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FOR IMMEDIATE RELEASE

March 17, 1970

DOW RESEARCH ON 2,4,5-T
BLAMES BIRTH DEFECTS ON IMPURITY

The Dow Chemical Company scientists presented detailed evidence today showing that a contaminant rather than the compound 2,4,5-T was probably the cause of birth abnormalities reported in test animals in a recent study.

2,4,5-T herbicides produced by several companies are widely used throughout the world for brush control purposes on agricultural lands and are used for weed control in a few food crops. The material in combination with 2,4-D, another herbicide, has also been used in Vietnam as a defoliant.

2,4,5-T has been under fire since October of last year when it was announced that a study conducted by Bionetics Laboratories, Inc., under contract to the National Cancer Institute, indicated higher than normal rates of birth defects in test animals treated with massive doses of 2,4,5-T. Examination of data from the Bionetics tests suggested to scientists at Dow that rather than 2,4,5-T, the real culprit might have been a toxic contaminant that has from time to time been a problem in the manufacture of the material.

The Bionetics sample material was analyzed and found to contain approximately 27 parts per million of the contaminant, 2,3,7,8-tetrachlorodibenzo-p-dioxin. Production standards for the

-more-

herbicide as produced by Dow require that 2,4,5-T contain less than one part per million of the dioxin. Dow established this specification in 1965 to assure safety in the production of the material.

In papers presented today at the meeting of the Society of Toxicology in Atlanta, V. K. Rowe and Dr. J. L. Emerson cited detailed studies just completed that indicate no fetal abnormalities are produced by the herbicide when the Dow standard for dioxin content is met. The animal studies involved the feeding of rats with 2,4,5-T containing less than one PPM of the dioxin contaminant at levels comparable to those used in the earlier studies.

Results indicated very clearly that the herbicide containing less than one part per million of the dioxin had no effect on either mothers or fetuses.

In addition, another group of test animals was given the dioxin alone at levels comparable to those in the impure sample used in the Bionetics work. Results in the test with the pure dioxin indicated a high level of maternal and fetal toxicity of the material. Abnormalities observed in these tests were similar to those reported by Bionetics Laboratories.

In a comment on the test work, V. K. Rowe, toxicologist at Dow and principal investigator in one of the studies, said, "We simply proved again what we already knew. 2,4,5-T is a material of low toxicity while the dioxin is highly toxic. That is precisely why we set a rigid production standard for our products many years ago."

# # #

ABSTRACT

Teratogenic Study of 2,4,5-Trichlorophenoxy acetic acid in the Rat. J. L. Emerson, D. J. Thompson, C. G. Gerbig and V. B. Robinson, The Dow Chemical Company, Zionsville, Indiana.

A study to determine the embryotoxicity or teratogenicity of 2,4,5-trichlorophenoxyacetic acid containing less than one part per million of 2,3,7,8-tetrachlorodibenzo-p-dioxin has been completed in Sprague-Dawley derived rats. Five treatment groups, each consisting of 25 females were administered 1, 3, 6, 12 or 24 mg/kg/day of the compound via gavage in 0.25% METHOCEL® on days 6 through 15 of gestation. A single group of 50 females received the suspending vehicle and served as controls. The following parameters were examined: clinical observations, maternal body weights (prebreeding and day 20), number and position of fetuses and resorptions, number of corpora lutea, pup weight and sex, gross external examination of pups, and macroscopic examination for intestinal hemorrhage in pups. Two-thirds of each litter were fixed in Bouin's solution and one-third was prepared for alizarin red-S staining and skeletal examination. Examination of Wilson sections under the dissection microscope or of alizarin stained skeletons of all fetuses from the 24 mg/kg/day group and an equal number of control fetuses was performed. Representative stained histologic sections through the head, thorax, and abdomen of 10 control and 10 high level fetuses were studied for histopathologic changes.

SOCIETY OF TOXICOLOGY
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No clinical or gross pathologic signs of adverse chemical effect were observed in treated dams during the period of treatment or gestation. Similarly, litter size, number of fetal resorptions, birth weights and sex ratio of pups appeared to be unaffected by chemical treatment. Skeletal and visceral examination of high level and control fetuses as well as histopathologic examination of certain fetuses failed to reveal any teratogenic or embryotoxic effects.

The results of this study fail to substantiate the findings reported recently (unpublished data: Bionetics Research Laboratories, Bethesda, Maryland) of serious effects in fetuses obtained from dams given comparable daily doses of 2,4,5-T containing approximately 27 parts per million of the contaminant, 2,3,7,8-tetrachlorodibenzo-p-dioxin.

ABSTRACT

Teratogenic Study of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in the Rat. G. L. Sparschu, F. L. Dunn and V. K. Rowe, The Dow Chemical Company, Midland, Michigan.

2,3,7,8-Tetrachlorodibenzo-p-dioxin has been found to occur in small amounts as a contaminant in some commercially manufactured samples of 2,4,5-trichlorophenoxy acetic acid. The purpose of this study was to learn whether the presence of this impurity possibly could account for the fetal abnormalities in test animals reported in a recent study (unpublished data: Bionetics Research Laboratories, Bethesda, Maryland).

The dioxin was administered by gavage in 9:1 corn oil - acetone solution in doses of 0 (control), 0.03, 0.125, 0.5, 2.0 and 8.0 micrograms per kilogram body weight per day to groups of 24 (control) and 12 (treatment) pregnant female Sprague-Dawley derived rats on days 6 through 15 of gestation.

On day 20 of gestation, each dam was sacrificed and a cesarean section performed. The number of viable and dead fetuses and early and late resorptions was recorded. Each fetus was examined for any gross abnormalities. Two-thirds of each litter were fixed in Bouin's solution, Wilson sections were examined under the dissection microscope, and tissues were studied for histopathology. One-third of each litter were fixed in alcohol and examined for skeletal abnormalities by alizarin red-S staining.

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No differences were observed in the fetuses taken from dams treated at the dosage of 0.03 µg/kg/day and those taken from dams that received the solvent vehicle only. At the 0.125 µg/kg/day dosage, all parameters studied were within normal limits except for a very slight decrease in average weight, and the occurrence of intestinal hemorrhage (18/127) and subcutaneous edema (22/80) in the fetuses from dams that received this treatment. At the 0.5 µg/kg/day level, the number of fetuses was reduced and the number of resorptions and fetal deaths was increased. The average weight of the viable fetuses was very slightly decreased. The incidence of intestinal hemorrhage (36/99) and subcutaneous edema (31/65) was markedly increased over that seen in the 0.125 µg/kg/day treatment.

At the 2.0 µg/kg/day level, only 7 viable fetuses were obtained. These were from 4 of the 11 litters examined. Resorptions were numerous, intestinal hemorrhage was frequent (4/7), and subcutaneous edema was present in all of the 4 fetuses examined by Wilson section. One fetus from this treatment level was found to have a kinked tail and two of its feet were somewhat misshapen. Skeletal examination, however, revealed no evidence of bone abnormalities.

The 8.0 µg/kg/day dosage level proved to be toxic to the dams. There were no viable fetuses in the dams which were examined on day 20 of gestation. All resorptions occurred early and no evidence of fetal tissue was found.

Skeletal examinations revealed delayed ossification of some sternebrae and skull bones. This occurred generally throughout the various groups, including controls, and is not considered to be of practical significance.

The results of this study indicate a high level of maternal and fetal toxicity to be associated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Its presence in the sample tested in the Bionetics Laboratories study could well have accounted for the observations reported and attributed to 2,4,5-trichlorophenoxy acetic acid.

-45- Dunn

DEPOSITION EXHIBIT
Allen-45
3-8-84 RD

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...CH DEPARTMENT
...S INCORPORATED
...RESEARCH CENTER

CC: Dr. R. B. Scott - M.O.Sym.
Dr. C. L. Dunn - M.O.Sym.

Dr. J. F. Walker/Bldg. 8100
Mr. A. Z. Conner/Bldg. 8100

Dr. A. E. Sidwell -
Jacksonville

March 19, 1970

TO: DR. M. A. TAVES, SYNTHETICS RESEARCH DIVISION

FROM: J. J. FORD, ANALYTICAL DIVISION

ANALYSIS OF 2,4,5-T ACID FOR "DIOXIN" CONTENT

A summary of the analytical data obtained for the "dioxin" content of Hercules 2,4,5-T Acid is given in the attached table. A total of 13 samples have now been analyzed by our modified analytical procedure. This series includes seven samples representing 2,4,5-T produced between 1967 and 1970 and six samples of 2,4,5-T produced in 1965. The latter samples were retained from our previous work (1965) on this problem.

No significant amounts of "dioxin" were detected in any of the 2,4,5-T representing the 1967 to 1970 production. Based on recovery data from "add back" experiments, the "dioxin" content of these samples is less than 0.2 ppm.

The samples of 2,4,5-T representing 1965 production yielded "dioxin" values in the range of 1.3 to 3.5 ppm. These values agree well with the results previously reported for these samples. (See letter Ford to Taves, 8/26/65)

We now feel we have an adequate analytical procedure for the analysis of 2,4,5-T for "dioxin" content. Bob Fisher, a chemist at the Jacksonville plant visited with us during the week of March 2nd to learn this method. Jacksonville Lab is presently "tooling up" to apply this procedure.

John J. Ford

JJF/paw
Attach.

DEPOSITION EXHIBIT
Dunn 20
6-27-90 DF

DEFENDANT'S EXHIBIT
1647

"Dioxin" Content of 2,4,5-T Acid Samples

Sample Designation	Description	Reference	PPM	"Dioxin"
X17394-21-1	Composite 10/11 + 10/12 1968	A	N.D.	<0.2 ppm.
-21-2	Composite 11/11 + 11/14 1968	A	N.D.	<0.2 ppm.
-21-3	Composite 12/6 + 12/7 1968	A	N.D.	<0.2 ppm.
-21-4	Composite 1/15 + 1/19 1969	A	N.D.	<0.2 ppm.
-21-5	Tote Bin 2/23/70	A	N.D.	<0.2 ppm.
-21-6	Composite 5/8/68	B	N.D.	<0.2 ppm.
-21-7	Composite 4/29 + 4/30 1967	B	N.D.	<0.2 ppm.
X14867-2-A1	Lot L 71965 4/15/65	C	3.1	
-2-A2	Lot M 71965 6/1/65	C	2.4	
-2-A3	Lot N 71965 6/15/65	C	3.5	
-2-A4	Lot P 71965 7/1/65	C	2.2	
-2-A5	Lot Q 71965 7/19/65	C	1.3	
-2-A6	Current 7/7/65	C	1.5	

Reference A = Letter Treisback to Lowe 2/23/70.
Reference B = Samples delivered by Bob Fisher.
Reference C = Letter Sidwell to Taves 7/19/65.

"Dioxin" = 2,3,7,8-Tetrachlorodibenzo-p-dioxin.

HQ 033

5009

HERCULES 4(E) 0078

6006

NATIONAL AGRICULTURAL CHEMICALS ASSOCIATION

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WASHINGTON, D.C. 20005

CARL HARRIMAN

PH. 202 • 296-1585

HERCULES 4(K) 0001

March 24, 1970

Mr. J. O. King
Diamond Shamrock Chemical Co.
300 Union Commerce Building
Cleveland, Ohio 44115

Dear Jim:

Thanks for your letter of March 2 regarding possible industry public relations value in publicizing the full dioxin story. When the Federal dioxin testing program was first announced, I talked with some of our member companies about it, especially those most closely involved. The concensus was that these companies could handle the matter more appropriately and expeditiously themselves, at least during that early stage which required quick action and responsive flexibility on their part.

Since that time, I have discussed the matter with our own public relations people and I will bring it up again to the members of the Phenoxy Herbicide Task Force when they get together again.

Yours very truly,

Kenneth K. Krausche
Director of Technical Services

KKK:pm

bcc: Mr. Charles Dunn

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DEPOSITION EXHIBIT
Dunn 21
6-27-90 KF

DEFENDANT'S EXHIBIT
1648

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Government steps up pressure on pesticides

Recent joint action restricting use of 2,4,5-T herbicide portends changes in pesticide regulations and testing

When Sen. Philip A. Hart (D.-Mich.) opened a Congressional inquiry into the hazards of 2,4,5-T earlier this month, he cautiously suggested that questions on the widely used herbicide's safety "might in the end appear to be much ado about very little indeed" or portend "the most horrible tragedy ever known to mankind."

The hearings fell short of proving the latter. But they did provide new evidence that catalyzed government suspension and cancellation of consumer and food crop uses of 2,4,5-T and a halt to its use in Vietnam. What's more, pesticide producers and formulators were again put on notice that Congress intends to scrutinize other products and that pesticide regulations and testing will likely change.

The multipronged action suspended use of liquid formulations containing 2,4,5-T around the home, near lakes and ponds, and on ditch banks and canceled use of nonliquid formulations around the home and on apples, blueberries, barley, corn, oats, rye, rice, and sugar cane. Not restricted are uses for weed and brush control on range, pasture, forest, rights-of-way, and nonagricultural land. But defoliation in Vietnam with a 2,4,5-T and 2,4-D mixture ("agent orange") will be suspended; use of a 2,4-D and picloram mixture ("agent white") will continue.

Of the two steps against U.S. uses, suspension is the more drastic: It halts interstate sales immediately. Cancellation provides for a 30-day period for industry comment. Appeals are possible for both steps, and if a company appeals, only suspension prevents marketing during the appeal process. Dow Chemical, a major producer of the herbicide had not announced what action it would take, if any, at press time.

Some 10% of total 2,4,5-T sales are affected by the orders, Dow estimates. Production of the herbicide in 1968, the latest year for which figures are available, was 17.5 million pounds. With the home gardening season now in full swing, 2,4,5-T formulations are already on retailers' shelves. Although these products may continue to be sold, one industry source suggests that state agencies may be under pressure not to buy and may ride out the year without new purchases for those uses still registered.

New evidence. For some time 2,4,-5-T has been under attack for its use in Vietnam defoliation and because of research findings by Bionetics Research Laboratories that it caused birth defects in laboratory animals. Dow, one of three current producers along with Monsanto and Hercules, had contested these findings, however. The company contended that the teratogenic (fetus deforming) effects were due to dioxin contaminants in a Diamond Alkali (now Diamond Shamrock) sample taken in 1965. (Diamond Shamrock no longer makes 2,4,-5-T. Various estimates of that sample place one contaminant, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, at from 16 to 27 p.p.m.) And Agriculture witnesses, testifying before the Hart Commerce Subcommittee, early this month judged the evidence insufficient to recommend any new restrictions (C&EN, April 13, page 21).

But further research by the National Institute of Environmental Health Sciences (NIEHS) overturned the Agriculture position. The data were analyzed April 11 and 12, presented to HEW, federal regulatory officials, and Cabinet members on April 13, and disclosed by Surgeon General Jesse Steinfeld on April 15 to the Hart subcommittee. The joint Agriculture-Interior-HEW announcement for taking the action states that "2,4,5,-T, as well as its contaminant dioxines, may produce abnormal development in unborn animals. Nearly pure 2,4,5-T was reported to cause birth defects when injected at high doses into . . . pregnant mice, but not in rats. No data on humans are available."

A summary of NIEHS data indicates that the 2,4,5-T, comparable to that available commercially from Dow, Monsanto, and Hercules, was administered subcutaneously in dimethyl sulfoxide solution to three strains of mice—random bred Charles River, C57B1/6, and DBA/2. Charles River rats received an orally administered sucrose suspension of 2,4,5-T. Dioxin was also administered to both mice and rats.

Under questioning by the subcommittee, Dr. Steinfeld professed his "surprise" at the research results and said that HEW judged that an "imminent hazard" existed and that the suspension action was taken to protect women of child-bearing age. But he stressed that HEW was "not aware of any reliable evidence that 2,4,5-T, indeed any of the pesticidal chemicals, has resulted in human birth abnormalities."

Further scientific evidence against 2,4,5-T was presented by Dr. M. Jacqueline Verrett of the Food and Drug Administration. She testified that

C&EN: Tom Feare

Dow's Julius Johnson
Not an imminent hazard

chick embryo studies and preliminary hamster data indicate that current production 2,4,5-T with 0.5 p.p.m. of the tetradioxin "is teratogenic and embryotoxic." Surgeon General Steinfeld, however, expressed concern over the tests' "degree of reliance" and said that "they do not clarify the uncertainties as to the significance for man."

Climate of pressure. Confronted with the Government's ban, Dr. Julius E. Johnson, Dow vice president and director of research, told Sen. Hart that he could not agree with the decision "as far as [2,4,5-T] is an imminent hazard" but that he would have to agree "in the climate of pressure today." Dr. Johnson argued that:

- Low mammalian toxicity of 2,4,-

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5-T and absence of reports of increased incidence of birth defects in cattle or sheep grazing rangelands sprayed with 2,4,5-T make it "difficult to believe that any practical hazard existed" from registered uses.

• Tests with Sprague-Dawley rats administered both regular production-grade 2,4,5-T and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, at dosages bracketing those given in the Bionetics study, did not cause birth defects in the case of 2,4,5-T, but did indicate a high level of maternal and fetal toxicity from the dioxin. Dr. Ian Mitchell of the National Cancer Institute told Dow that the rat tests, according to Dr. Johnson, would be superior to tests with mice.

• Production of 2,4,5-T under specifications requiring less than 1 p.p.m. of the tetradioxin "presents no practical hazard when used in accordance with good agricultural practices.

• "If a 130-pound (60 kg.) person

C&EN: Tom Feare

Sen. Philip A. Hart
Safe or unsafe?

eats 3.3 pounds (1.5 kg.) of food daily and all of this food contains 0.2 p.p.m. 2,4,5-T (a proposed negligible residue tolerance), the total amount of 2,4,5-T ingested per day would be 300 micrograms. If the 2,4,5-T contained 1 p.p.m. of the tetradioxin, the food would contain 300 picograms. If a person ingested this amount of dioxin each day for 100 years, the total amount ingested would be only 11 micrograms . . . which represents a 6000-fold safety factor over the amount required to cause embryonic effects in rats. (By contrast, FDA monitored 5300 food samples for 2,4,-5-T, found 25 samples with trace residues, and only two with 0.19 and 0.29 p.p.m. 2,4,5-T.")

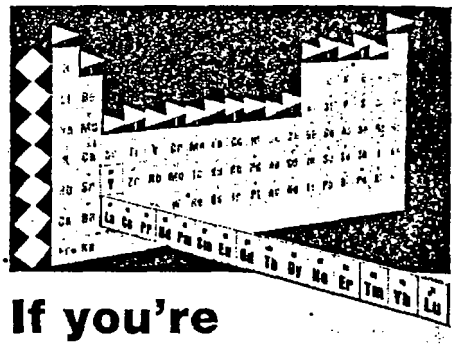
Support for the NIEHS and FDA studies came from Dr. Samuel S. Epstein, cochairman of the teratogenicity panel of HEW's Commission on Pesticides. Dr. Epstein testified that these studies "clearly confirm" 2,4,5-T's teratogenicity.

Although Dr. Epstein says that the teratogenic data on 2,4-D is "far less conclusive" than that for 2,4,5-T, he suggested, under questioning, that there is a "strong presumption" for suspending phenoxy herbicides "under any circumstances in the environment." He raises questions about restricting captan, carbaryl, organomercury compounds, and PCNB (pentachloronitrobenzene). And he concludes that there is an "urgent need" for restricting human exposure to dioxins—particularly in light of the lack of toxicology data—and that similar restrictions should extend to polychlorophenols, polychlorophenolic-containing compounds, and their combustion products.

Scientific challenge. What effect the 2,4,5-T hearings will have on other pesticides isn't immediately clear. But Dr. Steinfeld promises that HEW will, "in the very near future," set up a clearinghouse for information on all types of pesticides. On the related question of exchanging scientific information, Dow's Johnson strongly urges that research results be subject to open discussion and scientific challenge. The Bionetics results were leaked to the press and to Capitol Hill, but chemical company officials as well as members of the Mrak Commission (Secretary's Commission on Pesticides and Their Relationship to Environmental Health) had difficulty in obtaining the results.

Dr. Lee A. Dubridge, President Nixon's science adviser, in a statement submitted for the record, indicated that more federal funds might have to be spent on the "background research relating to health and other effects of environmental agents, including pesticides." He also pointed out that the Administration is considering a series of proposed amendments to federal laws regulating pesticides. One, not alluded to by Dr. DuBridge, would require Agriculture to inspect plants making pesticides. This is currently blocked, however, by the Bureau of the Budget. Another may involve what Dr. DuBridge called the lack of a mechanism for Government to "exercise prudent and unequivocally effective restraint temporarily on new, unexpected information and while awaiting more definitive results."

Meanwhile, an industry spokesman tells C&EN, "Everyone is looking at their costs and companies are either cutting back or combining their research efforts."



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Survey of Polychlorodibenzo-*p*-dioxin Content in Selected Pesticides

Edwin A. Woolson,* Ronald F. Thomas,[1] and Peter D. J. Ensor

One-hundred-twenty-nine samples of 17 different pesticides derived from chlorophenols were examined for polychlorinated dibenzo-*p*-dioxins by electron capture gas chromatography (ec-gc). The method of cleanup involved a concentrated sulfuric acid extraction of impurities from hexane and a mild nitration of the chlorophenol extracts. Seventy-six percent of the samples analyzed contained less than 0.1 μg/g of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in the technical material, whereas 7% contained between 0.1 to 1.0 μg/g, and 9% contained greater than 10 μg/g TCDD. No TCDD was detected in the 20 tri-, tetra-, or pentachlorophenol samples examined. However, high levels of other dioxins were found. All samples which contained more than 1.0 μg/g of dioxin by ec-gc were confirmed by gas chromatography using a flame ionization detector (fid-gc), a microcoulometric detector (mc-gc), *p* values, uv irradiation, and/or gas chromatography/mass spectrometry (gc-ms). Samples of phenoxy herbicides from current production contained less than 0.5 μg/g TCDD.

Polychlorodibenzo-*p*-dioxins may be contaminants in chlorophenols or in pesticides which use chlorophenols in the manufacturing process. Chlorinated dibenzo-*p*-dioxins are hazardous materials and may cause skin eruptions, teratogenesis, and are toxic to animals at low levels. The dioxins are formed usually when the reaction temperature for making *o*-chlorophenol by hydrolysis exceeds 160°C under pressure. The reaction may be an alkaline hydrolysis of polychlorobenzene or a chlorination of phenol to form a polychlorophenol.

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD, Figure 1) is the dioxin that may be formed when the reaction temperature for making 2,4,5-trichlorophenol from tetrachlorobenzene exceeds 160°C (Schultz, 1968). In chlorinating phenol to make tetra- or pentachlorophenol, heat must be supplied to the reaction mixture in order to maintain the mix as a melt. If too much heat is supplied, hexa-, hepta-, and/or octachlorodibenzo-*p*-dioxins may be formed. Since little or no heat is required to form di- and trichlorophenols by chlorination, there is little likelihood that di-, tri-, or tetrachlorodibenzo-*p*-dioxins will be formed in this process.

Interest in dioxins originated in 1957 from outbreaks of "chick edema (CE) disease." The disease was characterized by hydroparicardium in chickens. In 1958 a toxic substance, isolated from an unsaponifiable fraction of feed fats which caused CE, was identified (Cantrell *et al.*, 1969) by single crystal X-ray crystallography as 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin (HCDD). In 1970, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) was implicated as a potential teratogen in pregnant rats (Courtney *et al.*, 1970). Later tests indicated that the teratogenesis may have been caused by 27 ± 8 ppm of TCDD present as contaminant in the 2,4,5-T.

In order to assess possible environmental contamination with TCDD or higher chlorinated dioxins through pesticidal materials, samples of 17 pesticides based on use of chlorophenols in their manufacturing process were collected from U.S. Department of Agriculture's former Pesticide Regulation Division (PRD) laboratories.* Additionally, samples of 2,4,5-T from one manufacturer, covering a 3-year period, were collected. A method was developed for the analysis of dioxins in the 17 different pesticides. The method developed and results of the survey are reported in this paper.

PROCEDURE

Materials. No attempt should be made to analyze for dioxins without proper safety procedures. The following solvents were distilled in glass or were of pesticide grade quality: hexane, methanol, petroleum ether, acetonitrile, benzene, and diethyl ether.

The following apparatuses were required: chromatography columns (450 mm × 19 mm i.d.) with Teflon stopcock, gas chromatograph (gc), preferably equipped with a Ni^{63} detector (flame ionization or microcoulometric detectors also desirable for confirmation steps), glass gc columns (1.83-m × 4-mm), a sun lamp with maximum output at 310 nm, and thin-layer chromatography (tlc) apparatus.

The following compounds were examined for polychlorodibenzo-*p*-dioxins: (2,4-dichlorophenoxy)acetic acid, 2,4-D; 4-(2,4-dichlorophenoxy)butyric acid, 2,4-DB; 2-(2,4-dichlorophenoxy)propionic acid, 2,4-DP; (2,4,5-trichlorophenoxy)acetic, 2,4,5-T; 2-(2,4,5-trichlorophenoxy)propionic acid, silvex; 2-(2,4-dichlorophenoxy)ethyl sodium sulfate, sesone; 3,6-dichloro-*o*-anisic acid, dicamba; pentachlorophenol, PCP; tetrachlorophenol; trichlorophenol; 2,4-dichlorophenyl *p*-nitrophenyl ether, nitrofen; *O*-(2,4-dichlorophenyl) *O*-methyl isopropylphosphoramidothioate, DMPA; 2-(2,4,5-trichlorophenoxy)ethyl 2,2-dichloropropionate, erbon; tris[2-(2,4-dichlorophenoxy)ethyl]phosphite, 2,4-DEP; *O,O*-dimethyl *O*-2,4,5-trichlorophenyl phosphorothionate, ronnel; 2,4,5,4′-tetrachlorodiphenyl sulfone, tetradifon; and *O*-2,4-dichlorophenyl *O,O*-diethyl phosphorothioate, VC-13, Nemacide.

The cleanup procedure consisted of three steps which were dependent on the nature of impurities found in and the complexity of the sample.

Step A. Technical Salts and Acids of Phenoxy Acids. One-hundred milliliters of MeOH was added to 3.00 g of herbicide and 10 ml of 5 *N* KOH contained in a 1000-ml separatory funnel. Two-hundred milliliters of H_2O and 100 ml of hexane were added after 20 min and shaken. The aqueous phase was reextracted with 100 ml of hexane and the extracts were combined. The hexane extracts were washed twice with 100 ml of 1 *N* NaOH, twice with 1 *N* HCl, and twice with 100 ml of H_2O. The extracts were dried over anhydrous Na_2SO_4, transferred to a 250-ml beaker, and evaporated to *ca.* 10 ml. The sample was transferred to a pre-

Plant Science Research Division, Agriculture Research Service, U.S. Department of Agriculture, Beltsville, Maryland 20705.

[1] Present address: Pesticide Regulation Divison, Environmental Protection Agency, Beltsville, Maryland 20705.

Table I. Relative Retention Times of Several Chlorinated Hydrocarbon Insecticides and Polychlorodibenzo-*p*-dioxins on Five Gas Chromatography Columns[a]

	Relative retention times[b] on columns				
	5% OV-225	1.5% OV-17 + 2.0% QF-1 (1:1)	5% OV-17	5% UCW-98	15% QF-1 + 10% DC-200 (1:1)
Aldrin	1.00 (2.17)[c]	1.00 (1.80)	1.00 (0.91)	1.00 (1.26)	1.00 (4.2)
p,p'-DDE	2.63	2.50	1.98	1.67	1.90
p,p'-TDE	5.84	3.62	3.19	2.14	2.64
p,p'-DDT	5.62	4.17	*d*	2.70	3.14
Endrin	3.69	2.78	3.08	1.90	2.64
Endrin, Δ keto	15.76	6.89	8.57	3.25	5.48
2,7-CDD[e]	1.29	1.00	1.21	0.83	1.02
2,3,7-CDD	1.94	1.67	2.09	1.51	1.64
tri-CDD	2.30	1.83	7.10	1.57	1.83
tetra-CDD[f]	2.86	2.50	2.31	2.22	2.38
tetra-CDD[f]	3.27	2.52	2.33	2.24	2.52
2,3,7,8-CDD	4.33	3.44	3.41	2.86	3.19
penta-CDD	8.29	6.56		5.08	5.48
hexa-CDD (1)	11.61	9.28	7.18	7.06	7.26
hexa-CDD (2)	13.13	10.56	8.24	7.94	8.09
hexa-CDD (3)	16.45	12.44	11.10	9.97	9.45
hepta-CDD (1)	23.32	18.39	13.19	13.09	13.26
hepta-CDD (1)	26.96	21.17	15.82	14.68	14.83
octa-CDD	46.31	36.28	23.41	24.52	24.05

[a] Column conditions: length, 1.8-m × 4-mm glass; solid support, Chromosorb W, 80–100 mesh; injector, 240°C; column, 220°C; detector, Ni^{63}, 310°C; flow rate, 80–100 ml/min. [b] ±1%. [c] Time in minutes in parentheses. [d] Not resolved from TDE. [e] Chlorodibenzo-*p*-dioxin = CDD. [f] More than one isomer was present in the tri-, tetra-, hexa-, and heptachlorodibenzo-*p*-dioxins. Known isomers have the positions numbered.

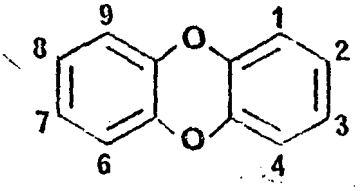

Figure 1. Structure of dibenzo-*p*-dioxin. Chlorines may be attached at the 1,2,3,4,6,7,8, and/or 9 positions to yield chlorodibenzo-*p*-dioxins

washed (petroleum ether) 15-g Al_2O_3 column (450 × 19 mm i.d.) and eluted with 100 ml of petroleum ether followed by 50 ml of 5% (v/v) diethyl ether in petroleum ether, which were discarded. One-hundred milliliters of 50% (v/v) diethyl ether in petroleum ether was collected, evaporated just to dryness, and adjusted to volume with hexane. The amount of each dioxin present was determined.

Step B. Low Organic Matter Soils, Phenol-Based Insecticides, Oil, and Ester Formulations of Phenoxy Herbicides. The following steps were performed prior to the Al_2O_3 column in Step A. The extract was shaken with concentrated H_2SO_4 until the acid was clear (not yellow or cloudy after standing *ca.* 10 min), washed with H_2O, and passed through a $NaHCO_3$–Na_2SO_4 column (1 cm of each layered in a 19 mm i.d. column). The eluant was evaporated to *ca.* 10 ml and continued with the Al_2O_3 column in Step A.

Step C. Chlorophenols, High Organic Matter Soils, and Other Samples Difficult to Clean Up. After completing parts A and B of the cleanup procedure, the eluant from the Al_2O_3 column was evaporated just to dryness, cooled to *ca.* 0°C on an ice bath, and 10 ml of 1:1 (v/v) HNO_3:H_2SO_4 mixture was added. The mix was gradually warmed to room temperature and added to 50 ml of ice water in a separatory funnel after 15 min. The beaker was rinsed with 5 × 10 ml of hexane. The combined hexane rinses were shaken for 1 min, washed with H_2O, and the hexane was drained through a $NaHCO_3$–Na_2SO_4 column. The volume was adjusted for analysis.

Quantitation was made on a 5% OV-225 column using electron-capture gas chromatography (ec-gc). Analysis was made with temperature programming from 220 to 260°C at 4°C/min and a 16-min hold at the final temperature.

Confirmation Techniques for Dioxins. If a positive response was found by ec-gc, the *p* value was determined for the dioxin between hexane and acetonitrile on a portion of the extract. The *p* value equals final concentration in hexane/initial concentration in hexane (Beroza and Bowman, 1965). Another portion of the extract was irradiated for 16 hr under a sun lamp (maximum output, 310 nm) at a distance of 30 cm since TCDD and the lower dioxins are destroyed under these conditions.

The remainder of the extract was condensed for confirmation on different gc columns using different detectors. The columns preferred were 1:1 (w/w) mix of 1.5% OV-17 plus 2.0% QF-1 and 5% UCW-98, both on Chromosorb W, 80–100 mesh. Flame ionization and microcoulometric detection were with these detectors. The ultimate confirmation was provided by a Perkin-Elmer Model 270 gc-mass spectrometer (gc–ms). There was very little fragmentation since the parent peak (*m/e* 322) was the parent ion and *m/e* 257 and 194 were the only fragments over 20% in relative abundance for the tetradioxin.

Two-dimensional tlc was used for cleanup and partial confirmation occasionally. The plate was developed first in acetonitrile followed by benzene. The spots were visualized under a uv lamp and were scraped off, extracted, and assayed by gc if desired. Infrared spectrometry was also used to confirm the identity of various chlorodioxins.

RESULTS AND DISCUSSION

Relative retention times of 13 dioxin isomers and a few selected chlorinated hydrocarbon insecticides are presented in Table I. The values were determined isothermally at

220°C. Because of the large value (rt_r = 46.31) for the octa-CDD, the 5% OV-225 column was normally used with temperature programming from 230 to 260°C at a rate of 4°C/min and a final temperature hold. Under these conditions, analysis was completed in about 40 min. The use of the three recommended columns (5% OV-225, 1.5% OV-17 plus 2% QF-1, and 5% UCW-98) prevented confusion of some chlorinated hydrocarbon insecticides in environmental samples with dioxins because relative retention times were sufficiently different.

p Values for dioxins are presented in Table II. Values for four specific isomers (2,7-, 2,3,7-, 2,3,7,8-, and 1,2,3,4,6,7,8,9-chlorodibenzo-*p*-dioxins) are given. Other values are for mixtures of isomers and were determined using total peak area or peak height. R_f values for all dioxin isomers by tlc in acetonitrile were 0.82 ± 0.08 and in benzene were 0.80 ± 0.02. The di-, tri-, tetra-, and hexadioxin were not separated from each other under our test conditions, but were separated from most interfering impurities in formulations. Care must be taken not to overload the spots or the material appears to stay on the origin. This behavior is presumably due to the low solubility of dioxins in most solvents.

In a further confirmatory step, dioxins were destroyed by uv light. The lower isomers (<4 Cl) were completely destroyed in 16 hr by irradiation (Crosby *et al.*, 1971) at concentrations less than 0.2 ppm in hexane. Nondestruction of the suspected di-, tri-, or tetrachlorodioxin is sufficient evidence that the peak is not a chlorodioxin. The higher the degree of chlorination, the more resistant the dioxins were to irradiation. Only 20% of the octa-CDD was destroyed in 16 hr at concentrations of about 0.3 ppm.

A total of 129 pesticide samples were analyzed for dioxins. Table III presents the occurrence and content of the dioxins in all samples. TCDD (tetra-) was found primarily in 2,4,5-T samples. Only one sample of silvex contained more than 0.5 ppm of TCDD. Detectable amounts of hexa-CDD were found in four 2,4,5-T samples, one 2,4-D, and two other samples other than the chlorophenols. Hepta- and octa-CDD also occurred in four other samples apiece in addition to their presence in chlorophenols. Most samples were made before 1970 and may not represent current production materials.

The TCDD concentration in selected pesticides is also presented in Table III. Twenty-two of 42 2,4,5-T samples collected contained less than 0.5 ppm of TCDD. Of the 20 samples containing more than 0.5 ppm of TCDD, 15 were obtained for the yearly survey of one manufacturer. The samples were from 1966-1970, with four samples usually collected each year. There was a tenfold drop in TCDD content by this manufacturer between 1968 and 1969. However, their technical 2,4,5-T still contained 2–3 ppm of TCDD in 1970. Four of the five remaining samples containing over 0.5 ppm of TCDD also came from this same manufacturer and were received from the PRD laboratories. Recent (1970) samples from another manufacturer contained <0.5 ppm of TCDD. No other samples tested had over 0.5 ppm of TCDD. Any sample could contain one or more different chlorodioxins.

The higher polychlorodibenzo-*p*-dioxin content of the same selected pesticides is also presented in Table III. Four samples of 2,4,5-T contained greater than 0.5 ppm of the hexa isomers. No higher dioxins were found in silvex or dicamba.

Table II. *p* Values for Chlorodibenzo-*p*-dioxins in a 1:1 (v/v) Acetonitrile:Hexane Solvent System[a]

Isomer	*p* Value	std dev
2,7-CDD	0.76	±0.03
2,3,7-CDD	0.86	±0.03
2,3,7,8-CDD	0.51	±0.06
hexa-CDD	0.94	±0.03
hepta-CDD	0.90	±0.05
octa-CDD	0.90	±0.05

[a] Ratio of peak height in hexane solution before equilibration with hexane-saturated acetonitrile to peak height in hexane after equilibration.

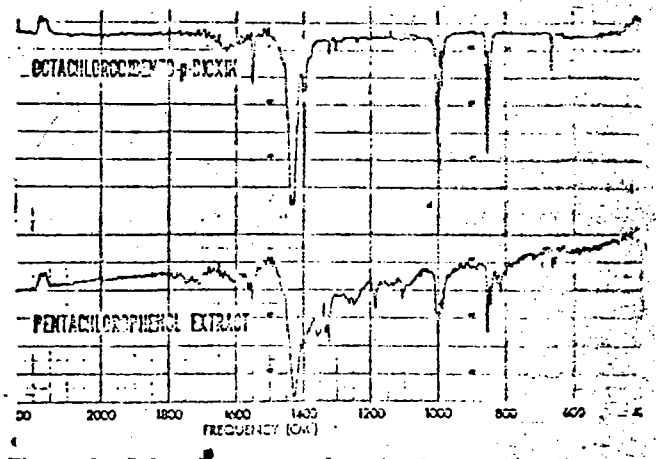

Figure 2. Infrared spectra of authentic octachlorodibenzo-*p*-dioxin and a cleaned-up pentachlorophenol extract. The material was incorporated in KBr and the spectra made on a Perkin-Elmer 625 infrared spectrometer

Table III. Number and Content of Polychlorodibenzo-*p*-dioxins in Selected Pesticides

Pesticide	ppm of chlorodibenzo-*p*-dioxin: tetra <10	tetra <100	hexa <10	hexa <100	hexa <1000	hepta <10	hepta <100	hepta <1000	octa <10	octa <100	octa <1000	No. of samples contaminated	Total no. of samples tested
	Number found												
2,4,5-T	7[a]	13[a]	3	1	0	ND[b]	....	...	ND	...	...	23	42
Silvex	1	0	ND	...	...	ND	...	....	ND	...	...	1	7
2,4-D (-DB,-DP)	ND	...	1	0	0	ND	...	...	ND	...	...	1	28
Dicamba	ND	...	ND	...	...	ND	...	....	ND	...	...	0	8
Chlorophenol													
tri-	ND	...	4	0	0	1	0	0	2	0	0	4	6
tetra-	ND	...	1	1	0	1	2	0	1	2	0	3	3
penta-	ND	...	0	7	0	0	4	6	0	4	6	10	11
Others	ND	...	1	0	1	3	0	1	3	1	0	7	24

[a] Any sample may contain one or more different dioxins. [b] ND = <0.5 ppm of any one chlorodioxin.

6014

and only one sample of 2,4-D contained measurable amounts the hexa isomers. The hexa isomers present presumably were there because of tetrachlorophenol impurities which condensed with each other. Higher dioxins were found in some samples of several other pesticides, including erbon, tetradifon, ronnel, sesone, and DMPA.

The dioxin content of the 20 chlorophenol samples is also presented in Table III. No TCDD was detected in any sample at levels above 0.5 ppm. However, the higher dioxins were plentiful. Trichlorophenol contained only small amounts of hexachlorodibenzo-*p*-dioxin and no sample contained over 10 ppm. Tetrachlorophenol contained less than 100 ppm of hexa-, hepta-, and octachlorodibenzo-*p*-dioxins, while six of 20 pentachlorophenol samples contained over 100 ppm of the hepta- and octachlorodibenzo-*p*-dioxin isomers. An infrared spectrum of a pentachlorophenol extract is presented in Figure 2. It is quite obvious that the extract contains octachlorodibenzo-*p*-dioxin when the spectrum is compared to the standard octachlorodibenzo-*p*-dioxin spectrum. Analysis by ec-gc indicated both hepta- and octachlorodioxins were present in the sample. This may account for the peak broadening. The reason for the high amounts of dioxin in chlorophenol is probably due to heat treatment during synthesis. As chlorination of phenol proceeds past the dichlorophenol stage, heat must be supplied in order to keep the reaction mixture in a melt condition. Since heat is being supplied in the presence of chlorophenols, the formation of higher chlorinated dibenzo-*p*-dioxins might be expected. The rate and time of melt heating probably governs the formation and amounts of the various dioxin isomers. If the chlorination temperature is raised too high too quickly, the lower chlorinated dioxins may be formed since the lower chlorophenols would be present and available for reaction with each other. If the temperature is raised too high after nearly all chlorophenol is in the penta form, octachlorodibenzo-*p*-dioxin would be the predominant impurity formed.

In conclusion, TCDD has been present at levels above 0.5 ppm in the past, but was less than 0.5 ppm in the current production samples examined. Higher chlorodioxins are present predominantly in chlorophenols with the highest amounts present in pentachlorophenol. Thirty-eight percent of all samples examined contained at least one chlorodioxin, with many containing more than one.

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The Insecticidal and the Anticholinesterase Activity of *meta*-Acylamidophenyl and *meta*-Thioureidophenyl *N*-Methylcarbamates

R. M. Sacher* and J. F. Olin

Fifty-nine new *N*-methyl and *N,N*-dimethylcarbamates were synthesized and tested as insecticides and as inhibitors of fly and bovine cholinesterases. In spite of the high anticholinesterase activity exhibited by many of these compounds, only few chemicals have shown insecticidal activity. Furthermore, these compounds could not be synergized effectively by 2,3-methylenedioxynaphthalene. Structure-activity correlation revealed that maximal anticholinesterase activity is associated with a definite size of the alkyl substituent on the amide or the thiourea grouping. In all series tested, alkyl substituent with four to six carbon atoms produced the most potent cholinesterase inhibitors.

The insecticidal properties of *N*-methyl and *N,N*-dimethylcarbamic esters of various alcohols and phenols have been demonstrated by several investigators (Gysin, 1954; Kolbezen *et al.*, 1954). A systematic evaluation of the structure-activity correlation of various aromatic carbamates was published in a series of papers by Metcalf, Fukuto, and coworkers (*e.g.*, Metcalf *et al.*, 1960, 1962; Metcalf and Fukuto, 1965). This paper presents a discussion of two new groups of insecticidal carbamates, the *meta*-acylamidophenyl and the *meta* thioureidophenyl *N*-methylcarbamates.

