. If the human subject was assumed to be 50% covered by any form of clothing, then maximum theoretical body deposition is 16 mg/kg body weight.

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APPENDIX C

Toxicity of Herbicides in Various Animal Species

Presented By

Dr. B. F. McNamara

19794

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Appendix C

Considerable data can be found in the literature on phenoxyacetates. However, most of this information concerns the parent acids or salts. Although our interests are in the butyl esters of 2,4,D and 2,4,5-T, the information on the parent acids and salts are pertinent because there are definite relationships between the parent compounds and the esters.

The data in Table 1 indicate a low order of toxicity for all of the compounds mentioned in the various animal species for the routes of administration shown. There are no significant differences in the toxicities of the various types of compounds by the intraperitoneal and intragastric routes of administration. By these routes of administration the toxicity of 'purple' is similar to that of the other compounds mentioned. By percutaneous application, 'purple' is less toxic than by the intraperitoneal, intragastric or intratracheal administration routes.

The information on the toxicity of the parent phenoxyacetates in dogs is sparse. These data indicate that dogs are more sensitive than other species to the toxic effects of phenoxyacetates. However, in dogs "purple" appears to be less toxic than the parent compounds.

The data shown in Table 1 refers to the LD50 values. Table 2 gives the predicted dose (mg/kg) of the parent phenoxyacetates which might cause death in 1%, 0.1% and 0.01% of a population. Doses which might produce one death in a population of 10,000 are considerably higher than the maximum dose (30 mg/kg) which could have been delivered in the Viet Nam operations. It would be expected that the lethal dose for "purple' would be similar to those shown in Table 2.

A summary of the available data from toxicity studies now in progress are shown in Table 3. These data indicate that "purple" will be no more toxic that predictions from information contained in Tables 1 and 2. This suggests that it is very unlikely that "purple" would produce any fatalities as used in the operations in Viet Nam.

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Appendix C - Table 1

TOXICITY OF PHENOXYACETATES

Species	Route	LD50 mg/kg					
		2,4-D			2,4,5-T		Purple (4)
		Acid	Salt	Mixed But Esters	Acid	Mixed Butyl Esters	
Rat	ip		512(2)-589(2)				436
	ig	375(1)	666(2)-805(1)	620(1)	527(1)	481(1)	448
	it						545
	pc						4000
	pce						>12500
Rabbit	iv		400 (2)				
	ip						1130
	ig		800(2)	424(1)		712(1)	>630
	it						550
	pc						1330
	pce						-
Dog	ip						353
	ig		100(3)		100(3)		-
	it						305
	pc						>1250
Mouse	ip		369(2)-426(2)				
	ig	300(1)	375(1)	713(1)	389(1)	940(1)	
Guinea P	ip		567(2)-800(2)				
	ig	469(1)	551(1)-1000(2)	848(1)	531(1)	750(1)	
Chicks	ig	541(1)		2000(1)	319(1)		

(1) Rowe & Hymas, Am J. Vet Med, Vol XV, No. 57, p 622, 1954.
(2) Hill & Carlisle, J Ind Hyg & Tox, 29:85, 1947.
(3) Hill & Piratzka, Arch Ind Hyg & Occup Med, 7:61, 1953.

Appendix C - Table 2

LETHAL DOSES FOR PHENOXYACETATES

Species	Route	No. of Animals	LD50 mg/kg	LD1 mg/kg	LD0.1 mg/kg	LD0.01 mg/kg	References
			2,4-D				
t	ip	72	512	268	170	138	Hill, 1947
inea Pig	ip	48	590	296	235	195	Hill, 1947
use	ip	200	369	200	165	140	Hill, Fitzhugh
t	ig	90	637	240	180	138	Hill (Martin,)
t	ig	165	630	231	170	130	Rowe & Fitzhugh (Ma
inea Pig	ig	18	481	390	375	340	Rowe, 1954
use	ig	30	557	257	205	165	Rowe, 1954
			2,4,5-T				
t	ig	40	527	285	230	195	Rowe, 1954
inea Pig	ig	20	389	252	220	195	Rowe, 1954
use	ig	27	373	196	118	93	Rowe, 1954

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Rats pe (clothed) >12,500

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Appendix C - Table 3

TOXICITY OF PURPLE

Species	Route	LD50 mg/kg
Rats	ip	430
Rabbits		1130
Dogs		358
Rats	ig	448
Rabbits		<625
Rats	it	549
Rabbits		ca550
Dogs		358
Rats	pc	4000
Rabbits		1330
Dogs		>1250

INVENTORIED MAY 8 1964
INVENTORIED & FILED JUN 20 1967

Technical Note Number
62-68

THE PRESENT STATUS OF CHEMICAL CONTROL OF VEGETATION IN RELATION TO MILITARY NEEDS

J. H. COATES
L. M. SHARPE
H. POLLACK

Institute for Defense Analyses

Research and Engineering Support Division

December 1962

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TECHNICAL NOTE 62-68

THE PRESENT STATUS OF CHEMICAL CONTROL OF VEGETATION IN RELATION TO MILITARY NEEDS

December 1962

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INSTITUTE FOR DEFENSE ANALYSES
RESEARCH AND ENGINEERING SUPPORT DIVISION

Contract SD-50
Project AGILE

Technical Note 62-68

19808

The authors wish to express their appreciation to Mr. S.J. Deitchman of the Institute for Defense Analyses for his many valuable suggestions and advice.

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TABLE OF CONTENTS

19802

INTRODUCTION

Under Project AGILE, a subtask was undertaken to provide "technical advice on the state-of-the-art in the United States, both governmental and non-governmental," on chemical means for controlling vegetation. The problem was broken down into the following categories:

1. Commercially available agents which could be applied in military operations within six months.

2. Chemicals in commercial production or laboratory development which could be brought to the operational status within 18 months.

3. Fundamental studies on plant physiology relevant to these short and intermediate range problems.

4. Botanical studies in relation to the task.

5. The proper function and distribution of intramural effort at Fort Detrick in relation to these objectives.

6. Relevancy of non-military government efforts to the problem.

7. Liaison, proprietary rights, and contractural arrangements in facilitating this program.

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RECOMMENDATIONS

1. Short-range Problem

a. The evaluation of commercially available agricultural chemicals along the lines of herbicide-herbicide, herbicide-defoliant, herbicide-desiccant mixtures has the greatest promise for developing operational agents in the next six months. Formulations must be investigated as a key part of these evaluations. The particular choice of agents can probably be best made by Fort Detrick with the USDA in consultation with representatives from industry, or by the panel discussed below.

b. The initial evaluations can be best conducted in industrial laboratories, second choices are the USDA facilities and Fort Detrick.

c. The field evaluation for tropical areas preliminary to operational testing can be carried out immediately at the facilities available to several of the larger companies. A good second choice is the Puerto Rican Commonwealth Agricultural Station. Independent USDA supervised facilities would have to be set up and manned; Fort Detrick supervised sites could be used if the others were unavailable.

2. Intermediate-range Solution

a. Industrial laboratories are the best source of candidate chemicals for phytotoxic evaluation. This should be implemented through 8 to 12 modest ($100,000) synthesis and screening contracts. The contractor should be given maximum latitude in pursuing the program; primary and secondary screening should be their responsibility.

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c. Closer interaction is required between those responsible for designing delivery equipment and those preparing the chemical agent regardless of their Service.

d. Fort Detrick should utilize a wide range of consultants from industry, the universities, research foundations, and the federal, state, and commonwealth agricultural stations, representing divergent points of view.

4. Advisory Panel

An advisory panel on the anti-vegetative program could play a critical role in meeting the present difficulties and laying out an effective plan for the future. In addition to the required statutory representation, it should include both military and civilian representation from the Air Force and Navy. It would be desirable to have a representative of the Office of the Assistant Secretary of the Army for R&D and the Office of the Chief of Research and Development, Department of the Army also represented. The panel should freely utilize consultants as suggested in Paragraph 3 (d) above.

5. Systematic Botany

An immediate effort should be made to compile a botannical register, from a qualitative and quantitative point of view, for Southeast Asia. A corresponding effort should be started for other potential trouble spots.

6. Phytotoxic Susceptibility

The relationship between phytotoxic susceptibility and phylogenetic strain should be studied.

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7. Program Management

It would be an intrusion of an unnecessary administrative layer to have some institution such as Stanford Research Institute or Armour undertake a supervisory function in the expanding anti-vegetation program. The supervision of the anti-vegetation program as it applies to the military rightly belongs to Fort Detrick.

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DISCUSSION

The consensus in and out of government, with which we concur, is that the Crops Division of the U.S. Army Biological Laboratory at Fort Detrick has responded splendidly to the present operational military requirements. In view of their history of budgetary caprice, intramural resistance, and lack of support by the military command, a far less effective response could have been expected. Now that the anti-vegetation program at Fort Detrick is being re-funded, it is appropriate to review the functions of the expanded staff in terms of the short and longer range objectives. Conclusions based on discussions with government and industrial contacts on the proper function of Fort Detrick are presented below.

It was made evident by our industrial contacts that rapport with the anti-vegetative program varied from satisfactory to antagonistic. Most companies appeared to be confused as to objectives and it was evident that the relationship was reciprocally unresponsive. Since no satisfactory utilization of the industrial capability can be made without improved rapport, this problem also will be discussed. Unlike many other technical fields, in which the principal expertise and competence lies in the military, the development of new anti-vegetation chemicals is fundamentally an activity of the commercial chemical industry. The military applications are peripheral to, and derivative of, the industrial competence. Industry must be utilized to a much greater extent if a more effective anti-vegetation program is to be developed.

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From a botanical point of view, the above problem includes various aquatic plants, mangrove, and a wide range of grasses, ferns, palms, palmettos, trees, and herbaceous plants throughout South Vietnam. Although time did not permit an exhaustive search, conversations with a number of knowledgeable individuals make it appear unlikely that there exists an adequate botanical collation of this area from either the qualitative or quantitative point of view.

Our information indicates that mangrove is controllable. However, there is a paucity of information on the relative susceptibility of the various other species to herbicides. It is known that:

1. There are no rain forests in the area of military interest.
2. The upland area has a dry season in the winter in which there is less than one inch of rain. The tree species there are largely non-deciduous broadleafs.
3. In the virgin forest, the principal obstruction to vision requiring defoliation is the broadleaf evergreens which grow up to a height of 100 feet. The ground has relatively little cover.
4. There is a tropical scrub growth consisting largely of such flora as broadleaf evergreens which are often mingled with bamboo (running up to 40 feet in height) and imperata grass. This tropical scrub appears to be typical of those areas in which civilization has intruded.

The above categories do not clarify fully the tactical objective of the military defoliation program. The chemicals now in operational

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trials, as of November 1962, are effective against all of the categories described above to a greater or lesser extent. The tactical problem to which research must be directed is the development of agents which attack a broader range of botanical species more rapidly. The agents must be applicable by air or ground spray devices. They should be non-toxic to the troops using it, to the natives in or passing through the area treated, and harmless to their livestock. Certainly, acute effects must be guarded against and the likelihood of chronic effect minimized. Since any agent will, in most areas, be used once, or at most a few times, it is not necessary to conform to the high safety standards required by the Food and Drug Administration for commercial agriculture. It is important also to guard against cosmetic effects, however transient, because of the propaganda value.

There appears to be a difference between the military and commercial terminology. The term "defoliant" appears to be used by the military to mean an agent which causes the leaves to drop whether it kills the plant or not. In commercial terminology an agent which kills a plant is a herbicide, whereas "defoliants" are exclusively non-herbicide agents which cause the leaves to drop from a commercial crop plant in order to facilitate harvesting. Desiccant appears to have the same meaning for the military and industry; namely, an agent which causes the dehydration of leaves and their withering but not necessarily causing them to drop from the plant. Another category of agent, the soil sterilant is recognized commercially as an agent which prohibits the growth of all flora in an area whether temporarily or permanently.

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There was some confusion among our industry contacts as to whether the military wanted, didn't want, or didn't care whether the agents offered were herbicidal or soil sterilizing. This needs clarification. In our understanding, sterilants have a definite place in roadside clearance whereas they might bring about erosion problems in the forest proper.

Several companies which bid on the two recently granted contracts had only a vague understanding as to what the military objectives are. This lack of clarity undoubtedly hampered some in the preparation of a satisfactory proposal. More specific information on the now classified aspects of military requirements would assist the bidders in submitting more responsive proposals.

II. Commercial Agents Immediately Applicable in the Field

The most promising source of new operational agents for use in the next six months lies in the combination of commercially available herbicides, defoliants, and/or desiccants. Formulation is the key to the successful field application of such agents.

The United States Department of Agriculture appears to be aware of the performance capabilities of all commercially available herbicides, defoliants, desiccants, and soil sterilants. They are familiar with the published literature as well as the results from the several state agencies. In addition, they have an extensive research program of their own. It is not clear that the able but overworked staff at Fort Detrick, since the arrest of their efforts in 1958 and its resumption

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in 1961, have been able to apprise themselves of the performance capabilities of all marketed agents. It is ironic that the Fort Detrick anti-vegetation program was aborted in 1958 since this is approximately the time that a number of new agents representing different chemical types became available. The ready availability of the components of the agent used and the generally recognized range of effectiveness made it the logical first contender.

Our contacts in industry were unable to suggest any agent as promising as those being tested operationally for two reasons:

1. They had not been given the military requirements specifically in terms of the situation in Vietnam; and
2. They had no reliable, comprehensive, organized body of data on the effects of their chemicals in tropical environments.

We make no specific suggestions as to commercially available agents which should be investigated in the field. We do, however, recommend that mixtures of one or more different herbicides either with currently used agents or in various combinations, such as dinitrophenols and 2,4,5-T, should be tried. This type of combination should bring about rapid leaf drop and subsequent kill. One would expect that a defoliant (in the commercial sense) by itself would be of military interest only in certain tactical situations since growth in a few months would undo its short-term effect. A combination of defoliant and herbicide, however, presents problems which call for specific experimental work. One anticipates that if leaf-drop should occur too rapidly, the herbicide may not have time to be absorbed and bring about a subsequent

kill. Similarly, combinations of herbicides and desiccants also should be evaluated.

The third aspect of the utilization of current materials lies in formulation. The latter is the addition of additives, solvents, emulsifiers, etc., to basic agents in order to enhance their effectiveness. Effective formulation requires an individual with long experience and a knack bordering on art. This competence is best embodied in a few private consultants and some industrial laboratories.

It is our opinion that the recommendation of the commercial agents to be investigated can be best made by Fort Detrick and USDA at Beltsville in consultation with some of the larger corporations such as American Cyanamid, Dow, Monsanto, Shell, Amchem Products, and Giegy Chemical Corporation. We believe that the formulation and initial evaluation of these mixtures can be most rapidly, effectively, and economically accomplished through industrial contracts, whereas Fort Detrick's major contribution should be in large-scale field evaluation.

III. Industrial Chemicals at the Developmental Stage

In the intermediate and long-range efforts of the anti-vegetative program, the accumulated laboratory and screening data as well as the current developmental activities of the herbicide manufacturers could be profitably applied to the program.

In any technically oriented big business, such as agricultural chemicals, there is a build-up of unused technical information available only to company employees. In wartime, in the name of patriotism and national defense, the barriers of industrial security are lowered. In

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a cold war, demands of proprietary self-interest are still dominant. In peacetime industry, by and large, is reluctant to give to the military proprietary information which has been accumulated at great expense. In the herbicide-defoliant field, a small company easily can accumulate data on 200 to 300 potential agricultural chemicals in a year. A large company can accumulate data on that many in a month. A vanishingly small percentage of the compounds initially screened for herbicide activity, because of unfavorable economics, toxicity, or an inappropriate spectrum of biological activity, is ever commercially developed. It still may be to the company's interest to keep the performance data on these unsuccessful compounds secret to avoid aiding its competitors.

The Food and Drug Administration requirements which must be met by agents that are to be applied to crops make the development of a crop chemical exceedingly expensive - ranging from $250,000 to $2,000,000. This expense is incurred largely in animal feeding studies, field evaluations, residue determinations, and investigations of the metabolic disposition of the chemical in the plant. Such expensive studies probably are not necessary for a military agent.

Several of the larger companies indicated that they did have, or might have, agents in their accumulated files which they would be willing to make available to the military if they were approached with a specific objective. It should be pointed out that the staffs of the state and federal agricultural agencies also are largely uninformed of the behavior of these test chemicals because of industrial security.

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Chemicals under development present a delicate problem to industry. The revelation of performance characteristics might reduce a company's lead time over its competitors by several years. The opinion was expressed frequently that a specific military request, coupled with a better safeguard of the companies proprietary rights, would induce them to reveal data on promising compounds. An additional inducement would be to give the companies more responsibility than is presently the case for the screening and evaluation of their compounds.

IV. Fundamental Studies

There is a slow but accelerating production of fundamental studies on phytotoxic action. In spite of more than 15 years of investigation, there is no definitive account of the mode of action of 2,4-D, the oldest of the commercial organic herbicides. In contrast, there has been marked success in investigating the mode of action of several of the newer herbicides. Monuron, chlorophenyldimethylurea, has been shown by Todd and others to interfere with the Hill reaction in photosynthesis. Hilton of DuPont and others of Beltsville have shown that Dalapon, salts of 2,2-dichloropropionic acid, and other chloro-acids compete for pantoate in the enzyme involved in pantothenate synthesis. There also has been increasing activity in the study of absorption and translocation of phyto-active chemicals.

These basic advances are being made largely in the universities and the USDA facilities in the United States and by a group of workers in England.

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Fundamental studies at present are largely irrelevant to the short and intermediate range problems. In the long pull, these studies present the greatest promise since they are the foundation upon which our understanding of phytotoxicity rests and this knowledge could be crucial in the selection of compounds to be studied in the future.

At one time, Fort Detrick was a center of fundmental studies. It is no more and, in our opinion, it should not be. Fundamental work is best conducted in an uninhibited environment of free exchange such as exists at the universities. In our opinion, therefore, the military should provide support for basic research. We believe, also, that Fort Detrick should be given the opportunity to take full advantage of this information by the appointment of consultants representing disparate points of view.

V. Proper Function of Fort Detrick in the Anti-Vegetative Program

As pointed out above, the military applications of defoliants are a relatively minor but specialized aspect of the general technology of plant chemistry. The military have specific problems peculiar to their needs, but the principal resources to solve them are located in industry. Fort Detrick should, therefore, play the primary role in formulating these unique problems and in developing the appropriate technology to solve them. To do this, they need a capability which ranges from basic research to applied technology. One of the key problems is to achieve the proper balance of these activities. The Fort Detrick operation should go into the fundamental aspects of plant chemistry only far enough to maintain a competence at the installation

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which will enable it to interpret fundamental research reports from all sources. On the other hand, fundamental studies in plant chemistry are currently under-funded at the universities and the Department of Defense would do well to support this activity.

The second activity, that of evaluating new agents, can be divided into two parts - synthesis of new agents, and their screening. By the very nature of organic synthesis, small installations cannot have a full spectrum of synthetic capability. Fundamentally, indsutry and, to a lesser extent, the universities should be the source of new chemicals. The synthesis of these new compounds can be best done on a contract basis and these laboratories should be given wide latitude to investigate new chemical structures. However, Fort Detrick must have sufficient synthetic organic chemical capability to permit it to follow up promising synthetic leads where an in-house effort is desirable.

The other aspect of new agent evaluation is primary screening to select those chemicals which have the slightest promise of phytochemical activity. Whenever possible, screening should be the responsibility of the organization synthesizing the compounds in order to provide a high rate of feedback of the results to the synthetic program. In this way, interest in the research would be heightened and economies in both time and money effected.

Thirdly, the application of plant chemicals for military purposes should be the strong point of the Fort Detrick operation, i.e., problems connected with modes of delivery as well as operational evaluations, and

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large-scale testing in those environments of military interest.

In summary, the use of phytochemically active agents is primarily a special facet of a much larger technology. Fort Detrick needs a full range of capability to stay abreast of developments but its emphasis should be overwhelmingly on those aspects which are peculiar to military applications.

VI. Other Government Efforts in Plant Chemistry

The principal focus of non-military federal government activity in phytotoxic agents is the United States Department of Agriculture; comparable agencies exist at the state levels. Their interests range from the improvement of agricultural yields without impairing the wholesomeness of food, control of undesirable plants in wooded lands to help the lumbering industry, control of growth along rights of way used for power transmission lines and transportation, to control of weeds in navigable waters and aquatic sports areas.

These agencies conduct extensive evaluation programs at the applied level which are designed primarily to measure the effectiveness of new agents in their various fields of interest. The state and federal agencies usually are given only those materials which the manufacturer has decided, on the basis of his own evaluations, have a good chance of being commercially successful. Thus, the governmental agencies' forte is the knowledge of the effectiveness of commercial chemicals being marketed or being offered for commercial development. Their weakness is a lack of information with respect to the far greater number of materials rejected by the manufacturer for commercialization.

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For the current military needs, therefore, the agricultural stations, in particular the USDA, are in a key position to recommend to Fort Detrick those commercially available agents which should be brought immediately to operational evaluation.

On the level of secondary plot size screening, the U.S. Department of Agriculture and the state agricultural stations have conducted field evaluations for many years, especially in temperate zones. They do not have the manpower, which can be applied immediately to the short and intermediate range military problems.

Industry with its long experience in formulation must be utilized to the maximum. The proper function of Fort Detrick is to coordinate these two competences and to channel their efforts into a productive, efficient program. Particular attention should be given to the Puerto Rican Commonwealth Agriculatural station which has a climate similar to that of Southeast Asia. The flora may not be comparable in their reactions to the phytotoxic agents.

The Forest Service is, in general, interested in removing undesirable trees from those areas which are commercially significant, for example, the selective killing of scrub oak in pine forests. Rapidity of response, a military necessity, has not been a Forest Service requirement. Secondly, their interest is directed toward selectivity or specificity of action. Thirdly, many of their tree-killing techniques such as frilling (prying a ring of wedges of bark away from the tree and applying the chemical to the wound) are militarily impractical.

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In summary, due consideration and emphasis should be given to the various aspects of the development program. The prime responsibility for formulation and its associated screening should be assigned to industry, directly or indirectly. The facilities for plot-size screening are most frequently found in the state, commonwealth, and federal agricultural stations.

VII. Industrial Liaison

It became apparent early in our investigation that the principal focus of phytochemical technology lies in industry. The military has not been receiving full advantage of this technology because of a failure to communicate its unique problems, and industry's fear of losing its proprietary rights.

Economic Difficulties - Contact after contact in the industrial laboratories made the point that the agricultural chemical business is highly competitive. An awareness by the competition of the performance of a developmental chemical or even the general trend of new research, can mean large dollar losses. When data is submitted to the various government agencies, it is with the understanding that secrecy will be maintained on proprietary information. In a few regrettable instances, this confidence has been violated, causing the suppliers to become over-cautious. Most of our contacts agreed that the individuals to whom the information is given initially act in good faith. Two effects act to undercut their good intentions. One is a relatively rapid turnover

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of personnel and the other appears to be a needlessly broad dissemination of information to those who have no real "need-to-know." Other difficulties are the failure to clarify and publicize industry's opportunity to retain commercial rights and concern that an agent might be classified "secret" thus preventing the development of a patent position.

In spite of these adverse reactions, the industrial representatives expressed a desire to serve the country, even at some risk to proprietary interest, provided:

1. The problems were made explicit preferably through face-to-face contact; and
2. There is an opportunity to earn a fair profit.

The salient features of the last point are the firm guarantee of commercial rights to any agent developed in a government program, and the opportunity to turn previous laboratory investigations to profit by developing military uses for agents which the company had previously rejected for commercialization. In this manner they will be able to retrieve some of their research expenditures.

Cost Sharing - In connection with the granting of two recent contracts by Fort Detrick which went to Penn Salt and Monsanto, respectively, a number of complaints were made with respect to cost sharing. In this arrangement, the contractor absorbs part of the program's cost presumably because his commercial interests are being aided by the contract. Cost sharing tends to be promoted by those who will gain the most through federal subsidy, whereas cost sharing tends to be discouraged or not engaged in by those who have the least to gain but the most to give to the federal effort. A company with no great

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commitment in a field may undertake a great deal of cost sharing, thus providing for itself an opportunity to break into a new field. In effect, rather than subsidizing a federal effort, it is utilizing federal money to subsidize its own interests. In contrast to this, the large company with a tremendous backlog of information and technology, when asked to engage in cost sharing, is subsidizing the federal effort.

The industrial reaction to cost sharing, in most cases, was unfavorable. This attitude is based on the fear that in some cases purchase price may take precedence over quality of research.

Communication Problem - The failure to communicate adequately the military needs to industry has been a major factor in retarding response. We will discuss the problem in terms of (a) the Industrial Liaison Office which was organized officially to bring new chemicals into the military program, and (b) the handling of the two recent Fort Detrick contracts as specific examples of difficulties.