Agricultural Division, Monsanto Company, St. Louis,

MATERIALS AND METHODS

Chemicals. The *meta*-acylamidophenyl *N*-methylcarbamates were prepared according to Leuckart (1892) by heating the corresponding *meta*-hydroxyacylanilide with methyl isocyanate. Anhydrous alcohol-free ethyl acetate was substituted for toluene as solvent, and triethylamine was used as a catalyst.

The *meta*-thioureidophenyl *N*-methylcarbamates were prepared *via meta*-hydroxyphenyl isothiocyanate; the latter was synthesized by the procedure of Dyson and George (1924). It is noteworthy that this hydroxyphenyl isothiocyanate reacts exothermically with methyl isocyanate in the absence of a catalyst, a behavior which had not been previously noted

6015

TRANSVAAL, INC.

P. O. Box 69 / Marshall Road
Jacksonville, Arkansas 72076
Phone 501-982-2132

TECHNICAL 2,4-D ACID

DESCRIPTION:	Off-white to white, coarse, crystalline solid.
SOLUBILITY:	Relatively insoluble in water; soluble in alcohol and aromatic solvents.
BULK DENSITY:	52 lbs./cu. ft. packed
LOSS ON DRYING:	0.4% (w/w), maximum
DICHLOROPHENOL:	0.4% (w/w), maximum
SODIUM CHLORIDE:	0.5% (w/w), maximum
ACID EQUIVALENT:*	99% (w/w) - A.O.A.C., Tenth Edition
PACKAGING:	Bags; Fiber Drums (200 lbs. net.)

If requested, certified analysis supplied on materials shipped.

*Name:	2,4-Dichlorophenoxyacetic Acid (2,4-D)
Chemical Formula:	$Cl_2C_6H_3OCH_2COOH$
Formula Weight:	221.04
Acid Equivalent:	100% (w/w)

EPA Reg. No. 11687-29
Prod. Code No. AC

Spec. Sheet 11/72

6017

TRANSVAAL, INC.

P. O. Box 69 / Marshall Road
Jacksonville, Arkansas 72076
Phone 501-982-2132

TECHNICAL 2,4,5-T ACID

DESCRIPTION:	Off-white to tan, granular solid.
SOLUBILITY:	Insoluble in water; soluble in alcohol and aromatic solvents.
BULK DENSITY:	48 lbs./cu. ft. packed
LOSS ON DRYING:	0.4% (w/w), maximum
TRICHLOROPHENOL:	0.05% (w/w), maximum
SODIUM CHLORIDE:	1.0% (w/w), maximum
ACID EQUIVALENT:*	98% (w/w) - A.O.A.C., Tenth Edition
TCDD CONTENT:	Less than 0.50 ppm.
PACKAGING:	Bags; Fiber Drums (200 lbs. net.)

If requested, certified analysis supplied on materials shipped.

*Name:	2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T)
Chemical Formula:	$Cl_3C_6H_2OCH_2COOH$
Formula Weight:	255.49
Acid Equivalent:	100% (w/w)

EPA Reg. No. 11687-30
Prod. Code No. AD

Spec. Sheet 11/72

6018

TRANSVAAL, INC.

P. O. Box 69 / Marshall Road
Jacksonville, Arkansas 72076
Phone 501-982-2132

TECHNICAL 2,4,5-TP ACID

DESCRIPTION:	Off-white to tan, granular solid.
SOLUBILITY:	Insoluble in water; soluble in alcohol and aromatic solvents.
BULK DENSITY:	48 lbs./cu. ft. packed
LOSS ON DRYING:	0.4% (w/w), maximum
TRICHLOROPHENOL:	0.06% (w/w), maximum
SODIUM CHLORIDE:	1.0% (w/w), maximum
ACID EQUIVALENT:*	97% (w/w) - A.O.A.C., Tenth Edition
PACKAGING:	Bags; Fiber Drums (200 lbs. net.)

If requested, certified analysis supplied on materials shipped.

*Name:	2-(2,4,5-Trichlorophenoxy) Propionic Acid (2,4,5-TP)
Chemical Formula:	$Cl_3C_6H_2OCH(CH_3)COOH$
Formula Weight:	269.52
Acid Equivalent;	100% (w/w)

EPA Reg. No. 11687-38
Prod. Code No., AL

Spec. Sheet 11/72

TRANSVAAL, INC.

P. O. Box 69 / Marshall Road
Jacksonville, Arkansas 72076
Phone 501-982-2132

TECHNICAL BUTYL ESTER OF 2,4-D

DESCRIPTION:	Amber colored, oily liquid.
SOLUBILITY:	Insoluble in water; soluble in alcohol, aromatic and aliphatic solvents.
SPECIFIC GRAVITY:	1.24 at 20°C., Average
WEIGHT PER GALLON:	10.3 lbs. at 20°C., Average
ACTIVE INGREDIENT * CONTENT:	98.0% (w/w), Minimum
ACID EQUIVALENT:	78.2% (w/w), Minimum - A.O.A.C., Tenth Edition
PACKAGING:	1, 5, 30, and 55 gal. containers

If requested, certified analysis supplied on materials shipped.

*Name:	Butyl 2,4-Dichlorophenoxyacetate
Chemical Formula:	$Cl_2C_6H_3OCH_2COO(C_4H_9)$
Formula Weight:	277.15
Acid Equivalent:	79.76% (w/w) as 2,4-D

EPA Reg No. 11687-36
Prod. Code No. AJ

Spec. Sheet 11/72

A-1-a AMINE SALTS

6020

TRANSVAAL, INC.

P. O. Box 69 / Marshall Road
Jacksonville, Arkansas 72076
Phone 501-982-2132

TECHNICAL 2-ETHYLHEXYL ESTER OF 2,4-D

DESCRIPTION:	Straw to amber colored, oily liquid.
SOLUBILITY:	Insoluble in water; soluble in alcohol, aromatic and aliphatic solvents.
SPECIFIC GRAVITY:	1.155 at 20°C., Average
WEIGHT PER GALLON:	9.62 lbs. at 20°C., Average
ACTIVE INGREDIENT * CONTENT:	98.0% (w/w), Minimum
ACID EQUIVALENT:	65.0% (w/w), Minimum - A.O.A.C., Tenth Edition
PACKAGING:	1, 5, 30, and 55 gal. containers

If requested, certified analysis supplied on materials shipped.

*Name:	2-Ethylhexyl 2,4-Dichlorophenoxyacetate
Chemical Formula:	$Cl_2C_6H_3OCH_2COO(CH_2CH(C_2H_5)CH_2CH_2CH_2CH_3)$
Formula Weight:	333.27
Acid Equivalent:	66.32% (w/w) as 2,4-D

EPA Reg. No. 11687-32
Prod. Code No. AF

Spec. Sheet 11/72

TRANSVAAL, INC.

P. O. Box 69 / Marshall Road
Jacksonville, Arkansas 72076
Phone 501-982-2132

TECHNICAL BUTYL ESTER OF 2,4,5-T

DESCRIPTION:	Amber colored oily liquid.
SOLUBILITY:	Insoluble in water; soluble in alcohol, aromatic and aliphatic solvents.
SPECIFIC GRAVITY:	1.330 at 20°C., Average
WEIGHT PER GALLON:	11.08 lbs. at 20°C., Average
ACTIVE INGREDIENT* CONTENT:	96.0% (w/w), Minimum
ACID EQUIVALENT:	78.7% (w/w), Minimum - A.O.A.C,, Tenth Edition
PACKAGING:	1, 5, 30, and 55 gal. containers

If requested, certified analysis supplied on materials shipped.

*Name:	Butyl 2,4,5-Trichlorophenoxyacetate
Chemical Formula:	$Cl_3C_6H_2\ OCH_2COO(C_4H_9)$
Formula Weight:	311.6
Acid Equivalent:	82.0% (w/w) as 2,4,5-T

EPA Reg. No. 11687-31
Prod. Code No. AE

Spec. Sheet 11/72

TRANSVAAL, INC.

P. O. Box 69 / Marshall Road
Jacksonville, Arkansas 72076
Phone 501-982-2132

TECHNICAL 2-ETHYLHEXYL ESTER OF 2,4,5-T

DESCRIPTION:	Amber color, light to dark, oily liquid.
SOLUBILITY:	Insoluble in water; soluble in alcohol, aromatic and aliphatic solvents.
SPECIFIC GRAVITY:	1.210 at 20°C., Average
WEIGHT PER GALLON:	10.08 lbs. at 20°C., Average
ACTIVE INGREDIENT * CONTENT:	96.0% (w/w), Minimum
ACID EQUIVALENT:	66.7% (w/w), Minimum - A.O.A.C., Tenth Edition
PACKAGING:	1, 5, 30, and 55 gal. containers

If requested, certified analysis supplied on materials shipped.

*Name:	2-Ethylhexyl 2,4,5-Trichlorophenoxyacetate
Chemical Formula:	$Cl_3C_6H_2OCH_2COO(CH_2CH(C_2H_5)CH_2CH_2CH_2CH_3)$
Formula Weight:	367.71
Acid Equivalent:	69.48% (w/w) as 2,4,5-T

EPA Reg. No. 11687-33
Prod. Code No. AG

Spec. Sheet 11/72

6023

TRANSVAAL, INC.

P. O. Box 69 / Marshall Road
Jacksonville. Arkansas 72076
Phone 501-982-2132

TECHNICAL 2-ETHYLHEXYL ESTER OF 2,4,5-TP

DESCRIPTION:	Dark amber-colored oily liquid.
SOLUBILITY:	Insoluble in water; soluble in alcohol, aromatic and aliphatic solvents.
SPECIFIC GRAVITY:	1.196 at 20°C., Average
WEIGHT PER GALLON:	9.96 lbs. at 20°C., Average
ACTIVE INGREDIENT* CONTENT:	95.0% (w/w) Minimum
ACID EQUIVALENT:	67.1% (w/w) Minimum - A.O.A.C., Tenth Edition
PACKAGING:	1, 5, 30, and 55 gal. containers

If requested, certified analysis supplied on materials shipped.

*Name:	2-Ethylhexyl 2(2,4,5-Trichlorophenoxy)propionate
Chemical Formula:	$Cl_3C_6H_2OCH_2(CH_3)COO[CH_2CH(C_2H_5)CH_2CH_2CH_2CH_3]$
Formula Weight:	381.74
Acid Equivalent:	70.6% (w/w) as 2,4,5-TP

EPA Reg. No. 11687-34
Prod. Code No. [illegible]H

Spec. Sheet 11/72

6024

CONFIDENTIAL - SUBJECT TO INJUNCTION
D.C., ... MI. 4-4-73; DOW/EPA AGREEMENT, -79

TO: M. Long

This must not be sent out until we have a clearer image of EPA policy in regard to handling the residue tolerance petitions. If pressure vegetables were "safe" as Bill Upholt indicated in his report on June 24, then EPA should give us the proposed tolerances with no more data than the ±5 in your list.

I asked John Ritch for the "policy" on July 2. Let's not stir up the preparation for a "hearing" and new Tolerance petitions in mind of Dow people at this time.

FROM: DDMc

EXHIBIT Long 10/26/77

NO ENVELOPE REQUIRED — DO NOT FOLD — DROP IN DOW MAIL
STOCK FORM C-3030 PRINTED 6-0-71 — USE REVERSE SIDE FOR REPLY

CON-O-GRAM — WRITE-DO NOT TYPE — DOW — DATE 7/8/74

TO: D. D. McCollister

As requested I will hold this letter. However I believe we are dividing ourselves if we think the problem will go away. Regarding the Corps of Engineers petition for sites, I answered a question about TCDD existence in fish after canning. As we are not obligated to submit any information pertinent to residues and tolerances. Such as are our not informing the government about TCDD in 2,4,5-T is what got us in all this trouble in the first place. Withholding information at this time (which they have not found) can only create ill will. We will not still happy to have

FROM: [illegible]

NO ENVELOPE REQUIRED — DO NOT FOLD — DROP IN DOW MAIL
STOCK FORM C-3030 PRINTED 6-0-71 — USE REVERSE SIDE FOR REPLY

PLAINTIFF'S EXHIBIT 25

6026

TRAN VAAL, INC.

P. O. Box 69 Marshall Road
Jacksonville, Arkansas 72076
Phone 501 982-2132

TECHNICAL 2-ETHYLHEXYL ESTER OF 2,4,5-TP

DESCRIPTION:	Dark amber-colored oily liquid
SOLUBILITY:	Insoluble in water; soluble in alcohol, aromatic and aliphatic solvents.
SPECIFIC GRAVITY:	1.190 at 20° C., Average
WEIGHT PER GALLON:	9.91 lbs. at 20° C., Average
ACTIVE INGREDIENT* CONTENT:	95.0% (w/w) Minimum
ACID EQUIVALENT:	67.1% (w/w) Minimum - A.O.A.C., 12th Edition
TRICHLOROPHENOL:	0.5%, Maximum
WATER:	0.2%, Maximum
FREE HERBICIDE ACID:	2.0%, Maximum
TCDD CONTENT: (2,3,7,8-Tetrachloro-dibenzoparadioxin)	< 0.1 ppm.
PACKAGING:	1, 5, 30, and 55 gallon containers and bulk

If requested, certified analysis supplied on materials shipped.

*Name: 2-Ethylhexyl 2(2,4,5-Trichlorophenoxy)propionate
Chemical Formula: $Cl_3C_6H_2OCH_2(CH_3)COO[CH_2CH(C_2H_5)CH_2CH_2CH_2CH_3]$
Formula Weight: 381.74
Acid Equivalent: 70.6% (w/w) as 2,4,5-TP

EPA Reg. No. 11687-34
Prod. Code No.: AH

11/76

6028

TECHNICAL ISOOCTYL ESTER OF 2,4,5-T

DESCRIPTION:	Amber color, light to dark, oily liquid.
SOLUBILITY:	Insoluble in water; soluble in alcohol, aromatic and aliphatic solvents.
SPECIFIC GRAVITY:	1.222 at 20° C., Average
WEIGHT PER GALLON:	10.18 lbs. at 20° C., Average
ACTIVE INGREDIENT* CONTENT:	96.0% (w/w), Minimum
ACID EQUIVALENT:	66.7% (w/w), Minimum - A.O.A.C., 12th Edition, 1975
TRICHLOROPHENOL:	0.4% maximum
WATER:	0.2% maximum
FREE HERBICIDE ACID:	2.0% maximum
TCDD CONTENT:	Less than 0.1 ppm.
PACKAGING:	1, 5, 30, and 55 gallon containers and bulk

If requested, certified analysis supplied on materials shipped.

*Name:	Isooctyl 2,4,5-Trichlorophenoxyacetate
Chemical Formula:	$Cl_3C_6H_2OCH_2COO(C_8H_{17})$
Formula Weight:	367.71
Acid Equivalent:	69.48% (w/w) as 2,4,5-T

EPA Reg. No. 11687-33
Prod. Code No. AG

Spec. Sheet 9/76

6029

WEED-RHAP A-6-MCPA

DESCRIPTION:	Amber-colored liquid with slight ammoniacal odor.
SOLUBILITY:	Forms stable solutions in 1710 ppm hard water.
SPECIFIC GRAVITY:	1.172 at 20° C., Average
WEIGHT PER GALLON:	9.76 pounds at 20° C., Average
ACTIVE INGREDIENT* CONTENT:	75.0% (w/w) Dimethylamine Salt of 2-Methyl-4-Chlorophenoxyacetic Acid
ACID EQUIVALENT:	61.2% (w/w) or 6 pounds per gallon - A.O.A.C., 11th Edition
PACKAGING:	1, 5, 30, and 55 gallon containers and bulk

If requested, certified analysis supplied on materials shipped.

*Name:	Dimethylamine Salt of 2-Methyl-4-Chlorophenoxyacetic Acid
Chemical Formula:	$CH_3ClC_6H_3OCH_2COOH \cdot HN(CH_3)_2$
Formula Weight:	245.7
Acid Equivalent:	81.65% (w/w) as MCPA

EPA Reg. No. 11687-52
Prod. Code No. AZ

Spec. Sheet 6/76

6030

TRANSVAAL, INC.

P. O. Box 69 / Marshall Road
Jacksonville, Arkansas 72076
Phone 501 982-2132

TECHNICAL 2,4,5-T ACID

DESCRIPTION:	Off-white to tan, granular solid.
SOLUBILITY:	Insoluble in water; soluble in alcohol and aromatic solvents.
BULK DENSITY:	48 lbs./cu. ft. packed
LOSS ON DRYING:	0.4% (w/w), maximum
TRICHLOROPHENOL:	0.5% maximum
SODIUM CHLORIDE:	0.5% (w/w), maximum
ACID EQUIVALENT:*	98% (w/w), - A.O.A.C., 12th Edition, 1975
TCDD CONTENT:	Less than 0.1 ppm.
PACKAGING:	Bags; Fiber Drums (200 lbs. net)

If requested, certified analysis supplied on materials shipped.

*Name:	2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T)
Chemical Formula:	$Cl_3C_6H_2OCH_2COOH$
Formula Weight:	255.49
Acid Equivalent:	100% (w/w)

EPA Reg. No. 11687-30
Prod. Code No. AD

Spec. Sheet 9/76

6031

TRANSCHEM, INC.

TECHNICAL BUTYL ESTER OF 2,4,5-T

DESCRIPTION:	Amber colored oily liquid.
SOLUBILITY:	Insoluble in water; soluble in alcohol, aromatic and aliphatic solvents.
SPECIFIC GRAVITY:	1.330 at 20° C., Average
WEIGHT PER GALLON:	11.08 lbs. at 20° C., Average
ACTIVE INGREDIENT* CONTENT:	96.0% (w/w), Minimum
ACID EQUIVALENT:	78.7% (w/w), Minimum - A.O.A.C., 12th Edition
PHENOL:	0.5%, Maximum
WATER:	0.2%, Maximum
FREE ACID:	2.0%, Maximum
PACKAGING:	1, 5, 30, and 55 gallon containers and bulk

If requested, certified analysis supplied on materials shipped.

*Name:	Butyl 2,4,5-Trichlorophenoxyacetate
Chemical Formula:	$Cl_3C_6H_2\ OCH_2COO\ (C_4H_9)$
Formula Weight:	311.6
Acid Equivalent:	82.0% (w/w) as 2,4,5-T

EPA Reg. No. 11687-31
Product Code, No. AE

Spec. Sheet 10/76

6032

Meet

Marion Moses 1979

2,4,5-T, Agent Oran
Tetrachlorodibenzo-p-d...

Evolution of the problem

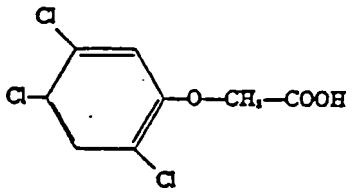
Marion Moses, M.D.
Presentation - Recent Advances in Occupational Medicine,
Environmental Sciences Laboratory,
Mount Sinai School of Medicine of The City University of New York
October 15, 1979.

ENVIRONMENTAL SCIENCES LABORATORY
MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

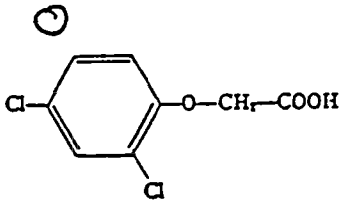
Use of 2,4,5-T in the
United States in 1974

Purpose	Pounds Used
Maintenance of right of way	3,960,000
Rangeland	1,980,000
Rice	220,000
Forestry	48,400
Other	990,000

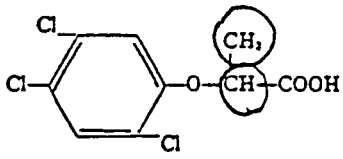
2,4,5-T
(2,4,5-trichlorophenoxy)acetic acid



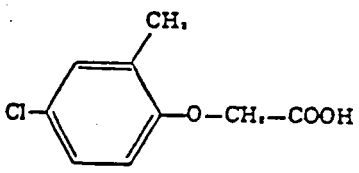
2,4-D
(2,4-dichlorophenoxy)acetic acid



SILVEX
2-(2,4,5-trichlorophenoxy)propionic acid

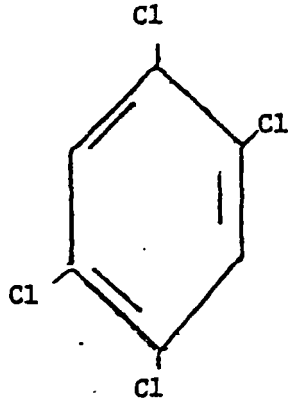


MCPA
[(4-chloro-*o*-tolyl)oxy]acetic acid
(2-methyl-4-chlorophenoxyacetic acid)



Possible Number of Isomers - Polychlorinated Dibenzodioxins

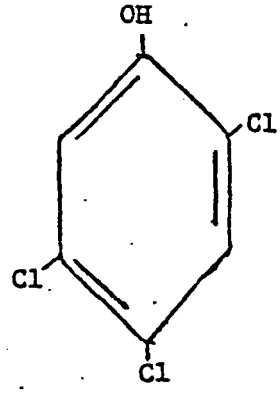
Chlorine Atoms	Number of Isomers
1	2
2	10
3	14
4	22
5	14
6	10
7	2
8	1



1,2,4,5-tetrachlorobenzene

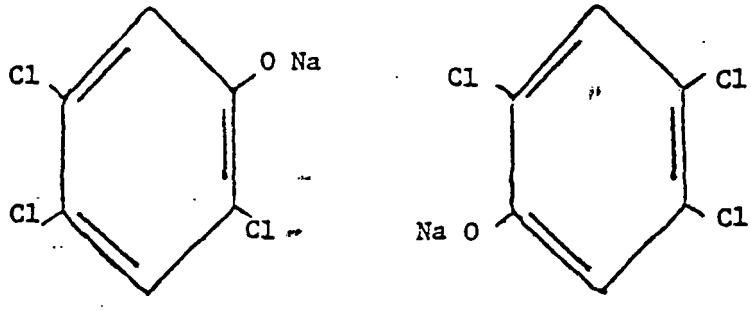
NaOH

CH_3OH



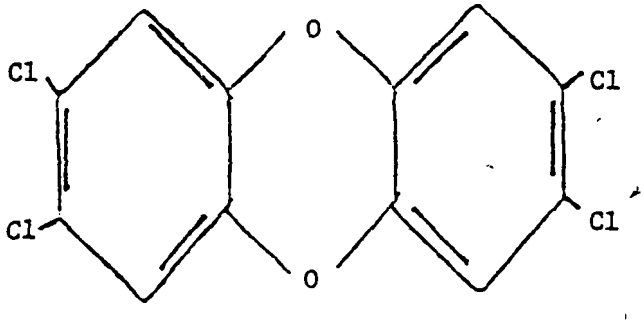
2,4,5-trichlorophenol

NaCl



sodium pentachlorophenate

Heat



2,3,7,8-tetrachlorodibenzodioxin

2,3,7,8-tetrachlorodibenzodioxin (TCDD)

Most toxic synthetic compound known

Persistent in the environment

Lipophilic

Concentrates mainly in the liver and fat

Lesser concentrations in thymus, spleen, liver

Crosses the placenta (pregnant rat)

Excreted unmetabolized in breast milk

Metabolism in humans unknown

Comparative Toxicity of Various Toxic Substances

Substance	Minimum Lethal Dose ug/kg
Botulinus Toxin A	0.00003
Tetanus Toxin	0.0001
Diphtheria Toxin	0.3
2,3,7,8-Tetrachlorodibenzobioxin	1.0
Saxitoxin	9.0
Tetrodotoxin	8 - 20
Bufotoxin	390
Curare	500
Strychnine	500
Muscarin	1100
Diisopropylflurophosphate	3100
Sodium Cyanide	10,000

LD_{50} of 2,3,7,8-TCDD in Laboratory Animals

Guinea Pig	1 µg/kg
Rat (male)	22 µg/kg
Rat (female)	45 µg/kg
Monkey	>70 µg/kg
Rabbit	115 µg/kg
Mouse	100-250 µg/kg
Dog	>300 µg/kg

Age Dependent Toxicity in Mice
Fed 25µg/kg of TCDD Weekly For
Four Doses

Age	Mortality (%)
4 months	0
2 months	17
1 month	44

Source: Vos, Moore, Zinkl 1974

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Botulinus Toxin A	0.00003
Tetanus Toxin	0.0001
Diphtheria Toxin	0.3
2,3,7,8-Tetrachlorodibenzobioxin	1.0
Saxitoxin	9.0
Tetrodotoxin	8 - 20
Bufotoxin	390
Curare	500
Strychnine	500
Muscarin	1100
Diisopropylflurophosphate	3100
Sodium Cyanide	10,000

LD_{50} in Selected PCDD Isomers in ppb

	GP	Mouse
2,3,7,8-tetra	2	283.7
1,2,3,7,8-penta	3.1	337.5
1,2,4,7,8-penta	1125	5000
1,2,3,4,7,8-hexa	72.5	825
1,2,3,6,7,8-hexa	70-100	1250
2,8-di	30,000	

Source: McConnell et al (1978)

2,3,7,8-tetrachlorodibenzodioxin (TCDD)

Most toxic synthetic compound known

Persistent in the environment

Lipophilic

Concentrates mainly in the liver and fat

Lesser concentrations in thymus, spleen, liver

Crosses the placenta (pregnant rat)

Excreted unmetabolized in breast milk

Metabolism in humans unknown

Herbicides used in Vietnam

Name	Composition	Pounds used (Active ingredient)	Years used
Agent Purple	n-butyl ester 2,4-D 50% n-butyl ester 2,4,5-T 30% isobutyl ester 2,4,5-T 20%	1,180,300	1962-1964
Agent Pink	isobutyl ester 2,4,5-T 40% n-butyl ester 2,4,5-T 60%	1,001,980	1962-1964
Agent Green	n-butyl ester 2,4,5-T 100%	66,980	1962-1964
Agent Orange	n-butyl ester 2,4-D 50% n-butyl ester 2,4,5-T 50%	99,172,750	1965-1971
Agent Blue	Cacodylic acid 4.7% Sodium cacodylate 26.4%	3,548,710	1962-1971
Agent White	Picloram 10% 2,4-D 40%	22,531,616	1965-1971

Source: Young, Alvin L. et al. The Toxicology, Environmental Fate, and Human Risk of Herbicide Orange and its Associated Dioxin. USAF, 1978.

60477

2,3,7,8-TCDD Contamination of
Herbicides Used in Vietnam

Agent Purple	17 to 47 ppm
Agent Pink Agent Green	65 ppm
Agent Orange	1 to 50 ppm

Estimation of the Amount of 2,3,7,8-TCDD
Released into the Environment in
Vietnam and in Seveso

Vietnam	368 pounds
Seveso	5 pounds

Industrial Accidents or Overexposures to TCDD
Resulting in Human Illness

1949	USA - Monsanto
1952	Germany - Boehringer
1953	Germany - BASF
1960	USA - Diamond Sham-Rock
1963	Holland - Philips Duphar
1964	Czechoslovakia - Spolana
1964	USA - Dow
1968	England - Coalite
1976	Italy - Givaudan

2,3,7,8-TCDD Contamination of
Herbicides Used in Vietnam

Agent Purple	17 to 47 ppm
Agent Pink Agent Green	65 ppm
Agent Orange	1 to 50 ppm

Sources of Human Environmental Exposure to Chlorinated Dibenzodioxins

Living in the household of an exposed worker

Pyrolysis products in the air from municipal waste incineration, burning of contaminated wood, etc.

Living in the vicinity of an industrial facility (e.g. Midland, Michigan; Jacksonville, Arkansas)

Drift from herbicide applications to forests, rights of way etc.

Herbicide defoliant sprays used in Vietnam

Living near a site where toxic wastes are buried (e.g. Love Canal)

Living in the vicinity where an industrial accident has occurred (e.g. Seveso, Italy)

Etc.

Effects on the Skin and Mucous Membranes in Humans Exposed to TCDD

Chloracne
Hyperpigmentation
Hypertrichosis
Edema and erythema
Blepharoconjunctivitis
Conjunctival cysts
Sties

Chloracne Chronology

1897	Von Bettman first described in workers manufacturing Hydrochloric acid
1901	Herxheimer describes in same workers - ascribes effects to chlorinated aromatic hydrocarbons
WWI	Chlorinated naphthalenes and chlorinated diphenyls used as halogenated waxes by Germans in manufacture of gas masks - chloracne seen in the workers
1912	First cases seen in US related to synthetic wax manufacture
1920's 1930's	Many cases reported in workers in the electronics and radio industry using Halowax for electrical wiring
1936	Schwartz published the first case in the US
WW II	Shipyard workers affected who were putting synthetic wax on ship to deter German magnetic mines
Post War	Most exposures have been related to the manufacture of the chlorinated phenols, especially 2,4,5-T and Pentachlorophenol manufacture
1957	Kimming and Schulz indentified 2,3,7,8-tetrachlorodibenzodioxin as the acneigen in 2,4,5-trichlorophenol
1972	Cases still being reported in Us (New York State) in workers exposed to synthetic waxes

Effects on the Nervous System in
Humans Exposed to TCDD

Headache
Lower extremity weakness
Difficulty in walking
Ataxia
Paresis
Hearing loss
Loss of sense of taste, odor
Lack of vigor, drive
Easy fatigability
Insomnia
Hypersomnolence
Personality change
Emotional instability
Depression
Diminished ability to learn
Memory deficits
Decreased libido
Impotence
Abnormalities in psychological tests
Abnormalities in tests of motor and
sensory peripheral nerve function
Abnormalities in nerve biopsy

Effects on the Liver in Humans Exposed to TCDD

Clinical Findings

- Hepatomegaly
- Right upper quadrant tenderness, pain
- Hepatitis
- Hepatic porphyria
- Increased excretion uroprophyrins
- Porphyria Cutanea Tarda
- Liver function test abnormalities
  - Alkaline phosphatase, SGOT, SGPT
  - Bilirubin, Bromosulfophthalein

Liver Biopsy Findings

- Mild steatosis
- Periportal fibrosis
- Chronic venostatis with Kupffer cell activation
- Red fluoresence

Effects on the Gastrointestinal System
in Humans Exposed to TCDD

Weight loss
Anorexia
Abdominal pain
Post prandial flatulence
Nausea/vomiting
Gastritis

Effects on the Cardiovascular System in Humans Exposed to TCDD

Excess cardiovascular death (myocardial infarction) in accident clean-up crew

Case report of rapidly progressive atherosclerosis in 2,4,5- TCP worker

Abnormalities in blood lipids (increased cholesterol and/or triglycerides) with as yet unknown possible effects on heart and blood vessels

Effects on the Cardiovascular System
in Humans Exposed to TCDD

Excess cardiovascular death (myocardial infarction) in accident clean-up crew

Case report of rapidly progressive atherosclerosis in 2,4,5- TCP worker

Abnormalities in blood lipids (increased cholesterol and/or triglycerides) with as yet unknown possible effects on heart and blood vessels

Reported Effects on Reproduction in Vietmanese Veterans

Increase in neural tube defects reported in offspring of soldiers from the north who had fought in the south as compared to soldiers who had remained in the north.

Chromosomal Changes in Human Peripheral Lymphocytes in Potential or Actual Exposure to Dioxin

why the difference ?

Herbicide workers

increased aberrations reported

Seveso populations

no differences from controls reported

2,4,5-TCP workers with chloracne

no differences from controls reported

Vietnamese populations

insufficient data available to draw any conclusions

Effects of TCDD on the Integument in Experimental Animals

Rabbit
- Acneigen (ear)

Rat, Mouse, Guinea Pig
- No effect

Monkey
- Periorbital and facial edema
- Alopecia (including eyelashes)
- Dry, crusty skin
- Hyperkeratosis palms, soles
- Loss fingernails, toenails
- Squamous metaplasia sebaceous glands
- Palpebral and scleral hyperemia with purulent exudate

Effects of TCDD on the Liver in
Experimental Animals

Rat
- Multiple foci hepatocellular degeneration, necrosis
- Fibrosis with periportal inflammation
- Cytomegaly
- Fatty metamorphosis
- Bile duct hyperplasia
- Cytoplasmic vacuolization
- Increased basophilia
- Multinucleated hepatocytes
- Increased RER with distortion and fragmentation
- Increased lysosomal activity
- Hyperplastic nodules (females)
- Hepatocellular carcinoma (females)

Mouse
- Centrilobular degeneration and necrosis
- Cellular infiltration
- Extensive lipid accumulation
- Bile duct hyperplasia

Guinea pig
- Minimal change

Monkey
- Few scattered necrotic hepatocytes
- Distended, thickened bile ducts

Immunological Effects of TCDD in Experimental Animals

Reduction in Peripheral Lymphocytes
Mouse, guinea pig, but not in rat

Decreased Resistance to Salmonella berne infection
Mouse

Humoral Antibody Response
No difference between treated and control in response to BGG (T dependent antigen - helper cells)
Mouse

Delayed Type Hypersensitivity Response
Decreased in guinea pig and rats exposed prenatally (still present 120 days post exposure with normal thymus size and histology)
No change in adult rats

Lymphocyte Response to Mitogen Stimulation
Decreased response spleen and thymus cells to PHA and Con A in rats exposed pre and post natally

Thymus Atrophy
Rat, mouse, guinea pig

Hematopoetic Effects of TCDD in Experimental Animals

Decreased hemoglobin, hematocrit
Rat, monkey

Decreased hemoglobin
Mouse

Lymphopenia, pancytopenia, hypocellular bone marrow
Monkey

Effects of TCDD on the Gastrointestinal System
in Experimental Animals

Monkey
- Microcystic dilitation crypts
- Loss of parietal cells with replacement by mucous secreting cells
- Gastric ulceration
- Degranulation of cells of exocrine pancreas
- Hemorrhage
- Edema

Mouse
- Submucosal edema of stomach, intestine
- Increased cellularity lamina propria

Rats
- Minimal change

Effects of TCDD on the Kidney and Urinary Tract
in Experimental Animals

Hyperplasia renal pelvis (monkey, guinea pig, rat)

Hyperplasia urinary tract (guinea pig)

Dilatation convoluted tubules (mouse)

Adenocarcinoma of kidney (rat)

Immunological Effects of TCDD in Experimental Animals

Reduction in Peripheral Lymphocytes
Mouse, guinea pig, but not in rat

Decreased Resistance to Salmonella berne infection
Mouse

Humoral Antibody Response
No difference between treated and control in response to BGG (T dependent antigen - helper cells)
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Rat, mouse, guinea pig

Hematopoetic Effects of TCDD in Experimental Animals

Decreased hemoglobin, hematocrit
Rat, monkey

Decreased hemoglobin
Mouse

Lymphopenia, pancytopenia, hypocellular bone marrow
Monkey

Effects of TCDD on the Cardiovascular System of Rats Fed 0.1 µg/kg [2200ppt] daily for 2 years

Brain hemorrhage (female)
Mesenteric/thoracic periarteritis with thrombosis and hematoma (male, female)
Myocardial degenerative changes (female)
Periarteritis with thrombosis of testicular and/or thoracic mediastinal vessels

Source: Kociba et al., 1978

Effects of TCDD on the Respiratory System in the Rat

Increase in focal alveolar hyperplasia
Accumulation of alveolar macrophages
Focal interstitial inflammation and fibrosis
Pulmonary edema
Squamous metaplasia
Squamous cell carcinoma of lung

Effect of a Single Dose of 25 µg/kg TCDD on Thyroid Function in Rats

increased biliary excretion of T_4

increased biliary clearance of T_4

increased ^{131}I uptake

increased thyroid gland weight

increased serum TSH

increased serum T_3

decreased serum T_4

Source: Bastomsky 1977

Concentrations at Necropsy in Rats Fed
TCDD for Two Years

Tissue	0.1ug/kg (2200 ppt)	0.01ug/kg (220 ppt)	0.001ug/kg (22 ppt)
Liver	24,000ppt	5100ppt	540ppt
Fat	8,100ppt	1700ppt	540ppt

Source: Kociba, 1978

Reproductive Effects of TCDD in Experimental Animals

Decreased size of testicles and degeneration of seminiferous components - guinea pig

Decreased spermatogenesis - Sprague-Dawley rats

Decrease in rate of synthesis of testicular DNA - mice

Decreased progesterone and estradiol levels, inability to carry infant to term and changes in menstrual cycle with increased bleeding - monkey

Embryotoxic Effects of TCDD
in the Rat

Effect	Dose
Decreased fetal weight	.125 ug/kg
Subcutaneous edema	.125 ug/kg
Intestinal hemorrhage	.125-.5 ug/kg
Fetal death	2.0 ug/kg

Teratogenic Effect of 2,4,5-T
and it's Associated Dioxin

Species	Effect	Compound and dose
Mice	Cleft palate	3 µg/kg TCDD
	Cystic kidney	1 µg/kg TCDD
Rat	Cystic kidney	113 mg/kg 2,4,5-T with 30 ppm TCDD
	Skeletal abnormalities	100 mg/kg 2,4,5-T with < .5 ppm TCDD
Hamster	Absence of eyelid	100 mg/kg 2,4,5-T with < .5 ppm TCDD
	Delayed head ossification	
	Exencephaly	

Embryotoxic Effects of TCDD
in the Rat

Effect	Dose
Decreased fetal weight	.125 µg/kg
Subcutaneous edema	.125 µg/kg
Intestinal hemorrhage	.125-.5 µg/kg
Fetal death	2.0 µg/kg

Mutagenic Effects of Dioxin

Salmonella Typhimurium

	2,3,7,8-TCDD	OCDD	Unsubstituted
TA1530	-	-	
TA1532	+	±	
TA1531	±	-	
TA1534	±	±	
TA1535	-	-	-
TA1537			-
TA1538	-	-	-

Dominant Lethal

No effect demonstrated in 20 Wistar rats fed 4,8,12 µg/kg daily for 7 days.

Chromosome Changes in Rat Bone Marrow

2,7-DDD	negative
OCDD	negative
2,3,7,8-TCDD	positive (weak)

Reproductive Effects of TCDD in Experimental Animals

Decreased size of testicles and degeneration of seminiferous components - guinea pig

Decreased spermatogenesis - Sprague-Dawley rats

Decrease in rate of synthesis of testicular DNA - mice

Decreased progesterone and estradiol levels, inability to carry infant to term and changes in menstrual cycle with increased bleeding - monkey

Neoplastic Changes in Rats Fed
2,3,7,8-TCDD for 78 Weeks

precipitate

Tumor	Dosage			
	5ppt	500ppt	1ppb	5ppb
Carcinoma of the ear duct	1			
Lymphocytic Leukemia	1			
Adenocarcinoma of Kidney	1	1		
Malignant Histiocytoma	1		2	
Angiosarcoma of Skin	1		1	
Leydig Cell Adenoma of Testes	1			
Sclerosing Seminoma of Testes		1		
Carcinoma of the Skin		1		
Cholangiosarcoma of the Liver			1	2
Glioblastoma (brain)			1	
Squamous Cell Lung Tumors				4
Neoplastic Liver Nodules				4

Source: Van Miller et al. 1977

Carcinogenic Effect in Rats Fed
2,3,7,8-TCDD for 2 Years

Squamous Cell Carcinoma Hard Palate	F, M	0.1ug/kg (2200ppt)
Squamous Cell Carcinoma Tongue	M	0.1ug/kg
Hepatocellular Carcinoma	F	0.1ug/kg
Hyperplastic Liver Nodules	F	0.01ug/kg (220ppt)
Squamous Cell Carcinoma of Lung	F	0.1ug/kg

Source: Kociba et al. 1978

TCDD Effects on Enzyme Induction in Chick Embryo Liver

30,000 times more potent as inducer of Aryl hydrocarbon hydroxylase than methylcholanthrene

1000 times more potent as inducer of delta-aminolevulinic acid synthetase than any other chemical tested

Effect of induction persists over a long period of time

Potency as inducer correlates with toxicity

TCDD Effects on Enzyme Induction in Mammalian Liver

Affects P448 mediated enzymes, e.g.
- Aryl hydrocarbon hydroxylase
- Biphenyl 2-and4-hydroxylase
- UDP-glucuronyltransferase

No effect on ALA in rat, guinea pig, mouse

Effect still present 2 to 3 months after dosing

Potency as inducer correlates with toxicity

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"2,4,5-T Agent Orange and Tetrachlorodibenzo-p-dioxin - Evaluation of the problem."

Marion Moses, Mount Sinai School of Medicine of The City University of New York, October 15, 1979 presentation.

PROTOCOL:

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FUNDED BY:

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DETERMINATION OF TCDD RESIDUES IN HUMAN MILK, BEEF LIVER, FISH, WATER, AND SEDIMENT

I. INTRODUCTION

The highly toxic compound 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) may be formed as a by-product in manufacturing processes utilizing tetrachlorobenzene to produce trichlorophenol. Under very basic, high temperature, high pressure conditions, 1,2,4,5-tetrachlorobenzene is hydrolyzed to the 2,4,5-trichlorophenate. Acidification yields the phenol. Unfortunately, a condensation can take place in this reaction resulting in formation of TCDD. Herbicides containing esters of 2,4,5-trichlophenoxyacetic acid (2,4,5-T) manufactured from trichlorophenol have been found to contain trace amounts of TCDD. TCDD has been recognized as an extremely toxic (oral LD_{50} 0.6 mg/kg, guinea pig), teratogenic compound that is stable in biological systems. The toxicological properties of TCDD have been well documented.

Because of its toxicity and occurrence as a trace contaminate in chemical products, it is necessary to analyze for TCDD at picogram/gram (low and sub-parts per trillion, ppt) levels, which are below the usual limits of detection for pesticide residue analysis. The analysis of human, biological, and environmental samples for possible TCDD contamination in the ppt concentration range is complicated by the presence of many interfering components ranging from naturally occurring compounds to industrial pollutants, such as PCBs, and the agricultural chemicals DDT, DDE, etc.

An extremely efficient and specific analytical cleanup procedure is a prerequisite for ppt TCDD analysis specifying GLC MS detection techniques. The GLC MS detection technique must be ultra sensitive and also highly specific because of the required low ppt detection limits. High resolution glass capillary column GLC interfaced with high resolution MS multiple ion selection analysis provides the required GLC resolution, MS sensitivity, and specificity for TCDD analysis in the 0.02-100 ppt concentration range.

Described below are the sample preparation procedures and capillary column GLC HRMS techniques developed and currently applied by EPA laboratories for isolation, detection, quantification, and confirmation of TCDD residues in human milk, beef liver, fish, water, and sediment extracts. The results of quality assurance samples and samples with unusual contamination are also discussed.