(a) Industrial Liaison Office - The general attitude toward the effectiveness of the Industrial Liaison Office varied all the way from "very favorable" to "ineffective." There is a tendency for those companies who are active participants or who have a long-standing history of involvement in military programs to consider the Industrial Liaison Office effective. Instances were reported where companies were recruited into the program by specific contacts with Dr. Metcalf, the Chairman. At the other extreme, the companies which had relatively few dealings with the military felt that the Industrial Liaison Office was not doing a good job. They tended to look upon the acquisition program as indiscriminate and ineffective.

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With respect to the herbicides, the opinion generally expressed was that the significant manufacturers already had screened most of the compounds before they submitted them to the Industrial Liaison Office. They felt that the military should not be conducting a redundant effort in screening these chemicals but rather should be consulting more closely with the synthesizer with reference to the phyto-activity of the compounds. More important was the statement that the compounds submitted to the Industrial Liaison Office were "highly filtered." It was said that only those compounds which were either known to be of low activity or for which there had been established a firm patent position were submitted.

The most interesting criticism of all came from one company which has submitted the names of hundreds of compounds in the recent past and has received no request for evaluation samples. The conclusion drawn by this supplier was that not even the military is interested in the Industrial Liaison Office acquisition program.

A contrast to these criticisms relating to herbicides is the awareness by industry of military interest in highly toxic materials. Almost without exception, industry has cooperated by submitting samples of new compounds for tests where the preliminary data was suggestive.

(b) Negotiation of Contracts - Our industrial contacts showed spontaneous interest in discussing the various aspects of submitting proposals for an anti-vegetation research contract with Fort Detrick. While none of the remarks below could be said to represent the opinion of all the industrial companies, there was sufficient consensus to merit presentation.

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The bidders' conference seems to have left some contractors confused on objectives. A request for bids for the synthesis of phosphorus, acetylenic and other compounds was made. Many interpreted the request to mean too heavy emphasis on the first two categories. Also, there was a great deal of criticism of the limited screening requested of the contractor. The latter was to screen the new compounds against one plant and Fort Detrick was to screen them against additional ones. One plant was not regarded as a singularly significant for diagnosis. Our contacts generally believed it was much more economical and efficient to permit the contractor to conduct the primary and possibly secondary screening.

We believe the contract work would be more efficient and effective were the contractor involved in goal planning, synthesis, formulation, primary and secondary screening, and field evaluations. Also, many of the large corporations and some of the smaller ones have tropical and subtropical evaluation facilities in operation or available to them which could respond almost immediately to the military requirements for secondary and field screening. Such a systems approach could be most effectively carried out in dealing with the larger companies such as Dow, Shell, DuPont, American Cyanamid, Monsanto, etc.

Some of the industrial contacts were sufficiently interested in the military program that they wished to initiate unsolicited contract proposals. Apparently the opportunity and the mechanism for doing this was not made clear to them at the bidders' meeting.

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VIII. Manufacturing Capability to Respond to Military Requirements

An important question is the ability of the manufacturer to produce large quantitites of a new chemical in response to military requirements. This problem has two important aspects - manufacturing facilities and the cost of the products.

For primary screening purposes, a few grams of material are quite adequate and are the scale on which a synthetic program is and should be conducted. Field or plot screening evaluation might call for one pound quantities. In almost all cases, it was felt by the manufacturers that they could respond to such a requirement within a month. Should an agent be successful at that time there probably would be a need for quantities in the range of 20 to 25 pounds for a large-scale field evaluation. The response time in this case probably would not exceed three months.

Application of a new agent at the operational level might involve synthesis of 50,000 to one million pounds per year. The larger manufacturers were, by and large, confident that such a need could be met provided fairly broad latitude in cost was allowed in order to cover the extra expenses inherent in the large-scale production of a new chemical.

It is our belief that in looking for this new military agent, one could justify, initially, several-fold higher costs than that allowable for an established commercial agent. We believe that if industry were explicitly informed that such an opportunity exists, it would be greatly stimulated in its search for new phytochemical agents.

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IX. Botany

Our observations indicate that there is significant literature available on the botany of the Indo-Chinese peninsula. This is not well organized nor is it available conveniently in the English language. We believe that some taxonomic botany would be most helpful to those attempting to develop improved herbicides and defoliants. The objectives should be:

1. To gain a clear understanding of the relative military importance of the specific species;
2. To explore the relationships between chemical sensitivity and taxonomy in temperate and tropical regions.

Our preliminary investigations suggest that considerable pertinent information is scattered among the various companies which have plantations or commercial interests in the tropics: these are primarily the rubber, coffee, banana, and cocoa growers. A taxonomist with a chemical orientation undoubtedly could perform a useful service in collecting and codifying this information. Of particular note is Maurice Schmid, a Frenchman, whose English, we understand, is excellent and who is considered to be the outstanding authority on the botany of Vietnam.

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APPENDIX

The following organizations and individuals have been contacted in our attempt to evaluate the current state of the art of vegetation control by means of chemicals:

1. Biology Department, Harvard University
   Cambridge, Massachusetts

   a. Dr. Duncan Clement
   b. Dr. Kenneth Thimann

2. United Fruit Company
   Boston, Massachusetts

   Dr. N. C. Thornton

3. Colonel K. C. Emerson
   Office of the Secretary of the Army(R&D), Pentagon

4. Smithsonian Institution
   Washington, D. C.

   a. Mr. Morton
   b. Dr. F. A. McClure

5. Esso Research Center
   Linden, New Jersey

   Dr. H. H. Yowell

6. W. R. Grace & Company
   Clarksville, Maryland

   Dr. W. K. Loughlin, Director of Research

7. Fort Detrick
   Fredericksburg, Maryland

   a. Dr. Minerick
   b. Dr. Brown
   c. Dr. Darrow
   d. Dr. Kingsolver

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8. U. S. Department of Agriculture
Washington, D. C.

   a. Forest Service, Dr. Donald Lynch
   b. Agricultural Research Center
      Dr. D. C. Haller
      Assistant Director
   c. Plant Industries Station, Beltsville, Maryland

      (1) Dr. W. D. McClellan
      (2) Dr. D. L. Klingman
      (3) Dr. Shaw

9. American Cyanamid
Princeton, New Jersey

   a. Dr. Frank Stark
   b. Dr. John King

10. Stauffer Chemical Company, New York City

   a. Dr. Chester Arnold
      Vice President in Charge of Research
   b. Dr. Donald Mastick,
      Assistant to the Vice President
   c. Dr. D. Dorman
      Associate Director of Biological Laboratories
   d. Mr. Obrecht
      Research Director, Chemical Division

11. Boyce Thompson Institute
Yonkers, New York

   Dr. George McNew, Research Director

12. Dupont Chemical Company
Wilmington, Delaware

   Dr. Max Goebel, Director of Research

13. Texaco Research Center
Beacon, New York

   Dr. C. L. W. Swanson

14. Pennsylvania State University
University Park, Pennsylvania

   Dr. Donald Frear

15. National Geographic Society
Washington, D. C.

16. Ethyl Corporation
Detroit and Baton Rouge

a. Dr. Ellis Rifkin
b. Mr. J. D. Libby, Jr.

17. Shell Development
Emeryville and Modesto, California

a. Dr. R. G. Larsen,
Director of Agricultural Research
b. Dr. J. Van Overbeak
c. Other staff members

18. Standard Oil of California
Richmond, California

a. Dr. B. F. Quisenberry
b. Dr. I. Levine
c. Dr. L. R. Gardiner,
Director of Agricultural Research
d. Other staff members

19. University of California
Davis, California

Dr. A. S. Crafts

20. California State Department of Forestry
Sacramento, California

Dr. L. Burcham

21. Dow Chemical
Midland, Michigan

a. Dr. W. P. Schambra, Defense Liaison and Planning
b. Dr. K. C. Barrons, Plant Scientist
c. Dr. L. C. Chamberlain, Assistant to the
Director of Research

22. Chemagro
Kansas City, Kansas

Dr. vonRumker

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onsanto

M
ME—LOCATION—PHONE) D. R. Bishop

E : May 11, 1983 CC:

JECT : "Removing the hysteria from dioxin"

ERENCE :

CONFIDENTIAL

O : J. F. Hussey

As you know, Dow is currently engaged in a major effort to try to "take the hysteria out of dioxin." They have two-man teams of scientists, recently trained in media interview techniques, traveling throughout the country in a media blitz. Dow also hired Hill & Knowlton to aid them in this effort. Their motives are two-fold: 1) to refute charges that they have seriously compromised health and the environment in the Midland area and 2) to articulate their position vis-a-vis the Agent Orange lawsuit.

Obviously, we could put together our own road show, employing basically the same techniques. We do have the Suskind mortality study to point to and hopefully, soon, the morbidity study which we're currently restrained by the court from exploiting.

In my opinion, Dow's efforts and, indeed, ours if we choose to emulate them, will do little more than give our management the proverbial "nice warm feeling." In the case of dioxin, we've got two very major things working against us: 1) dioxin is a completely worthless, highly toxic, unwanted contaminant, i.e., it's impossible to defend it on any logical grounds, and 2) we have virtually no credibility on this subject because of the lawsuits, i.e., the news media and the public say "What would you expect a company that is being sued for billions of dollars to say about dioxin?"

If any real progress is to ever be made in the battle to bring a sense of reason to the dioxin health debate, it is my belief that it must come from independent scientists, prestigious technical organizations like the National Science Academy and the Congressional Office of Science and Technology and the regulatory community, e.g., EPA, CDC, NIOSH, etc.

Not many people are going to believe the extreme ends of this highly polarized body of experts (Monsanto/Dow versus Epstein, et al). It's these so-called independent scientists and government experts who can make a difference -- if a way can be found to motivate them -- and that's a big IF!

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What's clearly needed is a "truce." This situation is very much out of control. A major scientific symposium might be an appropriate mechanism to bring all interested parties together. It should be jointly sponsored by organizations like the AMA, CMA, NSF, NRDC, possibly the WHO, etc.

I don't pretend to have all the answers on how this could be orchestrated, assuming it makes sense. It might be an appropriate agenda item for the Environmental Policy Committee to address -- or perhaps the CMA's Executive Committee under Lou Fernandez's leadership could take it on.

In my view, the analogy to AN in Dick Mahoney's note is inappropriate:

- 50,000 Vietnam Vets aren't suing anyone over exposure to AN.
- The CDC never said 1 ppb of AN is a health hazard.
- The government isn't buying out any towns contaminated with AN.
- AN is a highly beneficial product of commerce, notwithstanding its potential hazards.

These are my thoughts. Hope they are helpful.

Dan R. Bishop

DRB:ec

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FEDERAL GOVERNMENT EXPRESSION OF CONCERN

March 5, 1971, Meeting With U.S. Producers

"'Penta' Is A Useful Preservative For Wood."

"Unless Pentachlorophenol Can Be Cleaned Up, We Will Probably Lose It."

"The Subject Of Dioxins Is Pretty Explosive And Could Blow Up At Any Time."

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SUBJECT TO PROTECTIVE ORDER

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DOWV

INCIDENTS ATTRIBUTED TO NON-PHENOLIC IMPURITIES IN POLYCHLORINATED PHENOL PRODUCTS

Government Hearings On 2,4,5-T Herbicides	4-14-70
Kimmig & Schultz	1957
Cook, F.D.A. - Report To 1970 I.U.P.A.C.	1970
Poland, et al.	1970
Chick Edema Disease	1958-1972
PROCTER & GAMBLE (Cantrell, et al.)	
F.D.A. (Firestone, Campbell)	
U.S.D.A. (Kearney, Woolson)	
SWEDISH ENVIRONMENT PROTECTION BOARD - JENSEN	
Thomas Whiteside Articles In The *"New Yorker"*	1970

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BULK COMPOSITION OF PENTACHLOROPHENOL

PENTACHLOROPHENOL	90%[a]
TETRACHLOROPHENOL	8%[a]
TRICHLOROPHENOL	0.1%[a]
HIGH MOLECULAR WEIGHT PHENOLS .	1%[b]
NON-PHENOLIC COMPONENTS	0.5%[c]

[a] Determined by infra-red spectroscopy and gas-liquid chromatography for major and minor components. Precision = ± 0.5% r.s.d.