REFERENCE:

Sample Preparation Procedures and Gas Chromatography/Mass Spectroscopic Methods of Analysis for TCDD, Harless, R. L., Oswald, E. O., and Wilkinson, M. K., Analytical Chemistry Branch, U.S. EPA, HERL, ETD, Research Triangle Park, NC 27711. Submitted for publication to Anal. Chem.

II. PRINCIPLE:

Tissue, milk, water, soil, and sediment samples are subjected to an "acid-base" sample preparation procedure involving saponification with hot caustic followed by extraction with hexane, washing with concentrated sulfuric acid, cleanup by alumina column chromatography, and capillary column GLC/high resolution mass spectrometric multiple ion selection (GLC HRMS) analysis for TCDD residues. Fish tissue is subjected to a "neutral" cleanup procedure that is similar except that extraction is carried out with acetonitrile, and cleanup by solvent partitioning and Florisil column chromatography precedes the alumina column cleanup. ^{37}Cl-TCDD is added to all samples as an internal standard or marker to monitor and determine the analytical cleanup procedure efficiency.

III. SAFETY PRECAUTIONS:

TCDD is toxic and can pose grave health hazards if used improperly. Techniques for handling radioactive and infectious materials are applicable to TCDD. Only qualified individuals who are trained in laboratory procedures and familiar with the dangers of TCDD should handle this substance. Females of childbearing age should not work with this material.

A good laboratory practice involves routine physical examinations and blood checks of employees working with TCDD. Also, facial photographs using oblique photoflood lighting should be periodically taken to detect chloroacne, which is an early sign of overexposure.

IV. EQUIPMENT:

1. Gas chromatograph, Varian Model 2700, equipped with an SE-30 WCOT glass capillary column, 30 m x 0.25 mm, i.d. The capillary column yielded an efficiency of 113,000 effective plates measured at the ^{35}Cl-TCDD peak. Splitless injection incorporating n-tetradecane was employed.

2. Mass spectrometer, Varian 311A, interfaced to the chromatograph so as to ensure maximum transfer efficiency. The spectrometer was equipped with a turbo-molecular vacuum pumping system, combination chemical ionization (CI) and electron impact (EI)

ion source, and a Varian eight channel hardware (manual control) multiple ion selection (MIS) device. This vacuum system easily accommodated the 5 ml/minute helium flow from the GLC MS interface and did not contribute detectable background contamination. The MIS device was operated in the normal coupled electric mode (jumping the acceleration voltage). Each MIS channel was equipped with individual controls for selecting the acceleration voltage, measuring range, output signal bandwidth, compensation for background contamination, and intergration rate. The intensities of the selected masses were monitored in a time division multiplex system, setting alternately to each of the selected masses and recording their intensities simultaneously on an eight channel Soltec recorder. The adjustable integration rate, 0.01 second to 1 second was sufficient to accurately reproduce capillary column peaks two seconds wide at half height.

Alternative Instrumentation: Current MS instrumentation used by other laboratories (EPA contract laboratories) for TCDD analysis include (1) AEI MS-30, (2) AEI MS-50, and (3) Varian CH-5DF. These instruments are interfaced with a packed column gas chromatograph and use high resolution MS double ion monitoring techniques.

The general requirements for the GLS MS instrumentation are:

(1) Packed or preferably capillary column GLC introduction of the sample.

(2) High resolution (10,000 minimum) MS mass analysis.

(3) Ultra high sensitivity (1 to 50 pg TCDD quantification standards).

3. Pasteur pipets, 5.75 inches (14.6 cm) x 0.5 cm i.d.

4. Glass column, 50 cm x 11 mm, equipped with a Teflon stopcock and removal glass tip.

5. Desiccator, equipped with Drierite, which can accommodate adsorbent-packed Pasteur pipets.

6. Reflux condenser, water cooled, equipped with 100 ml boiling flasks.

7. Separatory funnels, 250 ml.

8. Evaporation apparatus including a 12 ml distillation receiver, micro-Snyder column Kontes K-569251, and steam bath.

9. Filter funnel.

10. Filter tube, glass, 16 cm x 42 mm.

11. Glass column, 39 cm x 11 mm i.d., with a 125 ml reservoir and Teflon stopcock.

12. Kuderna-Danish (K-D) evaporative concentrator, 250 ml.

13. Chromaflex sample tube, 2 ml, graduated, Kontes K-422560.

14. Glass tubing, 7 cm x 3 mm i.d.

15. Blender, Waring, or equivalent.

16. Magnetic stirrer.

17. Hotplate, explosion proof.

18. Mills type concentrator tube, Kontes K-570050.

V. REAGENTS:

1. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), ^{37}C labeled, isotopic purity >98% ^{37}Cl, Eco-Control, Inc., 71 Rogers St., Cambridge, MA 02142.

2. TCDD analytical standard, Dow Chemical Co., Midland, MI; ITT Research Institute, Chicago, IL; and Eco-Control, Inc.

3. Hexane, acetone, benzene, methylene chloride, ethyl alcohol, acetonitrile, Mallinckrodt Nanograde.

4. Carbon tetrachloride, Fisher ACS grade, 0.01% water maximum; a greater water content can cause TCDD to elute in the incorrect fraction.

5. Alumina, neutral, activity grade 1, Woelm.

6. Florisil, 60-120 mesh, suitable for pesticide residue analysis by the criteria in Section 3,D, activated at 225°C for 24 hours before use.

7. Sodium carbonate, sodium sulfate, and ammonium chloride, Mallinckrodt AR grade, Soxhlet extracted overnight with methylene chloride and dried at 200°C.

8. Potassium hydroxide and sulfuric acid, Mallinckrodt AR grade.

9. Glass wool, pre-extracted with methylene chloride.

10. Water, passed through a column of activated carbon and distilled.

11. Nitrogen for solvent evaporation, Zero Grade, Liquid Air, Inc., New Orleans, LA.

12. Dry ice.

VI. PREPARATION OF CHROMATOGRAPHIC CLEANUP COLUMNS:

1. Alumina

   a. Prewash and dry a disposable Pasteur pipet and plug the tip with glass wool.

   b. Pack the pipet with 4.5 cm of neutral alumina and top the column with 0.5 cm of anhydrous, granular sodium sulfate.

   c. Wash the column with 4 ml of methylene chloride and force the residual solvent from the column with a stream of dry nitrogen.

   d. Store the prepared columns in an oven at 225°C at least 24 hours.

   e. Before use, equilibrate the oven-activated columns to room temperature in a desiccator over Drierite.

2. Florisil

   a. Pack a 500 x 11 mm glass column with 15 grams of activated Florisil.

   b. Pack a 2.5 cm layer of anhydrous sodium sulfate on top of the Florisil.

   c. Hold at 225°C until ready for use (a minimum of 24 hours).

   d. Cool the column to near room temperature and prewash with 100 ml of hexane.

VII. SAMPLE PREPARATION AND CLEANUP - ACID-BASE PROCEDURE:

1. Lean Tissue

   a. Grind tissue samples to obtain a homogeneous sample.

b. Weigh a 10-20 gram sample into a 100 ml boiling flask and add 20 ml of ethyl alcohol and 40 ml of 45% KOH solution.

c. Add 5-10 ng of ^{37}Cl-TCDD standard solution.

d. Attach the flask to a water cooled reflux condenser and heat under reflux with stirring for 2.5 hours.

e. Cool and transfer the solution to a 250 ml separatory funnel.

f. Rinse the boiling flask with 10 ml of ethyl alcohol followed by 20 ml of hexane, and add to the separatory funnel.

g. Extract the solution with four 25 ml portions of hexane and combine the hexane extracts.

2. Adipose Tissue

a. Grind or render adipose samples, if necessary, to obtain a representative sample free of connective or other tissue.

b. Add 5-10 ng of ^{37}Cl-TCDD to 10 grams of sample.

c. Add 15 ml of distilled water to the sample. Extract and continue as described in Subsection 1, b-g, for lean tissue.

3. Milk

a. Add 2.5 ng of ^{37}Cl-TCDD standard solution to 10-20 grams of milk.

b. Extract the sample as described in Subsection 1, b-g, for lean tissue.

4. Water

a. Fortify one kilogram of a well mixed water sample (including particulate matter, if present) with 2.5 ng of ^{37}Cl-TCDD standard solution.

b. Extract the sample with three 100 ml portions of methylene chloride.

c. Evaporate the combined extracts to near dryness in a K-D concentrator with an attached Snyder column utilizing a steam bath. Complete the evaporation to dryness by placing the tube in a warm water bath under a gentle stream of dry nitrogen.

d. Transfer the residue to a separatory funnel with several rinsings of hexane totaling 100 ml.

e. Wash the hexane solution with 50 ml of 1 N KOH solution followed by concentrated H_2SO_4 as described in Subsection 6 on cleanup.

5. Soil and Sediment

a. Fortify 10-20 grams of well mixed sample with 2.5 ng of ^{37}Cl-TCDD.

b. Extract as described in Subsection 1, b-g, for lean tissue.

c. After refluxing and cooling, decant the solution into a separatory funnel through a filter funnel packed with glass wool.

d. Rinse the boiling flask and filter funnel with two 10 ml portions of ethyl alcohol followed by 20 ml of hexane.

e. Extract the combined solution with four 25 ml portions of hexane that had previously been used to rinse the boiling flask and filter funnel.

6. Cleanup

a. Wash the combined hexane extracts, obtained as describe above in Subsections 1-5, with 25 ml of 1 N KOH solution followed by four 50 ml portions of concentrated H_2SO_4.

b. Add 25 ml of water and shake. Neutralize the water and hexane layers by addition of powered Na_2CO_3 in small portions with mixing until CO_2 evolution ceases.

c. Discard the aqueous layer, and dry the hexane layer by passage through the 39 cm x 11 mm i.d. glass column containing 10 cm of anhydrous powered Na_2CO_3.

d. Transfer the hexane concentrate to an alumina column, prepared as described in Subsection VI, 1, that was prewetted with one ml of hexane.

e. Wash the column with 6 ml of CCl_4 and discard the wash.

f. Elute the column with 4 ml of methylene chloride and collect in a 21 ml distillation receiver.

g. Cap the distillation receiver with a micro-Snyder column and evaporate the methylene chloride just to dryness on a hot water or steam bath.

h. Add two separate 2 ml portions of hexane to the distillation receiver and evaporate each just to dryness.

i. Dissolve the residue in 3 ml of hexane and chromatograph on a second alumina column as just described.

j. Evaporate the methylene chloride eluate from the second column just to dryness.

k. Add 2 ml of benzene to the receiver and concentrate to ca 100 µl.

l. Transfer the benzene solution quantitatively to a 2 ml graduated Chromaflex sample tube.

m. Carefully concentrate the benzene ca 100 µl under a gentle stream of dry nitrogen. Quantitatively transfer with two 25 µl benzene rinses to a glass tube (7 cm x 3 mm i.d.) that is sealed at one end.

n. Carefully concentrate the extract to 60 µl and flame seal the tube. Store below 0°C until analysis by GLC MS.

VIII. SAMPLE PREPARATION AND CLEANUP - NEUTRAL PROCEDURE:

1. Extraction of Fish Tissue

a. Grind fish tissue to obtain a homogeneous sample.

b. Place a 15 gram sample and 150 grams of anhydrous granular sodium sulfate in a blender jar and blend for one minute.

c. Blend next with 50 gram portions of dry ice until the sample is thoroughly powered.

d. Transfer the powder to an Erlenmeyer flask and add 10 ng of ^{37}Cl-TCDD directly onto the powder.

e. Rinse the blender jar with acetonitrile.

f. Add the rinsings plus enough additional acetonitrile to the flask to make a total of exactly 150 ml.

g. Mix vigorously on a magnetic stirrer for 2 hours.

h. Filter the mixture through a glass filter tube containing 30 grams of anhydrous granular sodium sulfate.

2. Cleanup

a. Partition exactly a 100 ml aliquot of the acetonitrile extract, representing 10 grams of the original sample, with 50 ml hexane that is saturated with acetonitrile. Draw the acetonitrile (bottom) layer into a 500 ml separatory funnel.

b. Partition the hexane layer with two 100 ml portions of acetonitrile saturated with hexane followed by one 50 ml portion of the same solvent and combine with the above acetonitrile (350 ml total volume).

c. Partition the combined acetonitrile layers with 10 ml of hexane saturated with acetonitrile.

d. Draw the acetonitrile layer into a 500 ml flat bottom 20/40 S Florence flask and concentrate to ca 10 ml under a Snyder column on an explosion-proof hotplate.

e. Transfer the concentrate by repeated rinsings with a total of 200 ml of hexane to a K-D apparatus with a 10 ml Mills tube attached. Concentrate each of 5-10 ml on a hot water or steam bath.

f. Transfer the hexane concentrate to a Florisil column, prepared as described in Section VI,2, using three 5 ml portions of hexane.

g. Elute the column with 100 ml of hexane-methylene chloride (90:10 v/v) and discard this eluate.

h. Elute with 100 ml of hexane-methylene chloride (75:25 v/v) and collect in a Kuderna-Danish evaporator equipped with a 100 ml Mills tube.

i. Concentrate to ca 3 ml on a hot water or steam bath.

j. Dissolve the concentrate in 100 ml of hexane and again evaporate to ca 3 ml.

k. Transfer the concentrate to an alumina column and proceed with chromatography as described in the acid/base procedure (Subsection VII,6), but use only one alumina column.

IX. CAPILLARY COLUMN GC/HRMS MULTIPLE ION SELECTION ANALYSIS:

1. Tune the magnet current to perfluorokerosene (PFK) m/e 318.9793 and adjust the spectrometer from 5000 to 9000 mass resolution.

2. Monitor the ESA voltage and use in calculating the exact acceleration voltage required for the masses m/e 327.8847 $C_{12}H_4O_2{}^{37}Cl_4$, m/e 321.8936 $C_{12}H_4O_2{}^{35}Cl_3{}^{37}Cl$, and m/e 319.8965 $C_{12}H_4O_2{}^{35}Cl_4$.

3. Introduce the calculated values of MIS channels 2, 3, and 4.

4. Inject 2 µl of TCDD quantification standard, 500 pg/µl ^{37}Cl-TCDD (labeled 2,3,7,8-tetrachlorodibenzo-p-dioxin, ^{37}Cl, isotopic purity greater than 98%) and one pg/µl TDCC, and 0.5 µl of n-tetradecane (keeper) into the capillary column (on-column splitless injection) maintained at 80°C.

5. Rapidly turn the GLC oven manual temperature control to 265°C exactly 6 minutes after injection of the sample; the manual control provides an accurate and rapid heating rate of 34°C/minute.

6. Close the solvent vent valve exactly 14 minutes after injection of the sample.

7. Optimize the MS sensitivity for the source operating pressure, 6×10^{-6} Toor, using PFK m/e 318.9793.

8. Initiate the MIS analysis 16 minutes after injection of the sample.

9. Adhering to a strict (stopwatch) time schedule of events, the GLC HRMS experimental retention time for TCDD was 23 minutes ± 15 seconds with the following GLC and MS parameters:

30 m SE-30 WCOT glass capillary column
injection port temperature, 260°C
GLC transfer line into the MS ion source, 255°C
ion source temperature, 240°C
variable acceleration voltage 3 kV maximum
electron energy, 70 eV
filament emission, 1 mA
mass resolution 5,000-10,000
multiplier gain, greater than 10^6

X. COCl LOSS ANALYSIS:

1. Tune the magnet current to PFK m/e 254.9856.

2. Introduce the exact acceleration voltages required for TCDD masses m/e 256.9327, m/e 258.9298, m/e 319.8965, m/e 321.8936, and m/e 327.8847 into respective MIS channels (M^+—COCl peak, m/e 258.9298, is used to confirm TCDD structure).

3. Perform the analysis, adhering to the previously described time schedule of events.

4. Observe the GLC HRMS five channel simultaneous response for ^{37}Cl-TCDD and TCDD and record at the correct GLC retention time for TCDD.

XI. ELEMENTAL COMPOSITION ANALYSIS:

1. Adjust the mass spectrometer for 10,000 mass resolution using PFK m/e 318.9793 as reference.

2. Initiate the peak matching analysis, adhering to the exact time schedule of events utilized in the GLC HRMS MIS analyses.

3. Display alternately the reference mass and the exact mass range of interest and view simultaneously on the MS oscilloscope.

XII. DETECTION AND RECOVERY RESULTS AND DISCUSSION OF METHODS:

1. Glass capillary columns enhanced the GLC HRMS method of analysis because (a) they provided the required resolution of complex mixtures into individual components before they entered the mass spectrometer; (b) the narrow band width of the TCDD component enhanced MS sensitivity; (c) direct coupling of the capillary column to the mass spectrometer ensured maximum transfer efficiency; (d) capillary column bleed rate was low, therefore background contamination was minimized and MS sensitivity was enhanced.

2. The requirements imposed on the mass spectrometer used as a GLC detector in these analyses were (a) extremely stable electronic circuits; (b) ultra high sensitivity; (c) specific mass detection. The requirements were satisfied by optimizing all components that influenced sensitivity, noise, and mass resolution. The MIS response for a quantification standard, ^{37}Cl-TCDD and TCDD, is shown in Figure 1.

3. Precision and Accuracy of GLC HRMS Technique

When adjusted for 7500 mass resolution and used as a GLC detector in MIS analyses, the mass spectrometer will give positive responses for those components eluting from the gas chromatograph that yield a molecular or fragment ion in the range ± 30 millimass units of TCDD masses m/e 319.8965, m/e 321.8936, and m/e 327.8847. This minimizes the interference from contaminating components, thus yielding responses that are reproducible and linear relative to the amount of TCDD injected. Two concentration ranges, 0.2-2 pg and 2-10 pg, were used to provide the most efficient and accurate quantification of TCDD because of the extremely high sensitivity and manual control attenuation used in these analyses. Sample extracts should be diluted or concentrated as required for quantification purposes. The reproducibility of peak height response for TCDD standards, 1 pg/µl or 5 pg/µl, during daily operation was ± 20%. The TCDD m/e 320 and m/e 322 chlorine isotope ratio ranged from 0.75-0.95 to 1. The variation from the theoretical chlorine ratio, 0.8 to 1.0, was attributed to the MIS integration rate, very narrow capillary column GLC peaks, and the small amount of TCDD being analyzed.

The GLC HRMS peak matching accuracy for known elemental compositions was determined to be ± 2 millimass units at 9500 mass resolution with PFK as reference. The reference mass and TCDD mass were observed to be exactly superimposed on the mass spectrometer oscilloscope at the exact GLC HRMS retention time of TCDD.

4. Recovery of ^{37}Cl-TCDD and Measurement of TCDD

The MIS simultaneous peak height responses (m/e 328, m/e 322, and m/e 320) of sample and sample fortified with a known amount of ^{37}Cl-TCDD and TCDD were used to determine the sample preparation procedure efficiency (percentage recovery), TCDD residue level, and limit of detection. The criteria utilized for confirmation of TCDD are shown in Table 1. The percentage recovery experimental value was used to correct the TCDD residue level and limit of detection for ^{37}Cl-TCDD recovery losses. A minimum acceptable percentage recovery (50%) was established for reporting TCDD analyses. The infrequent analyses exhibiting less than 50% recovery were discarded. TCDD results were not corrected for recovery values greater than 100%. Recovery values between 100 and 135% were attributed to interference from PCBs and unidentified contamination. Due to the widespread distribution of PCBs, the accuracy of ^{37}Cl-TCDD determination primarily depends on the sample preparation procedure efficiency and specificity, and the capillary column GLC resolution of

components. The MS mass resolution, ca 45000, required to separate ^{37}Cl-TCDD m/e 327.8847 and PCB m/e 327.8758 is not feasible owing to MS limitations. For occasional and highly contaminated sample extracts, the ^{37}Cl-TCDD m/e 328 peak height was determined utilizing the PCB m/e 326 peak height to calculate the PCB contribution to the m/e 328, a mixture of ^{37}Cl-TCDD and PCB.

5. Limit of Detection

The limit of detection was defined as the quantity of TCDD that would provide a signal to noise ratio greater than 2.5:1 with clearly defined peak shapes (m/e 320 and m/e 322) in the proper isotopic ratio. The limit of detection varied from sample to sample because of percentage recovery, sample size, matrix effects, and electronic noise present in the time frame of measurements.

6. Isotopic Purity of ^{37}Cl-TCDD Fortification Standard

The ^{37}Cl-TCDD standard, 1 ng/µl in benzene, was subjected to MIS analyses for determination of purity and possible interferences for sub-ppt TCDD analyses prior to human milk studies. A TCDD isomer was detected at 1 pg/ng ^{37}Cl-TCDD. The GLC HRMS peak matching technique with PFK as reference was used to confirm the elemental composition of m/e 319.8965 and 321.8936, both corresponding to TCDD, in a concentrated solution of ^{37}Cl-TCDD standard. The elemental compositions, the m/e 320/322 Cl ratio, and the GLC retention time of ^{37}Cl-TCDD fortified with 2,3,7,8-TCDD were criteria used to confirm the presence of a TCDD isomer in ^{37}Cl-TCDD standard that satisfies the analytical criteria for 2,3,7,8-TCDD. These results indicated that 10 ng ^{37}Cl-TCDD foritification levels in 10 gram samples would produce 1 ppt TCDD analyses. This was confirmed experimentally. The fortification level was reduced from 10 to 2.5 ng ^{37}Cl-TCDD per sample to avoid false positive results in 0 to 2 ppt TCDD analyses.

7. Human Milk Studies

EPA has initiated a study to determine the possible presence of TCDD in human milk. Sample locations were selected based on the aerial application of 2,4,5-T for conifer release as part of a forestry management program. The samples were subjected to the described acid-base extraction and cleanup procedure prior to GLC HRMS MIS analysis.

The 60 µl human milk extracts were quantitatively concentrated to 7-20 µl using dry nitrogen gas for sub-ppt TCDD analysis. The MIS analysis sequence was sample, sample fortified with

^{37}Cl-TCDD, and TCDD. A typical analysis for TCDD residues in a QC sample of human mother's milk is shown in Figure 2. The corrected experimental results indicated the sample contained 1.2 ppt TCDD residue. This 10 gram sample had been fortified with 10 pg of TCDD, which corresponds to 1 ppt TCDD. The total TCDD analyses, analytical cleanup efficiency, TCDD residue level, and limit of detection were performed on injections of a sample and fortified sample. Duplicate analyses were usually performed on each sample to establish precision values.

The results of a quality assurance study incorporating human milk fortified with 2.5 ng ^{37}Cl-TCDD and 0-5 ppt TCDD are shown in Table 2. Evaluation of the experimental results and theoretical results after completion of study indicate: (a) the analytical cleanup procedure and MIS method of analysis provided reasonably accurate TCDD analysis in the 0.2-5 ppt concentration range; (b) false positive results were not detected; (c) 2.5 ng ^{37}Cl-TCDD fortification levels were adequate for recovery purposes; (d) the small amount, (2.5 pg) of TCDD, in adverse effects in 0-5 ppt TCDD analyses, with a 0.2 ppt detection limit. A representative number of positive results generated at this level of detection should be confirmed with supplemental techniques such as COCl loss, peak matching analyses, etc.

Contamination was a constant problem in 0-5 ppt TCDD analysis. A very efficient and optimized capillary column was required to resolve TCDD from contamination, and its effectiveness could be destroyed in the presence of high amounts of contamination. In general, PCBs were the contaminants of major concern. The mass resolutions 12,476 and 45,539 required to separate PCB masses 321.8677 and 327.8758 from TCDD masses 321.8935 and 327.8847 could not be used in 0-5 ppt TCDD analysis because of instrument design and sensitivity. The PCB interference to TCDD analysis was observed to have the following effects: (a) recovery of ^{37}Cl-TCDD became greater than 100% and (b) the TCDD m/e 320/322 chlorine isotope ratio was destroyed. Mass resolution of 5,000 to 8,000 was sufficient to resolve TCDD from other contamination present.

8. Fish Analysis

Edible portions (2.5 to 10 grams) of fish samples were fortified with 2.5 to 10 ng ^{37}Cl-TCDD and subjected to the described acid/base extraction and cleanup procedures. An MIS analysis is shown in Figure 3, for sample and fortified sample. Unusual and high concentrations of contaminate masses were detected at m/e 320 and m/e 322 in fish collected from polluted waters. The contamination was not detected in analyses of ocean perch, fish from specific locations, and beef liver during the analysis

sequence. The high concentration of co-extractable components in fish caused serious problems (capillary column overload, co-elution of components, and decreased MS sensitivity). To minimize or cancel these effects, very high MS sensitivity (4-9 pg quantification standard) and small sample size (0.5 to 3 µl from 55 µl equivalent to a 10 gram sample) were used in analysis of fish.

A small number of highly contaminated fish extracts were subjected to additional GLC HRMS analyses and to a "neutral" cleanup procedure to confirm the presence of TCDD:

(a) MIS simultaneous response for the molecular ion cluster m/e 320, m/e 322, and m/e 324 to confirm the tetrachloro isotope ratio.

(b) MIS simultaneous response for m/e 320, m/e 322, m/e 257, and m/e 259 to confirm the M^+-COCl loss indicative of the TCDD structure.

(c) GLC HRMS peak matching analysis to confirm the elemental composition of the TCDD molecular ion, m/e 319.8965.

Two exact masses corresponding to TCDD isomers were observed eluting before and after TCDD. Contaminant masses, differing from the exact mass of TCDD, were also observed during the time frame of the analysis. Highly contaminated fish samples were subjected to a "neutral" cleanup procedure described in Section 9G. Capillary column GLC HRMS MIS analysis yielded positive ^{37}Cl-TCDD and TCDD responses essentially free of contamination. The quality assurance sample results utilized in these studies are shown in Table 3.

9. Water and Sediment Analysis

Water and sediment samples were collected from specific areas of the United States and subjected to the described analytical extraction and cleanup procedures prior to MIS analysis. The analytical results for quality assurance samples incorporated in these studies are shown in Table 4.

Evaluation of the results shown in Table 4 indicates that the analytical extraction and cleanup procedure and MIS technique provided reasonably accurate analysis for 10-1000 parts per quadrillion (10^{-15}) TCDD in water and 0-35 ppt TCDD in sediment. Water extracts were very clean. Significant amounts of contamination differing from the exact mass of TCDD were detected in specific sediment samples but did not interfere with TCDD analysis.

10. TCDD Isomers

The toxicological properties of TCDD isomers are known to be significantly different. The mass spectra of known TCDD isomers are identical except in the low mass range, and this minor difference would not be of significant value in ppt analysis of environmental or biological extracts. Therefore, it is extremely important that the gas chromatograph be equipped with high resolution capillary columns to resolve TCDD isomers before they enter the mass spectrometer. The 2,3,7,8-, 2,3,6,8-, and 1,2,3,4-TCDDs and a mixture consisting of 70% 1,3,6,8-TCDD and 30% of an unknown TCDD isomer have been separated in this laboratory using glass capillary column GLC HRMS. The SE-30 WCOT glass capillary column resolution of TCDD isomers and order of elution were similar to separations reported in the literature on an OV-101 glass capillary column. The 2,3,6,8-TCDD isomer was only partially resolved from 1,2,3,4-TCDD.

Several TCDD isomers have been detected and confirmed in environmental, biological, and chemical formulation samples using the described capillary column GLC HRMS techniques and coinjection of specific TCDD isomers.

Preliminary studies using the acid-base cleanup procedure and nanogram quantities of hexa-, hepta-, and octa-substituted dioxins (analytical standards) suggest that tetrachlorodioxin isomers are not formed from the degradation of higher chlorinated dioxins by acid-base sample preparation conditions. Nanogram quantities of 2,4,5-trichlorophenol showed no evidence of condensation to 2,3,7,8-TCDD under the same acid-base conditions.

XIII. ANALYTICAL QUALITY CONTROL:

The analytical cleanup laboratory should assign identification numbers to all samples. The samples and QC samples are fortified with 2.5-10 ng of ^{37}Cl-TCDD. The QC samples are fortified with 0 to 1, 250 pg (p to 125 ppt) of TCDD before extraction and cleanup. A method blank is included as part of the QC sample package. All sample extracts and quantification standards, ^{37}Cl-TCDD and TCDD, are submitted to the GLC MS laboratory in a blind fashion, i.e., there should be no way to distinguish QC and actual samples.

The efficiency, accuracy, precision, and validity of ppt TCDD analyses depend on an incorporated quality assurance program. The supplemental and conclusive GLC HRMS validation techniques involving analyses for M^{+}-COCl loss and GLC HRMS peak matching analysis (real time) can not easily be applied to 0-30 ppt TCDD analyses at this date, using the described procedures. Based on the incorporated

quality assurance program, analytical criteria, GLC HRMS techniques, and multiple laboratory participation, the described methodologies have been shown to be effective for isolation, detection, and quantification of 0.02-100 ppt levels of TCDD in specific types of samples. Samples containing high ppt or part per billing (ppb) levels of TCDD can cause serious contamination problems in the sample preparation laboratories, which result in erroneous low ppt TCDD analysis of the sample next in the series. Extreme care and very clean laboratory practices are mandatory for low ppt TCDD analyses.

Results of some quality assurance studies are presented in Subsection XII.

TABLE 1. CRITERIA USED FOR CONFIRMATION OF 2,3,7,8-TCDD RESIDUES IN HUMAN, ENVIRONMENTAL AND FISH SAMPLES

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

TABLE 2. ANALYTICAL RESULTS FOR 2,3,7,8-TCDD RESIDUES IN QUALITY ASSURANCE SAMPLES OF HUMAN MILK

Experimental Results			TCDD Fortification Level	
^{37}Cl-TCDD % Recovery	TCDD Detection Limit* (ppt)	TCDD Detected* (ppt)	(pg)	(ppt)
50	0.3	1.9	10	1.0
72	0.2	0.6	3	0.3
68	0.1	0.2	1	0.1
64	0.3	ND	0	0
68	0.4	0.9	9	0.9
84	0.2	1.4	20	2.0
64	0.2	0.4	5	0.5
51	0.2	ND	2	0.2
73	0.4	0.6	7.5	0.75
52	0.3	1.4	6.5	0.65
72	0.5	3.0	30	3.0
100	0.5	4.0	50	5.0
50**	0.2	ND	0	0

Each 10 gram sample was fortified with 2.5 ng ^{37}Cl-TCDD.

* Corrected for recovery.
** Method blank.
ND = Not detected.
ppt = Parts per trillion.

TABLE 3. SUMMARY OF ANALYTICAL RESULTS FOR QUALITY ASSURANCE SAMPLES (OCEAN PERCH, LAKE TROUT, BEEF LIVER) GENERATED DURING ANALYSIS OF FISH FOR TCDD RESIDUES

Experimental Results						
Sample Weight (gram)	^{37}Cl-TCDD Fortification Level (ng)	^{37}Cl-TCDD % Recovery	^{35}Cl-TCDD Detection Limit (ppt)*	TCDD Detected (ppt)*	TCDD Fortification Level (pg)	TCDD Fortification Level (ppt)
5 (1)	5	62	2	20	110	22
5 (1)	5	52	4	34	185	35
5 (1)	5	82	3	ND	0	0
5 (4)	5	100	3	ND	0	0
5 (3)	5	54	1	19	70	14
5 (3)	5	100	2	ND	0	0
5 (3)	5	78	2	ND	0	0
5 (1)	5	92	2	19	55	11
5 (1)	5	97	5	45	240	48
10 (1)	10	100+	1	8	130	13
10 (1)	10	100+	4	43	600	60
10 (2)	10	100+	7	ND	0	0
10 (2)	10	100+	3	ND	0	0
10 (1)	10	100+	4	76	1250	125
10 (4)	10	67	1	ND	0	0
10 (1)	5	93	3	56	650	65
10 (1)	10	84	4	73	620	62

* Corrected for recovery (1) ocean perch (2) lake trout (3) beef liver (4) method blank

ND = Not detected.

TABLE 4. SUMMARY OF ANALYTICAL RESULTS FOR QUALITY ASSURANCE SAMPLES GENERATED DURING ANALYSIS OF WATER AND SEDIMENT FOR 2,3,7,8-TCDD RESIDUES

	Experimental Results					
Sample Type	Sample Weight (gram)	^{37}Cl-TCDD Fortification Level (ng)	^{37}Cl-TCDD % Recovery	Detection Limit*	TCDD Detected*	TCDD Fortification Level
water	1000	2.5	73	15 ppqd	85 ppqd	75 ppqd
water	1000	2.5	90	50 "	730 "	1000 "
water	1000	2.5	66	14 "	ND	10 "
water	1000	2.5	95	10 "	50 "	50 "
water	1000	2.5	78	15 "	116 "	100 "
water	1000	2.5	78	15 "	28 "	25 "
water	1000	2.5	100+	41 "	422 "	500 "
sediment	50	2.5	69	0.13 ppt	1.0 ppt	1.0 ppt
sediment	50	2.5	100+	0.14 "	1.0 "	1.4 "
sediment	10	2.5	100+	0.6 "	2.5 "	1.6 "
sediment	10	2.5	96	0.5 "	3.3 "	4.6 "
sediment	10	2.5	100+	2.0 "	23.0 "	17.0 "
sediment	10	2.5	68	4.0 "	30.0 "	35.0 "
sediment	10	2.5	100	0.7 "	ND	0 "

ppqd = Parts per quadrillion (10^{-15}).

ppt = Parts per trillion (10^{-12}).

* Corrected for recovery.

ND = Not detected.

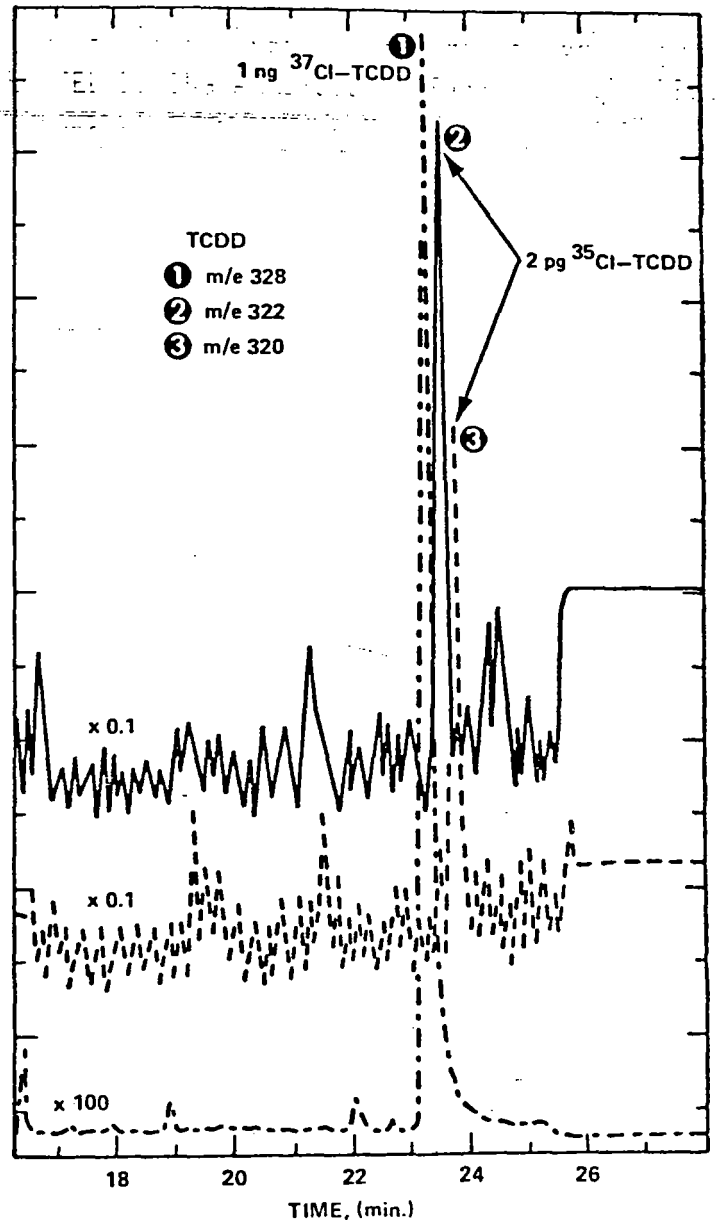

FIGURE 1. GLC/HRMS multiple ion selection response for 1 ng ^{37}Cl-TCDD and 2 pg ^{35}Cl-TCDD.

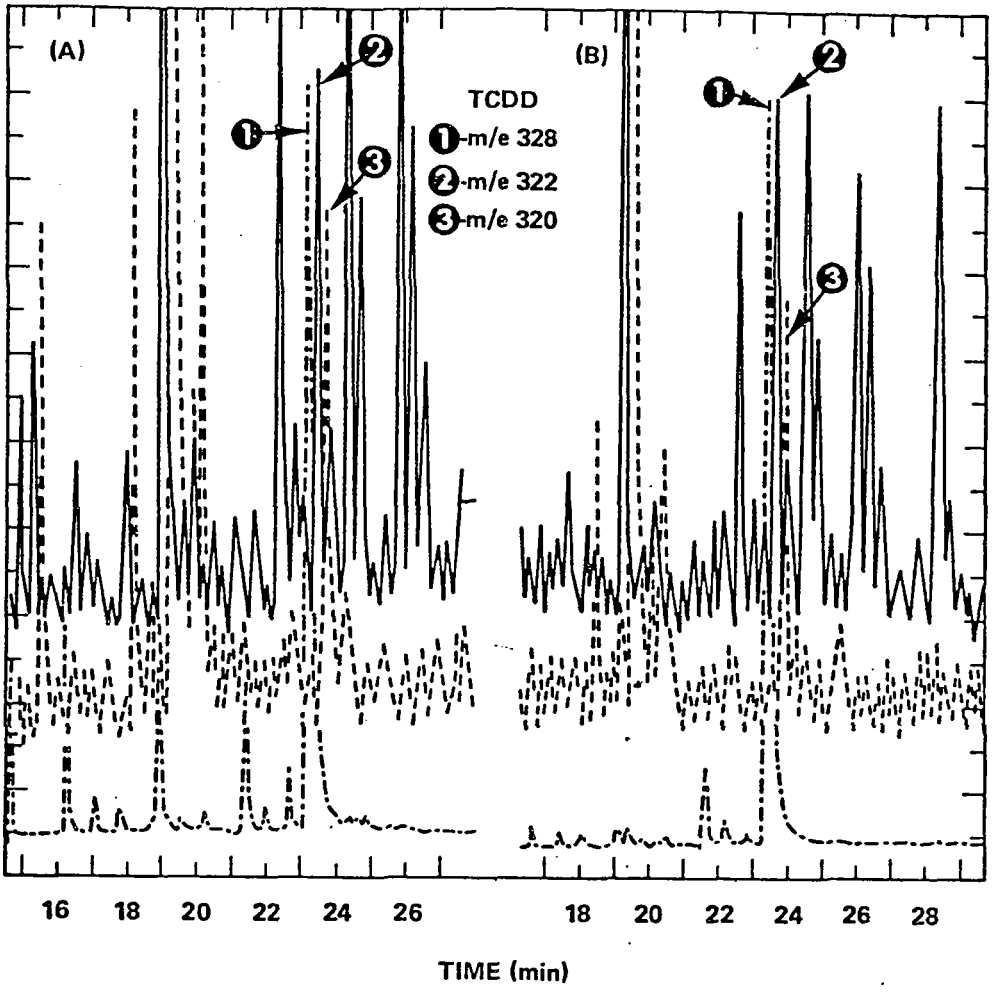

FIGURE 2. GLC/HRMS MIS monitoring analysis for TCDD residues in a human milk QA sample. (A) 2 µl of sample (fortified with 1 ppt TCDD). (B) 1 µl of sample fortified with 500 pg ^{37}Cl-TCDD and 1 pg ^{35}Cl-TCDD.

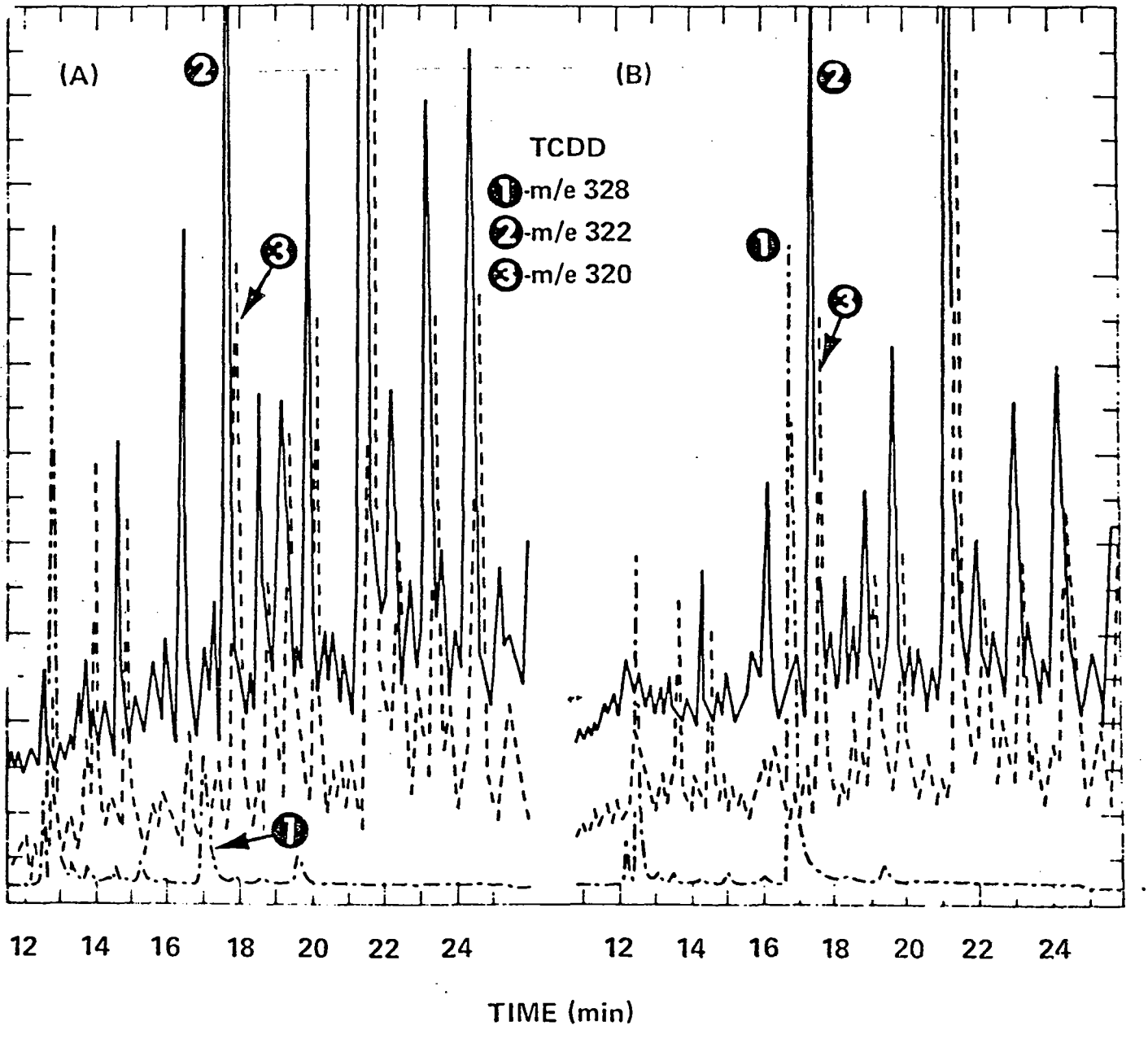

FIGURE 3. GLC/HRMS MIS monitoring analysis of a fish extract. (A) Sample 1 l from 50 µl; (B) Fortified sample, 0.5 µl from 50 l plus quantification standard.

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PUBLIC CONCERNS ABOUT 2,4,5-T

Wendell R. Mullison, Ph.D.

April, 1980

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He is a charter member of the Weed Science Society of America, a life member of the American Society of Plant Physiologists and the Botanical Society of America. He was chairman of the committee that revised the Herbicide Handbook which was published as the fourth edition in 1979 by the Weed Science Society of America. Wendell Mullison earned a doctoral degree in botany from the University of Chicago.

PUBLIC CONCERNS ABOUT 2,4,5-T

Wendell R. Mullison*

There appears to be considerable apprehension among certain sectors of the public about the use of the herbicide 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) which is used in many herbicidal formulations. These concerns are usually based upon inaccurate and often outright misstatements of fact that are frequently cited in the news media. This paper discusses certain public concerns about 2,4,5-T. The 2,4,5-T discussed in this paper contains the trace contaminant TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin). The legal limit for TCDD in 2,4,5-T acid in Denmark, Australia, New Zealand, and many other countries is 0.1 ppm[1]. Recent production runs of Dow products contain significantly less TCDD (0.02-0.04 ppm).

There has been a great deal of unfavorable publicity in the news media about the toxicity of 2,4,5-T. According to many accounts this herbicide is a harbinger of doom. The allegations are that 2,4,5-T causes tremendous human health hazards. However, the ... overwhelming scientific data clearly show that 2,4,5-T with its trace contaminant TCDD does not cause human health problems.

These alleged health problems have been grouped in the following classifications:

1. Miscarriages and birth defects
2. Cancer
3. Diseases or illnesses possible from a multiplicity of causes
4. Rare diseases with an unknown or obscure etiology

MISCARRIAGES AND BIRTH DEFECTS: BACKGROUND

The worldwide rate of spontaneous abortions or miscarriages has been estimated to be 15 to 20% according to the World Health Organization.[2] This estimate is probably low. Other authorities quote higher figures. A recent Great Britain report said 25% of all pregnancies result in miscarriage. One scientist[3] says "a pregnancy wastage of between 30 and 50% seems to afflict laboratory and wild animals, domestic breeds and man."

It is generally recognized that the majority of the miscarriages result from chromosomal or developmental abnormalities in the fertilized egg or the developing fetus. Thus, a miscarriage is Nature's way of handling a mistake.

*This paper was presented at the 33rd Meeting, Western Society of Weed Science March 18-20, 1980, Salt Lake City, Utah.

Birth defects also are far more common than is usually realized. In the United States[4] it has been estimated that 7% of all live babies born each year have a serious birth defect.

The U.S. Department of Health, Education and Welfare in a recent article[5] surveyed the incidence of 16 selected birth defects in the United States in 1970 and 1971 as well as in 1976-1977. They said, "There is no evidence for an overall increase or decrease in malformation rates (birth defects) since 1970." This same study indicated the rate of encephaly declined 5.4% while spina bifida declined by 6.7%.

The etiology of birth defects is not easily characterized although viral infections such as German measles are known to be a common cause. Based on surveys and case reports in medical literature, the following causes of birth defects and their frequency are: genetics — 20%; chromosomal aberration — 3-5%; radiation less than 1%; disease — 2-3%; maternal metabolic imbalance — 1-2%; drugs and environmental chemicals — 4-5%; and unknown causes — 65-70%.[6] It is noteworthy that 65% to 70% of birth defects still have an unknown cause today. Thus, even with our modern medical knowledge this is still a very poorly understood field.

The importance of the figures previously cited is that they show the chances of a woman having a miscarriage or a child with a birth defect are far greater than ordinarily realized. In fact, such problems really are not uncommon.

These problems of birth defects and miscarriages have been with mankind since prehistoric times, long before 2,4,5-T was manufactured. It therefore seems quite unreasonable to assume that 2,4,5-T is necessarily implicated as a cause of these problems, particularly when the charges are based on anecdotal reports. This is especially true when there is a large body of scientific evidence that indicates the use of 2,4,5-T does not cause human birth defects or miscarriages.

MISCARRIAGES AND BIRTH DEFECTS: 2,4,5-T SCIENTIFIC FACTS

2,4,5-T has been carefully studied in scientific experiments on seven species of mammals to determine whether it would cause birth defects. In six species of animals tested (monkeys, rats, rabbits, hamsters, sheep, and reindeer)[7-14], 2,4,5-T has been found to cause no birth defects and no spontaneous abortions or miscarriages (or the animal equivalent thereof). However, 2,4,5-T has been found to cause the birth defect of cleft palate in mice. Mice, however, are so highly susceptible to cleft palate that this defect can be caused by an experimental stimulus as mild as an airplane ride during pregnancy. Since this defect is so easily caused, its occurrence in mice is not a reliable indicator of hazard to humans.

Governmental committees in Australia and New Zealand, after studying the question of whether human birth defects are caused by 2,4,5-T, have found these allegations to be unfounded and have given a clean bill of health to 2,4,5-T. Dr. Donald P. Morgan, a physician in the Environmental Toxicology Division at the University of Iowa, reviewed the Australian report for EPA. He stated[15]:

> "The calculations confirm what one would expect on the grounds of common sense alone, i.e., that absorption of sufficient amounts of these agents to cause reproductive morbidity is extremely unlikely, if not impossible."

Dr. Morgan made some additional observations that are of interest:

> "Similar reviews of the same literature must have been completed by at least a hundred government agencies in the last five years. A study by the government of New Zealand in June, 1977, arrived at the same conclusions, using essentially the same investigative methods .... Interest in this aspect of human health (reproductive morbidity and congenital defects) will probably increase in the years ahead, and the public will be inclined to fasten on one or another agent as causative of birth defects, according to the fashion of the times."

Any discussion of alleged human miscarriages being caused by 2,4,5-T must include the Alsea II Oregon Study conducted for EPA. This came about as a result of a well-written letter to EPA and subsequent media publicity concerning eight women in the Alsea, Oregon area who had suffered 10 miscarriages[16]. The Alsea II Study is important because EPA said, in a press conference of March 1, 1979, when announcing the emergency suspension action to halt the use of 2,4,5-T and silvex:

> "We are taking emergency action today to halt the spring spraying of the herbicide 2,4,5-T on the basis of new information indicating its potential link to human miscarriages .... We have just received the results of a study which show a high probability that the herbicide is linked to actual human miscarriages in an area where 2,4,5-T is used regularly. New studies in the Alsea basin area of Oregon show a high miscarriage rate shortly after the spraying of 2,4,5-T in the forests."

According to EPA's press conference statement this Alsea II report was instrumental in prompting the Agency's emergency suspension action against 2,4,5-T and silvex.

Unfortunately, this Alsea II report is seriously flawed scientifically. The following common-sense points indicate why this report is considered to be invalid:

(1) There is no exposure data in the report that show the affected women ever came in contact with the herbicide. For instance, only

Birth defects also are far more common than is usually realized. In the United States[4] it has been estimated that 7% of all live babies born each year have a serious birth defect.

The U.S. Department of Health, Education and Welfare in a recent article[5] surveyed the incidence of 16 selected birth defects in the United States in 1970 and 1971 as well as in 1976-1977. They said, "There is no evidence for an overall increase or decrease in malformation rates (birth defects) since 1970." This same study indicated the rate of encephaly declined 5.4% while spina bifida declined by 6.7%.

The etiology of birth defects is not easily characterized although viral infections such as German measles are known to be a common cause. Based on surveys and case reports in medical literature, the following causes of birth defects and their frequency are: genetics — 20%; chromosomal aberration — 3-5%; radiation less than 1%; disease — 2-3%; maternal metabolic imbalance — 1-2%; drugs and environmental chemicals — 4-5%; and unknown causes — 65-70%.[6] It is noteworthy that 65% to 70% of birth defects still have an unknown cause today. Thus, even with our modern medical knowledge this is still a very poorly understood field.

The importance of the figures previously cited is that they show the chances of a woman having a miscarriage or a child with a birth defect are far greater than ordinarily realized. In fact, such problems really are not uncommon.

These problems of birth defects and miscarriages have been with mankind since prehistoric times, long before 2,4,5-T was manufactured. It therefore seems quite unreasonable to assume that 2,4,5-T is necessarily implicated as a cause of these problems, particularly when the charges are based on anecdotal reports. This is especially true when there is a large body of scientific evidence that indicates the use of 2,4,5-T does not cause human birth defects or miscarriages.

MISCARRIAGES AND BIRTH DEFECTS: 2,4,5-T SCIENTIFIC FACTS

2,4,5-T has been carefully studied in scientific experiments on seven species of mammals to determine whether it would cause birth defects. In six species of animals tested (monkeys, rats, rabbits, hamsters, sheep, and reindeer)[7-14], 2,4,5-T has been found to cause no birth defects and no spontaneous abortions or miscarriages (or the animal equivalent thereof). However, 2,4,5-T has been found to cause the birth defect of cleft palate in mice. Mice, however, are so highly susceptible to cleft palate that this defect can be caused by an experimental stimulus as mild as an airplane ride during pregnancy. Since this defect is so easily caused, its occurrence in mice is not a reliable indicator of hazard to humans.

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Governmental committees in Australia and New Zealand, after studying the question of whether human birth defects are caused by 2,4,5-T, have found these allegations to be unfounded and have given a clean bill of health to 2,4,5-T. Dr. Donald P. Morgan, a physician in the Environmental Toxicology Division at the University of Iowa, reviewed the Australian report for EPA. He stated[15]:

> "The calculations confirm what one would expect on the grounds of common sense alone, i.e., that absorption of sufficient amounts of these agents to cause reproductive morbidity is extremely unlikely, if not impossible."

Dr. Morgan made some additional observations that are of interest:

> "Similar reviews of the same literature must have been completed by at least a hundred government agencies in the last five years. A study by the government of New Zealand in June, 1977, arrived at the same conclusions, using essentially the same investigative methods .... Interest in this aspect of human health (reproductive morbidity and congenital defects) will probably increase in the years ahead, and the public will be inclined to fasten on one or another agent as causative of birth defects, according to the fashion of the times."

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3% of the basin was sprayed and in addition this was a forest area with the majority of people living elsewhere.

(2) There was no dose response effect; that is, when 2,4,5-T was applied to the forests at twice the dosage there was not a corresponding substantial increase of miscarriages.

The Environmental Health Sciences Center of Oregon State University has published a 93-page report with a 21-page supplement entitled "A Scientific Critique of the EPA Alsea II Study and Report with November 16, 1979 Supplement." This Oregon State University evaluation points out in detail the many inaccuracies and erroneous assumptions of EPA's Alsea II Report. The critique states that due to the many flaws in the study methodology the conclusions of EPA's Alsea II Report are wrong. The Oregon State University study is merely the latest criticism. The Alsea II data and report have been critically analyzed by highly respected statisticians, physicians, and other scientists from foreign countries including Canada, Great Britain, Australia, and New Zealand. Their scientists could find no justification for the claims stated in the Alsea II Report.

The Alsea II report was also carefully studied by the Scientific Dispute Resolution Conference on 2,4,5-T[17]:

> "The miscarriages reported in this study were not demonstrated to result from the spraying of the forests with 2,4,5-T."
>
> "The group found no evidence for an abortifacient (causing abortion) effect of TCDD in the human."

It is seldom indeed that a scientific report has received such detailed and universal criticism.

The Lancet[18], the leading medical journal of Great Britain, and one of the most influential in the world, characterized the Alsea II Report in this manner:

> "Independent statisticians have been unable to find any evidence in the data of a link between abortion and 2,4,5-T; and, the EPA, it seems, is now having second thoughts."

The Lancet 2,4,5-T article concluded:

> "To reduce the risks of chemical accidents, we need an inspectorate which is skilled, properly trained, and adequately paid. Getting the technology right is important, too. But it is a waste of effort, resources, and credibility to cry 'wolf' about 2,4,5-T when there is no wolf."

CANCER ASSESSMENT

Human cancer generally develops slowly over a latency period of many years and usually is a disease of old age. Thus, in studying possible causative agents, especially at low levels of exposure, it is

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necessary to go back approximately 20 years or more before there is proper human data to study. Since 2,4,5-T has been a commercial product for more than 30 years, there has been sufficient time for a possible carcinogenic effect to have been identified in humans.

During the Vietnam war and subsequently, a physician from North Vietnam, Dr. Ton That Tung, has alleged that there has been an increase in liver cancer from spraying of Herbicide Orange* for defoliation in Vietnam. Research[19] by Dr. Tung on this matter was presented at a scientific meeting in France.

In the discussion that followed, Dr. R. Favre made the following comments:

> "I have no opinion whatsoever concerning the role of defoliants promoting the appearance of primary cancer of the liver since my stay in Indochina goes back to 1949-1952 (prior to the Vietnam war). On the other hand, I was able to verify at this time, with astonishment, the extraordinary frequency of cancer of the liver with respect to its frequency in Europe. One should discuss the difference in diagnosis with amoebic hepatitis, especially since more frequently primary cancer of the liver in Vietnam is a febrile form accompanied by a localized and painful hepatomegalia."

Thus, Dr. Tung's allegation as to the cause of the high frequency of liver cancer in Vietnam is invalid since historically there has been a high incidence of this disease there. Tung also did not take into account other possible confusing causative factors such as aflatoxin. Aflatoxin is a common very poisonous mold that causes liver cancer.[20] Aflatoxin in spoiled grain could certainly have increased in Vietnam under wartime conditions. Another criticism of Tung's paper is that enough time had not elapsed to draw such conclusions about the increased incidence of liver cancer.

It is not surprising, therefore, that reviews by both the World Health Organization and the Cancer Assessment Group of EPA concluded that Tung's data was inadequate and did not prove Herbicide Orange caused an increase of liver cancer in Vietnam.

There have been nine long-term carcinogenic studies with rats and mice. The two most recent studies, reported last year, were done with rats; these were lifetime studies that used the latest and best technology available.[21,22] One of these studies was done in Germany, the other in the United States. The authors in both cases concluded that 2,4,5-T was not a carcinogen.

* Herbicide Orange was the code-name of a 50:50 mixture of the n-butyl esters of 2,4-D and 2,4,5-T. It contained 4.21 lb. of 2,4-D and 4.41 lb. 2,4,5-T acid equivalent per gallon.

These rat data are confirmed by seven long-term carcinogenic experiments with mice.[23] Review of these studies of 2,4,5-T with varying quantities of TCDD confirm each other and clearly show that 2,4,5-T does not cause cancer.

Medical surveillance of the workers engaged in the manufacture of Dow's 2,4,5-T has been carried out and is continuing. A recent published report[24] of some of these studies shows that among these workers there was no excess mortality from cancer caused by exposure to 2,4,5-T. The number of individuals studied is relatively small, due to the small work force involved. However, the results strongly indicate that 2,4,5-T is not carcinogenic. Since this chemical has been in production and use for over 30 years, there has been ample time for cancer to appear if it were a problem. Thus, the limited human data available are in agreement with the extensive animal data as to the non-carcinogenic effects of 2,4,5-T.

DISEASES AND ILLNESSES

Human illnesses mistakenly associated with 2,4,5-T are those with symptoms such as nervousness, chronic tiredness, and mental illness. Such symptoms are very common and are associated with many every day ailments having a multiplicity of causes such as normal menstrual difficulties, respiratory problems, flu, overwork, stress, and psychological factors. There are also obscure and rare medical problems that may arise with an unknown or poorly understood etiology. However, there is no scientific evidence that indicates 2,4,5-T causes such disorders.

The question of the toxicity of 2,4,5-T and whether it causes human health problems has been complicated by the trace contaminant TCDD which is an extremely toxic material.

TCDD TOXICITY: ANIMALS

Most of the toxicological investigations have been done with 2,4,5-T that contained various amounts of TCDD. However, in carefully controlled animal experiments with rats using only TCDD in both lifetime feeding studies[38] and three-generation reproduction studies[31], no-effect levels for TCDD have been found. These results were confirmed upon review by the Scientific Advisory Panel.[37]

A no-effect level has been demonstrated in chronic feeding studies[21] in rats using 2,4,5-T containing 0.05 ppm of TCDD. Such results support the findings from the experiments using TCDD alone. These studies clearly show that TCDD is not a practical hazard at the very low levels at which it is present as a trace contaminant in the herbicide 2,4,5-T.

The Council for Agricultural Science and Technology (CAST) reported that 200 to 2,000 toxic doses of 2,4,5-T would have to be administered, depending on the species, before a single toxic dose of TCDD would be received based on the trace amounts of TCDD

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present in 2,4,5-T.[25] This same report concludes, "T[illegible], the current level of TCDD in 2,4,5-T does not contribute significantly to the toxicity of herbicidal preparations of 2,4,5-T."

To further illustrate the negligible practical hazard from this trace contaminant in 2,4,5-T, CAST also said that if you assume a grazing animal about the size of a sheep or deer (175 lb or 80 kg and also the average weight of many a human) with the sensitivity of the most sensitive species known, the guinea pig, this animal would have to consume all the treated vegetation on more than nine acres of land to get a lethal dose. This assumes all the material is on the vegetation and that none of it decomposes. As a practical matter, TCDD on leaf surfaces is rapidly decomposed by sunlight. TCDD contacting the soil is immobilized immediately and gradually decomposes.

TCDD TOXICITY: HUMANS

There is some toxicological data on the effects of TCDD on humans that has been documented from industrial accidents. This information strongly suggests that the trace contaminant TCDD in 2,4,5-T does not constitute a problem to human health.

Trichlorophenol is used in the manufacture of 2,4,5-T and it is during this process that the impurity TCDD is formed. Subsequently, this impurity becomes the trace contaminant in 2,4,5-T. Data from industrial accidents indicate that chloracne is the first visible symptom of human over-exposure to TCDD. At Nitro, West Virginia there was an accident on March 8, 1949 at a plant manufacturing trichlorophenol. Workers in this plant were exposed to TCDD. All of the 121 workers who developed chloracne were studied. Recently a medical evaluation of this 30-year history on the Nitro episode[26] has been published:

> "it is important that no apparent excess in total mortality or in deaths from malignant neoplasms or diseases of the circulatory system were observed in a group of workers with a high peak exposure to tetrachlorodibenzodioxin who were followed over a period of nearly 30 years."

They also note the small number of deaths observed. Unfortunately these results, as the authors acknowledge, are not conclusive because of the small number of subjects available to be studied.

To further put this trace contaminant TCDD in perspective, the incident at Seveso, Italy is summarized. As a result of an industrial accident on July 10, 1976 at Seveso, approximately 37,000 people living in an area of about 6 square miles were exposed to varying amounts of TCDD.[27] Estimates of the total quantity of TCDD that was released into the atmosphere vary, from 1.5 to 3.7 pounds. CAST estimated there is only one ounce of TCDD in all the 2,4,5-T used each year in the entire United States. This unfortunate incident at

Seveso was unrelated to 2,4,5-T or its manufacture but this accident continues to provide useful information on the toxicity of TCDD to humans.

It is important to consider that the people of Seveso were exposed to thousands of times more TCDD than would ever be encountered from an accidental exposure to an application of 2,4,5-T for an agricultural use. Seveso and the entire region has been under medical surveillance since the accident. Technical specialists in many fields including statisticians, sociologists, epidemiologists, biochemists, pathologists, pediatricians, dermatologists, obstetricians, and neurologists, have been involved in studying possible health effects on this population.

From such industrial accidents it appears that TCDD is less toxic to humans than would be expected from the animal toxicological data. Although the people at Seveso were exposed to extremely high concentrations of TCDD, no serious medical problems have been identified except the skin disorder, chloracne. A report[27], approximately three years after the accident, states that nearly all the chloracne has healed. No spontaneous abortions, fetal malformations, neurological or psychological changes, unfavorable immunoresponses, or other various problems have been attributed to TCDD. This information is strong evidence that TCDD when present as a trace contaminant in 2,4,5-T presents no unreasonable hazard to human health.

DISPUTE RESOLUTION CONFERENCE

Another group of scientists carefully studied the scientific data known about 2,4,5-T and its trace contaminant TCDD at the Dispute Resolution Conference[28] in Arlington, Virginia near Washington, DC in 1979. These experts came to several conclusions which address the potential effect of 2,4,5-T on human health. Some of their conclusions are:

"2,4,5-T is not a carcinogen nor mutagen in animal test systems studied to date."

"Phenoxy herbicides containing TCDD have not been shown to be carcinogenic in humans in retrospective epidemiologic studies to date."

"In studies conducted in rats and monkeys, the apparent no-effect level in rats (for TCDD) was 0.001 μg/kg/day; a level 10 times below the demonstrated no-effect level in Rhesus monkeys." This means rats are ten times more sensitive to TCDD than monkeys.

"Analysis of the available data* leads this group to the conclusion that no adverse effects on human reproduction have yet been demonstrated after exposure to 2,4,5-T or TCDD."

* Data from the United States, Sweden, New Zealand, Australia, Vietnam and Italy were studied.

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GENETIC CONCERNS

Data from *in vivo* mammalian tests for possible germ cell mutations are best for predicting genetic risk to humans. Such tests to date show there have been no mutagenic effects of 2,4,5-T in mammals. Chromosomal studies[29] have been made in humans at Seveso, Italy who had been exposed to high concentrations of TCDD. This exposure was thousands of times higher than the actual exposure from herbicidal applications as used in the United States. The Seveso population have shown no evidence of chromosome abnormalities due to TCDD exposure.

Three-generation reproduction studies with 2,4,5-T[30] as well as with TCDD alone have shown that these chemicals are not mutagenic in mammals.[31] In addition, a chromosomal study[32] done on the workers at one 2,4,5-T manufacturing plant in the United States showed no chromosomal abnormalities in the exposed work force. This is strong evidence as to its nontoxicity from a genetic viewpoint.

ECOLOGICAL CONCERNS

A unique one square mile (640 acres) test site at the Eglin Air Force Base, Florida, was sprayed over an eight-year period with thousands of pounds of 2,4,5-T with its trace contaminant TCDD.[33] One test site in this area received 947 pounds per acre of 2,4,5-T between 1962 and 1964 with a formulation that contained approximately 33 ppm TCDD. This test gives results obtained under unusually extreme conditions that would never be reached in actual practice. The highest use rate currently for Dow's 2,4,5-T product, ESTERON® 245 Herbicide containing less than 0.1 ppm TCDD, is 16 pounds in 3 to 100 gallons of diluent applied to the basal stems and stumps of brush. This is a spot treatment and not an overall per acre treatment. Furthermore, it is not an annual application. The usual overall treatment is one-half to two pounds per acre and, except for rice, such treatments would not be applied annually. Range applications are made only once every three to five years. Forests are treated once or twice during their life span.

This area at Eglin has been the subject of an intensive ecological study of plant and animal life. The beach mouse, *Peromyscus polionotus,* one of the major inhabitants of the area, was thoroughly studied. There was no gross or histological evidence of any carcinogenic or teratogenic effect in adults or fetuses. The area originally defoliated after the application of this tremendous quantity of 2,4,5-T is now covered with vegetation going through the normal succession stages for the area. Species diversity and food chain studies showed no significant differences from the untreated area.

This ecological study[33] on 2,4,5-T has clearly shown that there were no permanent harmful effects to wildlife forms and flora of the region even when tremendously excessive amounts of 2,4,5-T containing very large amounts of TCDD (33 ppm) were applied.

- .The [onal Academy of Sciences (NAS) offers another noteworthy study on the uses of 2,4,5-T in Vietnam.[34] Also remember that the application rate of Herbicide Orange in Vietnam was approximately 26 pounds per acre of a mixture of 2,4-D and 2,4,5-T. This application was a much higher rate than would be encountered during normal agricultural uses. Their conclusions varied greatly from many sensational news articles that have appeared and still occasionally appear on this subject. NAS concluded that crops could be planted within one year or less from the last spraying (1971). They also point out there has been significant reforestation. It was specifically noted that much of the necessary reforestation was due to causes other than war. NAS concluded the sprayed forests would eventually be restored to productive levels if proper reforestation practices were followed.

Thus, there is substantial evidence that no ecological problems have developed or will develop from the commercial use of 2,4,5-T with its trace contaminant TCDD.

2,4,5-T USE HISTORY

How safe has 2,4,5-T really been when used for a long time? Manufacturers know a variant of Murphy's Law should be: If a product can be made to cause a problem, the public will find the way to make it happen. Therefore, the record of public usage can be important in judging the safety of a product. Two states which have used 2,4,5-T extensively have studied the herbicide's safety record.

The California Department of Food and Agriculture completed a detailed study April 6, 1978 on the aerial application of phenoxy herbicides in California.[35] Public hearings were also held on this subject. 2,4,5-T and 2,4-D have been in use in this state for 25 years. In their summary it was stated:

> "At the public hearings, allegations were made concerning gross, readily apparent effects of the herbicides, and these alleged gross effects were the target of a subsequent investigation by the Phenoxy Herbicide Investigation Team. None of these effects, such as human illness, animal deaths or deformities, plant damage, or environmental damage, could be attributed to or associated with spraying of phenoxy herbicides. Similarly, no substantiation could be provided for any correlation between geographical locations of residents in relationship to the spray site and the etiology of disease. Examination of pesticide illness reports from California physicians by this Department have not revealed any significant health hazards that can be attributed to the phenoxy herbicides as used today in California."

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Texas is the state where the most 2,4,5-T has been us Therefore, it is an excellent area to consider when studying the safety question of 2,4,5-T. Also, 82% of all the rangeland and pasture acreage treated with 2,4,5-T is in Texas and it is the largest producer of beef cattle in the United States. Comments of Texas Agricultural Authorities[36] on the safety of 2,4,5-T to humans and animals are extremely pertinent. Their comments on this subject are quoted in their entirety:

> "The chemical has been used in Texas since 1949-1978 (29 years). In this span of years, approximately 50,000,000 acres have been treated, with many areas of land receiving 3 to 5 applications. To date there has not been a single lawsuit because of attributed health damage to man or animal. There have been lawsuits on damage to vegetation outside of target areas. Percentage of calf, lamb and kid crop is up in Texas. There are less deformities in newborn animals than in the history of the livestock industry. The cause of practically all deformities has been traced to plants that historically cause deformities to fetuses."

The Texas and California summations of their experiences is convincing evidence that in the real world 2,4,5-T with its trace contaminant TCDD is safe for humans and the environment.

INDEPENDENT RISK ASSESSMENT OF 2,4,5-T

Another independent group of scientists have recently reviewed the scientific data pertaining to the safety of 2,4,5-T. The Scientific Advisory Panel (SAP) consisting of seven members was authorized by Congress under FIFRA to advise EPA on scientific questions related to suspension or cancellation actions or any new proposed regulations of EPA. The SAP is particularly concerned with the effect of EPA's proposed actions on human health and the environment.

The SAP on September 26, 1979 issued their review of EPA's proposed notice of intent to hold a hearing on the presently non-suspended uses of 2,4,5-T and silvex. The Panel's initial recommendation stated:

> "The Scientific Advisory Panel recommends that the Agency not hold such a meeting at this time. After extensive review of the data we find no evidence of an immediate or substantial hazard to human health or to the environment associated with the use of 2,4,5-T or silvex on rice, rangeland, orchards, sugarcane, and non-crop uses specified in the decision documents."[37]

This reference pertains to the present non-suspended uses of 2,4,5-T and silvex. But recognize that the Scientific Advisory Panel's safety evaluation of 2,4,5-T with its trace contaminant TCDD would also apply to the presently suspended uses of 2,4,5-T.

CONCLUSIONS

In summary, there is a tremendous volume of scientific information available on 2,4,5-T. This herbicide has been the subject of many carefully controlled toxicological experiments, perhaps more than any other pesticide on the market today. The known scientific data about this chemical, combined with a 30-year history of safe use, fully support these following conclusions: 2,4,5-T is a safe, efficient, and selective herbicide to control weeds and brush and its use has not caused cancer, birth defects, or miscarriages. 2,4,5-T with its trace contaminant TCDD can be and has been used safely and effectively without harm to people, animals, or the environment.

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Dr Garfalo

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The Development and Prognosis of Chronic Intoxication by Tetrachlordibenzo-p-dioxin in Men

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ABSTRACT. During 1965 to 1968, 80 workers who had been engaged in the production of 2, 4, 5-sodium trichlorphenoxyacetate and butylester of trichlorphenoxyacetate acid became ill. The cause of the illness was 2, 4, 7, 8-tetrachlordibenzo-*p*-dioxin. A 10-yr study has been conducted for 55 exposed individuals. The majority of the patients developed chloracne, and 11 manifested porphyria cutanea tarda. Approximately one-half of the patients suffered from metabolic disturbances, i.e., pathologically elevated lipids with abnormalities in the lipoprotein spectrum, and two-fifths of the patients had pathological changes in the glucose tolerance test. One-third of the patients had biochemical deviations indicative of a mild liver lesion. Histological examination revealed light steatosis, or periportal fibrosis, or activation of Kupffer cells. Fluorescence of the liver tissues was present in ultraviolet light. In 17 persons symptoms of nervous system focal damage existed, with predominance of peripheral neuron lesion of the lower extremities (verified by EMG examination). The majority of patients suffered from various psychological disorders. As of this date, two patients have died of bronchogenic lung carcinoma; one of liver cirrhosis; one of a rapidly developed, extremely unusual type of atherosclerosis precipue cerebri; and two patients have died in traffic accidents. The conditions of most other patients have improved.

PERHAPS THE most potent man-made toxin presently known is 2, 3,7,8-tetrachlordibenzo-*p*-dioxin (TCDD), a solid substance that is insoluble in water and slightly soluble in fats and chlorinated solvent. It is a heat-stable, amphoteric substance, and exerts its biological effects at extremely low concentrations. TCDD is not translocated in plants, and has a half-life in soil of about 1 yr. Microbial degradation of TCDD is reported to rarely occur in nature. Irradiation of TCDD in water produces few changes after 14 days.[1] Due to its extreme toxicity, its chemistry has not been fully evaluated. There are considerable differences in species susceptibility, but in all laboratory animals the lethal effect is slow and ensues several days or weeks after a single dose.[2]

TCDD is formed as a by-product during the synthesis of 2,4,5-trichlorphenol, which involves the hydrolysis of 1,2,4,5-tetrachlorbenzene using methanol and caustic soda at atmospheric pressure. TCDD is formed in the distillate by the condensation of two molecules of sodium trichlorphenolate influenced by the highly exothermic decomposition of sodium-2-hydroxyethanol. Trichlorphenoxyacetic acid (2,4,5-T), a herbicide produced commercially prior to 1965, contained 30 mg/kg TCDD. Currently, 2,4,5-T, containing < 0.05 mg/kg TCDD is produced in several countries and is available in commercial quantities.[1]

Several accidents have occurred during the industrial synthesis of 2,4,5-trichlorphenol and 2,4,5-T, the consequences of which are well described in the literature.[2-7]

The most recent large-scale TCDD intoxication that occurred in Seveso, Italy in 1976 renewed the interest of specialists and the general public. Since we have acquired considerable information during the 10 years we have observed patients with chronic TCDD intoxication, we have chosen to present our findings in this study.

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Table 1.—Physiologic, Neurologic, Psychiatric, and Dermatologic Observations for Fifty-Five Males with TCDD Intoxication*

	Percent of patients (N = 55)
Medical lesions	
Porphyria cutanea tarda	20
Only uroporphyrinuria	21
Hypercholesterolemia	56
Hyperlipemia	67
Hyperphospholipemia	42
Diabetes mellitus	8
Low glucose tolerance test value	19
Hepatic lesions	20
Increased total blood proteins	13
Increased plasma	
γ globulins	36
α_1 globulins	44
Decreased plasma albumin	33
Neurological lesions	
Pathological changes without any connection with exposure exposure to TCDD	8
Polyneuropathy	23
Encephalopathy	7
Psychiatric changes	
Severe neurotic symptoms and signs with disorders of vegetative nervous system	64
Neurasthenia syndromes with depressive component	11
Depressive syndromes with endogenous component	8
Pseudeoneurasthenia syndromes in patients with arteriosclerosis of central nervous system	14
Skin lesions	
Chloracne of different severity	95

*All results were obtained at the beginning of intoxication.

MATERIALS AND METHODS

The Department of Occupational Diseases University Hospital in Prague admitted 55 males for the first time in 1968 and 1969 suffering from chronic TCDD intoxication, who had been engaged in the production of sodium 2,4,5-trichlorphenoxyacetate and butyl ester of 2,4,5-trichlorphenoxyacetate acid. This incidence of mass intoxication occurred during a time when alkaline hydrolysis of tetrachlorbenzene at atmospheric pressure was used to increase and shorten reaction time, and probably during the same time the mother liquor, which was originally disposed of, was put back into production. The concentration of TCDD in the work atmosphere was never measured; however, TCDD was found in the final product—Arboricide E—and several years later, was also found in the building and on wall paintings.

Originally, 80 of 400 persons who were engaged in this production became ill. Only 55 of those persons have been observed on a long-term basis; the remaining 25 persons either refused to be examined in our hospital or moved, leaving no address. Those who moved were usually foreigners who returned home. The mean age of the 55 intoxicated individuals was 36.3 [standard error (SE) = 11.2] at the time the outbreak of illness occurred. We do not provide any further details about production conditions and the course of the illness during the initial 3 to 4 yr in this article, since these were described in our 1974 report;[7] therefore, we shall only provide the most important data required for understanding the development of the illness.

RESULTS

The first symptoms of intoxication which occurred at the time of exposure were: gradual, but rarely sudden, formation of chloracne; a feeling of sickness; fatigue; weakness in the lower extremities; and frequently, pain under the right coastal arch. In 10 patients, however, the first symptoms of intoxication appeared several months after work with TCDD was completed. The intoxication affected several organs and systems (Table 1). It should be noted that only the most severely affected patients exhibited all of the above-listed symptoms, and the extent of organ damage was not uniform for these patients. The severity of illness was not related to the duration of exposure, job status, or age.

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Table 2.—Cause of Death for Six Patients with TCDD Intoxication

	Age (yr)	Duration of Exposure	Duration of Intoxication	Severity of TCDD Intoxication Cause of Death and Post-Mortem Findings
1.	57	9 mo	2 yr	Severe type of TCDD intoxication. Unusual type of very severe arteriosclerosis of cerebri, liver, pancreas, and kidneys. Dementia cerebri. Immediate cause of death: bronchopneumonia.
2.	59	3 yr	2 yr	Severe type of TCDD intoxication. Bronchogenic carcinoma.
3.	47	2, 5 yr	3 yr	Severe type of TCDD intoxication. Bronchogenic carcinoma.
4.	31	15 shifts	4 yr	Slight signs of TCDD intoxication. Traffic accident—comminuited fractures of lower extremities. Immediate cause of death: fat embolisation to lungs.
5.	63	7 mo	5 yr	Severe chloracne and slight signs of lipid metabolism disorder. Traffic accident—fractura colli femoris. Cause of death: bronchopneumonia hypostatica.
6.	40	32 shifts	9 yr	Severe type of TCDD intoxication; about 3 yr before death; complicated with hepatitis epidemica, type B. Macronodular cirrhosis with signs of portal hypertension, ascites. Cause of death: hepatic coma.

The progression of illness was not linear. In some patients, symptoms and signs of intoxication that were present from the very beginning of the illness, became more severe during the 3-4 yr that followed intoxication. In others, however, organs and systems that were functionally normal during the beginning of illness later became impaired. Deterioration occurred suddenly, the eliciting factors sometimes being intercurrent illness, stress, or unusual physical exertion. In other patients, however, deterioration could not be ascribed to specific factors, but was probably attributable to the spontaneous course of the illness proper. Deterioration and subsequent improvement did not occur consistently in individual organs and systems. During 5 yr of intoxication, the health status of most patients was stabilized; some patients' status even improved. During this time 6 patients died, the causes of which are listed in Table 2, and 5 refused our systematic medical care. The authors are therefore providing medical care to 44 of the original 55 patients; all patients' conditions have improved, but no patient is entirely healthy. Most of these individuals gradually re-entered the workforce, and established themselves in society. During their illness, 18 healthy children were born. The wives of two patients had spontaneous abortions in their third month of pregnancy, but the cause is not known because the cases were not autopsied.

The impact of the intoxication varies. There are still pathological deviations in lipid metabolism in most of the patients. Figure 1 shows mean values of total cholesterol measured when the illness was first noted and "to-date" values, both compared with a control group. Figure 2 shows similar results for phospholipid measurements. At the beginning of intoxication, lipid values were pathologic in more than one-half of the patients (mean = 13.85 g/L). Currently, the mean values of lipids do not significantly differ from controls. Lipoproteins could be examined only in recent years; we found elevated mean values in the pre-beta fraction [VLDL (Fig. 3)]. In the blood protein spectrum, pathologically increased alpha 1 and gamma globulin levels have normalized, but there are still elevated mean values of total blood proteins in comparison to controls: 7.5404 (SE = 0.5499) against 7.0296 [SE = 0.4462 ($P = .01$)]. For all internal examinations we used the Student's t test for statistical evaluation.

Currently, one-fifth of the patients has a pathological diabetic glucose tolerance test and another one-fifth has a pathological flat glucose tolerance test. Pathologically high excretion of uroporphyrins, together with other signs of porphyria cutanea tarda, were present at the outset of intoxication in one-fifth of the patients. The same fraction had a slightly increased uroporphyrin excretion in urine (to 100 μg/24 hr) without any skin manifestations. Excretion of coproporphyrin in urine was, only rarely, substantially affected; mean values of delta-aminolevulnic acid in

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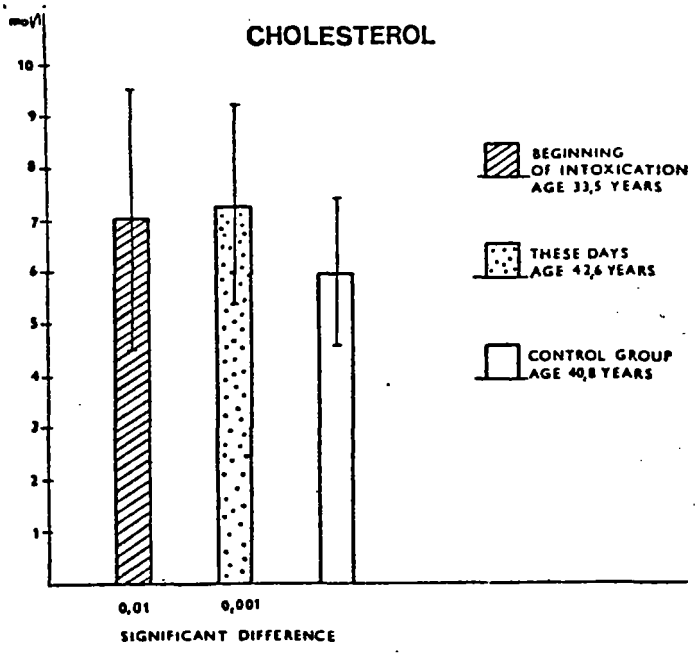

Fig. 1. Values of cholesterol in serum of patients at the "beginning of intoxication" and "these days" in correlation with "control group."

urine were, during the first years of intoxication, significantly higher than in controls. At present, pathological excretions of uroporphyrins and skin manifestations of porphyria cutanea tarda are very rare. Similarly, functional liver tests (i.e., bilirubin, thymol pyruvic transaminase in serum, bromsulphalein test) are seldom pathological, whereas in the beginning of the illness, one-fifth of the patients had mild hepatic lesions. Liver necropsy and biopsy showed that even for the most severe forms of intoxication, only slight morphological deviations in terms of mild steatosis or periportal fibrosis occurred; even when most severely affected patient, who was the first victim of intoxication, showed only slight activation of Kupffer cells. Only one patient, who died in hepatic coma attributable to concommitant infectious hepatitis B (HBAG positive), displayed large-nodule active cirrhosis with manifestations of portal hypertension and ascites.

In all decreased patients and for those in whom liver biopsy was performed, liver tissue fluorescence in ultraviolet (UV) light was present, even in cases where repeated examinations revealed normal values of urinary porphyrins. Throughout the entire observation period of the whole patient group, goal-directed examinations did not indicate any signs of toxic lesions in the myocardium or kidneys, and hemopoiesis was not affected. There were no pathological values of phosphatase alkaline serum and iron in serum, nor ophtalmological impairments that could be attributed to the effect of TCDD.