[b] Determined by gas-liquid chromatography of trimethylsilyl-derivatives and extraction from caustic solution and ion-exchange chromatography

[c] Determined by ion-exchange chromatography

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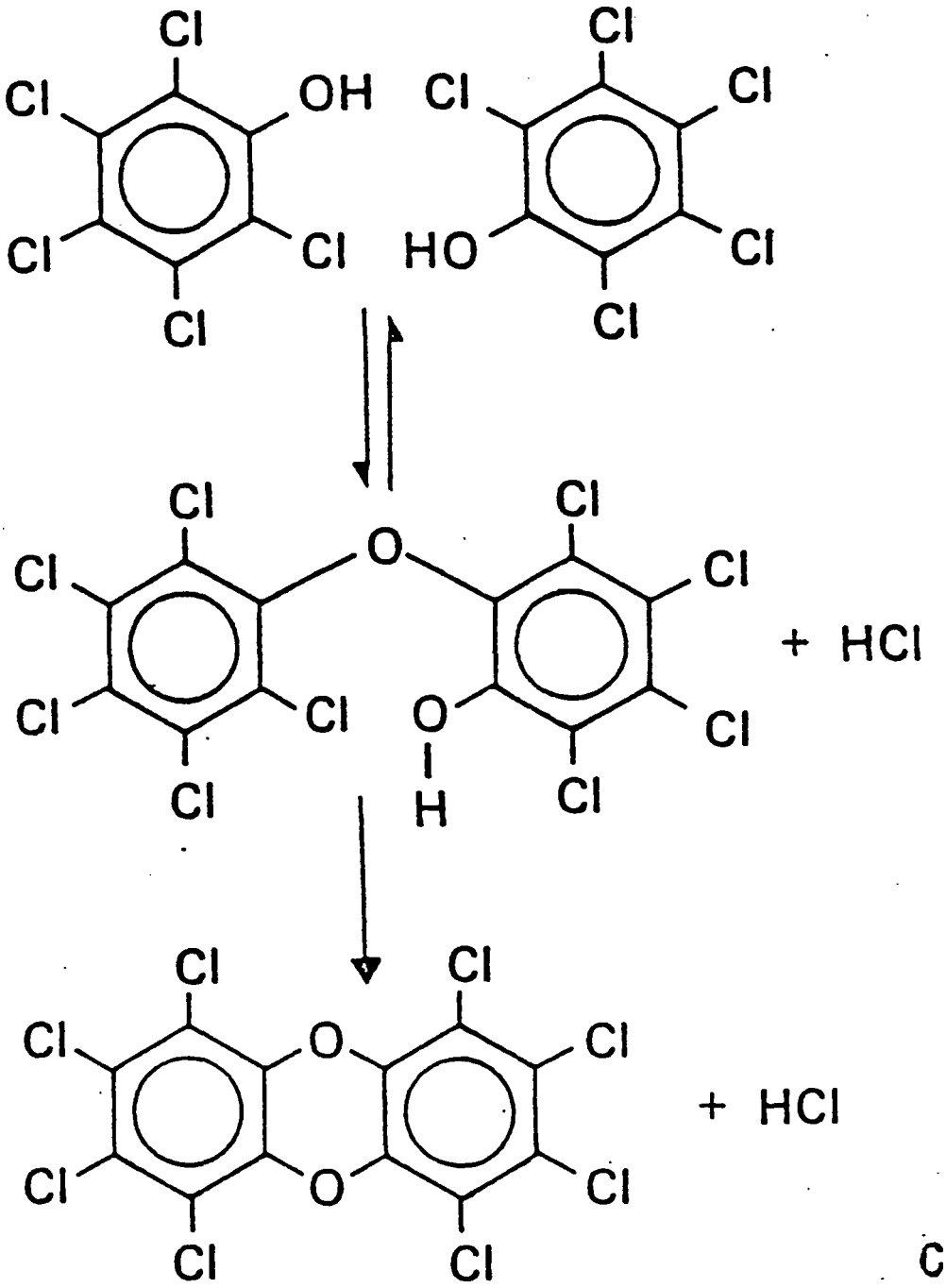
1983

EXAMPLE OF A POTENTIAL ROUTE TO FORMATION OF NON-PHENOLIC IMPURITIES IN COMMERCIAL PENTACHLOROPHENOL



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TOXICOLOGY OF 2,3,7,8-TETRACHLORO-DIBENZO-p-DIOXIN

- Acute Lethality
  Single Oral LD50 — 0.6 mg/kg - 115 mg/kg
- Acnegenic Response — Positive Response At 0.04 mg/ml
- Chick Edema Factor — Positive At 1 And 10 mg/kg/Day. No Effect Dose Level, 0.1 mg/kg/Day
- Embryotoxicity — Positive At 0.6 mg/kg/Day

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TOXICOLOGY OF HEXACHLORODIBENZO-p-DIOXIN

- Acute Lethality — Not Documented As Yet
- Acnegenic Response — Positive At 10 - 50 mg/ml
- Chick Edema Factor — Positive At 10 And 100 mg/kg/Day
- Embryotoxicity — Positive At 10 mg/kg/Day
- Teratogenicity — Positive At Dose Level Of 100 mg/kg/Day

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TOXICOLOGY OF OCTACHLORODIBENZO-p-DIOXIN

- Acute Lethality
  - NOT LETHAL TO FEMALE RATS, ORAL DOSES OF 1 g/kg
  - NOT LETHAL TO MALE MICE, ORAL DOSES OF 4 g/kg
- Acnegenicity — Negative
- Teratogenicity — Negative At 500 mg/kg/Day
- Embryotoxicity — Positive At 500 mg/kg/Day

C192
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COMMERCIAL PENTACHLOROPHENOL
Monsanto Company

Pentachlorophenol	86.3%
Tetrachlorophenol	4.2%
Highers	9.4%
Octachlorodibenzo-p-Dioxin	1550 ppm
Hexachlorodibenzo-p-Dioxins	18 ppm

Chloracne Response — Positive

C19225

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RESULTS OF COMPARATIVE TOXICOLOGY STUDIES

COMMERCIAL PENTACHLOROPHENOL, DOWICIDE 7

- Responsible For Chloracne
- Responsible For Production Of Chick Edema
- Responsible For Histopathological Changes
  - BLOOD CHEMISTRY CHANGES
  - GROSS ORGAN CHANGES
- Is Not Teratogenic But Is Embryotoxic

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RESULTS OF COMPARATIVE TOXICOLOGY STUDIES

Improved Pentachlorophenol (Dowicide EC-7) And Pure Pentachlorophenol

Do Not Cause Chloracne

Do Not Cause Production Of Chick Edema

Do Not Cause Histopathological Changes

Not Teratogenic But Are Embryotoxic

Are Equal In Acute Toxicity

Are Equal In Chronic Dietary Feeding Toxicity Studies

C19227

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CONCLUSIONS DERIVED FROM COMPARATIVE TOXICOLOGY STUDIES

- Acute Oral Toxicity Of Dowicide EC-7 Is Greater Than Dowicide 7
- Dowicide EC-7 Does Not Cause Chloracne, Dowicide 7 Does
- Dowicide EC-7 Does Not Produce Chick Edema, Dowicide 7 Does
- Dowicide EC-7 Does Not Cause Histopathological Changes In Chronic Feeding Studies, Dowicide 7 Does
- Pentachlorophenol, Regardless Of "Grade," Is Not Teratogenic
- Pentachlorophenol Is Embryotoxic

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PCP C192

178841

DOWICIDE EC-7:
WHY HAS TOXICITY BEEN IMPROVED?

- Total Chlorinated Dioxin (And Furan) Content Has Been Significantly Reduced
- Specification Of 30 ppm, Maximum Octachlorodibenzo-p-Dioxin Has Been Imposed
- Limit Of 1.0 ppm Hexachlorodibenzo-p-Dioxins Assures Absence Of:
  - CHLOROACNE CAUSING IMPURITIES
  - CHICK EDEMA FACTOR
  - HISTOPATHOLOGICAL CHANGES RESULTING FROM TOXIC IMPURITIES

PCP C1923

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19843

DOWMICIDE EC-7 TOXICITY CONCLUSIONS

- Does Not Cause Chromosome Damage
- Does Not Produce Chronic Endocrine
- Minimal Acute Peripheral Neurotoxicity

Both Acute And Chronic Toxicity

DOW

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PC-C19232
19844

☆ DOWICIDE EC-7, WITH REDUCED CHLORINATED DIBENZO-p-DIOXIN CONTENT, DOES NOT CAUSE:

- Chloracne
- Chick Edema
- Histopathological Changes In Chronic Feeding Studies

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DOW

PC 19233
19845

ANALYSIS AND SPECIFICATIONS OF DOWICIDE EC-7 PENTACHLOROPHENOL

PENTACHLOROPHENOL	88-93%
TETRACHLOROPHENOL	12-7%
TRICHLOROPHENOL	< 0.1%
HIGHERS	0.1%
DIOXINS	
2,2,7,8-TETRACHLORODIBENZO-p-DIOXIN	< 0.05 ppm
HEXACHLORODIBENZO-p-DIOXINS	1.0 ppm MAX.
OCTACHLORODIBENZO-p-DIOXIN	30 ppm MAX.

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ANTIMICROBIAL EFFICIENCIES

TEST FUNGI	% DOWICIDE EC-7 FOR INHIBITION
Trichoderma viride, ATCC No. 8678	0.0025-0.005
Trichoderma sp., Madison P-42	0.001-0.0025
Ceratocystis pilifera, ATCC No. 15457	0.0005-0.001
Polyporus tulipiferae, ATCC No. 11245	< 0.0001
Rhizopus stolonifer, ATCC No. 6227a	0.0001-0.00025
Lenzites trabea, Madison 617	0.0001-0.00025
Ceratocystis ips, ATCC No. 12860	0.001-0.0025
Chaetomium globosum, ATCC No. 6205	0.0001-0.00025
Aspergillus niger, ATCC No. 6275	0.001-0.0025

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PSP C196

94861

ANTIMICROBIAL EFFICIENCIES

TEST BACTERIA	% DOWICIDE EC-7 FOR INHIBITION
Bacillus cereus var. mycoides, ATCC No. 11778	0.0005-0.001
Staphylococcus aureus, ATCC No. 6538	0.00025-0.0005
Bacillus subtilis, ATCC No. 8473	0.005-0.01
Escherichia coli, ATCC No. 11229	0.025-0.05
Salmonella choleraesuis, ATCC No. 10708	0.01-0.025
Pseudomonas aeruginosa, ATCC No. 15442	0.1-0.25
Enterobacter aerogenes, ATCC No. 13048	0.05-0.1
Streptomyces griseus, ATCC No. 10137	0.0005-0.001
Flavobacterium arborescens, ATCC No. 4358	0.00025-0.0005

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8+861

From The Desk Of
LARRY ATKINS

WD Mackay

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0031188 PEP 01923

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

BEFORE THE ADMINISTRATOR

In re:	
The Dow Chemical Company, et al.	FIFRA Docket Nos. 415, et al.

DIRECT TESTIMONY OF DR. LENNART HARDELL */

Scheduled Date of Testimony: September 29, 1980

Dorothy E. Patton
Kevin M. Lee
Patricia A. Roberts
Richard P. Bozof
Timothy D. Backstrom
Andrew G. Gordon
Karl O. Bayer
John W. O'Donnell

Counsel for Respondent

U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

*/ EPA Exhibit No. 762

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

BEFORE THE ADMINISTRATOR

In re:	)	
	)	FIFRA Docket Nos. 415, et al.
The Dow Chemical Company, et al.	)	

DIRECT TESTIMONY OF DR. LENNART HARDELL*/

My name is Lennart Hardell. I received my medical degree from the University of Uppsala in Sweden and have subsequently specialized in internal medicine and oncology. I am currently employed by the Department of Oncology at the Regional Hospital in Umea, Sweden. My work at the Department of Oncology includes diagnosis, treatment, and evaluation of possible causes of human cancer.

My testimony concerns several epidemiological studies which my colleagues and I recently conducted in Sweden. We examined the relationship between the risk for two forms of cancer, soft tissue sarcoma and malignant lymphoma,**/ and exposure to phenoxyacetic acid herbicides and chlorophenols (Hardell and Sandstrom 1979, Exhibit 594; Eriksson et al.

*/ EPA Exhibit No. 762

**/ Soft-tissue sarcomas are rare cancers of certain connective tissues, such as muscle and fat. Since connective tissues are widely distributed throughout the body, soft-tissue sarcomas are not restricted to a single physiologic site. Lymphomas are cancers of lymphatic tissue.

1980, Exhibits 763a, 763b; Hardell et al. 1980, Exhibit 764). We found that exposure to phenoxy acids or to chlorophenols is related to a significantly elevated risk for these types of cancers.