The results of repeated neurological examinations are presented in Table 3. During the initial 3-4 yr of illness, the lesion in the peripheral neuron of the lower extremities deteriorated, which in most patients, was present from the onset of intoxication. In some cases, polyneuropathy appeared only during the course of the illness; in these patients it could be reliably documented that clinical and electromyographic examinations were normal at the

Table 3.—Results of Neurological Examinations for Individuals Exposed to TCDD

	Onset ($N = 55$)	At Present ($N = 44$)
Normal neurological examination	62%	51%
Pathological changes without any connection with exposure to TCDD	8%	9%
Polyneuropathy	23%	31%
Encephalopathy	7%	9%

outset of intoxication. In addition, in four patients there was peripheral lesion N VII, which occurred either in connection with polyneuropathy of the lower extremities, or was isolated. After 4 yr of illness, the neurological picture stabilized; three patients even showed improvement. Encephalopathy sometimes develops in persons aged 50-65 yr, accompanied by organic psychosyndrome on the basis of atherosclerosis of cerebral arteries. Very rarely is ischemic heart disease concurrently present. The patient who presently has the most severe form of the illness is also afflicted with paroxysms of temporal epilepsis and

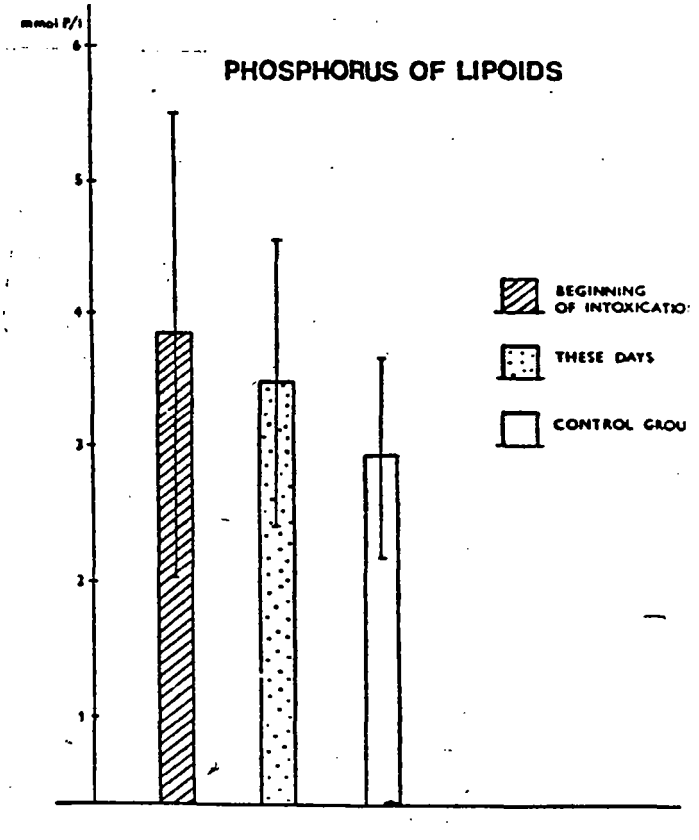

Fig. 2. Phosphorus of lipoids in serum at the "beginning of intoxication" and "these days" in correlation with "control group."

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processes which still remain disturbed at a time when TCDD, in view of its short biological half-life of 21 days, should be eliminated from the organism. There is a considerable species-specificity in the sensitivity of laboratory animals to this toxic substance, and the impact on individual organs differs in different species. In monkeys, as in humans, a permanent sign is skin lesions, while hepatic impairment is in the background.

The long-term and relatively complex observation of our patient sample with chronic TCDD intoxication permits us to express a hypothesis on the nature and prognosis of this illness in man. There is no doubt that TCDD was present in the air of the workshop, and because of the constantly changing technology, its concentration in air was inconstant. TCDD caused intoxication which in turn, nonuniformly affected a number of important organs and systems. The course of the illness was more severe in individuals when the illness started during exposure than when the first symptoms appeared several months after cessation of this study.

Even though most of the patients did not experience all symptoms and signs of intoxication, and some patients showed only symptoms and signs in different combinations, we assume that in this type of intoxication all the systems and organs mentioned in this study were simultaneously affected, although some only slightly. This assumption is supported by several facts. Fluorescence of liver tissues in UV light, which is a sign of pathological porphyrin metabolism, was present in all cases of necropsy and biopsy, i.e., in persons in whom long-term monitoring of porphyrin excretion in urine and delta-aminolevulinic acid values were constantly within normal limits. Probably a slight subclinical lesion was present. Further evidence was furnished in repeated neurological examinations. Polyneuropathy of the lower extremities was manifest in some patients only in the third or fourth year of illness; we have definite clinical and electromyographic evidence that the first examinations conducted when the illness commenced were entirely normal. The manifestation of these lesions was promoted by unspecific stress (e.g., greater physical exertion, intercurrent inflammation of upper respiratory pathways, stress situations, etc.), none of which could, by itself, produce a similar illness. Similarly, slight hepatic lesions and diabetes mellitus—manifest or latent—appeared in some patients 1 or 2 yr *after* intoxication, and were related with some unspecific stress, or sometimes they occurred independently. The alteration of many metabolic processes and functional disturbances of several organs indicate a high probability that TCDD affects general enzymatic processes that are present and necessary for the activity of more systems.

Other than the direct toxic effect of TCDD on nervous tissues, we also assume that indirect intervention may exist, i.e., impaired metabolic processes in lipid and hydrocarbon metabolism. The incidence of polyneuropathy was more frequent in patients with manifest or latent diabetes. Changes were also marked in the central nervous system on the basis of atherosclerosis of cerebral arteries, the development of which might be enhanced by hypercholesterolemia, hyperlipemia, hyperphospholipemia, and higher pre-beta fraction (VLDL) in the lipoprotein spectrum. Unfortunately, we could not arrange the autopsy of all deceased patients in a qualified, university surgery where detailed attention could have been given to atherosclerosis. The patient who was the first to die, and who had demonstrated the most severe clinical and laboratory signs of intoxication, was thoroughly examined in this respect and autopsy revealed very severe, entirely untypical atherosclerosis. Detailed information is given in our study of 1974.[7]

The mass occurrence of psychic disturbances, predominantly anxiety and depression, was in the first years of illness mainly due to exogenous influences: fear of death; disfigurement; invalidity; marital problems; and in young individuals, the difficulty of entering intimate, close relationships because of the disfigurement resulting from chloracne. Gradual adjustment to the illness, its improvement (especially on the visible skin area), and return to normal work and social life all contributed to decrease psychic disturbances, thus facilitating better adaptation to life.

It does not appear that chronic intoxication in our patients unfavorably affected the quality of offspring. All of the 18 children born to intoxicated individuals were free of the developmental anomalies; their postnatal development has also been normal. Two spontaneous abortions in 10 (10%) pregnant wives of our patients is less than the number of worldwide spontaneous abortions relative to the number of pregnancies (15-20%).[2]

In recent years the possible carcinogenicity of TCDD has been widely discussed.[1] Even though two of our patients died of bronchogenic lung carcinoma after 2 and 3 yr of the intoxication, no definite conclusions can be drawn in view of the small number of persons in the group.

This illness is characterized by its non-uniformity, both in its developments and its effects on individual organs. Deterioration was always sudden, followed by less gradual improvement. This is a rather cheerless balance of an illness, where the mechanism of origin and cause of unusual development we know virtually nothing. Being aware of this poor understanding, we were very careful in our therapy and concentrated on the prevention of further possible stressful situations that could have aggrevated the illness. We attempted to remove all neurotoxic, hepatotoxic, and dermatotoxic substances from the work and living areas. Each patient received a list of drugs known for their hepato- or neurotoxicity, and those drugs suspected of producing porphyria cutanea tarda, which he was instructed to avoid. Rarely did we apply medicines to alleviate symptoms which were particularly distressing. The treatment of chloracne is discussed elsewhere by the dermatologist, Jirásek.[8,9]

In our paper we wished to indicate the importance of having a thorough understanding and knowledge of undesired by-products resulting from synthesis or manufacture of various products, being alert to changes in technology and to systematically protect the health of workers.

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

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ABSTRACT. The presence of 3,3',4,4'-tetrachloroazobenzene (TCAB) was determined by high performance liquid chromatography in 3, 4-dichloroaniline and herbicides made therefrom. The concentrations of TCAB in 3, 4-dichloroanilines and in different herbicides from a variety of manufacturers ranged from 9 to 1400 μg/g (ppm). The chloracnegenic potential of these products, as determined by rabbit ear test, suggests that it is in the same range of 2, 3, 7, 8-tetrachlorodibenzodioxin, a known potent chloracnegenic agent.

RECENTLY, some outbreaks of chloracne in groups of chemical workers have been attributed to 3,3',4,4'-tetrachloroazobenzene (TCAB) and 3,3',4,4'-tetrachloroazoxybenzene (TCAOB) as contaminants in 3,4-dichloroaniline and its herbicidal derivatives.[1,2] These contaminants are by-products of the commercial synthetic process.[3] In addition, several workers have reported that the herbicides degrade in soil to produce TCAB and TCAOB.[4] Chlorinated azobenzenes are structurally similar (isosteric) to the chlorinated dibenzodioxins and dibenzofurans, which also cause chloracne. Poland has reported that chlorinated dibenzofurans, dibenzodioxins,

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PROCEDURE FOR DETERMINATION OF MONO-,DI-,TRI-, AND TETRACHLORO DIBENZO-P-DIOXINS IN 2,4-D ESTERS

Reagents:

1. Silica gel 60 (E. Merke) 70-230 mesh activated overnight at 125°C.
2. Alumina Basic (Woelm Al_2O_3 Activity I)
3. Anhydrous Na_2SO_4.

Procedure:

1. Prepare a silica gel column using a glass column ~~25~~ 60 cm x ~~1.5~~ 2.0 cm I.D. fitted with a teflon stopcock. Add 50 mL. hexane to the column. With a glass rod, pack the bottom of the column with a plug of glass wool. Top the plug with Ottawa sand to about 1 cm. Weigh 50.0 g. of activated silica gel, make a slurry of silica gel in hexane using about half of it, and pour into column with solvent flowing at a very slow rate. Slurry the remaining silica and pour it in. Allow the column to settle and the solvent to fall to just above the level. Wash down the gel from the sides of the glass column. Top off the silica gel with about 1.0 cm of anhydrous sodium sulphate. Allow the level of solvent to fall just below the sodium sulphate.

2. Weigh 2.0 g. of ester sample and transfer onto silica gel column by using 5-10 mL. of 30% CH_2Cl_2/hexane.

3. Allow the level of the sample to fall below the top of the Na_2SO_4 layer. Elute using 150 mL. of 30% CH_2Cl_2/hexane. Discard first 30 mLs. Collect the remaining eluate into a 250 mL. R.B. flask.

4. Concentrate the eluate to 1-2 mL. under reduced pressure on a rotavapor.

5. Prepare a basic alumina column (Woelm basic Alumina Activity I as is) using a glass column 25 cm x 1.5 cm I.D. fitted with a teflon stopcock. Pour about 10 mL. hexane into the column. Using a glass rod, pack a small glass wool plug at the bottom of the column making sure all air bubbles are removed. Pour Ottawa Sand Standard sand to about 0.5 cm height on top of glass wool. Fill column to just below full. Pour 15 g. of alumina slowly into column while allowing solvent to slowly run out so that a well-packed, uniform bed of alumina is made. Wash down the column wall to remove adhering particles. With solvent a few cms above the top of the alumina, pour anhydrous sodium sulfate to a height of 0.5 cm on alumina. Wash wall and allow solvent to just fall below the top of the sulfate layer.

6. Transfer residue from concentration step quantitatively onto the basic alumina column with 3 x 2 mL. hexane washings of flask.

7. Elute the column with (1) 100 mL. hexane
(2) 100 mL. 2% CH_2Cl_2/ hexane
(3) 100 mL. 5% CH_2Cl_2/hexane
(4) 100 mL. 10% CH_2Cl_2/hexane
(5) 50 mL. 30% CH_2Cl_2/hexane
Discard 1 and 2 and collect fractions 3, 4 and 5 in a 500 mL. R.B. flask.

8. Concentrate the fraction to 1-2 mL. under reduced pressure on a rotavapor.

9. Quantitatively transfer the residue to a 5 mL. graduated centrifuge tube with 3 x 1 mL. wash with benzene. Take the residue to dryness under a gentle stream of nitrogen with warming in a water bath.

10. Make the residue to 0.100 mL. with hexane for GC/MS analysis.

Mass Spectrometry Laboratory,
Laboratory Services Division,
Food Production and Inspection Branch,
Agriculture Canada.

May, 1981.

DIOXIN STANDARDS

COLUMN: 25M FUSED SILICA COATED WITH SP2100; 225 DEG; PRESSURE 20 PSI.

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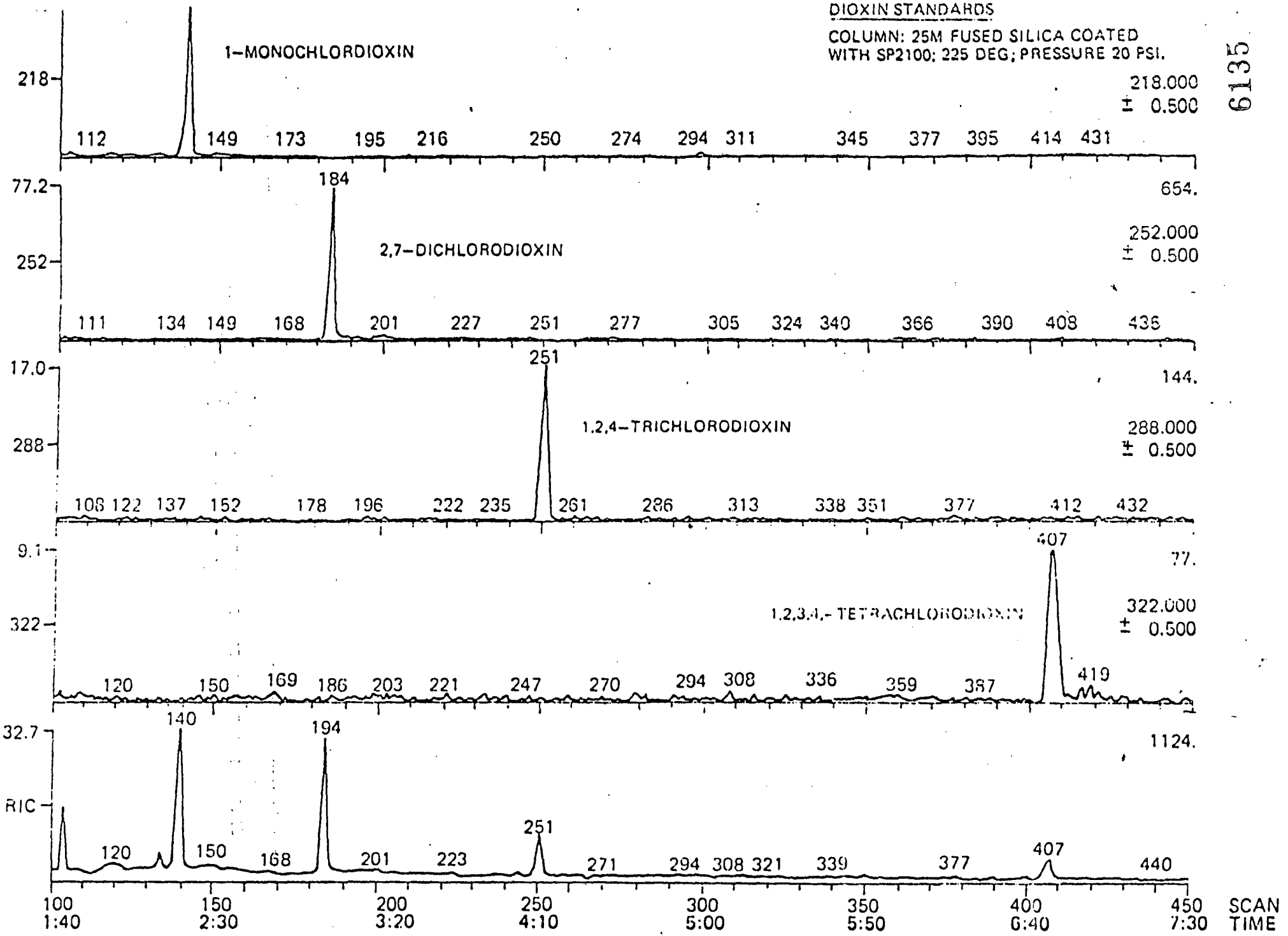

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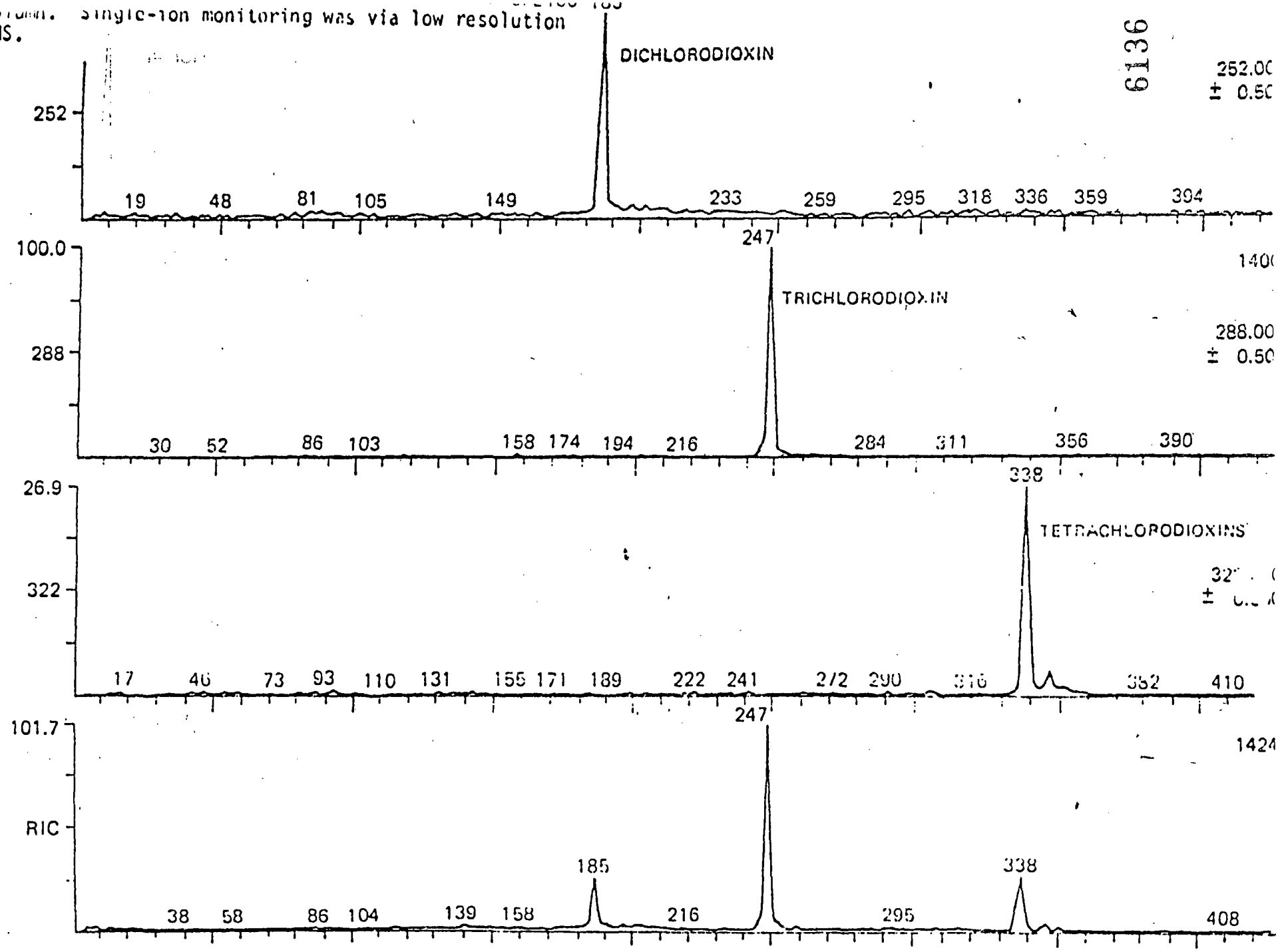
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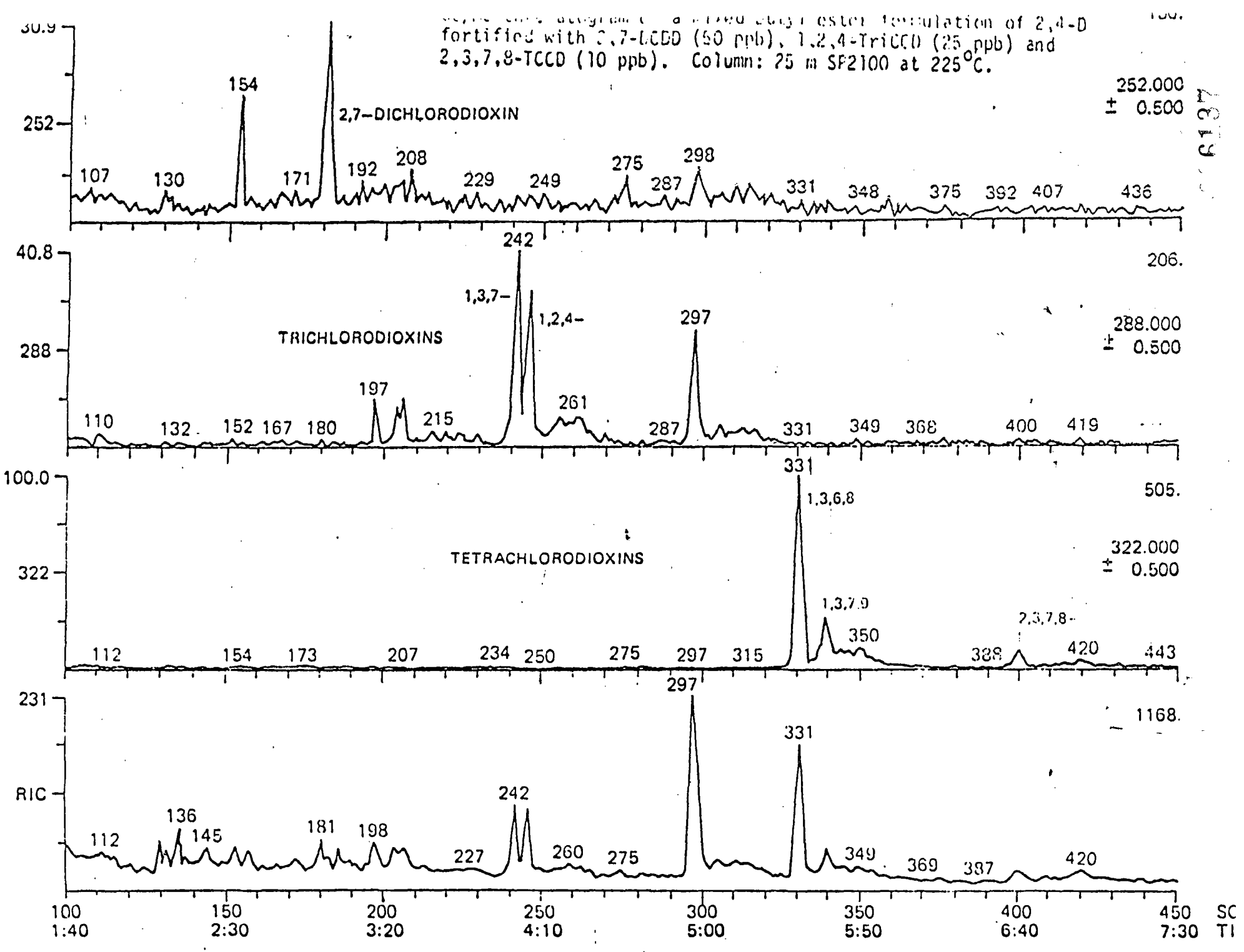
DICHLORODIOXIN
252
252.00
± 0.50
19 48 81 105 149 233 259 295 318 336 359 394
100.0
247
TRICHLORODIOXIN
288
288.00
± 0.50
30 52 86 103 158 174 194 216 284 311 356 390
26.9
338
TETRACHLORODIOXINS
322
17 46 73 93 110 131 155 171 189 222 241 272 290 316 352 410
101.7
247
RIC
185
338
38 58 86 104 139 158 216 295 408


fortified with 2,7-DiCDD (50 ppb), 1,2,4-TriCDD (25 ppb) and
2,3,7,8-TCDD (10 ppb). Column: 25 m SP2100 at 225°C.
30.9
252
154
2,7–DICHLORODIOXIN
252.000
± 0.500
107
130
171
192
208
229
249
275
287
298
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348
375
392
407
436
40.8
288
242
1,3,7–
1,2,4–
297
TRICHLORODIOXINS
206.
288.000
± 0.500
110
132
152
167
180
197
215
261
287
331
349
368
400
419
100.0
322
331
1,3,6,8
505.
TETRACHLORODIOXINS
322.000
± 0.500
1,3,7,9
2,3,7,8–
350
112
154
173
207
234
250
275
297
315
388
420
443
231
RIC
297
331
1168.
242
136
145
181
198
227
260
275
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369
387
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100
1:40
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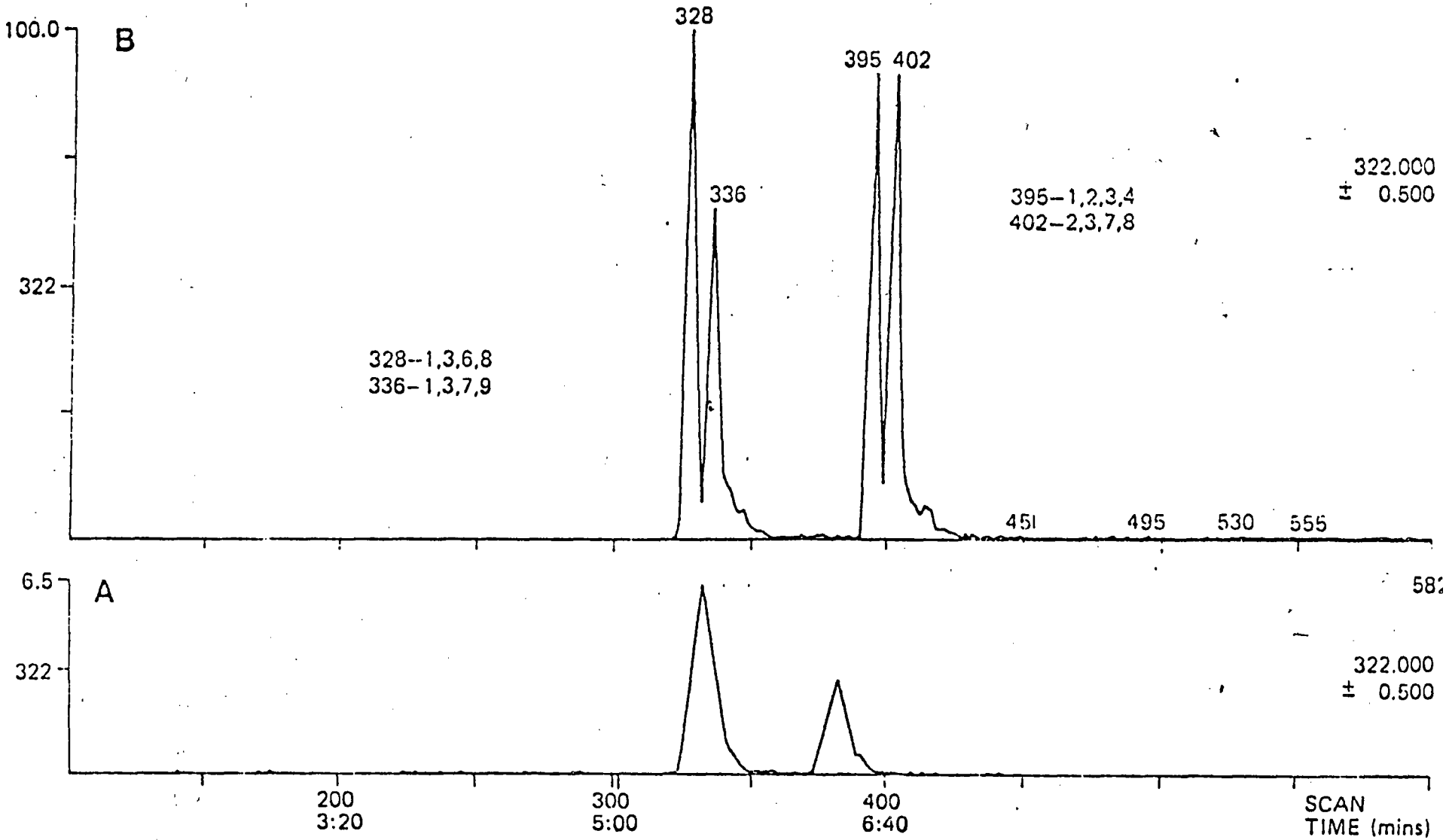
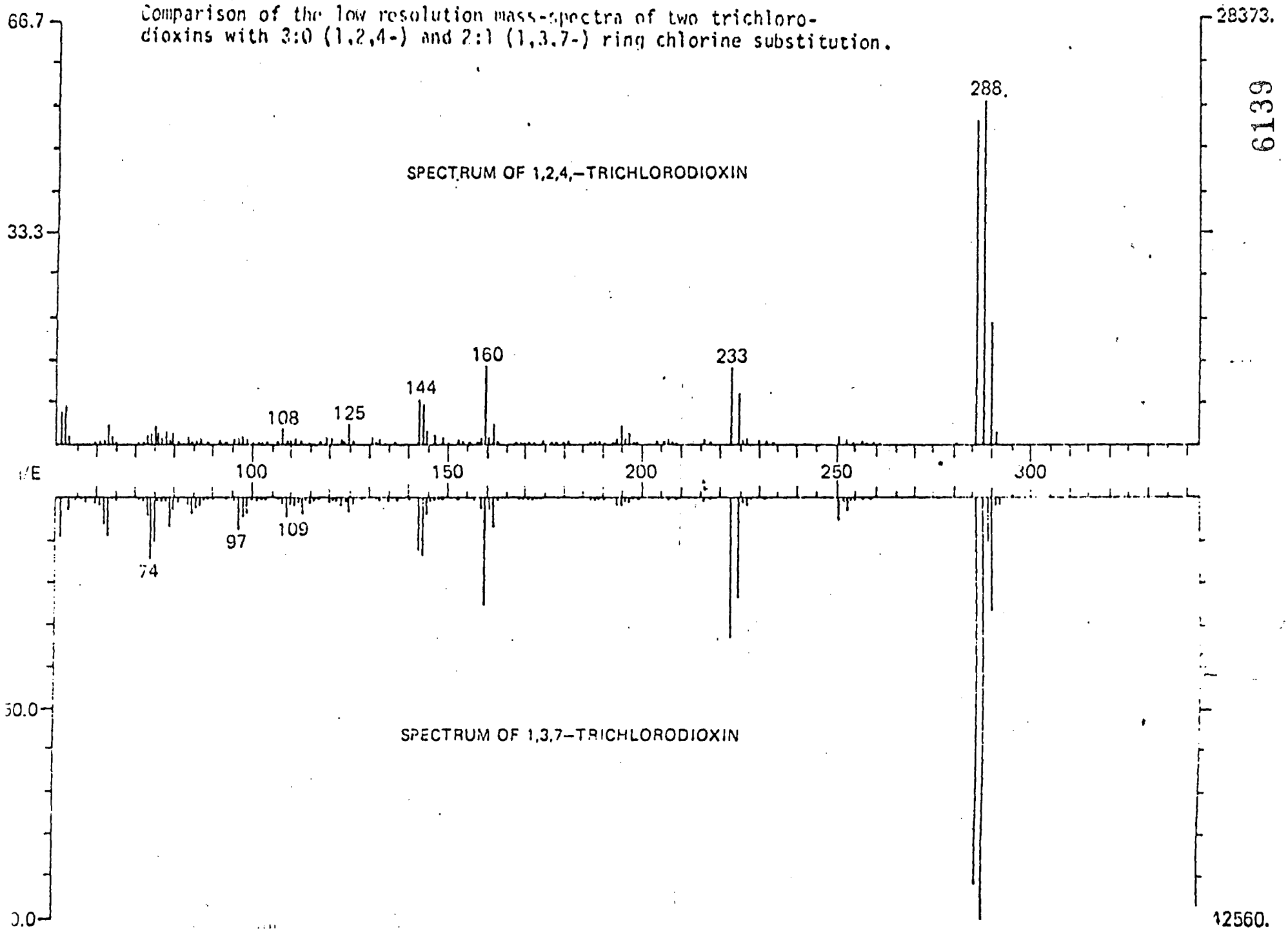


Fig: Chromatograms showing separation of four tetrachlorodioxin isomers on (A) 1m x 2mm 3% SE-30 ultraphase packed column and (B) 25m SP2100

Comparison of the low resolution mass-spectra of two trichloro-dioxins with 3:0 (1,2,4-) and 2:1 (1,3,7-) ring chlorine substitution.

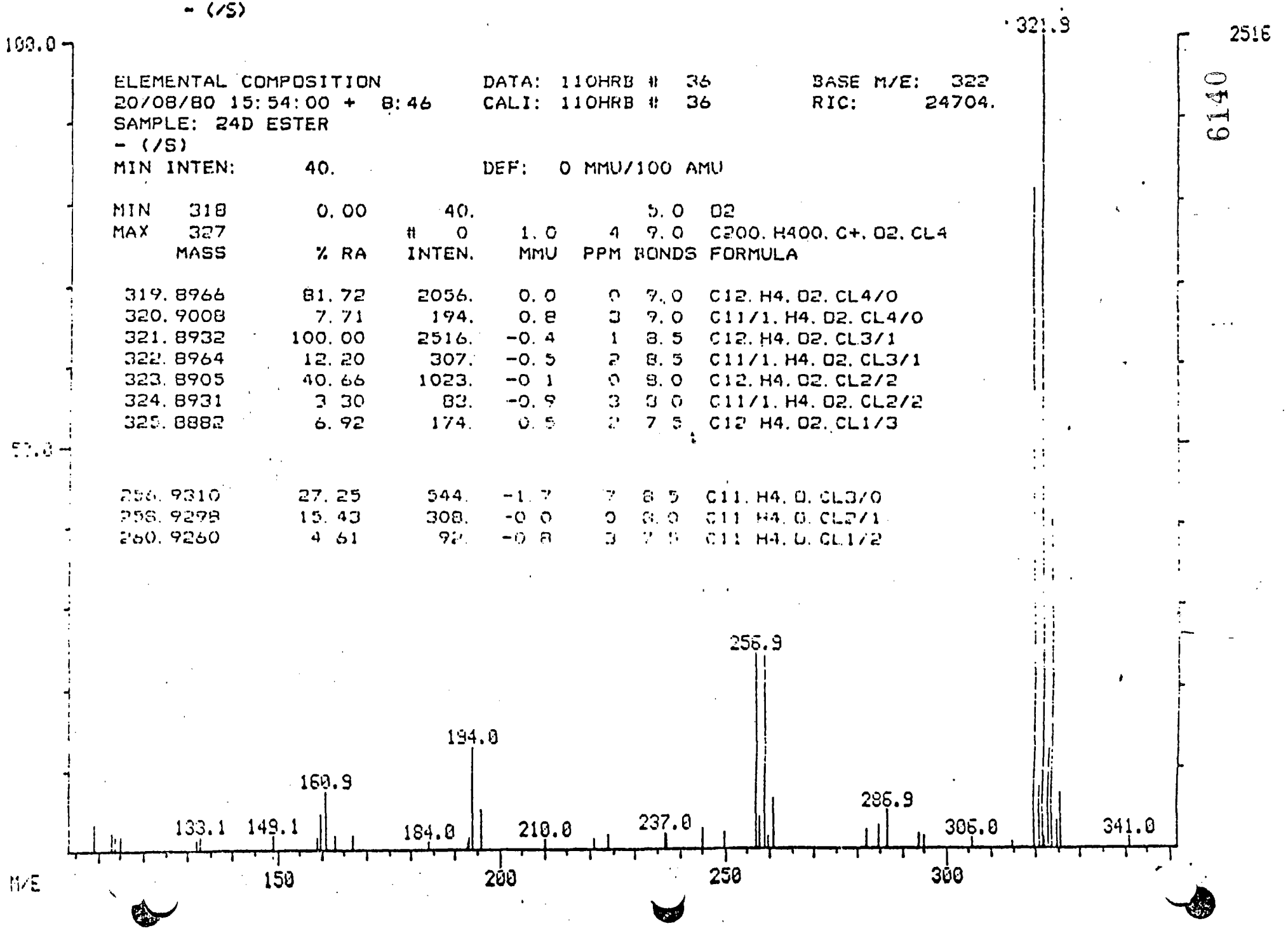


dioxin from a 2,4-D iso-octylester sample together with accurate mass measurements on m/z 320, 322 and 324 ions.

DATA: 110HRB #36
CALI: 110HRB #36

BASE M/E: 322
RIC: 20896.

SAMPLE: 24D ESTER
- (/S)



ELEMENTAL COMPOSITION
20/08/80 15:54:00 + 8:46
SAMPLE: 24D ESTER
- (/S)
MIN INTEN: 40.

DATA: 110HRB # 36
CALI: 110HRB # 36

BASE M/E: 322
RIC: 24704.

DEF: 0 MMU/100 AMU

MIN	318	0.00	40.			5.0	D2
MAX	327		# 0	1.0	4	9.0	C200. H400. C+. O2. CL4
	MASS	% RA	INTEN.	MMU	PPM	BONDS	FORMULA
	319.8966	81.72	2056.	0.0	0	7.0	C12. H4. O2. CL4/0
	320.9008	7.71	194.	0.8	3	7.0	C11/1. H4. O2. CL4/0
	321.8932	100.00	2516.	-0.4	1	8.5	C12. H4. O2. CL3/1
	322.8964	12.20	307.	-0.5	2	8.5	C11/1. H4. O2. CL3/1
	323.8905	40.66	1023.	-0.1	0	8.0	C12. H4. O2. CL2/2
	324.8931	3.30	83.	-0.9	3	8.0	C11/1. H4. O2. CL2/2
	325.8882	6.92	174.	0.5	2	7.5	C12 H4. O2. CL1/3
	256.9310	27.25	544.	-1.7	7	6.5	C11. H4. O. CL3/0
	258.9278	15.43	308.	-0.0	0	6.0	C11 H4. O. CL2/1
	260.9260	4.61	92.	-0.8	3	7.5	C11 H4. O. CL1/2

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Environmental Protection
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January 1982

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Recognition and Management of Pesticide Poisonings

Third Edition

RECOGNITION AND MANAGEMENT OF PESTICIDE POISONINGS

Donald P. Morgan, M.D., Ph.D.*

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Third Edition

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INTRODUCTION

This manual is designed to help professionals responsible for the health of persons exposed to pesticides to recognize and treat properly poisonings by these substances. This third edition discusses many more compounds than were dealt with in previous editions, and it updates particular management methods according to recently published clinical literature.

No text or manual on so complex a topic can presume to take the place of good clinical judgment. But it is unrealistic to expect health professionals confronted with a pesticide poisoning emergency to assemble quickly the many details of toxicology, diagnosis, and treatment that are essential to optimal management. This manual provides such information in a concise format.

A deliberate effort has been made to suggest treatment that can be implemented (or at least initiated) in small hospitals and clinics where victims of pesticide poisonings are likely to be received. At the expense of some repetition, details of treatment have been spelled out sequentially for the common classes of chemical poisonings.

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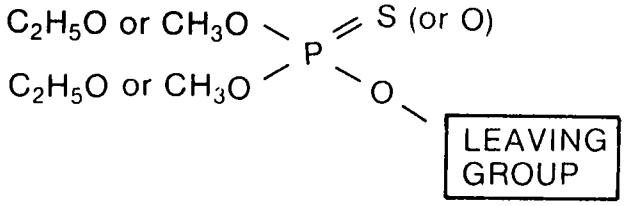
Chapter 1

ORGANOPHOSPHATE CHOLINESTERASE-INHIBITING PESTICIDES

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS*

Highly toxic: tetraethyl pyrophosphate (TEPP), phorate (Thimet), disulfoton† (Di-Syston), fensulfothion (Dasanit), demeton† (Systox), terbufos (Counter), mevinphos (Phosdrin), methidathion (Supracide), chlormephos (Dotan, MC2188), sulfotepp (Bladafum, Dithione), chlorthiophos (Celathion), monocrotophos (Azodrin), fonofos (Dyfonate), prothoate (Fac), fenamiphos (Nemacur), phosfolan (Cyolane), methyl parathion (Dalf, Penncap-M), schradan (OMPA), chlorfenvinphos (Birlane), ethyl parathion (Parathion, thiophos), azinphos-methyl (Guthion), phosphamidon (Dimecron), methamidophos (Monitor), dicrotophos (Bidrin), isofenphos (Amaze, Oftanol), bomyl (Swat), carbophenothion (Trithion), EPN, famphur, (Warbex, Bo-Ana, Famfos), fenophosphon (Agritox, trichloronate), dialifor (Torak), cyanofenphos (Surecide).

Moderately toxic: bromophos-ethyl (Nexagan), leptophos (Phosvel), dichlorvos (DDVP, Vapona), coumaphos (Co-Ral), ethoprop (Mocap), quinalphos (Bayrusil), triazophos (Hostathion), demeton-methyl† (Metasystox), propetamphos (Safrotin), chlorpyrifos (Lorsban, Dursban), sulprofos (Bolstar), dioxathion (Delnav), isoxathion (Karphos), phosalone (Zolone), thiometon (Ekatin), heptenophos (Hostaquick), crotoxyphos (Ciodrin), cythioate (Proban), phencapton (G28029), DEF (De-Green, E-Z-off D), ethion, dimethoate (Cygon, De-Fend), fenthion (Baytex, Entex, Tiguvon, Spotton, Lysoff), dichlofenthion (Mobilawn), EPBP (S-Seven),

---

* These are listed approximately in order of descending toxicity. "Highly toxic" organophosphates have listed oral LD_{50} values (rat) less than 50 mg/kg; "moderately toxic" agents have LD_{50} values in excess of 50 mg/kg.

† These organophosphates are systemic; i.e., they are taken up by the plant and translocated into foliage and sometimes into the fruit.

diazinon (Spectracide), phosmet (Imidan, Prolate), formothion (Anthio), profenofos (Curi 1), naled (Dibrom), phenthoate, trichlorfon (Dylox, Dipterex, Neguvon), pyrazophos (Afugan, Curamil), fenitrothion (Agrothion, Sumithion), cyanophos (Cyanox), pyridaphenthion (Ofunack), propylthiopyrophosphate (Aspon), acephate (Orthene), merphos (Folex), malathion (Cythion), etrimfos (Ekamet), phoxim (Baythion), pirimiphosmethyl (Actellic), iodofenphos (Nuvanol-N), bromophos (Nexion), tetrachlorvinphos (Gardona, Rabon), temephos (Abate, Abathion).

TOXICOLOGY

Organophosphates poison insects and mammals primarily by phosphorylation of the acetylcholinesterase enzyme at nerve endings. The enzyme is critical to normal transmission of nerve impulses from nerve fibers to innervated tissues. Some critical proportion of the tissue enzyme mass must be inactivated by phosphorylation before symptoms and signs of poisoning are manifest. At sufficient dosage, loss of enzyme function allows accumulation of acetylcholine (the impulse-transmitter substance) at cholinergic neuroeffector junctions (muscarinic effects), and at skeletal myoneural junctions and in autonomic ganglia (nicotinic effects). Organophosphates also impair nerve impulse transmission in the brain, causing disturbances in sensorium, motor function, behavior, and respiratory drive. Depression of respiration is the usual cause of death in organophosphate poisoning. Recovery depends ultimately on generation of new enzyme.

Organophosphates are efficiently absorbed by inhalation, ingestion, and skin penetration. To a degree, toxicity depends on the rate at which specific organophosphates are metabolized in the body (principally by hydrolysis in the liver), thus limiting the amount of pesticide available to attack acetylcholinesterase enzyme in other tissues.

Many organophosphates readily undergo conversion from -thions to -oxons (replacement of sulfur by oxygen). In general, -oxons are much more toxic than -thions. This conversion occurs in the environment under the influence of sunlight and in the body, mainly by the action of liver microsomes. Ultimately, both -oxons and -thions are inactivated by hydrolysis at the ester linkage, yielding alkyl phosphates and phenols which are readily excreted. The hydrolysis products present little toxic hazard.

One to two days after organophosphate absorption, depending on the specific organophosphate, some phosphorylated acetylcholinesterase enzyme can be de-phosphorylated (reactivated) by certain oxime antidotes. After this interval, the nature of the enzyme-phosphoryl bond changes, rendering the enzyme inactivation irreversible. New enzyme must then be generated.

Very rarely, organophosphate pesticides have produced a different type of neurotoxicity, consisting of damage to the myelin substance of peripheral nerves. This leads to a protracted peripheral neuropathy, characterized by numbness, pain, and weakness in the extremities, which persists for months or years. Organophosphates associated with these chronic illnesses have included

some whose acute toxic potential is low; i.e., there appears to be no relationship between acute toxicity and the likelihood of a chronic neuropathic effect. Particularly suspect as neurotoxic agents of this type are the phenylphosphonothioate series, cyanofenphos, EPN, leptophos, and EPBP.

Other unusual properties of specific organophosphates may render them more hazardous than basic toxicity data suggest. By-products can develop in long-stored malathion which strongly inhibit the hepatic enzymes operative in malathion catabolism, thus enhancing its toxicity. Certain organophosphates are exceptionally prone to storage in fat tissue, prolonging the need for antidote when stored pesticide is released back into the circulation. It is possible that other unrecognized factors modify the toxicity of organophosphates.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

Symptoms of acute poisoning develop during exposure or within 12 hours (usually within four hours) of contact. **HEADACHE, DIZZINESS, WEAKNESS, INCOORDINATION, MUSCLE TWITCHING, TREMOR, NAUSEA, ABDOMINAL CRAMPS, DIARRHEA,** and **SWEATING** are common early symptoms. Blurred or dark vision, confusion, tightness in the chest, wheezing, productive cough, and **PULMONARY EDEMA** may occur. Incontinence, unconsciousness and convulsions indicate very severe poisoning. **SLOW HEARTBEAT,** salivation, and tearing are common. **TOXIC PSYCHOSIS,** with manic or bizarre behavior, has led to misdiagnosis of acute alcoholism. Slowing of the heartbeat may rarely progress to complete sinus arrest. **RESPIRATORY DEPRESSION** may be fatal. Continuing daily absorption of organophosphate at intermediate dosage may cause an **INFLUENZA-LIKE ILLNESS** characterized by weakness, anorexia, and malaise.

The very few individuals who have suffered peripheral neuropathy following organophosphate exposure exhibited diverse clinical courses. Onset of symptoms was generally slow, sometimes after an asymptomatic interval of several days following exposure. Principal symptoms have been numbness, tingling, pain and weakness of the arms and legs. Some recovered fully in a few weeks; a few others experienced muscle atrophy, leaving a degree of paresis and sensory loss.

CONFIRMATION OF DIAGNOSIS

CAUTION: If there are strong clinical indications of organophosphate poisoning, treat patient immediately. **DO NOT WAIT** for laboratory confirmation.

Depressions of plasma pseudocholinesterase and/or RBC acetylcholinesterase enzyme activities are the most satisfactory and generally available biochemical indices of excessive organophosphate absorption. A *minimum* amount of organophosphate must be absorbed to depress blood cholinesterase activities, but activities are lowered by dosage considerably less than are required to cause symptomatic poisoning. The enzyme depression is usually apparent immediately after, or within 12-24 hours of, significant absorption of

organophosph- Depression of the plasma enzyme generally persists several days to a few -eks; the RBC enzyme activity usually remains depressed longer, sometimes 1-3 months. Table 1 lists **APPROXIMATE LOWER LIMITS OF NORMAL FOR PLASMA** and **RBC CHOLINESTERASE ACTIVITIES** of human blood, measured by generally available methods. **LOWER LEVELS usually** indicate excessive absorption of a cholinesterase-inhibiting chemical. Whenever possible, comparison of the test sample with a pre-exposure value offers the best confirmation of organophosphate absorption: a depression of 25% or more is strong evidence of excessive absorption.

In certain conditions, the activities of plasma and RBC cholinesterase are depressed in the absence of chemical inhibition. About 3% of individuals have a genetically determined low level of plasma cholinesterase. These persons are particularly vulnerable to the action of cholinesterase-inhibiting pesticides and to the drug succinylcholine, often administered to surgical patients. Patients with advanced liver disease, malnutrition, chronic alcoholism and dermatomyositis exhibit low plasma cholinesterase activities. A number of toxicants, notably carbon disulfide, benzalkonium salts, organic mercury compounds, ciguatoxins, and solanines may reduce plasma pseudocholinesterase activity. The RBC acetylcholinesterase is less likely than the plasma enzyme to be affected by factors other than organophosphates. It is reduced, however, in certain conditions that damage the red cell membrane, such as hemolytic anemias.

The alkyl phosphates and phenols to which organophosphates are hydrolyzed in the body can often be detected in the urine during pesticide absorption and up to 48 hours thereafter. These analyses are useful in identifying the actual pesticide to which workers have been exposed. Alkyl phosphate and phenol analyses can demonstrate organophosphate absorption at lower dosages than those required to depress cholinesterase activities.

Detection of intact organophosphates in the blood is usually not possible except after extreme exposures, such as ingestions of pesticide. Few organophosphates remain unhydrolyzed in the blood more than a few minutes or hours, unless the quantity absorbed is extraordinary or the hydrolyzing liver enzymes are inhibited.

TREATMENT

CAUTION: Persons attending the victim should avoid direct contact with heavily contaminated clothing and vomitus. Wear rubber gloves while washing pesticide from skin and hair.

1. Establish **CLEAR AIRWAY** by aspiration of secretions. Administer **OXYGEN** by mechanically assisted pulmonary ventilation. Improve tissue oxygenation as much as possible before administering atropine to minimize the risk of ventricular fibrillation.
2. Administer **ATROPINE SULFATE** intravenously, or intramuscularly, if IV injection is not possible. Atropine protects the muscarinic end-organs from excessive concentrations of acetylcholine. It does not reactivate the

TABLE 1. *Approximate Lower Limits of Normal Plasm[illegible]id Red Cell Cholinesterase Activities in Humans**

METHOD	PLASMA	RBC	WHOLE BLOOD	UNITS
Δ pH (Michel)	0.45	0.55		Δ pH per hr per ml
pH Stat (Nabb-Whitfield)	2.3	8.0		μM per min per ml
ChE-tel (Pfizer)	40			ChE-tel units
A ChE-tel (Pfizer)		210		A ChE-tel units
BMC Reagent Set (Ellman-Boehringer)	1875		3000	mU per min per ml
1-Test Cholinesterase (EM Diagnostics)	3.6			Units per ml
Acholest Test Paper	>20			Minutes
Dupont ACA	< 8			Units per ml
Garry-Routh (Micro)			Male 7.8 Female 5.8	μM-SH per 3 min per ml
Merckotest			3.0	Units per ml
GLC Method (Cranmer)	2.1	8.2		μM per min per ml
Technicon	2.0	8.0		μM per min per ml

* Because measurement technique varies among laboratories, more accurate estimates of minimum normal values are usually provided by individual laboratories.

cholinesterase enzyme. Recrudescence of poisoning may occur if tissue concentrations of organophosphate remain high when the effect of atropine wears off. Atropine is the ideal antidote for muscarinic manifestations; it is ineffective against nicotinic actions: muscle weakness and twitching, and respiratory depression.

In **MODERATELY SEVERE** poisoning:

Adult dosage, including children over 12 years: 0.4-2.0 mg repeated every 15 minutes until atropinization is achieved: tachycardia (pulse of 140 per minute), flushing, dry mouth, dilated pupils. Maintain atropinization by repeated doses for 2-12 hours or longer depending on severity of poisoning. Râles in the lung bases indicate inadequate atropinization. Miosis, nausea, bradycardia, and other cholinergic manifestations are also indicative.

Dosage for children under 12 years: 0.05 mg/kg body weight, repeated every 15 minutes until atropinization is achieved. Maintain atropinization with repeated dosage of 0.02-0.05 mg/kg.

SEVERELY POISONED individuals may exhibit remarkable tolerance to atropine; two or more times the dosages suggested above may be

needed. Persons not poisoned or only slightly poisoned, however, may develop signs of atropine toxicity from such large dosages: **FEVER,** muscle fibrillations, and delirium are the main signs of atropine toxicity. If these signs appear while the patient is fully atropinized, atropine administration should be discontinued, at least temporarily.

3. Draw a **BLOOD SAMPLE** for **PLASMA** and **RBC CHOLINESTERASE** analysis.
4. Administer **PRALIDOXIME** (Protopam®-Ayerst, 2-PAM) in cases of severe poisoning by **organophosphate** pesticides in which respiratory depression, muscle weakness and twitchings are severe. When administered early (usually less than 36 hours after poisoning) pralidoxime relieves the nicotinic effects of poisoning.

   Note: Pralidoxime is of questionable value in poisonings by the cholinesterase-inhibiting **carbamate** compounds. (See Chapter 2).

   Adult dosage (including children over 12 years): 1.0 gm intravenously at *no more* than 0.5 gm per minute.

   Child's dose (under 12 years): 20-50 mg/kg (depending on severity of poisoning) intravenously, injecting *no more* than half the total dose per minute.

   Dosage of pralidoxime may be repeated in 1-2 hours, then at 10-12 hour intervals if needed. In very severe poisonings, dosage rates may be doubled.

   Note: *slow administration of pralidoxime is strongly recommended,* and may be achieved by administering the total dose in 250 ml 5% glucose solution over 30-60 minutes.

   If intravenous injection is not possible, pralidoxime may be given by deep intramuscular injection.

   CAUTION: Be prepared to assist pulmonary ventilation mechanically if respiration is depressed during and after pralidoxime injection.

5. **OBSERVE PATIENT CLOSELY** for *at least* 24 hours to insure that symptoms (sweating, visual disturbances, vomiting, diarrhea, chest and abdominal distress and sometimes **PULMONARY EDEMA**) do not recur as atropinization wears off. In very severe poisonings by ingested organophosphates, particularly the more lipophilic and slowly hydrolyzed compounds, metabolic disposition of toxicant may require as many as 5-10 days, during which atropinization must be maintained. Rising levels of blood cholinesterase activity are a useful signal that atropine dosage can be tapered off by lengthening the intervals between doses. As dosage is reduced, the lung bases should be checked frequently for râles. If râles are heard, or if there is a return of miosis, bradycardia, sweating or other cholinergic signs, atropinization must be re-established promptly.
6. **BATHE** and **SHAMPOO** victim with soap and water if there is any chance that **SKIN** and **HAIR** are contaminated.

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7. **IF PESTICIDE HAS BEEN INGESTED** in quantity sufficient to cause poisoning, empty the stomach and intestine.

   A. **IF** victim is **ALERT** and respiration is not depressed, give **SYRUP OF IPECAC,** followed by 1-2 glasses of water to induce vomiting. **Adults** (12 years and over): 30 ml; **children** under 12 years: 15 ml.

      CAUTION: **OBSERVE** victim closely **AFTER** administering **IPECAC.** If consciousness level declines, or if vomiting has not occurred in 15 minutes, proceed immediately to **INTUBATE** the stomach.

      Following emesis, have victim drink a suspension of 30-50 gm **ACTIVATED CHARCOAL** in 3-4 ounces of water to limit absorption of toxicant remaining in the gut.

   B. **IF** victim is **OBTUNDED** or respiration is depressed, empty stomach by **INTUBATION, ASPIRATION,** and **LAVAGE,** using isotonic saline or 5% sodium bicarbonate. Because many pesticides are dissolved in petroleum distillates, emesis and intubation of the stomach involve a serious risk that solvent will be aspirated, leading to chemical pneumonitis. For this reason:

      (a). If victim is unconscious or obtunded and facilities are at hand, insert **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.

      (b). Keep victim's **HEAD BELOW LEVEL OF STOMACH** during intubation and lavage (Trendelenburg, or left lateral decubitus, with head of table tipped downward). Keep victim's head turned to left.

      (c). **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.
      After aspiration of gastric contents and washing of stomach, instill 30-50 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through stomach tube to limit absorption of remaining toxicant.

   C. **SAVE A SAMPLE** of emesis, or the initial gastric washings, for chemical analysis.

   D. If bowel movement has not occurred in 4 hours, and if patient is fully conscious, give **SODIUM SULFATE,** 0.25 gm/kg, in 1-6 ounces water, as a cathartic. Magnesium sulfate and citrate are equally suitable at similar dosage if renal function is adequate. Retained magnesium may depress CNS function.

8. **DO NOT** give morphine, aminophylline, phenothiazines, reserpine, furosemide, or ethacrynic acid in poisonings by organophosphates.

9. Give adrenergic amines **ONLY** if there is a specific indication, such as marked hypotension.

10. Rarely, in severe organophosphate poisonings, **CONVULSIONS** occur which are unresponsive to atropine and pralidoxime. Insure that causes unrelated to pesticide toxicity are not responsible: head trauma, cerebral anoxia, or mixed poisoning. **DIAZEPAM** (Valium), 5-10 mg for adults, 0.1 mg/kg for children under 6 years or 23 kg is probably the safest and most reliable anticonvulsant to use under these circumstances. Give **SLOWLY** (no more than half the total dose per minute) intravenously. Severe protracted convulsions may require additional medication, as suggested in the chapter on *Solid Organochlorine Pesticides.*

    CAUTION: Be prepared to assist pulmonary ventilation mechanically if respiration is depressed; to intubate the trachea, if laryngospasm occurs; and to counteract hypotensive reactions.

11. Persons who have been clinically poisoned by organophosphate pesticides should not be re-exposed to cholinesterase-inhibiting chemicals until symptoms and signs have resolved completely and blood cholinesterase activities have returned to at least 80 percent of pre-poisoning levels. If blood cholinesterase was not measured prior to poisoning, blood enzyme activities should reach at least minimum normal levels (Table 1) before the patient is returned to a pesticide-contaminated environment.
12. **DO NOT** administer atropine or pralidoxime prophylactically to workers exposed to organophosphate pesticides. It is neither practical nor medically sound to do so.

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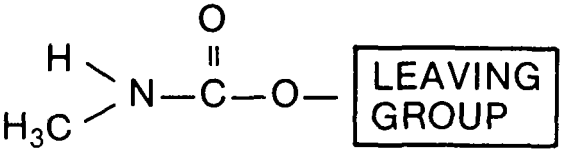
Chapter 2

CARBAMATE CHOLINESTERASE-INHIBITING PESTICIDES

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS*

Highly toxic**: aldicarb† (Temik), oxamyl (Vydate), carbofuran (Furadan), methomyl (Lannate, Nudrin), formetanate HCl (Carzol, Dicarzol), aminocarb (Matacil), dimetilan (Snip Fly Bands).

Moderately toxic***: promecarb (Carbamult), methiocarb (Mesurol, Draza), propoxur (Baygon), pirimicarb (Pirimor, Aphox, Rapid), bufencarb (Bux), carbaryl (Sevin).

TOXICOLOGY

Insecticides of this class cause reversible carbamylation of acetylcholinesterase enzyme, allowing accumulation of acetylcholine at cholinergic neuroeffector junctions (muscarinic effects), and at skeletal muscle myoneural junctions and in autonomic ganglia (nicotinic effects). Poison also impairs CNS function. The carbamyl-enzyme combination dissociates more readily than the phosphorylated enzyme produced by organophosphate insecticides. This lability tends to mitigate the toxicity of carbamates, but also limits the usefulness of blood enzyme measurements in diagnosis of poisoning. Carbamates are absorbed by inhalation, ingestion, and dermal penetration. They are actively metabolized by the liver, and the degradation products are excreted by the liver and kidneys.

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* Listed approximately in order of decreasing toxicity.

** Acute oral LD_{50} in the rat less than 50 mg/kg.

*** Acute oral LD_{50} in the rat above 50 mg/kg.

† This carbamate is a systemic, i.e., it is taken up by the plant and translocated into foliage and sometimes into the fruit.

A few carbamate insecticides are formulated in methyl (wood) alcohol. In cases of inges ' of these formulations, the toxicology of the methanol must be taken fully ....o consideration: severe gastroenteric irritation, acidosis, CNS injury, and neuropathy.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

DIARRHEA, NAUSEA, VOMITING, ABDOMINAL PAIN, PROFUSE SWEATING, SALIVATION, and **BLURRED VISION** are frequently reported. Other common symptoms have been dyspnea, tremor, muscle twitching, ataxia, and headache. Temporary paralysis of the extremities has also occurred. Most reported illnesses have not exceeded a few hours, and the prognosis is generally better than in organophosphate intoxications. However, in severe poisonings, one should anticipate the possibility of **RESPIRATORY DEPRESSION,** pulmonary edema, and convulsions. Continuing absorption of intermediate quantities may cause protracted **MALAISE,** weakness, and anorexia, resembling influenza.

CONFIRMATION OF DIAGNOSIS

CAUTION: If there is strong clinical evidence of poisoning, treat patient immediately. **DO NOT WAIT** for laboratory confirmation.

Depressions of plasma and/or RBC cholinesterase activities may be observed following absorption of extraordinary amounts of carbamate insecticide. However, enzyme activities commonly revert to normal within a few minutes or hours. They are not, therefore, reliable detectors of carbamate poisoning; i.e., intoxication may exist when blood cholinesterase activities are normal. The rapid methods for cholinesterase estimation (ACHOLTEST, ChE-tel, MERCKOTEST) are more likely to detect depressions than the longer test methods.

Table 1 in the chapter on **ORGANOPHOSPHATE PESTICIDES** lists the approximate lower limits of normal plasma and red cell cholinesterase-inhibiting carbamates. A normal value does not preclude carbamate insecticide poisoning. Whenever possible, comparison of the test sample with pre-exposure values offers the best confirmation of excessive carbamate absorption: a depression of 25% or more is strong evidence of excessive absorption.

Consult the chapter on **ORGANOPHOSPHATE PESTICIDES** for detailed interpretation of the blood cholinesterase tests.

Measurement of carbamate metabolites in urine within 48 hours of exposure represents a specific and sensitive method for confirming absorption of several pesticides of this class. A number of government and university laboratories in contact with poison control centers can perform these tests. Specimens for such analysis should be collected as promptly as possible after exposure.

TREATMENT

CAUTION: Persons attending the victim should avoid direct contact with heavily contaminated clothing and vomitus. Wear rubber gloves while decontaminating skin and hair.

1. Establish **CLEAR AIRWAY** and **TISSUE OXYGENATION** by aspiration of secretions, and if necessary, by assisted pulmonary ventilation with oxygen. Improve tissue oxygenation as much as possible before administering atropine to minimize the risk of ventricular fibrillation.
2. Administer **ATROPINE SULFATE** intravenously, or intramuscularly if IV injection is not possible. Atropine protects the end-organs from excessive concentrations of acetylcholine. It does not reactivate the cholinesterase enzyme. Recrudescence of poisoning may occur if tissue concentrations of carbamate remain high when the effect of atropine wears off. Atropine is the ideal antidote for muscarinic symptoms; it is ineffective against nicotinic actions such as muscle weakness and twitching, and respiratory depression.

   In **MODERATELY SEVERE** poisoning: **Adult dosage,** including children over 12 years: 0.4-2.0 mg repeated every 15 minutes until atropinization is achieved (tachycardia, flushing, dry mouth, mydriasis). Maintain atropinization by repeated doses for 2-12 hours, or longer, depending on severity of poisoning. The appearance of râles in the lung bases, miosis, salivation, nausea, bradycardia, are all indications of inadequate atropinization.

   Dosage for children under 12 years: 0.05 mg/kg body weight repeated every 15 minutes until atropinization is achieved. Maintain atropinization with repeated dosage of 0.02-0.05 mg/kg.

   SEVERELY POISONED individuals may exhibit remarkable tolerance to atropine; twice the doses suggested above may be needed. Persons not poisoned, or only slightly poisoned, may develop signs of atropine toxicity if large doses are given: **FEVER,** muscle fibrillations, and delirium. If these appear while the patient is fully atropinized, atropine should be discontinued, at least temporarily.
3. Pralidoxime (Protopam®-Ayerst, 2-PAM) is of doubtful value in poisonings by carbamate inhibitors of cholinesterase. Atropine alone is almost always an adequate antidote. Pralidoxime is probably contraindicated in poisonings by carbaryl, specifically. If victim of carbamate poisoning exhibits severe muscle weakness and/or respiratory depression, or if poisoning involves a combination of carbamate and organophosphate, a dilute solution of pralidoxime (total dose in 250 ml 5% glucose solution) may be given cautiously IV. The infusion should be terminated if patient's condition worsens. Pralidoxime **dosage:** adults, 1.0 gm; for children under 12 years, 20-50 mg/kg.
4. **OBSERVE** treated patients closely **at least 24 HOURS** to insure that symptoms (possibly pulmonary edema) do not recur as atropinization wears off. In very severe poisonings, metabolic disposition of toxicant

may require several hours or days during which atropinization must be maintair Markedly lower levels of urinary metabolites indicate that atropine dosage can be tapered off. As dosage is reduced, check the lung bases frequently for râles. If râles are heard, or if nausea, salivation, or bradycardia returns, **RE-ESTABLISH ATROPINIZATION** promptly.

5. **BATHE** and **SHAMPOO** victim with soap and water if there is any chance that **SKIN** and **HAIR** are contaminated.
6. If pesticide has been **INGESTED** in quantity sufficient to cause poisoning, empty the stomach and intestine.

   A. If victim is alert and respiration is not depressed, give **SYRUP OF IPECAC,** followed by 1-2 glasses of water to induce vomiting; adults (including children over 12), 30 ml; children (under 12 years), 15 ml.

      CAUTION: **OBSERVE** victim closely **AFTER** administering **IPECAC.** If consciousness level declines, or if vomiting has not occurred in 15 minutes, proceed immediately to **INTUBATE** the stomach.

   Following emesis, have victim drink a suspension of 30-50 gm **ACTIVATED CHARCOAL** in 3-4 ounces of water to bind toxicant remaining in the gastrointestinal tract.

   B. If victim is **OBTUNDED** or respiration is depressed, empty stomach by **INTUBATION, ASPIRATION,** and **LAVAGE,** using isotonic saline or 5% sodium bicarbonate. Because many pesticides are dissolved in petroleum distillates, emesis and intubation of the stomach involve a serious risk that solvent will be aspirated, leading to chemical pneumonitis. For this reason:

      (a). If victim is unconscious or obtunded and facilities are at hand, insert **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.

      (b). Keep victim's **HEAD BELOW LEVEL OF STOMACH** during intubation and lavage (Trendelenburg, or left lateral decubitus, with head of table tipped downward). Keep victim's head turned to left.

      (c). **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.

   After aspiration of gastric contents and washing of stomach, instill 30-50 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through the tube to limit absorption of remaining toxicant.

   C. **SAVE A SAMPLE** of emesis or initial gastric washings for chemical analysis.

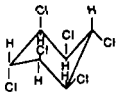
   D. If bowel movement has not occurred in 4 hours and patient is fully conscious, give **SODIUM SULFATE,** 0.25 gm/kg in 1-6 ounces of water, as a cathartic. Magnesium sulfate or citrate is equally suitable if renal function is satisfactory.

7. **DO NOT** give morphine, aminophylline, phenothiazines, reserpine, furosemide, or ethacrynic acid.
8. Give adrenergic amines **ONLY** if there is a specific indication, such as severe hypotension.
9. **CONVULSIONS** are **RARE** manifestations of poisoning by carbamates. If they occur, causes other than direct carbamate action should be considered: cerebral anoxia, head trauma, mixed poisoning. Although not tested in these circumstances, **DIAZEPAM** (Valium) is probably the anticonvulsant of choice. **Dosage** for adults and children over 6 years or 23 kg body weight is 5-10 mg given **slowly** intravenously (no more than half total dose per minute), or intramuscularly (deep). Dosage for children under 6 years or 23 kg body weight is 0.1 mg/kg. Repeat this dosage every 2-4 hours if needed to control convulsions. Be prepared to intubate and to assist pulmonary ventilaton mechanically if respiration is depressed. Hypotensive reactions may also occur.
10. Persons who have been clinically poisoned by carbamate pesticides should not be re-exposed to cholinesterase-inhibiting chemicals until symptoms and signs have resolved completely, and normal blood cholinesterase activities have been demonstrated.
11. **DO NOT** administer atropine prophylactically to workers exposed to carbamate insecticides. It is neither practical nor medically sound to do so.

Chapter 3

SOLID ORGANOCHLORINE PESTICIDES

CHEMICAL STRUCTURES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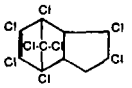
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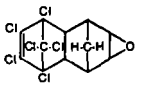
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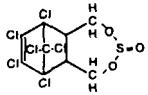
HEXACHLOROBENZENE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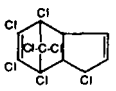
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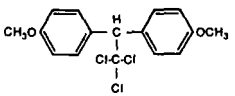
METHOXYCHLOR

COMMON COMMERCIAL PESTICIDE PRODUCTS*

Highly toxic: endrin (Hexadrin), a stereoisomer of dieldrin.

Moderately toxic: aldrin (Aldrite, Drinox), endosulfan (Thiodan), dieldrin (Dieldrite), toxaphene (Toxakil, Strobane-T), lindane (Gammexane), benzene hexachloride (BHC, HCH), DDT (chlorophenothane), heptachlor, kepone, terpene polychlorinates (Strobane), chlordane (Chlordan), dicofol (Kelthane), chlorobenzilate (Acaraben), mirex, methoxychlor (Marlate), dienochlor (Pentac), hexachlorobenzene (HCB), ethylan (Perthane). All except HCB are insecticides or acaricides; HCB is a fungicide.

The U.S. Environmental Protection Agency has sharply curtailed the availability of many organochlorines, particularly DDT, dieldrin, and chlordane. Others, however, are still the active ingredients of various home and garden products and some agricultural and structural pest control agents. Hexachlorobenzene is used as a seed protectant. Lindane may no longer be used in continuous vaporizers, but it is the active ingredient of many products for pest control in the home and on the farm. It is the active ingredient of the scabicide Kwell®.

TOXICOLOGY

Most organochlorines are efficiently absorbed from the gut and across the skin. In adequate dosage, they interfere with axonic transmission of nerve impulses and, therefore, disrupt the function of the nervous system, principally that of the brain. This results in behavioral changes, sensory and equilibrium disturbances, involuntary muscle activity, and depression of vital centers, particularly those controlling respiration. Adequate doses of some organochlorines increase myocardial irritability, and stimulate synthesis of hepatic drug-metabolizing enzymes.

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* Listed approximately in order of decreasing toxicity.

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Chlordane has apparently induced a few cases of self-limited megaloblastic anemia after protracted low-level exposures. The condi' has resolved following termination of exposure.

Kepone has caused nervousness, tremor, incoordination, weakness and infertility in excessively exposed workers. Clinical improvement has occurred as the pesticide was excreted.

Endrin is more toxic to the liver and kidneys than the other organochlorines at comparable dosages.

Prolonged ingestion of HCB-treated grain produced porphyria cutanea tarda in several thousand Turkish citizens who mistakenly ate the seed grain. Disease was manifest as excretion of red urine, bullous dermatitis, hyperpigmentation, generalized hair growth, muscle wasting and liver enlargement. Slow improvement occurred when HCB ingestion was stopped.

A series of anecdotal reports of bone marrow injury has tended to indict lindane as a hematotoxic agent in certain predisposed individuals, but no relationship has been proved.

Lindane, methoxychlor, terpene polychlorinates, chlorobenzilate, dicofol, and the constituents of chlordane, except heptachlor and oxychlordane, are excreted rapidly by humans, usually within 3-4 days of ingestion. Dieldrin, aldrin, endrin, hexachlorobenzene, heptachlor, and oxychlordane are excreted within weeks to several months of absorption by humans. DDT, kepone, mirex, and the beta isomer of benzene hexachloride are excreted very slowly, requiring months or years for elimination. The excretion kinetics of perthane, kelthane, and dienochlor are not known. Because of their lipophilicity, all organochlorines are likely to be excreted in the milk of lactating women.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

APPREHENSION, EXCITABILITY, DIZZINESS, HEADACHE, DISORIENTATION, WEAKNESS, PARESTHESIAE, muscle twitching, tremor, tonic and clonic **CONVULSIONS** (often epileptiform), and unconsciousness are the major manifestations. Soon after ingestion, nausea and vomiting commonly occur. When chemicals are absorbed dermally, apprehension, twitching, tremors, confusion, and convulsions may be the first symptoms. Respiratory depression is caused by the pesticide and by the petroleum solvents in which these pesticides are usually dissolved. Pallor occurs in moderate to severe poisoning. Cyanosis may result as convulsive activity interferes with respiration.

Even though convulsive activity may be severe, the prognosis in poisonings by these agents is far from hopeless. Although fatalities have occurred following absorption of large amounts of some organochlorines, there is a substantial likelihood of complete recovery if convulsions can be controlled, and vital functions sustained.

CONFIRMATION OF DIAGNOSIS

Pesticide and/or metabolites can usually be identified in blood or urine by gas-liquid chromatographic examination of samples taken within 72 hours of poisoning. These tests can be performed by some private laboratories, and by state health department and university laboratories supported by the U.S. Environmental Protection Agency. Such laboratories can be reached through poison control centers. Some chlorinated hydrocarbon pesticides (notably DDT) persist in the serum for weeks or months after absorption, but most are excreted in a few days. **DO NOT DELAY TREATMENT** of acute poisoning pending confirmatory blood analysis. Detection of chlorinated hydrocarbon residues in blood or tissues does not, of itself, indicate poisoning; actual concentrations are critical to a diagnosis of poisoning.

TREATMENT

1. Establish **CLEAR AIRWAY** and **TISSUE OXYGENATION** by aspiration of secretions, and, if necessary, by assisted pulmonary ventilation with oxygen.
2. **CONTROL CONVULSIONS. DIAZEPAM (VALIUM®)** is a valuable anticonvulsant.
   Adult dosage, including children over 6 years of age or 23 kg in weight: 5-10 mg (1-2 ml) slowly, intravenously (no faster than one ml per minute), or give total dose intramuscularly (deep). Repeat in 2-4 hours if needed.
   Dosage for children under 6 years or 23 kg in weight: 0.1 mg/kg (0.02 ml/kg) intravenously, no faster than half the total dose per minute, or give total dose intramuscularly (deep). Repeat in 2-4 hours if needed.

   CAUTION: Administer intravenous diazepam slowly to avoid irritation of the vein, hypotension, and respiratory depression.

   A. Persons suffering **SEVERE PROTRACTED CONVULSIONS** may require additional anticonvulsant medication. Agents that have been used successfully in the past are pentobarbital (Numbutal®), phenytoin (Dilantin®), thiopental (Pentothal®), and succinylcholine (Anectine®).

      CAUTION: Be prepared to maintain pulmonary ventilation mechanically if respiration is depressed during administration of anticonvulsants. Laryngospasm sometimes occurs during anticonvulsant therapy, and may necessitate tracheostomy.

      (a). **PENTOBARBITAL:** 5 mg/kg body weight, or 0.20 ml/kg body weight, using the usual 2.5% solution. If possible, inject solution intravenously, at a rate not exceeding 25 mg (one ml)

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per minute until convulsions are controlled If intravenous administration is not possible, give total d rectally, not exceeding 5 mg/kg body weight (0.20 ml/kg of 2.5% solution).

(b). **PHENYTOIN:** loading dose 15-18 mg/kg. Maintenance dose 4-8 mg/kg q 4-24 hours as needed. Intramuscular administration is not recommended. Give IV slowly at no more than 20% total dose per minute.

(c). **THIOPENTAL (PENTOTHAL):** a solution of one gm in 500 ml of 5% glucose in water is given by intravenous drip at a rate just sufficient to suppress convulsions.

(d). **SUCCINYLCHOLINE:** occasionally, curarization may be required to stop seizures. Prior to curarization, the trachea must be intubated, and pulmonary ventilation maintained mechanically. Blood gases and pH must be monitored. A person experienced in general anesthesia should conduct these procedures.

3. **BATHE** and **SHAMPOO** the victim vigorously with soap and water if skin and hair have been contaminated.
4. **IF PESTICIDE HAS BEEN INGESTED** in quantity sufficient to cause poisoning, the stomach and intestine must be emptied.

A. **IF** victim is **ALERT** and gag reflex is not depressed, give **SYRUP OF IPECAC** to induce vomiting (adults and children 12 years and older: 30 ml; children under 12: 15 ml), followed by 1-2 glasses of water.

CAUTION: **OBSERVE** the **VICTIM** closely after administering **IPECAC.** If consciousness level declines, or if vomiting has not occurred in 15 minutes, proceed immediately to **INTUBATE** stomach.

Following emesis, have victim drink a suspension of 30-50 gm **ACTIVATED CHARCOAL** in 3-4 ounces of water to limit absorption of toxicant remaining in the gut.

B. If the victim is **NOT FULLY ALERT,** empty the stomach immediately by **INTUBATION, ASPIRATION,** and **LAVAGE,** using isotonic saline or 5% sodium bicarbonate. Because many pesticides are dissolved in petroleum distillates, emesis and intubation of the stomach involve a serious risk that solvent will be aspirated, leading to chemical pneumonitis. For this reason:

(a). If victim is unconscious or obtunded and if facilities are at hand, insert an **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.

(b). Keep victim's **HEAD BELOW LEVEL OF STOMACH** and turned to left during intubation and lavage. (Trendelenburg, or left lateral decubitus, with head of table tipped downward).

(c). **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.

C. After ' 'ration of gastric contents and washing of stomach, instill 30-50 g... of **ACTIVATED CHARCOAL** in 3-4 ounces of water through stomach tube to limit absorption of remaining toxicant. **DO NOT** instill milk, cream, or other substances containing vegetable or animal fats, which enhance absorption of chlorinated hydrocarbons.

D. **SAVE A SAMPLE** of emesis or gastric washings for chemical analysis.

E. If bowel movement has not occurred in 4 hours and if patient is fully conscious, give **SODIUM SULFATE,** 0.25 gm/kg in 1-6 ounces of water, as a cathartic. Magnesium sulfate and citrate are as suitable as sodium sulfate if renal function is adequate. Retained magnesium may depress CNS function.

5. **DO NOT** give epinephrine or other adrenergic amines, because of the enhanced myocardial irritability induced by chlorinated hydrocarbons.
6. **CHOLESTYRAMINE** resin may accelerate the biliary-gastrointestinal excretion of the more slowly eliminated organochlorine compounds. This is usually administered in 3-8 gm doses, 4 times a day, before meals and at bedtime. Dose should be mixed with a pulpy fruit or liquid. Prolonged treatment (several weeks or months) may be necessary.
7. During convalescence, enhance **CARBOHYDRATE, PROTEIN,** and **VITAMIN** intake by diet or parenteral therapy to minimize injury to the liver.

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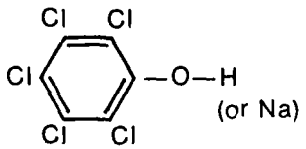
Chapter 4

PENTACHLOROPHENOL

CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS

Pentachlorophenol or Sodium Pentachlorophenate, PCP, Dow Pentachlorophenol, Dowicide EC-7, Penchlorol, Pentacon, Penwar, Veg-I-Kill, penta, Wood Preserver, Wood Tox 140, Purina Insect Oil Concentrate, Gardon Termi Tox, Usol Cabin Oil, Certified Kiltrol-74 Weed Killer, Ciba-Geigy Ontrack OS3, 4 or 5, Ortho Triox Liquid Vegetation Killer, Black Leaf Grass Weed and Vegetation Killer Spray, DP-2 Antimicrobial, Priltox, Sinituho.

Pentachlorophenol is used as an herbicide, defoliant, wood preservative, germicide, fungicide, and molluscicide. It is an ingredient of many formulated mixtures sold for one or more of these purposes.

Pentachlorophenol volatilizes from treated wood and fabric. Excessively treated interior surfaces may represent a source of intensive PCP exposure.

TOXICOLOGY

Pentachlorophenol irritates the skin, eyes, and upper respiratory mucous membranes. It is efficiently absorbed across the skin, the lung, and the gastrointestinal lining. Like the nitrophenolic compounds, it stimulates cellular oxidative metabolism by uncoupling phosphorylation. In common with other phenols, it is toxic to the liver, kidney, and central nervous system. Impurities in the technical formulation may be responsible for chloracne in workers regularly exposed.

Most severe poisonings have occurred in workers exposed to hot environments. However, a major epidemic of poisoning occurred in an American hospital among newborn infants who absorbed PCP from treated diapers. Dehydration and metabolic acidosis are important features of poisoning in children.

Albuminuria, glycosuria, and elevated BUN reflect renal injury. Liver enlargement has been observed in some cases. Anemia and leukopenia have occurred in some chronically exposed workers, but leukocytosis is more commonly found in acute poisoning.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

IRRITATION of nose, throat, eyes, and skin is the most common symptom of exposure to PCP. Severe or protracted exposure may result in **CONTACT DERMATITIS.** Intensive occupational exposure has resulted in chloracne.

PROFUSE SWEATING, HEADACHE, WEAKNESS, and **NAUSEA** are the most consistent presenting symptoms of systemic poisoning by absorbed PCP. **FEVER** is usually present but may be minimal or absent. **TACHYCARDIA, TACHYPNEA,** and **PAIN** in the **CHEST** and **ABDOMEN** are often prominent. **THIRST** is usually intense, but may be masked by nausea and vomiting. **DECLINING MENTAL ALERTNESS** may progress to stupor and/or convulsions. Protracted exposure may result in **WEIGHT LOSS** from increased basal metabolic rate.

CONFIRMATION OF DIAGNOSIS

PCP can be measured in blood, urine, and adipose tissue by gas-liquid chromatography. Up to about 100 parts per billion may be found in the blood and urine of persons having no recognized exposure. Based on studies of persons occupationally exposed to PCP, manifestations of systemic toxicity probably do not appear in adults until blood and urine concentrations reach at least one part per million (0.1 mg%, or 1,000 parts per billion).

If poisoning is strongly suspected on grounds of exposure, symptoms, and signs, **DO NOT POSTPONE TREATMENT** until diagnosis is confirmed.

TREATMENT

1. **BATHE** and **SHAMPOO** contaminated **SKIN** and **HAIR** promptly with soap and water, or water alone if soap is not available.
2. **FLUSH** chemical from **EYES** with copious amounts of clean water.
3. **IN EVENT OF SYSTEMIC POISONING:**
   - A. **REDUCE ELEVATED BODY TEMPERATURE BY PHYSICAL MEANS.** Administer sponge baths and cover victim with low-temperature blankets. In fully conscious patients, administer cold, sugar-containing liquids by mouth as tolerated.
   - B. Administer **OXYGEN** continuously by mask to minimize tissue anoxia.
   - C. Unless there are manifestations of cerebral edema, administer **INTRAVENOUS FLUIDS** at maximum tolerated rates to enhance urinary excretion of toxicant and to support physiologic mechanisms for heat loss. Monitor fluid balance, blood electrolytes and sugar, adjusting IV infusions to stabilize electrolyte concentrations, Follow urine contents of albumin and cells. In the presence of **CEREBRAL EDEMA,** intravenous **FLUIDS** must be administered very **CAUTIOUSLY** to avoid increasing the cerebral injury.

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D. Administer **SEDATIVES,** if necessary, to control apprehension and excitement. **DIAZEPAM®** (Valium) should be available, although its use has not been reported in this type of poisoning. Give slowly, intravenously, 5-10 mg in the adult, 0.1 mg/kg in children. Amobarbital or pentobarbital, 100-200 mg IM or slowly IV, every 4-6 hours may be needed. (Children's dose: up to 5 mg/kg.)

CAUTION: Be prepared to assist pulmonary ventilation mechanically in event of respiratory depression, and to counteract hypotensive reactions.

4. If toxicant has been **INGESTED,** evacuate the stomach and intestine.

A. If victim is alert and respiration is not depressed, give **SYRUP OF IPECAC,** followed by 1-2 glasses of water, to induce vomiting. (Adults, 12 years and older: 30 ml; children under 12: 15 ml).

CAUTION: **OBSERVE** the victim closely **AFTER** administering **IPECAC.** If consciousness level declines, or if vomiting has not occurred in 15 minutes, proceed immediately to **INTUBATE** the stomach.

Following emesis, have the victim drink a suspension of 30-50 gm **ACTIVATED CHARCOAL** in 3-4 ounces of water to bind toxicant remaining in the gastrointestinal tract.

B. If victim is not fully alert, empty the stomach immediately by **INTUBATION, ASPIRATION,** and **LAVAGE,** using isotonic saline or 5% sodium bicarbonate. Because PCP is commonly dissolved in petroleum distillates, emesis and intubation of the stomach involve a serious risk that solvent will be aspirated, leading to chemical pneumonitis. For this reason:

(a). If victim is unconscious or obtunded and facilities are at hand, insert an **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.

(b). Keep victim's **HEAD BELOW LEVEL OF THE STOMACH,** turned to left, during intubation and lavage. (Trendelenburg, or left lateral decubitus, with head of table tipped downward).

(c). **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.

(d). After aspiration of gastric contents and washing of stomach, instill 30 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through a stomach tube to limit absorption of remaining toxicant. Do **NOT** instill milk, cream, or other materials containing vegetable or animal fats, which are likely to enhance absorption.

C. If bowel movement has not occurred in 4 hours and patient is fully conscious, give **SODIUM SULFATE** as a cathartic: 0.25 gm/kg body weight in 1-6 ounces of water. Magnesium sulfate and citrate

are equally suitable unless renal function is impaired; retention of ma ium may depress CNS function and alter myocardial irritability.