I. BACKGROUND

My interest in the relationship between exposure to phenoxy acids and soft-tissue sarcoma began when three patients with sarcomas were admitted to the Department of Oncology in Umea in the autumn of 1976. Each of these patients reported substantial occupational exposure to phenoxy herbicides some 10-20 years earlier. Two of these patients were forestry workers who had previously worked with the phenoxy acids 2,4,5-T and 2,4-D and the third patient owned a workshop where large quantities of phenoxy acids had been stored, partly in open buckets. Prompted by these reports, I reviewed the Department of Oncology records for the period of 1970-1976 and found four additional soft-tissue sarcoma patients who reported previous exposure to phenoxy acids. I then brought this series of cases to the attention of the scientific community (Hardell 1977, Exhibit 765a, 765b).

Based on these observations, my colleagues and I decided to conduct a formal epidemiologic investigation to determine whether or not exposure to phenoxy herbicides increases the risk of developing soft-tissue sarcoma.*/ Because soft-tissue

*/ We also evaluated the risk associated with exposure to chlorophenols, which like 2,4,5-T and silvex are known to contain chlorinated dibenzodioxins as impurities.

sarcoma is a rare variety of cancer, it was apparent that a case-control (also called case-referent) study would be the most appropriate epidemiologic method to test our hypothesis. The case-control method is particularly well suited to the study of rare diseases because a case-control study begins with identification of a group of persons who have the disease (cases). After selection of an appropriate comparison group of persons free of the disease (controls), the nature of previous exposure to the suspected causal agent is then compared between the two groups and, with appropriate statistical analysis, the relative risk*/ for the disease can be estimated.**/

In our initial case-control study (Hardell and Sandstrom 1979, Exhibit 594), which utilized subjects residing in the Department of Oncology admission area in northern Sweden, we found that exposure to phenoxy acids and to chlorophenols was

*/ Relative risk is the rate at which a disease develops in exposed persons divided by the rate at which the disease develops in unexposed persons. In the absence of uncontrolled confounding factors or bias (see discussion below at p.6-9, 22-29), a relative risk of 1.0 indicates that a particular exposure is not related to the disease in question. A relative risk significantly greater than 1.0 indicates that exposure increases the risk of developing the disease, while a relative risk significantly less than 1.0 indicates that exposure provides protection against the disease.

**/ In contrast, a cohort study compares the incidence of disease in an exposed population directly to the incidence of disease in an unexposed population. In order to yield meaningful data on the risk for a rare type of cancer such as soft-tissue sarcoma, a cohort study would probably have to be large and cover a long period of time.

associated with a significantly elevated risk for soft-tissue sarcoma. We also employed the case-control method in a subsequent study of soft-tissue sarcoma and exposure to phenoxy acids and chlorophenols in an agricultural region in southern Sweden (Eriksson et al. 1980, Exhibits 763a, 763b). This second study, which was conducted at the request of the Swedish Board of Occupational Safety and Health, corroborated our initial findings in a separate and different population.

My interest in the possible relationship between exposure to phenoxy acids and malignant lymphoma began in May, 1978, when a patient with a tumor in the soft-tissue of his left femur was admitted to the Department of Oncology. Although the clinical picture resembled that of a soft-tissue sarcoma, histological examination indicated a malignant lymphoma of the histiocytic type. The patient reported prior exposure to phenoxyacetic acid herbicides. I then questioned seventeen male patients with the same type of tumor admitted to the Department of Oncology between January and September 1978 about their past and present occupation and possible exposure to phenoxyacetic acids or chlorophenols. Fourteen of these seventeen patients reported a current occupation consistent with the possibility of exposure and eleven of these patients reported prior exposure to phenoxy herbicides or chlorophenols (Hardell 1979, Exhibit 766).

Prompted by these clinical observations, my colleagues and I conducted a third case-control study (Hardell et al.

1980, Exhibit 764) in the same geographic region where the first soft-tissue sarcoma study had been conducted. In this study, we found that a significantly elevated relative risk for malignant lymphoma was associated with previous exposure to phenoxy acids and to chlorophenols.

In the following section, I will review methodologic considerations that were important in all three studies. Following that, I will discuss our findings in these studies, some general concerns in interpretation of our findings, and the conclusions that may be drawn from them.

II. METHODOLOGY

Each of our three case-control studies was carefuly designed to minimize the likelihood of spurious or misleading results and to enable a meaningful evaluation of the risks associated with the exposures studied. This section discusses some of our basic methodologic concerns and describes the techniques we utilized in selection of cases, selection of control subjects, assessment of exposure, and calculation of relative risk.

A. Selection of Cases

The first step in a case-control study is the selection of a group of subjects who have the disease in question. In our first soft-tissue sarcoma study and our lymphoma study, we identified cases by reviewing the records of patients previously treated at the Department of Oncology in Umea. Cases in the second soft-tissue sarcoma study were obtained from the Cancer

Registry of the Swedish Social Welfare Board and were sarcoma patients who resided in a particular region of southern Sweden at the time of diagnosis. In all three studies, tumor slides from each patient were examined by pathologists in order to verify the initial histologic diagnosis. In each instance, these pathologists had no information concerning any patient's prior exposure history.

B. Selection of Controls

After selection of each group of diseased patients, we selected a corresponding group of controls. In general, it is desirable to use a method for selecting controls which is designed to minimize the influence of confounding factors. These are factors that are associated with both the probability of developing the disease and the probability of exposure to the suspect agent. Inadequate attention to confounding factors can produce a misleading estimate of relative risk. For example, consider a hypothetical case-control study of breast cancer and exposure to household cleaners in which the investigators failed to consider sex in selection of control subjects. This oversight could result in a spurious elevation of the relative risk, if the group of cases (subjects with breast cancer) contained a higher proportion of women, who are both more likely to develop breast cancer and to use household cleaners, than the group of controls. In such a study, the sex of the subjects would be a confounding factor.

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One effective way of controlling for the possible influence of confounding factors is to match cases and controls individually for comparability as to possible confounding factors. For statistical reasons, matching should be limited to a small set of the most likely confounding factors. In each of our studies, we matched two or more controls to each case on the basis of three possible confounding factors: sex, age, and place of residence.*/ As will be discussed below, we also considered a number of other possible confounding factors in analyzing the results of each study.

C. Assessment of Exposure

After selection of cases and controls, we investigated the exposure history of each case and control, including information on possible carcinogenic agents to which the subject had previously been exposed and the nature and duration of such exposure. Although adequate exposure information may sometimes be derived from occupational or historical records, such records are often fragmentary or inadequate, especially when exposure is not limited to particular groups in the subject population or the disease in question exhibits a long latency period prior to clinical detection. Accordingly, exposure information in case-control studies is most commonly obtained by questioning or interviewing the subjects (McMahon and Pugh 1970, Exhibit 767).

*/ In addition, deceased controls were selected for deceased patients and matched for year of death.

In each of our studies, exposure information was obtained by written questionnaires and was supplemented by interviews.

When exposure information is obtained from the subjects, care must be taken to avoid the possibility that the subjects' attitudes and experiences will introduce bias into the investigator's ascertainment of exposure (Axelson 1980, Exhibit 597a). One possible source of such bias could be a tendency, conscious or not, for those suffering from a disease to overstate past exposure as compared to healthy controls. In recognition of this potential problem, we designed each of our studies to minimize the possibility of such recall bias. Each subject or next-of-kin of a deceased subject received a questionnaire by mail, which was subsequently supplemented by a telephone interview. Each questionnaire contained a variety of extraneous questions concerning previous and present occupation, conditions in the occupational environment, smoking habits, etc., avoiding any special attention to phenoxyacetic acid or chlorophenol exposure (see Exhibits 768a, 768b). Supplementary interviews were conducted by individuals who did not know whether the subjects were cases or controls. Employers, neighbors, and other individuals who might have special knowledge concerning a subject's past exposure were consulted by questionnaire or telephone to verify and monitor the accuracy of exposure information. In addition, deceased controls were selected for deceased patients, in order to avoid any bias which might

result from differences in recall between live subjects and deceased subjects' next-of-kin.

The potential risks associated with use of phenoxy acids, including their possible carcinogenic and teratogenic effects, have been vigorously debated in Sweden. Despite our precautions, we could not completely exclude the possibility that diseased individuals might be inclined to exaggerate their past exposure as compared to healthy controls. Thus, we also analyzed our results for indications of residual observational bias by utilizing a statistical technique recently developed by Dr. Olav Axelson (Axelson 1980, Exhibit 597a). Dr. Axelson is a leading Swedish epidemiologist who has also been conducting an ongoing study of a cohort of railroad workers exposed to phenoxy acids and other herbicides. He provided methodological assistance to my colleagues and me in designing and evaluating all three of our case-control studies. The results of our analyses using Dr. Axelson's technique are described in a later section. They suggest that bias in the observation of exposure, if present at all in our studies, was very slight.

After collecting exposure information, we classified each case and control as exposed or unexposed for each category of substances studied. Phenoxy acid preparations have been used extensively in Swedish forestry and agriculture (Barring 1978, Exhibit 769; Granstrom 1978, Exhibit 770), and individuals classified as exposed to phenoxy acids generally were or had

been forestry or agricultural workers.*/ Most subjects classified as exposed to phenoxy acids reported they had performed jobs involving application of phenoxy acids, such as knapsack spraying, basal-bark spraying, tractor-mounted spraying, operation of mistblowers, stump painting, and notching. A recent study has documented the presence of 2,4,5-T and 2,4-D residues in the blood and urine of Swedish forestry workers engaged in tractor-mounted spraying of 2,4,5-T and 2,4-D. (Kolmodin-Hedman et al. 1979, Exhibits 517a, 517b). In our studies, we also classified some subjects as exposed to phenoxy acids who reported wet clothes or skin contact while working on wet ground which had been sprayed with phenoxy acids. Individuals who worked in areas previously sprayed with phenoxy acids but who did not report any wet contact were classified as unexposed. In instances where the reported exposure to phenoxy acids was uncertain or less than one day in duration, subjects were classified as unexposed.

D. Calculation of Relative Risk

In studies where cases and controls have been individually matched to avoid confounding, different formulas for calculating the relative risk may be used, depending upon whether or not

*/ Subjects classified as exposed to chlorophenols consisted primarily of individuals employed in sawmills, (see Levin et al., 1976, Reference 1) paper pulp operations, or painting with wood preservatives.

the matching is taken into account. When, as in our studies, each case is assigned two or more controls, the calculation of relative risk using the matched material is relatively complicated (Miettinen 1970, Reference 2). Calculation of relative risk without matching is considerably simpler.

The procedure we followed in each of our studies was to calculate the relative risk both with and without matching in the initial analysis (including all subjects and considering exposure to phenoxy acids and/or chlorophenols). In each study, we found that the matched analysis gave slightly higher values for relative risk than the unmatched method. This indicated to us that the confounding factors we matched for did not bias the result (See Miettinen 1972, Reference 3). Consequently, we were able to greatly simplify the subsequent calculations in each study by dissolving the matching, recognizing that use of the matched material would yield somewhat higher, not lower, estimates of relative risk.

III. RESULTS OF OUR RESEARCH

A. The First Soft-Tissue Sarcoma Study

In our first study (Hardell and Sandstrom 1979, Exhibit 594), the 52 cases consisted of 21 living and 31 deceased male patients with soft-tissue sarcoma, ranging in age from 26 to 80 years, who were treated at the Department of Oncology between 1970 and 1977. We selected four control subjects for each case and matched the cases and controls on the basis of sex, age, place of residence, and vital status. Deceased cases and controls were matched for year of death.

In this study, 19 of the 52 sarcoma patients (36.5%) and 19 of the 206 controls (9.2%) reported previous exposure to phenoxy acids or chlorophenols. Of the 19 exposed cases, 12 reported exposure to phenoxy acids, 6 to chlorophenols, and one to both. Of the 19 exposed controls, 13 reported exposure to phenoxy acids, 5 to chlorophenols, and one to both. Among those reporting exposure to phenoxy acids, combined exposure to 2,4,5-T and 2,4-D was by far the most common exposure history (9/13 cases, 8/14 controls). Other subjects reported exposure to 2,4,5-T or 2,4-D separately or to MCPA (4-chloro-2-methyl phenoxyacetic acid).