5. **DO NOT** administer atropine, aspirin, or other antipyretics to control fever. These are likely to enhance the toxicity of phenolic compounds.
6. During convalescence, administer high-calorie, high-vitamin diet to restore body fat and carbohydrate.
7. Discourage subsequent contact with the toxicant for at least 4 weeks to allow full restoration of normal metabolic processes.
8. **HEMODIALYSIS** and **HEMOPERFUSION** may be considered in PCP poisoning, although phenols are extensively bound to plasma protein. **EXCHANGE TRANSFUSION** was used to rescue the infants inadvertently poisoned by PCP in a hospital. Unless renal and liver functions are impaired, PCP is rapidly eliminated from the blood and tissues.

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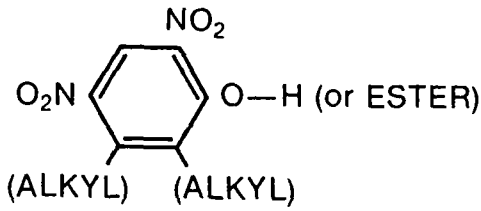
Chapter 5

NITROPHENOLIC AND NITROCRESOLIC HERBICIDES

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS

Dinitrophenol (Chemox PE), dinitrocresol (DNOC, DNC, Sinox, Chemsect DNOC, Elgetol 30, Nitrador, Selinon, Trifocide), dinoseb (DNBP, Dinitro, Basanite, Caldon, Chemox General, Chemox PE, Chemsect DNBP, Dinitro-3, Dinitro General, Dow General Weed Killer, Dow Selective Weed Killer, Dynamyte, Elgetol 318, Gebutox, Kiloseb, Nitropone C, Premerge 3, Sinox General, Subitex, Unicrop DNBP, Vertac Dinitro Weed Killer), dinosam (DNAP), dinoprop, dinoterbon, dinoterb, dinosulfon, binapacryl (Morocide, Endosan, Ambox, Dapacryl), dinobuton (Acrex, Dessin, Dinofen, Drawinol, Talan), dinopenton, dinocap (Crotothane, Karathane). Several combinations are widely used: Dyanap and Klean Krop = dinoseb + naptalam; Ancrack = sodium salts of dinoseb + naptalam; Naptro = dinitrophenol + naptalam.

TOXICOLOGY

These materials should be regarded as highly toxic to humans and animals. Most nitrophenols and nitrocresols are well absorbed from the gastrointestinal tract, across the skin, and by the lung when fine droplets are inhaled. Except in a few sensitive individuals, aromatic nitro-compounds are only moderately irritating to the skin. Like other phenols, they are toxic to the liver, kidney, and nervous system. The basic mechanism of toxicity is a stimulation of oxidative metabolism in cell mitochondria, by interference with the normal coupling of carbohydrate oxidation to phosphorylation (ADP to ATP). Increased oxidative metabolism leads to pyrexia, tachycardia, and dehydration, and ultimately depletes carbohydrate and fat stores. Most severe poisonings from absorption of these compounds have occurred in workers who were concurrently exposed to hot environments. Pyrexia and direct action on the brain cause cerebral edema, manifest clinically as a toxic psychosis and sometimes

convulsions. Liver parenchyma and renal tubules show degenerative changes. Albuminuria, pyuria, hematuria, and increased BUN are often prominent signs of renal injury.

Agranulocytosis has occurred in humans following large doses of dinitrophenol. Cataracts have occurred in some chronically poisoned laboratory species, but this effect has not been observed in humans.

Nitrophenols and nitrocresols are efficiently excreted by the kidneys, and there is some hepatic excretion into the bile. Unless the absorbed dose was extremely high, or kidney function is impaired, nearly complete elimination from the body can be expected within 3-4 days.

Death in nitrophenol poisoning is followed promptly by intense rigor mortis.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

YELLOW STAINING of skin and hair often signify contact with a nitrophenolic chemical. Staining of the sclerae and urine indicate absorption of potentially toxic amounts. **PROFUSE SWEATING, HEADACHE, THIRST, MALAISE,** and **LASSITUDE** are the common early symptoms of poisoning. **WARM, FLUSHED SKIN, TACHYCARDIA,** and **FEVER** characterize a serious degree of poisoning. **APPREHENSION,** restlessness, anxiety, manic behavior, or unconsciousness reflect severe cerebral injury. **CONVULSIONS** occur in the most severe poisonings. Cyanosis, tachypnea and dyspnea result from stimulation of metabolism, pyrexia, and tissue anoxia. Weight loss occurs in persons chronically poisoned at low dosages.

CONFIRMATION OF DIAGNOSIS

Unmetabolized nitrophenols and nitrocresols can be identified spectrophotometrically, or by gas-liquid chromatography, in the serum and urine at concentrations well below those necessary to cause poisoning. If poisoning is probable, **DO NOT AWAIT CONFIRMATION** before commencing treatment.

TREATMENT

1. **WASH** contaminated **SKIN** and **HAIR** promptly with soap and water, or with water alone if soap is not available.
2. **FLUSH** chemical from **EYES** with copious amounts of clean water.
3. **IN EVENT OF SYSTEMIC POISONING:**

   A. **REDUCE ELEVATED BODY TEMPERATURE BY PHYSICAL MEANS.** Administer sponge baths and cover victim with low-temperature blankets. In fully conscious patients, administer cold, sugar-containing liquids by mouth as tolerated.

   B. Administer **OXYGEN** continuously by mask to minimize tissue anoxia.

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C. Unless there are manifestations of cerebral edema, administer **INTRAVENOUS FLUIDS** at maximum tolerated rate enhance urinary excretion of toxicant and to support physiolo[illegible] mechanisms for heat loss. **IN** the presence of **CEREBRAL EDEMA,** intravenous **FLUIDS** must be administered very **CAUTIOUSLY** to avoid increasing the cerebral injury. Monitor fluid balance, blood electrolytes and sugar, adjusting IV infusions to stabilize electrolyte concentrations. Follow urine contents of albumin and cells. Follow serum alkaline phosphatase, GOT, and LDH to evaluate liver injury.

D. Administer **SEDATIVES,** if necessary, to control apprehension, excitement, and/or convulsions. Although not previously used in this type of poisoning, **DIAZEPAM** (Valium®) should help: adult dose, 5-10 mg **slowly** IV, or IM (deep); child's dose, 0.1 mg/kg. Repeat every 2-4 hours as needed. Amobarbital or pentobarbital may be needed. Dose in adults: 200 mg, IM or slowly IV, every 4-6 hours; child's dose: up to 5 mg/kg.

CAUTION: Be prepared to counteract respiratory depression and hypotension which may follow administration of anticonvulsants and sedatives.

4. If toxicant has been **INGESTED,** evacuate the stomach and intestine.

A. If victim is alert and respiration is not depressed, give **SYRUP** of **IPECAC,** followed by 1-2 glasses of water, to induce vomiting (adults 12 years and older: 30 ml; children under 12: 15 ml).

CAUTION: **OBSERVE** victim closely **AFTER** administering **IPECAC.** If consciousness level declines, or if vomiting has not occurred in 15 minutes, immediately **INTUBATE, ASPIRATE,** and **LAVAGE** the stomach.

Following emesis, have victim drink a suspension of 30-50 gm **ACTIVATED CHARCOAL** in 3-4 ounces of water to bind toxicant remaining in the gastrointestinal tract.

B. **IF VICTIM IS NOT FULLY ALERT,** empty the stomach immediately by **INTUBATION, ASPIRATION,** and **LAVAGE,** using isotonic saline or 5% sodium bicarbonate. Because these pesticides are usually dissolved in petroleum distillates, emesis and intubation of the stomach involve serious risk that solvent will be aspirated, leading to chemical pneumonitis. For this reason:

(a). If victim is unconscious or obtunded and facilities are at hand, insert an **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.

(b). Keep victim's **HEAD BELOW LEVEL OF THE STOMACH** and turned to the left, during intubation and lavage (Trendelenburg, or left lateral decubitus, with head of table tipped downward).

(c). **ASPIRATE PHARYNX** as regularly as possible to remove ;agged or vomited stomach contents.

(d). After aspiration of gastric contents and washing of stomach, instill 30-50 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through the stomach tube to limit absorption of remaining toxicant. Do **NOT** instill cream, milk, or other materials containing vegetable or animal fats, as these are likely to enhance absorption.

C. If bowel movement has not occurred in 4 hours, and if patient is fully conscious, give **SODIUM SULFATE** as a cathartic: 0.25 gm/kg body weight in 1-6 ounces of water. Magnesium sulfate and citrate are equally suitable unless renal function is impaired; retention of magnesium may depress CNS function and alter myocardial irritability.

5. **DO NOT** administer atropine, aspirin, or other antipyretics to control fever. Animal tests indicate that aspirin enhances, rather than reduces, the toxicity of nitrophenolic and nitrocresolic compounds.
6. During convalescence, administer high-calorie, high-vitamin diet to facilitate repletion of body fat and carbohydrate.
7. Discourage subsequent contact with the toxicant for at least 4 weeks, to allow full restoration of normal metabolic processes.
8. **HEMODIALYSIS** and **HEMOPERFUSION** may be considered in severe poisonings by aromatic nitro-compounds, although most phenols are extensively bound to plasma proteins. **EXCHANGE TRANSFUSION** is another option in poisonings characterized by impaired renal function. So long as renal and liver functions are intact, these compounds are efficiently excreted.

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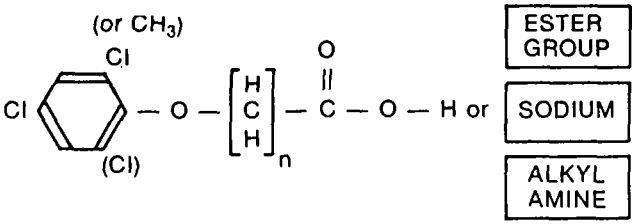
Chapter 6

CHLOROPHENOXY COMPOUNDS

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS

Several hundred commercial products contain chlorophenoxy herbicides in various concentrations and combinations. Following are names of widely advertised formulations. In some cases, the same name is used for products with different ingredients. Exact composition must therefore be determined from product label.

2,4-D, or 2,4-dichlorophenoxyacetic acid (Weedone†, Agrotec, Amoxone, Aqua-Kleen, BH 2,4-D, Chipco Turf Herbicide "D", Chloroxone, Crop Rider, D50, Dacamine 4D, Ded-Weed, Desormone, Dinoxol, DMA4, Dormone, Emulsamine BK, Emulsamine E-3, Envert DT or 171, Esteron 99 Concentrate, Esteron Four, Esteron Brush Killer, Estone, Fernoxone, Fernimine, Ferxone, Fernesta, Formula 40, Hedonal, Herbidal, Lawn-Keep, Macondray, Miracle, Netagrone 600, Pennamine D, Planotox, Plantgard, Rhodia, Salvo‡, Spritz-Hormin/2,4-D, Spritz-Hormit/2,4-D, Superormone Concentre, Super D Weedone, Transamine, U46, Verton 2D, Visko-Rhap, Weed-B-Gon, Weedar, Weed-Rhap, Weed Tox, Weedtrol, De broussaillant 600, Lithate, Dicotox, Field Clean Weed Killer). 2,4-DB is the butyric acid homologue of 2,4-D. Dichlorprop is the propionic acid homologue.

2,4,5-T or 2,4,5-trichlorophenoxyacetic acid (Brush-Rhap, Dacamine 4T, Debroussaillant Concentre, Ded-Weed Brush Killer, Esteron 245, Fence Rider, Forron, Inverton 245, Line Rider, Spontox, Super D Weedone, Tormona, Transamine, Trinoxol, Trioxone, U46, Veon 245, Verton 2T, Weedar, Weedone Envert T).

Common mixtures of 2,4-D and 2,4,5-T are: Dacamine 2D/2T, Esteron Brush Killer, Rhodia Low Volatile Brush Killer No. 2, U46 Special, Tributon, Visko-Rhap LV2D-2T, and Transamine.

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† A product of identical name containing pentachlorophenol (Chapter 4) as the active ingredient has been discontinued by Amchem Products Co.

‡ A product of identical name marketed by the Crystal Chemical Company contains cacodylic acid as the active ingredient (Chapter 10).

2,4,5-TP (Silvex) is the propionic acid homologue of 2,4,5-T. Kuron is a low volatile est f 2,4,5-TP. 2,4,5-TB is the butyric acid homologue of 2,4,5-T. Fenac or chlorfenac is 2,3,6-trichlorophenylacetic acid. Dicamba (Banvel) is dichloroanisic acid. MCPA, MCPB, MCPB-Ethyl, MCPCA and MCPP (Mecoprop) are 2-methyl, 4-chlorophenoxy aliphatic acids and esters.

TOXICOLOGY

Some of the chlorophenoxy acids, salts, and esters are moderately irritating to skin, eyes, and respiratory and gastrointestinal linings. In a few individuals, local depigmentation has apparently resulted from prolonged and repeated dermal contact with chlorophenoxy materials.

The chlorophenoxy compounds are absorbed across the gut wall, lung, and skin. They are not significantly fat storable. Excretion occurs within hours, or at most, days, primarily in the urine.

Given in large doses to experimental animals, 2,4-D causes vomiting, diarrhea, anorexia, weight loss, ulcers of the mouth and pharynx, and toxic injury to the liver, kidneys, and central nervous system. Myotonia (stiffness and incoordination of hind extremities) develops in some species and is apparently due to CNS damage: demyelination has been observed in the dorsal columns of the cord, and EEG changes have indicated functional disturbances in the brains of heavily dosed experimental animals.

Ingestion of large amounts of chlorophenoxy acids has resulted in severe metabolic acidosis in humans. Such cases have been associated with electrocardiographic changes, myotonia, muscle weakness, myoglobinuria, and elevated serum creatine phosphokinase, all reflecting injury to striated muscle. Because chlorophenoxy acids are weak uncouplers of oxidative phosphorylation, extraordinary doses may produce hyperthermia from increased production of body heat.

PolyChlorinated DibenzoDioxin (CDD) compounds are generated in the synthesis of 2,4,5-T. The 2,3,7,8-Tetra CDD form is extraordinarily toxic to multiple mammalian tissues. Hexa- hepta-, and octa-compounds exhibit less systemic toxicity, but are the likely cause of chloracne (a chronic, disfiguring skin condition) seen in workers engaged in the manufacture of 2,4,5-T, and certain other chlorinated organic compounds. Although toxic effects, notably chloracne, have been observed in manufacturing plant workers, they have not been observed in formulators or applicators regularly exposed to 2,4,5-T.

The medical literature contains several reports of peripheral neuropathy following what seemed to be minor dermal exposures to 2,4-D. It is not certain that exposures to other neurotoxicants were entirely excluded in these cases. Single doses of 5 mg/kg body weight of 2,4-D and 2,4,5-T have been administered to human subjects without any adverse effects. One subject consumed 500 mg of 2,4-D per day for 3 weeks without experiencing symptoms or signs of illness.

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FREQUENT SYMPTOMS AND SIGNS OF POISONING

Chlorophenoxy compounds are moderately **IRRITATING** to skin and mucous membranes. Inhalation of sprays may cause burning sensations in the nasopharynx and chest, and coughing may result. Prolonged inhalation sometimes causes dizziness.

When **INGESTED,** high concentrations of chlorophenoxy compounds may irritate the mouth, throat, and gastrointestinal tract. Prompt **EMESIS, CHEST PAIN** (from esophagitis), **ABDOMINAL PAIN,** and **DIARRHEA** commonly ensue. Injury to the GI tract does not usually progress to ulceration or perforation. Absorbed chlorophenoxy compounds have caused **FIBRILLARY MUSCLE TWITCHING,** skeletal muscle tenderness, and **MYOTONIA** (stiffness of muscles of the extremities). Ingestion of very large amounts has produced **METABOLIC ACIDOSIS,** fever, tachycardia, hyperventilation, vasodilatation and sweating. Particular cases have been characterized by coma and convulsions.

CONFIRMATION OF DIAGNOSIS

Gas-liquid chromatographic methods are available for detecting and measuring the chlorophenoxy compounds in blood and urine. These analyses are useful in confirming and assessing the magnitude of chlorophenoxy absorption. Urine samples should be collected as soon as possible after exposure because the herbicides may be almost completely excreted in 24-72 hours, depending on the extent of toxicant absorption. Analyses can be performed at special laboratories operated by state health departments, chemical companies, universities, and government facilities. If circumstances indicate strongly that excessive exposure to any of these compounds has occurred, initiate appropriate treatment measures immediately, not waiting for chemical confirmation of toxicant absorption.

TREATMENT

1. **BATHE** and **SHAMPOO** with soap and water to remove chemicals from skin and hair. Individuals with chronic skin disease or known sensitivity to chemicals should either avoid using these herbicides or take extraordinary measures to avoid contact.
2. **FLUSH** contaminating chemicals from eyes with copious amounts of clean water for 10-15 minutes.
3. If symptoms of illness occur during or following inhalation of spray, **REMOVE** victim **FROM CONTACT** with the material for at least two days. Allow subsequent contact with chlorophenoxy compounds only if effective respiratory protection is practiced.
4. IF substantial amounts of chlorophenoxy compounds have been **INGESTED,** spontaneous emesis usually occurs. Ordinarily, this empties the stomach as effectively as intubation and lavage. If vigorous emesis

has not occurred and **IF VICTIM IS FULLY ALERT,** induce **EMESIS** with S' JP **OF IPECAC** (adults 12 years and older, 30 ml; children under 12 years, 15 ml), followed by 1-2 glasses of water. Following emesis, administer 30-50 gm of **ACTIVATED CHARCOAL** in a slurry of 6-8 ounces tap water, to limit absorption of herbicide remaining in the gut.

5. **IF CONSCIOUSNESS LEVEL IS DEPRESSED** or other signs of **NEUROTOXICITY** appear, **SUSPECT** additional or alternative ingested toxicants. Evacuate the stomach by **INTUBATION, ASPIRATION,** and **LAVAGE.** Because petroleum distillates are commonly included in chlorophenoxy formulations, gastric intubation incurs a risk of hydrocarbon pneumonitis from aspiration. For this reason:

   A. If victim is unconscious or obtunded and facilities are at hand, insert an **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.
   B. Keep victim's **HEAD BELOW LEVEL OF THE STOMACH** during intubation and lavage (Trendelenburg, or left lateral decubitus, with head of table tipped downward). Keep victim's head turned to left.
   C. **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.

   After aspiration of gastric contents and washing of stomach, instill 30-50 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through the stomach tube to limit absorption of remaining toxicant. Do **NOT** instill milk, cream, or other materials containing vegetable or animal fats, as these are likely to enhance absorption.

6. If bowel movement has not occurred in 4 hours and patient is fully conscious, give **SODIUM SULFATE,** 0.25 gm/kg, as a cathartic. Magnesium sulfate and citrate, in comparable dosages, are equally suitable if renal function is adequate. Retained magnesium may depress CNS function.

7. In **SEVERE POISONINGS** by very large amounts of ingested chlorophenoxy acids, forced **ALKALINE DIURESIS** may save the victim's life. Assess serum electrolyte concentrations, and serum and urine pH. If a metabolic acidosis is present, infuse solutions of sodium bicarbonate at rates sufficient to keep the urine distinctly alkaline, continuing until plasma concentrations of chlorophenoxy compounds are less than about 10 μg/ml. [Prescott, L F. et al., Br. J. Clin. Pharmacol. 7:11 (1979)]

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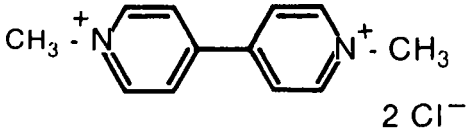
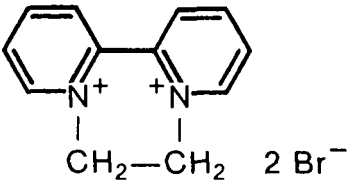
Chapter 7

PARAQUAT AND DIQUAT

CHEMICAL STRUCTURES





PARAQUAT DIQUAT

COMMON COMMERCIAL PESTICIDE PRODUCTS

Paraquat products: paraquat dichloride (usually as a 21% concentrate). Other names: Ortho paraquat-CL, Crisquat, Dextrone X, Esgram. Mixtures: Priglone, Preeglone, Weedol—with diquat; Simpar, Terraklene—with simazine; Gramonol, Mofisal—with monolinuron; Pathclear—with diquat and simazine; TotaCol, Dexuron—with diuron.

Diquat products: diquat (Reglone, Reglox, Aquacide, Dextrone, Weedtrine-D). Mixtures: Priglone, Preeglone, Weedol—with paraquat; Pathclear—with paraquat and simazine.

TOXICOLOGY

These dipyridyls injure the epithelial tissues: skin, nails, cornea, liver, kidney, and the linings of the GI and respiratory tracts. In addition to direct irritant effects, injury may involve peroxidation of intracellular and extracellular phospholipids and inhibition of surfactant synthesis by lung tissue. These toxic properties may derive from the capacity of dipyridyls to generate free radicals in tissues. The injury is usually reversible; however, the pulmonary reaction which follows ingestion of paraquat is often fatal.

Certain injuries have followed occupational contact with paraquat. Contact with the concentrate may cause irritation and fissuring of the skin of the hands, and cracking, discoloration, and sometimes loss of the fingernails. Splashed in the eye, paraquat concentrate causes conjunctivitis and, if not promptly removed, may result in protracted opacification of the cornea.

Although nearly all systemic intoxications by paraquat have followed ingestion of the chemical, occasional poisonings have resulted from excessive dermal contact. Absorption of toxic amounts is much more likely to occur if the skin is abraded. Persons who have experienced extraordinary dermal contact with paraquat (especially the concentrate) should be examined, and tested for hazardous concentrations of the agent in the blood and urine (see section on Confirmation of Diagnosis).

None of these agents is a cholinesterase inhibitor.

Thiram irritating to skin and mucous membranes. It has sensitized some individuals, generally after contact with rubber products containing residues of thiram used as a curing agent.

The metallo dithiocarbamates and ethylene dithiocarbamates are moderately irritating to skin and the respiratory mucous membranes following contact with sprays or dusts.

Thiram is the methyl analogue of disulfiram (Antabuse), an agent used to condition alcoholics against beverage alcohol. Much more is known of the toxic effects of disulfiram than of thiram, although the acute toxicity of thiram in laboratory animals is substantially greater. Given to animals in extreme doses, disulfiram has caused gastrointestinal irritation, demyelinization of CNS tissues, and necrosis of liver, splenic, and kidney tissues. Peripheral neuropathy and psychotic reactions have occurred in humans taking large doses of disulfiram regularly.

Functional and anatomic CNS damage has been demonstrated in rats on high chronic dosage regimens of iron and zinc dimethyldithiocarbamates. Because all of these agents are degraded partly to carbon disulfide in the body, a role of this metabolite in neurotoxic effects is suspected.

Both thiram and disulfiram inhibit aldehyde dehydrogenase, and are therefore capable of inducing "Antabuse" reactions in persons who consume beverage alcohol following substantial absorption of dithiocarbamates. Reactions may have occurred rarely in workers who imbibed after extraordinary occupational exposure to thiram. Theoretically, the metallo dithiocarbamates may also predispose to an "Antabuse" reaction. Peripheral vasodilation is the main pathophysiologic feature of the disulfiram-alcohol reaction, probably due to high tissue levels of acetaldehyde. This may occasionally lead to shock, and even more rarely, to myocardial ischemia, cardiac arrhythmias, circulatory failure, and death. Animal experimentation has suggested certain other biochemical mechanisms of toxicity involving reaction products of ethanol and disulfiram.

The ethylene bis dithiocarbamates do not inhibit aldehyde dehydrogenase, and there is no evidence of neurotoxicity from them. They do, however, degrade in the environment, and in mammalian tissues, to ethylene thiourea, a compound known as a goitrogen and carcinogen in laboratory animals. This feature mandates extra care in the protection of harvesters, and in removal of residues from harvested crops.

Except for some moderate irritant effects on skin, respiratory tract, and eyes, the (mono) thiocarbamate herbicides do not appear to be highly toxic. Extreme doses in laboratory animals do produce paralysis. There is a very remote possibility of "Antabuse" reactions from ethanol following extraordinary exposure to these (mono) thiocarbamates. They do not form ethylene thiourea on degradation.

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SYMPTOMS AND SIGNS OF POISONING

Thiram and metallo bis dithiocarbamates

Itching, redness, and eczematoid **DERMATITIS** have resulted when predisposed individuals have come into contact with these agents. Inhaled sprays and dusts have caused **NASAL STUFFINESS,** hoarseness, cough, and, rarely, pneumonitis. Repeated contact may produce sensitization. Ingestion of large amounts may produce nausea, **VOMITING,** and **DIARRHEA. HYPOTHERMIA** and ataxia are characteristic of poisoning. Muscle **WEAKNESS** and/or ascending paralysis may progress to respiratory paralysis if absorbed dosages are equivalent to those tested in experimental animals.

The reaction to beverage alcohol that may follow exceptional absorption of thiram and metallo bis dithiocarbamates is characterized by **FLUSHING, HEADACHE, SWEATING,** warm sensations, weakness, nasal congestion, labored breathing, tightness in the chest, tachycardia, palpitation, and hypotension. Extreme dosages may result in shock, convulsions, respiratory depression, and/or unconsciousness. Reactions are not likely to occur unless the absorbed dose is extraordinary.

Ethylene bis dithiocarbamates and (mono) thiocarbamates

Some of these agents are irritating to skin and respiratory mucous membranes, causing **ITCHING, SCRATCHY THROAT, SNEEZING,** and **COUGH,** if excessive amounts of spray or dust are inhaled. Apart from this effect, toxic potential is low. Neurotoxic and post-ethanol "Antabuse" reactions are not known to occur as a result of contact with these particular compounds.

CONFIRMATION OF DIAGNOSIS

Skin testing may be useful in identifying sensitization to these agents.

In general, these compounds are so rapidly metabolized in the body and excreted, that detection in blood is rarely possible. There are methods for detection of ethylene thiourea (from the ethylene bis dithiocarbamates) in urine.

TREATMENT

1. **WASH** contaminating chemical from **SKIN** and **HAIR** with soap and water. Persons sensitive to thiram (rubber-sensitive) should be permanently **REMOVED FROM CONTACT** with compounds of this nature.
2. **FLUSH** contaminant from **EYES** with fresh water for 10-15 minutes.
3. If **THIRAM** or **METALLO DITHIOCARBAMATE** compounds have been **INGESTED:**

A. If vigorous emesis has not already occurred and victim is fully alert, give **SYRUP OF IPECAC,** followed by 1-2 glasses of water to induce vomiting (adults, 12 years and older: 30 ml; children under 12: 15 ml).

CAUTION: **OBSERVE** victim closely **AFTER** administering **IPECAC.** If **CONSCIOUSNESS** level declines or vomiting has not occurred in 15 minutes, empty the stomach by **INTUBATION, ASPIRATION,** and **LAVAGE.**

B. **IF** consciousness level or respiration is **DEPRESSED,** empty the stomach by **INTUBATION, ASPIRATION,** and **LAVAGE,** using all available means to avoid aspiration of vomitus: left lateral Trendelenburg position, frequent aspiration of the pharynx and, in unconscious victims, tracheal intubation (using a cuffed tube) prior to gastric intubation.
After aspiration of the stomach and washing with isotonic saline or sodium bicarbonate, instill 30-50 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through the stomach tube to limit absorption of remaining toxicant.

C. If the irritant properties of the toxicant fail to produce a bowel movement in 4 hours, administer **SODIUM** or **MAGNESIUM SULFATE** as a cathartic: 0.25 gm/kg body weight in 1-6 ounces of water.

D. Administer glucose-containing fluids intravenously to accelerate excretion of toxicant.

E. For adults and children over 12 years, inject 1.0 gm **ASCORBIC ACID** (Vitamin C) intravenously at a rate not exceeding 0.2 gm/minute. For children under 12, give 10-20 mg/kg body weight. As a hydrogen-donor, ascorbic acid may have significant antidotal action against absorbed, but unreacted, dithiocarbamate compounds.

F. The victim must **AVOID** consumption of any **ALCOHOLIC** beverage for 3 weeks. Gastrointestinal absorption of these substances is slow, and the enzyme inhibition which they cause is slowly reversed.

4. Management of a reaction to **ETHANOL,** following absorption of a **DITHIOCARBAMATE:**

A. Administer **100% OXYGEN** as long as the reaction continues. Oxygen usually gives substantial relief from the distressing symptoms of vasodilation and hypotension.

CAUTION: If respiration is depressed, administer oxygen by an intermittent positive pressure breathing device and observe the victim closely to maintain pulmonary ventilation mechanically in case of apnea.

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B. Gastric evacuation, charcoal administration, catharsis. intravenous fluids, and ascorbic acid administration (3 A,B,C,D, E) may be appropriate, depending on the amount of dithiocarbamate absorbed, the time interval between exposure and treatment, and the severity of symptoms.

C. If the victim has suffered from arteriosclerosis, myocardial insufficiency, diabetes, neuropathy, cirrhosis, or other severe chronic disease, **OBSERVE** him **CAREFULLY** for 48 hours to insure that complications (especially myocardial infarction, toxic psychosis, and neuropathy) are treated promptly.

5. If an **ETHYLENE BIS DITHIOCARBAMATE,** or (mono) **THIOCARBAMATE** have been ingested:

   A. Give **SYRUP OF IPECAC,** followed by 1-2 glasses of water, to induce vomiting (adults: 30 ml; children under 12 years: 15 ml). Following emesis, administer 30-50 gm **ACTIVATED CHARCOAL** to bind toxicant remaining in the gut.

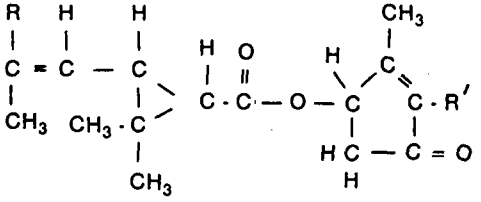
   B. Follow charcoal with **SODIUM** or **MAGNESIUM SULFATE,** 0.25 gm/kg, to remove toxicant from the gut by catharsis.

Chapter 9

PYRETHRUM, PYRETHRINS, PYRETHROIDS, AND PIPERONYL BUTOXIDE

Pyrethrum is the partly refined extract of the chrysanthemum flower which has been used as an insecticide for more than 60 years. Pyrethrins are the insecticidally active ingredients of pyrethrum, now known to consist of keto-alcohol esters of pyrethric and chrysanthemic acids. The alcohols are pyrethrolone, cinerolone, and jasmololone, whose respective esters are known as pyrethrins, cinerins, and jasmolins. Pyrethroids are synthetic compounds based structurally on the pyrethrin molecule but modified to improve stability in the natural environment (light, heat, etc.)

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS

Pyrethrins: There are several hundred commercial products containing pyrethrins and pyrethroids. Commonly, these products combine pyrethrins or pyrethroids with a synergist, such as piperonyl butoxide, and an additional pesticide, for increased killing power. Many of these combinations are packaged with a propellant in a spray can or bug-bomb.

Pyrethroids: Allethrin (Pynamin), barthrin, bioresmethrin, cypermethrin (Ripcord), decamethrin, fenothrin, fenpropanate, fenvalerate (Belmark, Pydrin), permethrin (Ambush, Ectiban, Pounce), phthalthrin or tetramethrin (Neo-Pynamin), resmethrin (Synthrin, Chrysron).

TOXICOLOGY

These esters rapidly paralyze the insect nervous system, making them famous for their quick "knockdown" effect. Mammalian toxicity, however, is extraordinarily low for pyrethrins and pyrethroids. Oral LD_{50} values for these compounds in rats are several hundred or thousand mg/kg body weight. There is apparently less efficient absorption of pyrethrins across the GI lining and

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skin than across insect chitin, and much more rapid biodegradation (hydrolysis and oxidation) by the mammalian liver than by insect tissues.

Some of the less purified pyrethrum extracts contain allergenic substances that induce attacks of allergic rhinitis and asthma in humans. Rarely, hypersensitivity pneumonitis has followed pyrethrum inhalation.

Administered orally to rodents in extraordinary dosage, pyrethrins and pyrethroids cause nervous irritability, tremors, and motor ataxia. Bloody tears and urinary incontinence have also been observed. Manifestations of toxicity occur at much lower dosage following intravenous administration than after oral dosing. Chronic feeding of these chemicals induces an increase in liver size and bile duct hyperplasia. To date, neither pyrethrins nor pyrethroids have been identified as mutagenic, carcinogenic, or teratogenic.

Piperonyl butoxide inhibits the mixed function oxidase enzymes of the liver which catabolize pyrethrins and pyrethroids. The amount absorbed by humans during ordinary exposure is not likely to affect liver function measurably.

FREQUENT SYMPTOMS AND SIGNS OF UNDUE EXPOSURE

A **STUFFY, RUNNY NOSE** and scratchy throat from inhalation of partly purified pyrethrum extract is the most common adverse effect of these agents. Asthmatic **WHEEZING** may be precipitated by exposure of predisposed individuals.

Sudden bronchospasm, swelling of oral and laryngeal mucous membranes, and shock (anaphylaxis) have been reported after pyrethrum inhalation. Delayed appearance of dyspnea, cough and fever, with patchy lung infiltrates on x-ray, suggest hypersensitivity pneumonitis.

Nervous irritability, tremors, and ataxia have occurred rarely in persons who have had massive inhalation exposure to pyrethrins.

Halocarbon propellents in bug-bomb products present a risk of **CARDIAC ARRHYTHMIA** and possibly fibrillation if inhaled to excess. Hydrocarbons used as solvents in spray products are likely to result in **COUGH, FEVER,** and **CHEST PAIN** (hydrocarbon pneumonitis) if these liquids are inadvertently aspirated.

CONFIRMATION OF DIAGNOSIS

Skin tests sometimes identify sensitivity to pyrethrum. Neither pyrethrins nor pyrethroids inhibit cholinesterase enzymes. There are gas-chromatographic methods for identifying some of these insecticides in environmental samples, but they are not likely to be useful in diagnosing poisoning because of the rapid metabolism of the esters following absorption. There are no methods for identifying urinary metabolites.

TREATMENT

1. **WASH** contaminating pesticide from the **EYE** with copious amounts of water. Wash contaminated **SKIN** with soap and water.
2. For life-threatening allergic reaction to pyrethrum (severe **ASTHMA** or **ANAPHYLAXIS**), give 0.1 to 0.5 ml of 1:1000 **ADRENALIN** intramuscularly, or **slowly** intravenously. Repeat if necessary to relieve respiratory distress and maintain blood pressure. Intravenous **AMINOPHYLLINE** (10 ml, slowly) may be indicated. Give **HYDROCORTISONE** (50-100 mg), or equivalent steroid, intravenously.

   Less severe allergic reactions (rhinitis) can be managed with **ANTIHISTAMINES** and **DECONGESTANTS**, given orally.

   HYPERSENSITIVITY PNEUMONITIS may require oxygen, steroids, antibiotics and several days bedrest, depending on severity.
3. **INGESTION** of a **SMALL AMOUNT** of a pyrethrin or pyrethroid formulation is not likely to cause poisoning. **EXAMINE THE LABEL** to identify additional insecticides, which may be more toxic. **BASE TREATMENT ON THE MOST TOXIC** ingredients.

   A. If a formulation contains **ONLY** pyrethrins, or pyrethroids, and synergists, ingestion of a small amount (up to about 5 mg/kg) is probably best treated by large doses of **ACTIVATED CHARCOAL**, 30-50 gm in 3-4 ounces of water, followed by cathartic doses of **SODIUM** or **MAGNESIUM SULFATE**, 0.25 gm/kg body weight in 1-6 ounces of water.

4. If **LARGE AMOUNTS** of pyrethrin or pyrethroid formulation have been **INGESTED**, the stomach and intestine must be evacuated:

   A. **IF** victim is **ALERT** and respiration is not depressed, give **SYRUP OF IPECAC**, followed by 1-2 glasses of water, to induce vomiting (adults and children 12 years and older: 30 ml; children under 12 years: 15 ml).

      CAUTION: **OBSERVE VICTIM** closely **AFTER** administering **IPECAC.** If consciousness level declines or vomiting has not occurred in 15 minutes, **INTUBATE** the stomach immediately.

   Following emesis, have victim drink a suspension of 30-50 gm **ACTIVATED CHARCOAL** in 3-4 ounces of water to limit absorption of toxicant remaining in the gut.

   B. IF victim is **NOT FULLY ALERT**, empty stomach immediately by **INTUBATION, ASPIRATION,** and **LAVAGE,** using isotonic saline or 5% sodium bicarbonate. Because many pesticides are dissolved in petroleum distillates, emesis and intubation of the stomach involve a risk that solvent will be aspirated, leading to chemical pneumonitis. For this reason:

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(a). If victim is unconscious or obtunded and facilities are at hand, insert an **ENDOTRACHEAL TUBE** (cuffed, available) prior to gastric intubation.

(b). Keep victim's **HEAD BELOW LEVEL OF THE STOMACH** during intubation and lavage (Trendelenburg, or left lateral decubitus, with head of table tipped downward). Keep victim's head turned to left.

(c). **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.

(d). After aspiration of gastric contents and washing of stomach, instill 30-50 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through stomach tube to limit absorption of remaining toxicant.

(e). If bowel movement has not occurred in 4 hours and patient is fully conscious, give **SODIUM** or **MAGNESIUM SULFATE** as a cathartic: 0.25 gm/kg body weight in 1-6 ounces of water.

5. Do **NOT** administer or instill milk, cream, or other substances containing vegetable or animal fats, which enhance absorption of lipophilic substances, such as pyrethrins and pyrethroids.
6. **DIAZEPAM** (Valium®), 5-10 mg in adults, 0.1 mg/kg in children, given orally or **slowly** IV, should control nervousness and tremors in rare cases having these symptoms after extraordinary exposure to pyrethrins and pyrethroids.

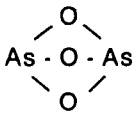
Chapter 10

ARSENICAL PESTICIDES

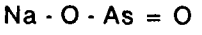
CHEMICAL STRUCTURES

INORGANIC ARSENICALS

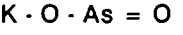
Extremely Toxic



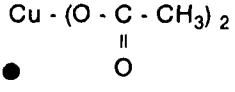
ARSENIC TRIOXIDE



SODIUM ARSENITE



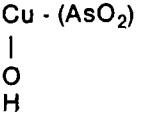
POTASSIUM ARSENITE



$3Cu \cdot (As\ O_2)_2$

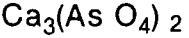
COPPER ACETOARSENITE

CALCIUM ARSENITE

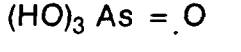


COPPER ARSENITE

Highly Toxic

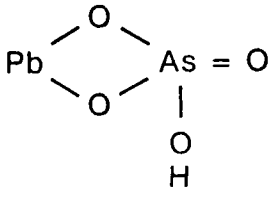


CALCIUM ARSENATE



ARSENIC ACID

Moderately Toxic



LEAD ARSENATE

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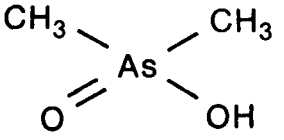
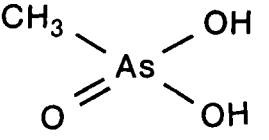
ORGANIC ARSENICALS

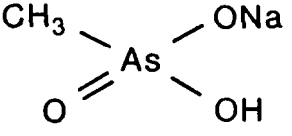
Moderately Toxic



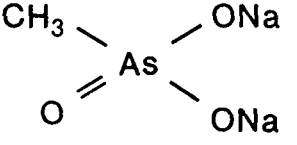
CACODYLIC ACID



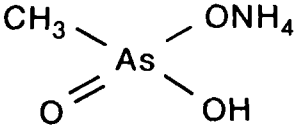
METHANE ARSONIC ACID
(MAA)



MONOSODIUM
METHYL ARSONATE
(MSMA)



DISODIUM
METHYL ARSONATE
(DSMA)



MONOAMMONIUM
METHANE ARSONATE

COMMON COMMERCIAL ARSENIC PRODUCTS

1.	Arsenic trioxide	"White arsenic," arsenious oxide (registered only for ant pastes, veterinary medicinals, and marine antifouling preparations).
2.	Sodium arsenite:	Chem Pels C, Chem-Sen 56, Kill-All, Penite, Prodalumnol Double.
3.	Calcium arsenite:	Mono-calcium arsenite.
4.	Copper arsenite:	Chemonite.
5.	Copper acetoarsenite:	Paris green, Schweinfurt green, emerald green, French green, mitis green.
6.	Arsenic acid:	Desiccant L-10, Hi-Yield Desiccant H-10.
7.	Sodium arsenate:	Jones Ant Killer, Terro Ant Killer.
8.	Calcium arsenate:	Pencal, Spra-cal, Security.
9.	Lead arsenate:	Gypsine, Security, Soprabel, Talbot.
10.	Methane arsonic acid:	MAA.
11.	Monosodium methyl arsonate:	MSMA, Ansar 17OHC, methane arsonate, Ansar 529HC, Arsonate liquid, Bueno 6, Daconate 6, Dal-E-Rad, Herb-All, Merge 823, Mesamate, Target MSMA, Trans-Vert, Weed-E-Rad, Weed-Hoe.
12.	Disodium methyl arsonate:	DSMA, Ansar 8100, methane arsonate, Ansar DSMA liquid, Arrhenal, Arsinyl, Chipco Crab Kleen, Crab-E-Rad, Dal-E-Rad 100, Di-Tac, DMA, DMA 100, Methar, Namate, Sodar, Weed-E-Rad, Weed-E-Rad 360, Weed-E-Rad DMA Powder, Weed-Hoe.
13.	Monoammonium methyl arsonate:	MAMA, monoammonium methanearsonate.
14.	Calcium acid methanearsonate:	CAMA, Super Crab-E-Rad-Calar, Super Dal-E-Rad "Calar".
15.	Cacodylic acid:	Dilic, Phytar 560, Rad-E-Cate 25, Salvo.† [Crystal Chemical Company)

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† A product of identical name marketed by Crystal Chemical Company contains 2,4-D as the active ingredient (Chapter 6).

TOXICOLOGY

Although there may be some degree of dermal and pulmonary absorption of arsenical liquids and sprays, ingestion is the route of intake involved in virtually all acute poisonings by the solid arsenicals.

Inhalation of arsine gas (sometimes generated inadvertently in pesticide manufacturing plants) has caused serious illness and death by hemolytic action.