The relative risk for soft-tissue sarcoma associated with exposure to phenoxy acids and/or chlorophenols in the matched material was 6.2 (95% confidence interval 3.0 - 12.6, $p < 0.001$).*/ Without matching, the relative risk was 5.7 (95% confidence interval 2.9-11.3, $p < 0.001$). These relative risks suggest that persons occupationally exposed to phenoxy acids and/or chlorophenols are approximately six times more likely to

*/ The 95% confidence interval indicates the range of values for relative risk in which there is a 95% probability that the actual value lies. The p-value, or level of statistical significance, is the probability that the calculated estimate of relative risk could have arisen solely by random variaton (in this case, less than 1 chance in 1,000). P-values were determined from the standard chi square test of statistical significance. 95% confidence intervals were calculated by the test-based method of Miettinen (Miettinen 1976, Reference 4). Therefore, if the lower limit of the 95% confidence interval is greater than 1.0, p is less than 0.05. All reported values for our studies are derived from two-tailed tests of significance.

develop soft-tissue sarcoma than similar persons not exposed to these substances. Since the relative risk by the matched method was slightly greater than by the unmatched method, we concluded that retention of matching was unnecessary and simplified subsequent calculations by dissolving the matching.

We determined the relative risk for soft-tissue sarcoma associated with exposure to phenoxy acids alone by excluding all cases and controls reporting exposure to chlorophenols and repeating the analysis. This procedure yielded a relative risk of 5.3 (95% confidence interval 2.4-11.5, $p < 0.001$). When all subjects reporting exposure to phenoxy acids were excluded, the relative risk associated with chlorophenol exposure was 6.6 (95% confidence interval 2.8-15.6, $p < 0.001$). Therefore, we could not attribute the increased risk for exposed individuals either to phenoxy acids or to chlorophenols, as both exposures were independantly associated with increased risk. However, we noted that both groups of chemicals contain chlorinated dibenzodioxins as impurities.

The inference that the excess risk for soft-tissue sarcoma associated with exposure to phenoxy acids and to chlorophenols may be related to dioxin contamination is consistent with the unexpected occurrence of soft-tissue sarcomas in relatively small cohorts of individuals occupationally exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). A single death from a soft-tissue sarcoma was observed in a cohort of 121 individuals

exposed to TCDD in a 1949 trichlorophenol process accident (Zack and Suskind, 1980, Exhibit 771). Although the investigators did not draw any conclusion from this observation, they described it as a "rare" event. Moreover, an additional death from a soft-tissue sarcoma has recently been reported in a cohort of only 61 trichlorophenol production workers exposed to TCDD in 1964 (Cook et al. 1980, Exhibit 772).

B. The Second Soft-Tissue Sarcoma Study

Following completion of the first soft-tissue sarcoma study, we conducted a second soft-tissue sarcoma study in another part of Sweden, using different patients and controls but the same study method (Eriksson et al. 1980, Exhibits 763a, 763b). The first study, in which the cases were patients treated at the University Hospital in Umea, included subjects residing in the three most northern counties in Sweden. In the first study, subjects exposed to phenoxy acids were primarily workers in forestry. In the second study, we studied patients and controls from an agricultural region in the five most southern counties in Sweden. This new study was initiated partly to determine whether or not the results we observed in the first study could be replicated in a different geographical area, and partly to determine whether or not agricultural exposure to phenoxy herbicides which are not known to contain measurable levels of chlorinated dibenzodioxins (e.g. 2,4,-D, MCPA, mecoprop, dichlorprop) might also be associated with an increased risk for soft-tissue sarcoma.

In the second study, the 110 cases consisted of 72 living and 38 deceased male patients with soft-tissue sarcomas diagnosed and reported to the Swedish Cancer Registry between 1974 and 1978. Patients ranged in age from 25 to 75 years and were living in the five southernmost counties of Sweden at the time of diagnosis. Two control subjects were selected for each case and matched on the basis of sex, age, place of residence, and vital status. Deceased controls were matched with deceased cases for year of death. Analyses were conducted in the same manner as in the first study.

In the second study, 25 of the 110 sarcoma patients (22.7%) and 13 of the 219 controls (5.9%) reported exposure to phenoxy acids or chlorophenols. Of the 25 exposed cases, 14 reported exposure to phenoxy acids and 11 to chlorophenols. Of the 13 exposed controls, 5 reported exposure to phenoxy acids and 8 to chlorophenols. Among those reporting exposure to phenoxy acids, exposure to 2,4,5-T was less prevalent than in our first study, although combined exposure to 2,4,5-T and 2,4-D was still a common exposure history (7/14 cases, 1/5 controls).

The relative risks associated with exposure to phenoxy herbicides and chlorophenols were essentially comparable to those obtained in the first study. (See Table 1). The relative risk for soft-tissue sarcoma associated with exposure to phenoxy acids and/or chloropehnols in the matched material was 5.1 (95% confidence interval 2.5-10.4, $p < 0.001$). Since the corresponding relative risk without matching was 4.7 (95% confidence interval 2.6-8.5, $p < 0.001$), matching was dissolved for all subsequent

TABLE 1

Relative Risks for Soft-Tissue Sarcoma in Two Case-Control Studies

Exposure category	Study location: Northern Sweden[a]	Study location: Southern Sweden[b]
Phenoxy acids and/or chlorophenols	5.7(6.2)*	4.7(5.1)*
Phenoxy acids only	5.3	6.8
Chlorophenols only	6.6	3.3**

*/ Estimates in parentheses were calculated from matched material. All others derived from unmatched material.

**/ $p<0.01$. For all other relative risks, $p<0.001$.

Sources: a. Hardell and Sandstrom 1979, Exhibit 594.
b. Eriksson et al. 1980, Exhibit 763a.

calculations. When all subjects reporting exposure to chloropenols were excluded, the relative risk for soft-tissue sarcoma associated with exposure to phenoxy acids was 6.8 (95% confidence interval 2.6-17.3, $p < 0.001$). After exclusion of subjects reporting exposure to phenoxy acids, the relative risk associated with chlorophenol exposure was 3.3 (95% confidence interval 1.3-8.1, $p < 0.01$).

In the second sarcoma study, we also looked for evidence of a dose-response relationship between exposure to phenoxy acids and the risk for soft-tissue sarcoma by calculating relative risks separately for groups of subjects with different exposure durations. Workers reporting exposure to phenoxy acids for more than 30 days had a relative risk of 8.5, while those reporting exposure for less than 30 days had a relative risk of 5.7. Although this difference in relative risk in relation to duration of exposure is not statistically significant, it is consistent with a possible dose-response relationship.

Because the second study was conducted in an agricultural region, sufficient numbers of cases and controls were exposed to phenoxy herbicides not known to be contaminated with dioxin (MCPA, 2,4-D, mecoprop, dichlorprop) to enable a separate analysis of the risk associated with these herbicides. Exposure to these substances was associated with a significantly elevated relative risk of 4.2 (95% confidence

interval 1.3-13.4, $p<0.025$).*/ This finding raised the possibility that the phenoxy acids themselves, rather than dioxin contaminants, might be responsible for the increased risk for soft-tissue sarcoma. Alternatively, it is possible that these phenoxy acids are contaminated with dioxin at concentrations below the limit of detection.

C. The Lymphoma Study

Like the first sarcoma study, our case-control study of malignant lymphoma was initiated in response to clinical observations at the Department of Oncology in Umea. Because lymphoma is also a relatively rare disease and our Department records provided a convenient source of cases, we again chose the case-control method of study (Hardell et al. 1980, Exhibit 764).

The 169 cases in this study consisted of 107 living and 62 deceased male patients with various types of lymphoma, ranging in age from 25 to 85 years, who were treated at the Department of Oncology in Umea between 1974 and 1978. We selected two control subjects for each case and matched for sex, age, place of residence, and vital status. Deceased controls were matched with deceased cases for year of death.

The relative risk for lymphoma associated with exposure to phenoxyacetic acids and/or chlorophenols in the matched

*/ In contrast, the relative risk for subjects reporting exposure to 2,4,5-T, alone or in combination with other phenoxy acids, was 17.0.

material was 6.0 (95% confidence interval 3.7-9.7, $p<0.001$). After dissolving the matching, the relative risk was 5.3 (95% confidence interval 3.4-8.3, $p<0.001$). As in the sarcoma studies, these results indicated that further analysis could be simplified by dissolving the matching.

After excluding persons reporting exposure to chlorophenols, the relative risk associated with exposure to phenoxy herbicides (primarily 2,4,5-T and 2,4-D) was 4.8 (95% confidence interval 2.9-8.1, $p<0.001$). Workers reporting exposure to phenoxy acids for more than 90 days had a relative risk of 7.0, while those reporting exposure for less than 90 days had a relative risk of 4.3. As in the second sarcoma study, this observed difference in relative risk was not statistically significant, but was consistent with a possible dose-response relationship. After excluding subjects reporting exposure to phenoxy acids, exposure to chlorophenols was associated with a relative risk of 4.3 (95% confidence interval 2.7-6.9, $P<0.001$). These findings were quite similar to those in the two soft-tissue sarcoma studies: a statistically significant increase in the relative risk for lymphoma was associated with exposure to phenoxy acids and to chlorophenols.

Because a recent study suggests an increased risk for malignant lymphoma in occupational groups exposed to benzene (Vianna and Polan 1979, Reference 5), and a number of subjects in our study reported exposure to substantial amounts of

various organic solvents, we also evaluated the risks associated with exposure to organic solvents. High exposure to organic solvents was associated with a significantly elevated relative risk for lymphoma, which was most pronounced for exposure to certain solvents which are suspected mutagenic or carcinogenic agents (benzene, trichloroethylene, perchloroethylene, and styrene). The relative risk for all individuals reporting exposure to organic solvents, excluding those also reporting exposure to phenoxy acids or chlorophenols, was 2.4 (95% confidence interval 1.5-3.8 $P<0.001$). An especially strong association with lymphoma was observed in individuals reporting exposure to both organic solvents and phenoxy acids or chlorophenols, who had a relative risk of 8.5 (95% confidence interval 4.2-17.2, $p<0.001$). These results suggest that the association of lymphoma with exposure to phenoxy acids and chlorophenols was not due to confounding by exposure to organic solvents, and that separate increases in risk are attributable to each category of substances.

This study indicates that exposure to phenoxy herbicides such as 2,4,5-T or to chlorophenols is a risk factor for malignant lymphoma. The presence of chlorinated dibenzodioxins as impurities in 2,4,5-T and chlorophenols suggests one possible mechanism underlying the observed excess risk for lymphoma. Animal tests indicate that dioxins, particularly 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), suppress cell-mediated immunity (Vos et al. 1973, Reference 6). Defects in cell-mediated immunity

in humans have been associated with Hodgkin's lymphoma (Bjorkholm et al. 1977, Reference 7), and the incidence of histiocytic lymphoma is 350 times greater in kidney transplant patients with deliberately induced immunological deficiencies than in the general population (Penn 1978, Reference 8). Thus, it is possible that the elevated risk for lymphoma associated with exposure to phenoxy herbicides such as 2,4,5-T and to chlorophenols is related to immunologic effects resulting from exposure to dioxin contaminants in these products.

The hypothesis that the observed excess risk for lymphoma among individuals reporting exposure to phenoxy herbicides or to chlorophenols is related to dioxin contamination is consistent with other epidemiological evidence of the effects of TCDD exposure. A recent cohort study of mortality among individuals exposed to TCDD in a 1949 trichlorophenol process accident (Zack and Suskind 1980, Exhibit 771) indicates that TCDD-exposed workers have an elevated incidence of lymphatic and hematopoietic cancer. Even though no hypothetical induction or latency period was used in evaluating cancer mortality, 3 deaths from lymphatic and hematopoietic neoplasms were observed as compared to 0.88 deaths expected. All three observed deaths occurred more than 20 years after exposure to TCDD. The investigators did not calculate risk ratios or significance levels for types of mortality with fewer than five observed deaths. However, the excess incidence of lymphatic and hematopoietic cancer would be statistically significant ($p < .05$) after inclusion of any reasonable latency period in the analysis.

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IV. INTERPRETATION OF OUR FINDINGS

Proper interpretation of epidemiological data depends in part on assessment of the possible effect of bias or confounding on the observed results. We designed each of our case-control studies to minimize the chance that our results would be influenced by bias or confounding. However, although we were able to control the potential impact of certain factors by application of proper study design techniques, we could not entirely eliminate the possibility of uncontrolled bias or confounding. Thus, we also evaluated the results in each of our studies for evidence of potential problems such as bias in the observation of exposure or confounding by concurrent exposure to causative factors other than phenoxy acids.

A. Observational Bias

The possibility of bias in the observation of exposure was an important methodological concern in each of our studies. Accordingly, we utilized a number of techniques to reduce the likelihood of observational bias, including addition of questions regarding extraneous matters, blinding of interviewers to whether a particular subject was a case or control, independent questioning of the subjects' employers and acquaintances, and selection of deceased controls for deceased cases. However, since the potential risks associated with the use of phenoxy acids have been the subject of considerable controversy in Sweden and the ascertainment of exposure in our studies was based primarily on recall, we were still concerned about the

possibility that diseased individuals or their next-of-kin might be inclined to overstate exposure as compared to controls or their next-of-kin. Therefore, we also used a statistical technique developed by Dr. Axelson (Axelson 1980, Exhibit 597a) to evaluate the results of our studies for evidence of the presence of observational bias.

Table 2, which is derived from the results of our second sarcoma study, provides an example of the application of Dr. Axelson's technique. */ By dividing the subjects between those employed in occupations where exposure to phenoxy acids is common (agriculture and forestry) and those employed in other occupations, separate relative risks can be calculated for exposed and unexposed workers in agriculture and forestry, as compared to unexposed persons in other occupations. If cases were inclined to substantially exaggerate their exposure, this bias would increase the number of exposed cases in occupations where exposure is common (in this instance, 13), creating an artifical deficit in unexposed cases in these occupations (in this instance, 17). Thus, the presence of substantial recall bias should result in a relative risk considerably below 1.0 when unexposed individuals in agriculture

*/ Dr. Axelson's observational bias technique had not yet been developed at the time our first sarcoma study was completed. The Swedish version of our second sarcoma study included a separate application of Dr. Axelson's technique in which subjects exposed to chlorophenols were also included.

TABLE 2

EXPOSURE TO PHENOXY ACIDS IN THE SECOND SARCOMA STUDY DIVIDED BY OCCUPATION

	Agriculture/forestry		Other Occupations
	Exposed	Unexposed	Unexposed
Cases	13	17	68
Controls	5	39	167
Relative Risk	6.4	1.1	(1.0)

Source: Eriksson et al. 1980. Subjects exposed to chlorophenols are excluded. One case and no controls exposed to phenoxy acids were employed in occupations other than agriculture and forestry.

TABLE 3

EXPOSURE TO PHENOXY ACIDS IN THE LYMPHOMA STUDY DIVIDED BY OCCUPATION

	Agriculture/forestry		Other Occupations
	Exposed	Unexposed	Unexposed
Cases	35	37	71
Controls	23	114	189
Relative Risk	4.1	0.9	(1.0)

Source: Hardell et al. 1980. Subjects exposed to chlorophenols are excluded. Six cases and one control exposed to phenoxy acids were employed in occupations other than agriculture and forestry.

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and forestry are compared to unexposed individuals in other occupations.*/ However, in this instance, the relative risk was 1.1. The comparable relative risk for our lymphoma study was 0.9 (see Table 3). These calculations indicate that bias in the observation of exposure to phenoxy acids, if present in either of these studies, did not substantially influence the results.

My colleagues and I have recently conducted a new case-control study to obtain further evidence concerning the likely magnitude of observational bias in our soft-tissue sarcoma and lymphoma studies. In this new study, we evaluated the relation between exposure to phenoxy acids and the risk for colon cancer, a type of cancer not previously suspected of being associated with exposure to phenoxy acids. We utilized the same basic study design employed in our first three studies. Discussion of phenoxy acids and their presumed risks in the Swedish media was especially intense during the period when this new study was conducted. Accordingly, any observational bias present in the first three studies should also be present in this study. We have just completed a preliminary

*/ In contrast, the presence of an independent risk factor among individuals in agriculture and forestry not also exposed to phenoxy acids could result in a relative risk above 1.0. Thus, it is theoreticaly possible that confounding by an occupational variable which is not closely related to phenoxy acid exposure could compensate for the statistical effect of a possible observational bias. However, since we found no evidence of this type of independent occupational risk factor, such an ad hoc hypothesis is inappropriate.

analysis of the data in this new study and will publish our findings soon.

B. Confounding Factors

In each of our studies, cases were individually matched to controls on the basis of sex, age, place of residence, and year of death. This procedure resulted in a comparable distribution of these characteristics in the cases and controls, thereby minimizing the influence of these characteristics as possible confounding factors. We also evaluated the possible confounding effect of smoking habits in each study and could detect no apparent difference between cases and controls.

Our studies found a higher incidence of soft-tissue sarcoma and of lymphoma in occupations where exposure to phenoxy acids or chlorophenols is common than in other occupations. Thus, we also evaluated the possible confounding influence of other types of occupational exposures, in order to determine whether or not the observed excess risk might be attributable to some occupational factor other than phenoxy acid or chlorophenol exposure. In the first sarcoma study, we studied DDT exposure and exposure to exhaust from motorized sawing and found no significant increase in risk was associated with these exposures.

In the second sarcoma study, we analyzed the possible confounding influence of a number of occupational factors, including exposure to organic solvents, DDT, exhaust from motorized sawing, mercury seed dressings, asbestos, glass fiber, and a variety of other pesticides. Although reported exposure

to these other occupational factors tended to be somewhat higher among cases than controls (see Table V, Exhibit 763a), no other studied exposure varied nearly as much between cases and controls as exposure to phenoxy acids and to chlorophenols. Moreover, none of the relative risks for soft-tissue sarcoma associated with more common exposures such as organic solvents, DDT, and mercury seed dressings were significantly elevated. The total percentage of subjects who reported exposure to pesticides other than phenoxy acids or chlorophenols was higher among cases (21.8%) than controls (11.0%). However, after excluding subjects who also reported exposure to phenoxy acids or chlorophenols, the percentage of subjects who reported exposure to other pesticides was roughly comparable among cases (9.5%) and controls (8.0%). Thus, the observed difference in exposure to other pesticides between cases and controls was probably due to an incidental occupational relationship between use of phenoxy acids or chlorophenols and use of other pesticides.

Each of our soft-tissue sarcoma studies found an association between exposure to phenoxy acids and a significantly elevated cancer risk, although the studies were conducted in different geographic and occupational settings. Phenoxy acid exposures in the first study in northern Sweden occurred primarily in forestry work, while phenoxy acid exposures in the second study in southern Sweden occurred more frequently in agricultural work. The similar results in each study, despite

differences in the occupational context in which phenoxy acid exposure occurred, increased our confidence that the observed association of exposure to phenoxy acids and soft-tissue sarcoma was not due to occupational confounding.

In our lymphoma study, we evaluated the possible confounding effect of a similar series of occupational factors, including exposure to DDT, mercury seed dressings, diesel oil, exhaust from motorized sawing, asbestos, glass fiber, and a variety of other pesticides. Although reported exposure to DDT, mercury seed dressings, asbestos, and glass fiber was somewhat higher among cases than controls, the differences were not nearly as pronounced as those for exposure to phenoxy acids and chlorophenols (See Table 6, Exhibit 764). As in our second sarcoma study, the differences in exposure to these other agents between cases and contols were probably due to an incidental occupational relationship between use of these other agents and use of phenoxy acids or chlorophenols.

In general, we found no evidence in any of our studies of any uncontrolled confounding factors which could account for the observed relation between phenoxy acid exposure and an elevated risk for soft-tissue sarcoma and lymphoma. On the other hand, we could not identify any specific phenoxy acid or contaminant as the principal causative factor.*/

*/For example, exposure to 2,4,5-T was most often reported in combination with exposure to 2,4-D. Thus, the observed excess risk for cancer associated with exposure to 2,4,5-T could be attributable to 2,4,5-T itself, TCDD contamination in the 2,4,5-T, concurrent exposure to 2,4-D, or a combination of these factors.

In addition, it is possible that the observed increases in relative risk were related to some as yet unidentified factor which is closely associated with use of phenoxy acids. Nevertheless, it is most likely that the observed excess risk for human cancer was associated with the phenoxy acids themselves, impurities in the commercial preparations, or a combination of these factors.

V. CONCLUSION

Two separate case-control studies have demonstrated that occupational exposure to phenoxyacetic acid herbicides (primarily 2,4,5-T and 2,4-D) is associated with a statistically significant fourfold to sevenfold increase in the risk for soft-tissue sarcoma. Exposure to chlorophenols, which like 2,4,5-T are contaminated with chlorinated dibenzodioxins, is also associated with a significantly elevated risk for soft-tissue sarcoma. However, in one study a significant association was also found between soft-tissue sarcomas and exposure to phenoxy acids which do not contain measurable dioxin. Thus, the excess risk for soft-tissue sarcoma in individuals reporting exposure to 2,4,5-T and 2,4-D may be related to TCDD contamination in the 2,4,5-T, the properties of the phenoxy herbicides themselves, or a combination of these factors.

Another case-control study indicates that exposure to phenoxyacetic acids and to chlorophenols is also associated with a significantly elevated risk for lymphoma. Since lymphomas are known to be more prevalent in individuals

with deficient immunological competence, it is possible that the observed increase in relative risk is related to immunologic depression caused by exposure to the dioxin contaminants in 2,4,5-T and chlorophenols.

Each of these studies was carefully designed to minimize the likelihood of spurious or misleading results. Cases and controls were individually matched on the basis of a set of potential confounding factors. A number of measures were employed to avoid systematic bias in the ascertainment of the subjects' exposure histories, including questions concerning extraneous variables, interviewers unaware of whether a subject was a case or control, verification of exposure by employers and acquaintances, and selection of deceased controls for deceased patients.

In addition to use of appropriate study design techniques, we also evaluated the results of each study for evidence of problems such as confounding by concurrent occupational exposure or residual observational bias. Although exposure to some factors other than phenoxy acids and chlorophenols tended to be higher among cases than controls, exposure to these factors among cases and controls not also exposed to phenoxy acids or chlorophenols was quite similar, indicating an incidental occupational connection. Thus, although we cannot absolutely rule out confounding by some unknown factor related to exposure to phenoxy acids and chlorophenols, we

found no evidence of any uncontrolled confounding factors which could account for the observed increases in relative risk found in our studies.

The potential hazards associated with use of phenoxy-acetic acid herbicides have been vigorously debated in Sweden. Thus, despite our precautions, a possibility remained that diseased individuals might be inclined to overstate their past exposure as compared to controls. In recognition of this possibility, we employed a new statistical technique to determine whether or not our findings were substantially influenced by observational bias. Utilizing this technique, we found no evidence of an observational bias sufficiently large to account for the observed increases in relative risk.

For each of our major findings, the chances were less than one in a thousand that the observed relative risk could have occurred solely as a result of random variation. Research into the health effects of environmental agents, whether conducted in the laboratory or the clinical setting, is seldom conclusive and additional research is nearly always warranted. Nevertheless, in the absence of any evidence that uncontrolled confounding factors or bias seriously distorted these stuies, our findings must be regarded as strong evidence of a causal relationship between exposure to phenoxy herbicides and human cancer.

Lennart Hardell (tdb)

Lennart Hardell, M.D.

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EXHIBITS

Exhibit No.

594 Hardell, L. and A. Sandstrom 1979. Case-control study: Soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols, Brit. J. Cancer 39: 711-717.

597a Axelson, O. 1980. A note on observational bias in case-referent studies, Scand. J. Work Env. Health 6: 80-82.

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763b Table: Type and duration of exposure for cases and referents exposed to phenoxyacetic acids in Eriksson et al. 1980.

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CERTIFICATE OF SERVICE

I hereby certify that copies of the foregoing DIRECT TESTIMONY (AND EXHIBIT*) OF DR. LENNART HARDELL were hand delivered or mailed first class postage prepaid on September 15, 1980 to the following persons.

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September 15, 1980

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

BEFORE THE ADMINISTRATOR

In re:	)	
	)	FIFRA Docket Nos. 415, et al.
The Dow Chemical Company, et al.	)	
	)	

DIRECT TESTIMONY OF DR. LENNART HARDELL*/

Scheduled Date of Testimony: February 9, 1981

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

BEFORE THE ADMINISTRATOR

In re:	
The Dow Chemical Company, et al.	FIFRA Docket Nos. 415, et al.

DIRECT TESTIMONY OF DR. LENNART HARDELL*/

My name is Lennart Hardell. I received my medical degree from the University of Uppsala in Sweden and have subsequently specialized in internal medicine and oncology. I am currently employed by the Department of Oncology at the Regional Hospital in Umea, Sweden. My work at the Department of Oncology includes diagnosis, treatment, and evaluation of possible causes of human cancer.

I have previously testified in this proceeding (Exhibit 762) concerning several case-control studies in which my colleagues and I found that exposure to phenoxy acids and/or to chlorophenols is associated with a significantly elevated relative risk for soft-tissue sarcoma and malignant lymphoma (Hardell and Sandstrom 1979, Exhibit 594; Eriksson et al. 1980, Exhibit 763; Hardell et al. 1980, Exhibit 764). In case-control studies, one important methodologic concern is the possibility of systematic bias in the ascertainment of the exposure histories of the subjects. Indeed, in prior

*/ EPA Exhibit No. 956

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testimony in this proceeding (Reference 1), Dow witness Dr. Philip Cole suggested that the excess risk for soft-tissue sarcoma and lymphoma associated with phenoxy acid exposure in our studies could be explained by bias in the recall and observation of exposure.

In my previous testimony, I described the techniques which we utilized to prevent observational bias from occurring and to evaluate our results for evidence of such bias. My colleagues and I have just recently completed a new epidemiologic study designed to provide further evidence concerning the likely magnitude of observational bias in our soft-tissue sarcoma and lymphoma studies (Hardell 1981, Exhibit 957). In this study, we evaluated the relation between exposure to phenoxy acids or to chlorophenols and the risk for colon cancer, a disease not previously suspected of being associated with exposure to these substances We found no significant association between exposure to phenoxy acids or to chlorophenols and the risk for colon cancer.

In my testimony today, I will describe the results of our colon cancer study. My testimony will also include further analysis of data from our previous studies of soft-tissue sarcoma and lymphoma and a discussion of new information concerning mortality among industrial workers exposed to 2,4,5-T. In each instance, the new data reinforce and

strengthen our previous conclusion that the positive association between exposure to phenoxy acids and soft-tissue sarcoma and lymphoma cannot be reasonably attributed to methodologic bias.

I. BACKGROUND

In case-control studies, the calculation of relative risk is based on the classification of each case or control subject as exposed or unexposed for each type of exposure studied. Although occupational or historical records may occasionally be sufficient to enable such classification, exposure information in case-control studies is generally obtained by questioning or interviewing the subjects. In our soft-tissue sarcoma and lymphoma studies, exposure information was obtained initially by written questionnaires completed by the subjects or their next-of-kin and was supplemented subsequently by oral interviews.

When exposure information is obtained from subjects or their next-of-kin, the investigator must be careful to use techniques which will prevent or minimize bias in the observation of exposure. As Dr. Cole has noted, observational bias might arise if the cases, who are suffering from a disease, are inclined to overstate past exposure as compared to healthy controls ("recall bias"), or if the manner in which an interviewer elicits exposure information is based on knowledge of the case or control status of the subjects ("observer bias"). In our soft-tissue sarcoma and lymphoma studies, we employed

a number of measures to reduce bias in the ascertainment of the subjects' exposure histories, including many questions concerning extraneous variables, interviewers unaware of whether a subject was a case or control, verification of exposure by employers and acquaintances, and selection of deceased controls for deceased patients.

Despite these precautions in the design of the soft-tissue sarcoma and lymphoma studies, we could not exclude all potential bias in the observation of exposure. (Indeed, it is not possible to design an epidemiologic study which is free of all potential bias). In particular, we were concerned about the possibility that diseased subjects or their next-of-kin might be inclined to overstate exposure as compared to controls or their next-of-kin. Therefore, we also used a statistical technique developed by Dr. Axelson (Axelson 1980, Exhibit 597a) to evaluate the results of our studies for evidence of the presence of observational bias. Calculations utilizing this technique indicated that bias in the observation of exposure to phenoxy acids, if present in our studies, was not of sufficient magnitude to substantially influence the results (see Tables 2 and 3, Exhibit 762).

One of the purposes of our new colon cancer study was to obtain further evidence concerning the validity of the observation of exposure in the previous studies. In our colon cancer study, we utilized the same basic questionnaire and the same interview procedure utilized in our prior studies. Since colon

cancer is a disease which has not been previously linked to phenoxy acids (a so-called "dummy disease"), detection of an excess risk for colon cancer of the same magnitude as the relative risks previously observed for soft-tissue sarcoma and lymphoma would suggest that our prior findings could be explained by observational bias. (McMahon and Pugh 1970, Exhibit 767). However, no significant association between exposure to phenoxy acids or to chlorophenols and the risk for colon cancer was found, as discussed below.

II. THE COLON CANCER STUDY

A. Methodology

The new case series utilized in our colon cancer study consisted of 92 living and 65 deceased male patients with adenocarcinoma of the colon, ranging in age from 25 to 85 years, who were residents of the admission area for the Department of Oncology in Umea and who had been reported to the Swedish Cancer Registry in 1978-79. As in our previous studies of soft-tissue sarcoma and malignant lymphoma, all prospective subjects satisfying the selection criteria were included in the case series.

Exposure was evaluated by the same basic questionnaire and the same interview procedure employed in our previous studies of soft-tissue sarcoma and lymphoma. However, unlike previous studies, the colon cancer study was conducted immediately before and during the Swedish spraying season,

when adverse publicity concerning phenoxy acids has generally been most pronounced. The completed questionnaires were supplemented as necessary by an interviewer who did not know whether or not a particular subject was a colon cancer patient */ and who had been provided with no information concerning the special purpose of the study. Colon cancer cases were classified as exposed or unexposed for each category of substances, including phenoxy acids such as 2,4,5-T, in the same manner as in previous studies. Information concerning exposure among the colon cancer patients was then evaluated in two ways, as described below.

B. Colon Cancer Patients as Controls

As one means of testing whether the previously observed association of soft-tissue sarcoma and lymphoma with phenoxy acids was due to disease-based differences in observation of exposure, we employed the colon cancer patients as an additional reference entity (or set of controls) **/ for the cancer patients

*/ The colon cancer questionnaires were mixed with a set of identical questionnaires for a study of nasopharyngeal cancer being conducted at the same time.

**/ During my previous appearance in this proceeding, I was asked why our previous studies did not utilize other patients at the Regional Hospital in Umea as controls ("hospital controls"). In general, non-diseased controls drawn from the same population as the cases are preferable to hospital controls. When hospital controls are used, the basic purpose is to control for potential bias in the selection of a treatment facility. Thus, conventional hospital controls have little utility in countries with centralized health care systems like that in Sweden, since the non-diseased controls would, if they had the disease in question, be admitted to the same treatment facility as the cases.

who were previously included in our studies of soft-tissue sarcoma (Hardell and Sandstrom 1979, Exhibit 594) and lymphoma (Hardell et al. 1980, Exhibit 764) in the same geographic region in northern Sweden. Since referents had not been individually matched to cases, we stratified all subjects according to the possible confounding factors of age and place of residence (urban vs. rural) and used the standard Mantel-Haenszel statistical techniques to calculate relative risks and p-values (Mantel and Haenszel 1959, Reference 2).

When we used the colon cancer patients as controls and stratified the material to control for differences in age and place of residence, the relative risk for soft-tissue sarcoma associated with exposure to phenoxy acids was 4.5 (95% confidence interval 2.0-10.0, $p.<0.001$). The corresponding relative risk for malignant lymphoma associated with exposure to phenoxy acids was 3.5 (95% confidence interval 1.9-6.5, $p<0.001$). The similarity of these findings to our previously observed values indicates that our findings in the original soft-tissue sarcoma and lymphoma studies cannot be reasonably attributed solely to observational bias.

C. Evaluation of Risk Factors for Colon Cancer

We also evaluated the risk for colon cancer associated with exposure to phenoxy acids and to chlorophenols by using all 541 controls included in our previous studies of soft-

tissue sarcoma and lymphoma in the same region in Northern Sweden.*/ All cases and controls were again stratified according to age and place of residence to control confounding. Relative risks and p-values were calculated utilizing the Mantel-Haenszel statistical techniques.

When we compared the colon cancer cases to previously studied controls drawn from the same geographic region and stratified the material to control for differences in age and place of residence, we found no significant association between phenoxy acid exposure or chlorophenol exposure and the risk for colon cancer.**/ The relative risk for colon cancer associated with exposure to phenoxy acids was 1.7 (95% confidence interval 0.4-6.6). Eleven of the 154 colon cancer patients (7.1%) and 43 of the 541 controls (7.9%) reported exposure to phenoxy

*/ Selection of new individually matched controls for each colon cancer patient was judged impractical because of the additional expenditure of time and resources which would have been involved.

**/ In the colon cancer study, we also analyzed the influence of a number of other possible etiologic factors, including exposure to organic solvents, antihypertensive drugs, asbestos, glass fiber, motor saws, DDT, and mercury seed dressings (see Table 6, Exhibit). Exposure to most of these factors was essentially comparable between cases and controls. One notable exception was exposure to asbestos, which was reported by 10.4% of the colon cancer cases, but only by 5.7% of the controls. After stratification by age and place of residence, the relative risk for colon cancer associated with exposure to asbestos was 1.9 (95% confidence interval 1.0-3.6), which is in agreement with the risk ratios for colon cancer of 2.1 and 2.9 previously reported in cohorts of asbestos workers (Selikoff and Hammond 1975, Reference 3).

acids. If there is no etiologic relationship between exposure to phenoxy acids and colon cancer, the relative risk for colon cancer associated with exposure to phenoxy acids should be one. The observed value of 1.7 may be the result of random statistical variation. It could also indicate that phenoxy acid exposure is associated with a small increase in the risk for colon cancer. Alternatively, it may indicate the presence of some methodologic bias. In any event, these data indicate that the substantially higher relative risks associated with exposure to phenoxy acids in each of our previous case-control studies of soft-tissue sarcoma and lymphoma cannot be reasonably attributed solely to methodologic bias.

III. ADDITIONAL ANALYSIS OF PREVIOUS DATA

In prior testimony in this proceeding (Reference 1), Dr. Cole cited a number of alleged problems or deficiencies in the design and conduct of our soft-tissue sarcoma and lymphoma studies.*/ Despite their hypothetical character,

*/ In other testimony, Dow witness Dr. Michel Ibrahim implied that recent negative case-control studies of reserpine and breast cancer demonstrate that three initial studies which reported a positive association between reserpine use and breast cancer were biased (Reference 4, at 25-7). I have not attempted to evaluate the adequacy of the methodology employed in any of the studies in question. Nevertheless, it is interesting to note that a recent National Cancer Institute bioassay of reserpine (Reference 5) reports a significant excess of tumors in treated male rats and in treated mice of both sexes, including an increased incidence of mammary cancer in treated female mice.

two concerns emphasized by Dr. Cole can be tested objectively and therefore warrant further analysis of the previous data.

In each of our studies, the interviewer who supplemented the written questionnaire responses was initially unaware of the case or control status of the subjects. However, Dr. Cole suggested that the disease status of some subjects might nevertheless have been subsequently disclosed to or discerned by the interviewer, thereby providing a basis for introduction of bias by the interviewer (Reference 1, at 13). To test this hypothesis, we evaluated the relative risks associated with exposure to phenoxy acids based solely on the written questionnaires as returned by the subjects, without considering the more detailed information obtained during subsequent oral interviews. After allowing for a minimum latency period of five years and excluding exposure of less than one day, the resultant relative risks for the first soft-tissue sarcoma, second soft-tissue sarcoma, and lymphoma studies were 4.2, 5.6, and 4.1 respectively (see Table 1, Exhibit), demonstrating that the excess cancer risk associated with phenoxy acid exposure cannot reasonably be imputed to bias introduced by the interviewer.

In his testimony, Dr. Cole also discussed some of the assumptions underlying the application of Dr. Axelson's observational bias technique. In general, the data indicate

that these assumptions were valid and reasonable in the context of our studies. As Dr. Cole noted, the most important assumption underlying application of the Axelson technique is that cases and controls will accurately report the occupations in which they have been employed. Dr. Cole then suggested that, if cases are more likely to recall exposure than controls, cases who were employed in a related occupation for a short duration many years ago might be more likely to recall such employment than comparable controls (Reference 1, at 17; Tr. 16491-2). In my view, it is implausible that such an effect would significantly bias the classification of subjects by occupational category. Nevertheless, in order to test Dr. Cole's hypothesis, subjects who had reported work in agriculture or forestry were subdivided into those who reported employment in agriculture or forestry during the entire period since 1950 (approximately when phenoxy acid preparations were first introduced in Sweden) and those who reported employment in agriculture or forestry for shorter durations. Relative risks were then calculated for exposed and unexposed workers in each group, as compared to unexposed workers employed exclusively in other occupations (see Tables 2 and 3, Exhibit). Utilizing this special application of the Axelson technique, no evidence of bias in the classification of subjects by occupational category could be detected.