Generally, the organic (methylated) pentavalent arsenicals are considerably less toxic than the trivalent inorganic arsenicals. In fact, methylation is the principal mechanism of detoxification of inorganic arsenicals in mammals. The less soluble inorganic forms (notably lead arsenate, and even arsenic trioxide) present less hazard than the highly soluble salts such as sodium arsenite and copper acetoarsenite. But because gastric pH, gastrointestinal motility, and gut bacterial action can enhance the absorption and toxicity of ingested compounds, it is safest to manage cases of arsenic ingestion as though all forms of arsenic are highly toxic.

Trivalent arsenicals (or, more likely, an arsenious acid metabolite) bind efficiently to the functional thiol groups of many tissue components, including enzymes. The affinity for thiol groups in keratin accounts for the accumulation of arsenic in skin, nails, and hair in cases of chronic poisoning. When absorbed across the gut wall, these arsenicals injure the splanchnic vasculature, causing abdominal pain, colic, and diarrhea. Once absorbed into the blood, they cause toxic damage to the liver, kidneys, brain, bone marrow, and peripheral nerves. Liver injury is manifest as hepatomegaly, jaundice, and increase in circulating hepatocellular enzymes LDH and GOT. Renal damage is reflected in albuminuria, hematuria, pyuria, cylindruria, then azotemia. Acute tubular necrosis may occur in severe poisoning. Injury to blood-forming tissues can take the form of agranulocytosis, aplastic anemia, thrombocytopenia, or pancytopenia. Toxic encephalopathy may be manifest as speech and behavioral disturbances. Peripheral neuropathy occurs in both acute and chronic forms.

Sequelae of arsenic poisoning include cirrhosis, hypoplastic bone marrow, renal insufficiency, and peripheral neuropathy. Excessive exposures to arsenicals have caused hyperkeratosis and skin cancers. Excessive inhalation of dusts may cause bronchitis and pneumonia; protracted inhalation has been associated epidemiologically with increased occurrence of lung cancer.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

ACUTE arsenic poisoning

COLIC, BURNING ABDOMINAL PAIN, VOMITING, and **WATERY** or **BLOODY DIARRHEA** are the primary manifestations of ingestion of solid arsenical poisons. Symptoms following ingestion of inorganic arsenicals are much more severe than those resulting from ingestion of pentavalent organic arsenicals. Symptoms are sometimes delayed for minutes or even hours after ingestion. **HEADACHE, DIZZINESS, MUSCLE SPASMS, DELIRIUM,**

and sometir **CONVULSIONS** reflect direct injury to the central nervous system, as we.. as extracellular electrolyte disturbances and shock. **A GARLIC ODOR** to the breath and feces helps to identify the responsible toxicant. **SHOCK, TOXIC NEPHROSIS, HEPATITIS** (hepatomegaly and jaundice), and **NEUROLOGIC INJURY** (delirium, paralysis, respiratory depression) may progress to a fatal outcome.

SUBACUTE arsenic poisoning

Repeated intakes less than those necessary to produce severe acute symptoms are known to cause **CHRONIC HEADACHE, ABDOMINAL DISTRESS, SALIVATION, LOW-GRADE FEVER,** and **PERSISTENT** symptoms of **UPPER RESPIRATORY IRRITATION.** Stomatitis and garlicky breath are characteristic.

CHRONIC arsenic poisoning

Prolonged low intakes of arsenic cause peripheral neuropathy (**PARESTHESIAE, PAIN,** anesthesia, paresis, ataxia), encephalopathy (**APATHY,** disorientation), dermatologic disorders (**KERATOSES,** pigmentation, eczema, brittle nails, loss of hair), toxic hepatitis (**HEPATOMEGALY,** sometimes progressing to cirrhosis with ascites), and bone marrow injury (**ANEMIA,** leukopenia, **WEAKNESS**). Local **EDEMA,** frequently of the eyelids, characterizes some poisonings.

ACUTE arsine gas poisoning

The gas causes hemolysis of red blood cells, in addition to inhibition of cellular sulfhydryl respiratory enzymes. Hemolysis causes **HEMOGLOBINEMIA** and **HEMOGLOBINURIA.** This in turn, causes acute tubular necrosis. Early symptoms of poisoning (**CHILLS,** weakness, burning sensations) are followed by abdominal **CRAMPS,** vomiting, and prostration. Failing renal function deteriorates to **ANURIA.**

CONFIRMATION OF DIAGNOSIS

Measurement of 24-hour urinary excretion of arsenic is probably the best way to confirm excessive arsenic absorption, although methods for blood arsenic concentration are available. Persons on ordinary diets usually excrete less than 20 μg/day but diets rich in seafood may generate as much as 200 μg/day. Excretions above 100 μg/day should be viewed with suspicion and tests should be repeated. Excretions above 200 μg/day reflect a toxic intake, unless seafood was ingested. (The arsenic in seafood is apparently bound firmly to an organic moiety that renders the arsenic essentially nontoxic and highly excretable.)

The qualitative Gutzeit test for arsenic in the urine is available in most hospital laboratories, and is useful in identifying acute poisonings promptly.

Chronic storage of arsenic can be detected by analysis of hair or fingernails. The hemoglobinuria caused by arsine is identified by fin , free hemoglobin in fresh urine.

TREATMENT OF POISONING BY SOLID ARSENICALS

1. Flush contaminated **EYES, HAIR** and **SKIN** with copious amounts of fresh water. **WASH SKIN** and **HAIR** with soap and water.
2. In poisonings by **INGESTED ARSENICALS**

   A. **INTUBATE** the stomach, **ASPIRATE,** and **LAVAGE** with 3 liters of isotonic saline or 5% sodium bicarbonate. Use all possible precautions to avoid aspiration of vomitus:

      (1) If victim is unconscious or obtunded, insert an **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.
      (2) Keep victim's **HEAD BELOW LEVEL OF THE STOMACH** during intubation (Trendelenburg, or left lateral decubitus, with head of table tipped downward). Keep victim's head turned to the left.
      (3) **ASPIRATE** pharynx as regularly as possible to remove gagged or vomited stomach contents.

   B. After lavage, **INSTILL** 30-50 gm **ACTIVATED CHARCOAL** in the smallest amount of water necessary to deliver the charcoal through the tube.
   C. If diarrhea or colic has not ensued within an hour of gastric lavage and charcoal administration, give **SODIUM SULFATE** as a cathartic 0.25 gm/kg body weight in 1-6 ounces of water.

3. An **ABDOMINAL X-RAY** film is useful in detecting concretions of the less soluble arsenicals (As_2O_3 and lead arsenate) in the gut. If not removed these may become a repository of slowly absorbed toxicant.
4. Administer **INTRAVENOUS ELECTROLYTE** and **GLUCOSE** solutions to maintain hydration and to accelerate toxicant excretion. **COMBAT SHOCK** with **TRANSFUSIONS** of **WHOLE BLOOD,** and by inhalation of 100% **OXYGEN.**

   CAUTION: Monitor urine flow via catheter. Monitor fluid balance, body weight, and/or central venous pressure to guard against fluid overload that may result if tubular necrosis (anuria) supervenes.

5. Administer **DIMERCAPROL** (BAL) and **PENICILLAMINE** to accelerate arsenic excretion.

   A. Give dimercaprol, 3-5 mg/kg q4h intramuscularly until abdominal pain and diarrhea subside and patient is regularly passing administered charcoal in the feces. **IF** victim is **ALLERGIC** to

PE[illegible]CILLIN, continue dimercaprol therapy at 3-5 mg/kg q6h × 4 dos then q12h × 2 doses, then q24h × 10 doses, monitoring urine arsenic excretion periodically to judge effectiveness.

CAUTION: **DIMERCAPROL** can cause troublesome side effects (hypertension, tachycardia, nausea, headache, paresthesiae and pain, lacrimation, sweating, anxiety, and restlessness). Although usually not so severe as to preclude treatment, they may require antihistaminic therapy.

B. **IF** victim is **NOT ALLERGIC** to **PENICILLIN**, oral **d-PENICILLAMINE** is the therapy of choice and should **REPLACE** dimercaprol treatment as soon as the feces are laden with charcoal, limiting gut absorption of arsenic. Adult dosage is 0.5 gm four times daily (2 gm/day), given before meals, for 5 days. Dosage for children is 0.025 gm/kg four times daily, not to exceed 2 gm/day for 5 days.

CAUTION: Although oral d-penicillamine therapy is usually better tolerated than intramuscular dimercaprol, serious reactions to it have occurred: the most common has been maculopapular rash, with fever, leukopenia, thrombocytopenia, eosinophilia, arthralgia and lymphadenopathy. It has also induced the nephrotic syndrome on occasion, and has caused thrombophlebitis, cheilosis, angioneurotic edema, and even fatal agranulocytosis in particular patients given the drug over long periods for conditions unrelated to arsenic poisoning. Penicillin sensitive individuals are likely to be sensitive to d-penicillamine.

(a). A single 5 day course of d-penicillamine therapy is usually sufficient. However, if symptoms recur after treatment, additional d-penicillamine should be given at a dosage just sufficient to abolish symptoms.

6. Intense abdominal pain may require morphine (adults, 12 years and older: 4-15 mg; children under 12 years: 0.1-0.2 mg/kg).
7. Severe poisoning (especially when renal function is impaired) may require **HEMODIALYSIS** to remove arsenic combined with dimercaprol from the blood, and to control extracellular fluid composition. **HEMOPERFUSION** may be useful, but its effectiveness has not been reported.

TREATMENT OF POISONING BY ARSINE GAS

1. **REMOVE** victim to **FRESH AIR.**
2. **MAINTAIN RESPIRATION** and **CIRCULATION** by resuscitation and cardiac massage, if necessary.

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3. Administer **INTRAVENOUS FLUIDS** promptly to dilute free hemoglobin and minimize tubular injury. Include enough sodium carbonate to keep the urine alkaline.

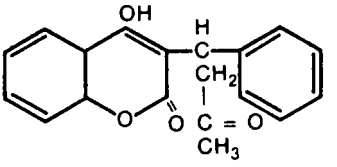
   CAUTION: Monitor urine flow via catheter. Monitor fluid balance, body weight, and/or central venous pressure to guard against fluid overload resulting from acute tubular necrosis.

4. Administer **DIMERCAPROL** as recommended in 5A even though it has only limited effect in arsine poisoning.
5. **EXCHANGE BLOOD TRANSFUSIONS** and **PERITONEAL DIALYSIS** have saved the lives of victims of arsine poisoning suffering acute tubular necrosis.

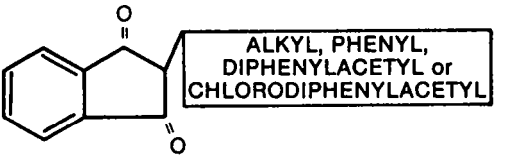
Chapter 11

RODENTICIDES

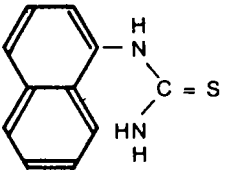
STRUCTURES OF PRINCIPAL COMPOUNDS



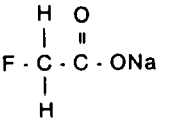
WARFARIN



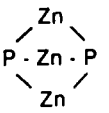
1,3 INDANDIONE



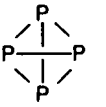
α - NAPHTHYL
THIOUREA



SODIUM
FLUOROACETATE



ZINC
PHOSPHIDE



YELLOW
PHOSPHORUS

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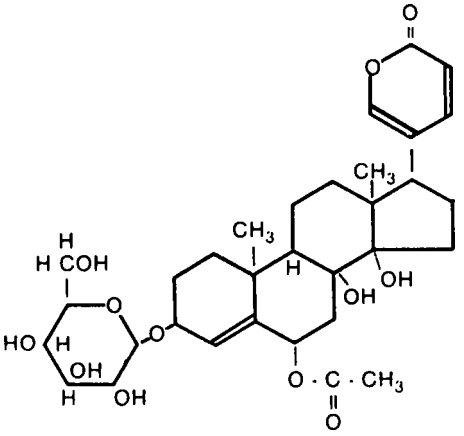
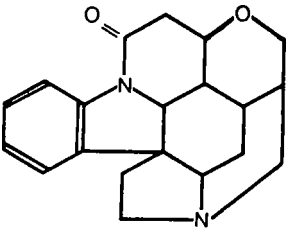
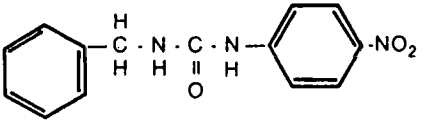


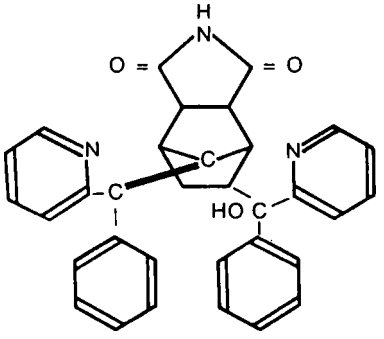
SCILLIROSIDE
(Active principle of Red Squill)



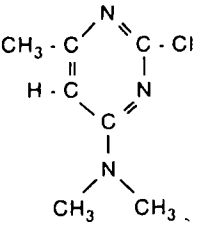
STRYCHNINE



RH- 787 (Active ingredient of VACOR and DLP-787)



NORBORMIDE



CRIMIDINE

COMMON COMMERCIAL RODENTICIDE PRODUCTS

Coumarins: warfarin, coumafene, zoocoumarin (Kypfarin, Ratox, RAX, Rodex, Tox-Hid, Warfarin Plus); coumafuryl (Tomarin, Fumarin); bromadiolone (Bromone, Super-Caid, Ratimus), coumachlor (Tomorin).

Indandiones: diphacinone (Diphacin, Promar, Ramik); chlorophacinone (Caid, Drat, Liphadione, Microzul, Ramucide, Ratomet, Raviac, Rozol, Topitox); pindone or pivaldione (Pival, Pivacin, Pivalyn, Tri-ban).

Other anticoagulant rodenticides of different structure: difenacoum (Ratak); brodifacoum (Talon).

Sodium fluoroacetate: 1080, Fratol, Yasoknock.

Zinc phosphide: Phosvin, Zinc-Tox.

Yellow phosphorus and **strychnine** have limited use and are generally identified by these long established common names.

Crimidine: Castrix.

RH-787: This product is no longer available for sale, but existing stocks present a continuing threat of poisoning. Commercial products are: Vacor Rat Killer (2% RH-787 in vehicle resembling corn meal); DLP-787 Bait (2% RH-787 in vehicle resembling corn meal); DLP-787 House Mouse Tracking Powder (10% RH-787 in a light green powder).

Red squill: Dethdiet, Rodine.

Antu: Krysid.

Norbormide: Shoxin, Raticate.

TOXICOLOGY

Rodent poisons are generally added to baits, i.e., grain or paste designed to encourage consumption. Safety for pets, domestic animals, and humans depends on the toxicity of the agents, concentration of active ingredients in the baits, and the likelihood that a toxic dose will be consumed by nontarget species. The *coumarins* are reasonably effective against pest rodents and have a good safety record. This is due mainly to the low concentration of active ingredient in the bait: about 100 gm of the commercial bait must be ingested to yield 25 mg of anticoagulant. This is important in evaluating suspected poisonings by anticoagulants, which are the most widely available rodenticides for public use.

Very small amounts of the extremely toxic rodenticides—sodium fluoroacetate, zinc phosphide, crimidine, strychnine, and yellow phosphorus—can cause fatal poisoning.

Vacor should be considered highly toxic. Ingestion of less than 1 gm by an adult has caused severe poisoning.

Antu, red squill, and norbormide present considerably less toxic hazard to humans and to domestic animals.

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† A rodenticide of identical trade name is still available in some areas which contains thallium sulfate as the active ingredient. Use of thallium in the United States is now restricted.

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Coumarins, indandiones, and other anticoagulants: Gastrointestinal absorption of these toxicants is efficient, beginning within minute ingestion and continuing for 2 to 3 days. Apparently warfarin can also be absorbed across the skin, although the circumstances under which this occurred were extraordinary.

These agents depress the hepatic synthesis of substances essential to blood clotting: prothrombin (factor II) and factors VII, IX, and X. The antiprothrombin effect is best known, and provides the basis for detection and assessment of clinical poisoning. Direct damage to capillary permeability occurs concurrently. The ultimate effect of these actions is to induce widespread internal hemorrhage. This generally occurs in the rodent after several days of bait ingestion, although the modern products (diphacinone, chlorophacinone, pindone, difenacoum, and brodifacoum) may be lethal after fewer feedings. These modern agents should be considered more toxic than warfarin.

In rare instances, coumarin-type anticoagulants have caused ecchymosis and extensive skin necrosis in humans for reasons not related to excessive dosage.

Unlike the coumarin anticoagulants, the indandiones cause symptoms and signs of neurologic and cardiopulmonary injury in laboratory rats; these often lead to death before hemorrhage occurs. These actions may account for the somewhat greater toxicity of this class of anticoagulants. Neither cardiopulmonary nor neurologic symptoms or signs have been reported in human poisonings.

Lengthened prothrombin time from a toxic dose is usually evident within 24 hours of ingestion and reaches a maximum in 36 to 72 hours. Without intervention, hypoprothrombinemia may persist 10 to 15 days, depending on the agent and dosage. Prothrombin depression occurs in response to doses much lower than those necessary to cause hemorrhage.

Sodium fluoroacetate: the fluorocitrate metabolite of this poison blocks energy production in mammalian cells at the level of the tricarboxylic acid cycle. The critical sites of toxic effect in humans are the myocardium (where ventricular fibrillation is the usual cause of death) and the brain, where seizures are induced and respiration is depressed. Seizures, respiratory depression, and ventricular fibrillation are all causes of death.

Zinc phosphide: this inorganic compound produces severe gastrointestinal irritation. It degrades in the gut to phosphine gas which, when absorbed, causes pulmonary edema and severe liver, kidney, CNS, and myocardial injury.

Yellow phosphorus: this agent causes severe gastrointestinal irritation resulting in vomiting, diarrhea, and melena. Circulatory collapse may occur and prove irreversible. Liver necrosis and acute renal tubular necrosis are equally ominous threats to life. Hemorrhage, from hypoprothrombinemia, and cardiac arrest or fibrillation, account for some deaths.

Strychnine: this natural poison acts directly on the cells of the brain and spinal cord to cause convulsions. Death is caused by convulsive interference with pulmonary gas exchange, by depression of respiratory center activity, or both.

Crimidine: this is a synthetic pesticide which, although unrelated chemically to strychnine exerts toxic effects similar to those of strychnine, producing violent convulsions and secondary tissue anoxia by its action on the CNS.

Vacor, DLP-787: the exact mechanism of RH-787 toxicity is not known although one established effect in rats is interference with nicotinamide metabolism. RH-787 has no anticoagulant action. Symptoms and signs in poisoned animals suggest toxic actions on the brain, peripheral nerves, myoneural junctions, pancreatic islet tissues, autonomic nervous system, and the conducting tissues of the heart. Abnormalities of renal and vascular function may be direct effects of poisoning, or they may reflect metabolic and autonomic nervous system disturbances, impaired vascular reactivity in particular.

Red squill: this biological agent is unlikely to present a serious toxic hazard to humans or other vomiting species, because 1) it usually induces prompt emesis, 2) it is poorly absorbed from the gut, and 3) the active principles are in low concentration, and are rapidly excreted. Natural squill contains digitalis-like glycosides, which might, theoretically, produce manifestations of digitalization in humans. The glycoside known as scilliroside is the probable cause of convulsive death in the rat; convulsions have not been observed in human poisonings.

Antu: this agent exhibits selective toxicity for the rat, causing pulmonary edema and pleural effusion. Only one human poisoning is recorded, and it was induced by a large suicidal dose. Vomiting was followed by dyspnea, cyanosis, and pulmonary râles, presumably reflecting pulmonary edema. The patient recovered.

Norbormide: this is selectively toxic to Norway and roof rats, which it kills by inducing a generalized, sudden, and intense vasoconstriction. Other varieties of rats are resistant, and the chemical is only moderately toxic to other mammals, including humans. Oral doses of 300 mg cause transient lowering of blood pressure and body temperature in humans.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

Coumarins, indandiones, and other anticoagulants: In most cases of ingestion of anticoagulants, victims have remained asymptomatic, due to the small dosage taken. Even in cases involving ingestion of substantial amounts of anticoagulant compound (more often medication than rodenticide), hypoprothrombinemia has occurred without symptoms of poisoning. Hemorrhage appears only when extraordinary amounts have been absorbed. In reported cases, the anticoagulants were either taken deliberately, were absorbed over long periods out of neglect of elementary hygienic standards, or were ingested by starving indigents who used quantities of rodent bait as food.

Victims of large doses exhibit **HEMATURIA, NOSEBLEED, HEMATOMATA, BLEEDING GUMS,** and **MELENA. ABDOMINAL PAIN** and **BACK PAIN** probably reflect hemorrhage in the abdominal and retroperitoneal tissues. **WEAKNESS** occurs as a result of **ANEMIA. RENAL COLIC**

often complicates severe hematuria. Nasal and gastrointestinal hemorrhages have occasionally caused death from exsanguination.

Sodium fluoroacetate: A delay of several minutes or even hours may be expected before symptoms appear. Epigastric distress and vomiting often occur. Apprehension, **PARESTHESIAE** and hallucinations are the usual premonitory symptoms, leading to epileptiform **CONVULSIONS. CARDIAC IRREGULARITIES** (ectopic beats, pulsus alternans, ventricular tachycardia and fibrillation) appear after seizures commence. These are frequently fatal.

Zinc phosphide: Intense **NAUSEA,** abdominal pain, excitement, and chills are early symptoms. Tightness in the chest, **DYSPNEA** and **COUGH,** productive of **FROTHY SPUTUM,** reflect pulmonary edema. **SHOCK** from toxic myocarditis is common. If these conditions are survived, **JAUNDICE** from liver necrosis, and **ANURIA** from renal tubular injury are later complications. Hypocalcemic **TETANY** and **PURPURA** have occurred in some poisonings.

Yellow phosphorus: BURNING PAIN in the throat, chest, and abdomen reflect severe mucosal irritation. Vomiting and diarrhea ensue. Breath has garlicky odor. Feces may luminesce and "smoke" from phosphorus fumes. **SHOCK** often progresses to death in 1 to 2 days. The patient who survives may then be relatively symptom-free for several hours or even days, after which the delayed manifestations appear due to liver, CNS, myocardial and renal injury. Nausea and **VOMITING** persist. **HEMORRHAGE** at various sites reflects mainly depression of clotting-factor synthesis in the liver. **SHOCK** may be due to hemorrhage and/or toxic myocarditis. **CONVULSIONS,** delirium, and coma are common. **ANURIA** usually ensues as a result of direct nephrotoxic effect of phosphorus, enhanced by biliary nephrosis (hepatorenal syndrome).

Strychnine: Within 10 to 60 minutes of ingestion of an adequate dose (as little as 16 mg), the victim suffers **VIOLENT CONVULSIONS** caused by clonic, then tonic contraction of all the skeletal muscles of the body. Cyanosis develops promptly. Brief periods of relaxation may occur, followed by even more severe seizures. Opisthotonus is common, and the muscles of the face are drawn into a grimace. Death is usually due to **ASPHYXIA,** a consequence of convulsive spasm of the respiratory muscles.

Crimidine: Ingestion is followed promptly by **VIOLENT CONVULSIONS,** essentially like those caused by strychnine (see preceding paragraph).

Vacor, DLP-787: Minimum toxic and lethal doses in humans are not known. Ingested amounts less than one gram have proved severely toxic.

Symptoms may not appear for 4 to 48 hours after ingestion. Earliest symptoms are usually **NAUSEA,** vomiting, abdominal cramps, **CHILLS,** and **CONFUSION.** Later manifestations are aching and fine tremors of the extremities, dilated pupils, plantar hyperesthesia, **MUSCLE WEAKNESS,** dysphagia, chest pain, postural hypotension, anorexia, diarrhea, urinary retention, and **HYPOTHERMIA.** Subsequently, **DIABETES MELLITUS** commonly develops, manifest as glycosuria, polyuria, ketoacidosis, and dehydration. Death may result from respiratory failure, cardiovascular collapse, or ketoacidosis. Survivors of the acute phase of the poisoning are often

left with permanent sequelae: postural hypotension, diabetes mellitus, bladder dystonia (r tion or frequency), bowel dystonia (constipation or diarrhea), and peripheral neuropathy.

Abnormal laboratory findings include hyperglycemia, glycosuria, ketosis (acidosis and electrolyte disturbances), and elevation of serum amylase and lipase activities.

Red squill: Nausea and **VOMITING** are the predominant effects. In the unlikely event that significant amounts of glycosides are absorbed, cardiac arrhythmias and slowing might be expected. Convulsions have not been observed in humans as they have in rats.

Antu: Pulmonary râles, **DYSPNEA** and cyanosis may be expected following ingestion of large amounts.

Norbormide: No human poisonings have been reported. Ingestion of 300 mg by an individual caused a slight fall in body temperature and blood pressure.

CONFIRMATION OF DIAGNOSIS

Coumarins, indandiones, and other anticoagulants: Increase of the prothrombin time (Quick) reflects a reduction in serum prothrombin concentration, and occurs in response to physiologically significant absorption of these toxicants. This widely available clinical test offers a sensitive and reliable diagnostic method for detecting a toxic effect of these compounds. Readily detectable change in prothrombin time appears within 24 to 48 hours of ingestion of anticoagulant.

Zinc phosphide and phosphorus: Zinc phosphide smells like rotten fish and imparts a garlicky odor to the breath. Luminescence of vomitus or feces indicates yellow phosphorus ingestion.

Other rodenticides: There are analytical methods available for identifying some remaining rodenticides in food or liquids suspected of contamination, in gastric contents, and sometimes in blood and urine. (See Sunshine, I., Handbook of Analytical Toxicology (1969) published by the Chemical Rubber Company, 18901 Cranwood Parkway, Cleveland, Ohio 44128.) These methods are generally complex and must be performed by a toxicology laboratory experienced in these tests. Analysis is often time-consuming, limiting the usefulness of the results in clinical management. Analyses may be important, however, for legal reasons.

TREATMENT

Coumarins, indandiones, and other anticoagulants

1. If only a few grains of anticoagulant bait have been ingested by an adult or child having no antecedent liver or blood clotting disease, treatment is probably unnecessary.

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A. If there is uncertainty about the amount of bait ingested or the general health of the patient, **PHYTONADIONE** (vitamin K_1, Mephyton®) given orally protects against the anticoagulant effect of these rodenticides. For adults, give 15-25 mg; for children under 12, give 5-10 mg. Alternatively, a colloidal solution of phytonadione, Aquamephyton®, may be given intramuscularly. For adults, give 5-10 mg; for children under 12, give 1-5 mg.

CAUTION: **PHYTONADIONE,** specifically, is required. Neither vitamin K_3 (menadione, Hykinone®) nor vitamin K_4 (menadiol) is an antidote for these anticoagulants.

B. Whatever the doage, insure that patients (especially children) will be **CAREFULLY OBSERVED** for 4-5 days after ingestion. The indandiones and the more recently introduced anticoagulants have toxic effects apart from anticoagulation that are not yet well defined.

2. If **LARGE AMOUNTS** of anticoagulant were ingested in the preceding 2-3 hours, **INDUCE VOMITING** with **SYRUP OF IPECAC,** followed by 1-2 glasses of water. For adults, give 30 ml; for children under 12, 15 ml. Following emesis, give 30-50 gm **ACTIVATED CHARCOAL** in 4-6 ounces of water to limit absorption of anticoagulant remaining in the gut.
3. If anticoagulant has been ingested any time in the preceding 15 days, determination of **PROTHROMBIN TIME** provides a basis for judging the severity of poisoning.

   A. If the prothrombin time is lengthened, give Aquamephyton®, intramuscularly: **adult dose,** 5-10 mg; **child's dose:** 1-5 mg. Decide dose according to the degree of prothrombin time lengthening and, in children, the age and weight of the child.
   B. Repeat prothrombin time in 24 hours. If it has not decreased from the original value, repeat Aquamephyton® dosage.

4. If victim shows **SYMPTOMS** or **SIGNS** of **ANTICOAGULANT POISONING** (bleeding) in addition to hypoprothrombinemia, administer Aquamephyton® intramuscularly, up to 25 mg in the adult, and up to 0.6 mg/kg in children under 12 years. Phytonadione administration may be repeated in 24 hours if bleeding continues.

   A. In cases of **SEVERE BLEEDING,** it may be necessary to give Aquamephyton® intravenously. This is especially true if the bleeding tendency is so severe that intramuscular injection is likely to cause hematoma formation. Dosage is up to 25 mg in the adult, up to 0.6 mg/kg in children under 12 years. Repeat this dose in 24 hours if bleeding continues. Inject at rates not exceeding 5% of the total dose per minute. **INTRAVENOUS INFUSION** of the Aquamephyton® **DILUTED IN SALINE OR GLUCOSE SOLUTION** is recommended. Bleeding is usually controlled in 3-6 hours.

CAUTION: Adverse reactions, some fatal, have occurred from **INTRAVENOUS** phytonadione injections, even when recommended dosage limits and injection rates were observed. For this reason, the **INTRAVENOUS** route should be used **ONLY IN** cases of **SEVERE POISONING.** Flushing, dizziness, hypotension, dyspnea, and cyanosis have characterized adverse reactions.

B. Antidotal therapy **IN** cases of **SEVERE BLEEDING** should be supplemented with **TRANSFUSIONS** of **FRESH BLOOD** or **FRESH FROZEN PLASMA.** Use of fresh blood or plasma represents the most rapidly effective method of stopping hemorrhage due to these anticoagulants.

C. Determine **PROTHROMBIN TIMES** (and hemoglobin concentrations, if appropriate) every 6-12 hours to assess effectiveness of antihemorrhagic measures.

D. When normal blood coagulation is restored, it may be advisable to drain large hematomata.

E. Ferrous sulfate therapy may be appropriate in the recuperative period to rebuild lost erythrocyte mass.

Sodium fluoroacetate

1. If this substance has been **INGESTED,** empty the stomach immediately by **INTUBATION, ASPIRATION,** and **LAVAGE,** using 5% sodium bicarbonate. Before withdrawing the lavage tube, instill a slurry of 30-50 gm **ACTIVATED CHARCOAL.**
2. **MONITOR** cardiac rhythm by continuous **ELECTROCARDIOGRAPHY.**
3. **MONOACETIN** (glyceryl monoacetate) has antidotal properties in experimental animals. The liberated acetate competes successfully with fluorocitrate in the tricarboxylic acid cycle. However, there is no sterile pharmaceutical preparation of this compound: high-quality, fresh laboratory grade material must be used.

   A. If victim is fully conscious and not convulsing, administer 100 ml of monoacetin in 500 ml of water, by mouth. Repeat in one hour. (Arena, J. M. *Poisoning,* 1970.)

   B. If victim is obtunded, unconscious, or convulsing, give 0.1-0.5 ml/kg of undiluted monoacetin by deep intramuscular injection every half hour for 4-6 hours, rotating the injection sites to minimize pain and swelling. Monoacetin can also be given intravenously on the same schedule, using a 1:5 dilution in sterile isotonic saline.

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CAUTION: The use of parenteral monoacetin is hazardous. Technical grade material contains glyc[illegible] which, in adequate dosage, may cause hemoly[illegible], hypotension, convulsions, and paralysis. If a nonsterile solution is injected, the monoacetin should be cultured to guide the administration of antibiotics if sepsis develops.

4. **CONTROL CONVULSIONS**

A. Administer 100% **OXYGEN** by positive pressure to provide as much pulmonary gas exchange as possible, despite seizures.

B. **ANTICONVULSANT DRUGS**

CAUTION: It may be difficult or impossible to stop the seizure activity without stopping respiration. Be prepared to maintain pulmonary ventilation mechanically. Tracheostomy may be necessary if seizures are prolonged.

(a). Diazepam (VALIUM®) usually controls mild convulsions. For adults, give 5-10 mg, slowly, intravenously; for children under 6 years or 23 kg body weight, give 0.1 mg/kg body weight, slowly, IV. Repeat in 4-6 hours if necessary.

(b). Pentobarbital may be needed in addition to control severe convulsions. Dosage: 5 mg/kg body weight, or 0.20 ml/kg body weight, using the usual 2.5% solution. If possible, inject solution intravenously, at a rate not exceeding 25 mg (one ml) per minute until convulsions are controlled. If intravenous administration is not possible, give total dose by deep intramuscular injection, not exceeding 5 mg/kg body weight (0.20 ml/kg of 2.5% solution).

(c). Phenytoin (DILANTIN®) has prolonged anticonvulsant action. Dosage: loading dose 15-18 mg/kg. Maintenance dose 4-8 mg/kg q 4-24 hours as needed. Intramuscular administration is not recommended. Give IV slowly at no more than 20% total dose per minute.

(d). Thiopental (PENTOTHAL®), by continuous intravenous infusion, may help to control severe seizures. Dissolve one gram in 500 ml of glucose solution, and infuse at a rate just sufficient to stop seizures.

CAUTION: Laryngospasm is a complication of anticonvulsant therapy and may require tracheostomy.

(e). In some instances, curarization with succinylcholine or a similar agent is required to stop convulsions. This requires tracheal intubation or tracheostomy and mechanical pulmonary ventilation, with regular monitoring of blood gases and pH.

5. Many other agents tested in fluoroacetate poisoning are **NOT EFFECTIVE:** [illegible]ium acetate, calcium chloride, ethanol, propylene glycol, digitalis [illegible]ycosides, di- and tri-acetates of glycerol.
6. Administer IV electrolyte solutions cautiously to avoid fluid overload in presence of a weak and irritable myocardium.

Zinc phosphide and yellow phosphorus

1. **WASH SKIN BURNS** due to yellow phosphorus with water and a 1% copper sulfate solution. Make sure all particles of phosphorus have been removed. Cover burned area with ointment.
2. Poisonings by **INGESTED** yellow phosphorus or zinc phosphide are extremely difficult to manage. The mortality rate of 50% is the result of either shock or pulmonary edema in the first few hours or days, or coma, seizures, and/or liver, kidney and myocardial damage in the ensuing days or weeks.

   CAUTION: Highly toxic phosphine gas may evolve from emesis, lavage fluid, and feces of victims of these poisons. The patient's room should be well ventilated.

   A. **INTUBATE** and **ASPIRATE** the stomach. **LAVAGE** with several quarts of 1:5000 potassium permanganate solution.

      CAUTION: Persons attending victim must avoid contact with yellow phosphorus, which causes skin burns.

   B. Combat shock and acidosis with **TRANSFUSIONS** of whole blood and **INFUSIONS** of glucose and electrolyte solutions. Monitor fluid balance and central venous pressure to avoid fluid overload. Monitor blood electrolytes and pH to guide choice of intravenous solutions.
   C. Administer 100% **OXYGEN** by mask or nasal tube.
   D. Combat pulmonary edema with intermittent or continuous **POSITIVE PRESSURE OXYGEN.**
   E. **MONITOR URINE** albumin, glucose, and sediment to detect early renal injury. Monitor EKG to detect myocardial impairment. Monitor serum alkaline phosphatase, LDH, prothrombin time, and bilirubin to evaluate liver damage.
   F. Include Aquamephyton® (vitamin K_1) in intravenous infusions if prothrombin level declines. Dosage of 10-50 mg per day may be required. Administer Aquamephyton® slowly, intravenously; stop infusion if flushing, cyanosis, paresthesiae, hypotension, or dyspnea occurs.
   G. **MORPHINE SULFATE,** 8-16 mg every few hours may be necessary to control pain. Child's dose: 0.1-0.2 mg/kg.
   H. **CONTROL CONVULSIONS** with diazepam, barbiturates, and/or phenytoin as suggested under *treatment of sodium fluoroacetate poisoning.*
   I. **CORTICOSTEROIDS** at high dosages may be beneficial.

Strychnine and crimidine

1. Administer **100% OXYGEN** by positive pressure.
2. **CONTROL CONVULSIONS.** This may be attempted with intravenous diazepam, barbiturates, and/or phenytoin, as described under *management of sodium fluoroacetate poisoning.*

   A. **CURARIZATION** is often required, using succinylcholine or similar agent. Tracheal intubation or tracheostomy and continuous mechanical pulmonary ventilation are necessary. Blood gases and pH must be monitored.

3. **FORCED DIURESIS** with mannitol accelerates the excretion of strychnine. Infusion of **SODIUM BICARBONATE** relieves metabolic acidosis. There may be some benefit from peritoneal dialysis, hemodialysis, and hemoperfusion.
4. Once seizures have been controlled, remove unabsorbed toxicant from the stomach by gastric **INTUBATION, ASPIRATION,** and **LAVAGE.** Leave a slurry of 30-50 gm **ACTIVATED CHARCOAL** in the stomach. Follow charcoal with **SODIUM** or **MAGNESIUM SULFATE,** 0.25 gm/kg, in 1-6 ounces of tap water, to induce catharsis. Repeat cathartic dosage as needed.

Vacor, DLP-787 (Active ingredient RH-787)

1. If toxicant was ingested recently, **EVACUATE** the **STOMACH** by **INTUBATION, ASPIRATION,** and **LAVAGE** with 2-3 liters isotonic saline.

   A. Before withdrawing stomach tube, instill 30-50 gm of **ACTIVATED CHARCOAL** as a slurry in 3-4 ounces of water, to limit absorption of remaining toxicant.
   B. As soon as patient can tolerate oral fluids after withdrawal of stomach tube, give **SODIUM** or **MAGNESIUM SULFATE,** 0.25 gm/kg body weight in 1-6 ounces of water to induce catharsis. Repeat dose in 4 hours if patient has had no bowel movement.

2. Administer **NICOTINAMIDE** (niacinamide) intravenously, slowly, or intramuscularly. For adults and children over 12 years, give 500 mg immediately, then repeat injections of 200-400 mg every 4 hours for 10-12 doses. Within this range, select the dose on the basis of body weight and the estimated quantity of RH-787 ingested. If manifestations of RH-787 toxicity appear, give nicotinamide by continuous IV infusion at about 100 mg per hour. There is probably no advantage in giving more than 3000 mg per day of nicotinamide.

   A. Dosage of nicotinamide for children under 12 years, or 23 kg, is about half the dosage suggested for adults.
   B. After 2-3 days of parenteral therapy, give nicotinamide by mouth, 100 mg four times daily, for 2 weeks.

3. **MONITOR** blood and urine sugar concentrations, serum alkaline phosphatase, amylase, LDH, and GOT activities, urine ketone concentrations, blood electrolytes and BUN. Examine the electrocardiogram for arrhythmias.
4. Unless the patient is able to void easily, put in place a **RETENTION CATHETER** to monitor urine flow and urinary glucose excretion.
5. Infuse **ELECTROLYTE SOLUTIONS** intravenously to accelerate toxicant excretion and correct errors in specific ion concentrations. If ketoacidosis appears, use bicarbonate or Ringer's-lactate to control acidosis.
6. If **DIABETIC KETOACIDOSIS** appears (ketonuria, metabolic acidosis, hyperglycemia) administer enough regular insulin to control the acidosis and hyperglycemia, as in naturally occurring diabetic ketosis. The diabetes resulting from RH-787 tends to be brittle and correspondingly difficult to control.
7. In all cases of ingestion of Vacor or DLP-787 (whether or not acute poisoning occurs), follow the patient's clinical status carefully for at least 6 months. Look for indications of diabetes mellitus (glycosuria, hyperglycemia), and for consequences of autonomic nervous system damage: orthostatic hypotension, urinary retention, constipation, diarrhea, abdominal cramping, pain and weakness in the limbs.

Red squill

1. Significant toxicity is not expected from this agent. If, for some reason, a significant amount is retained in the stomach, remove it by gastric **INTUBATION, ASPIRATION,** and **LAVAGE,** followed by 0.25 gm/kg **SODIUM** or **MAGNESIUM SULFATE** in 1-6 ounces water.
2. Monitor **ELECTROCARDIOGRAM** for arrhythmias and conduction disturbances characteristic of digitalis.

Antu

1. Significant toxicity is not expected from this agent. If an extraordinary amount has been ingested, empty the gut. Administer **SYRUP OF IPECAC,** then 1-2 glasses of water, to induce vomiting. Adult dose: 30 ml; dose for children under 12 years: 15 ml. Follow with 30-50 gm activated charcoal in 3-4 ounces of water, then 0.25 gm/kg **SODIUM** or **MAGNESIUM SULFATE** in 1-6 ounces water.
2. If dyspnea appears, administer **OXYGEN** by continuous flow or by intermittent **POSITIVE PRESSURE.**

Norbormide

1. Significant toxicity is not expected from this agent. If an extraordinary amount has been ingested, empty the gut. Administer **SYRUP OF**

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IPECAC, then 1-2 glasses of water, to induce vomiting. Adult dose: 30 ml; dose for children under 12 years: 15 ml. Follow wit' -50 gm **ACTIVATED CHARCOAL** in 3-4 ounces of water, the.. 0.25 gm/kg **SODIUM** or **MAGNESIUM SULFATE** in 1-6 ounces water.

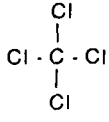
2. Monitor **BLOOD PRESSURE** and **BODY TEMPERATURE** for several hours, if a large amount has been absorbed.

Chapter 12

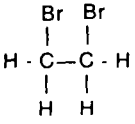
FUMIGANTS

CHEMICAL STRUCTURES

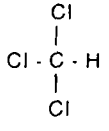
HALOCARBONS



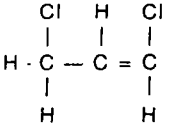
Carbon Tetrachloride



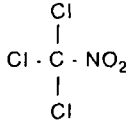
Ethylene Dibromide



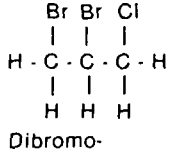
Chloroform



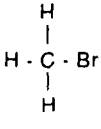
1,3-Dichloropropene



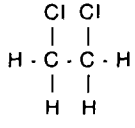
Chloropicrin



Dibromochloropropane

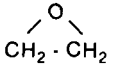


Methyl Bromide

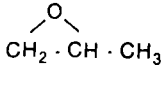


Ethylene Dichloride

OXIDES AND ALDEHYDES

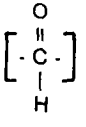


Ethylene Oxide

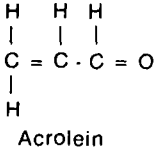


Propylene Oxide

Formaldehyde

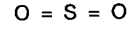


Paraformaldehyde

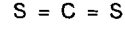


Acrolein

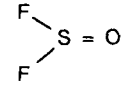
SULFUR AND PHOSPHORUS COMPOUNDS



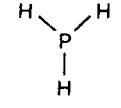
Sulfur Dioxide



Carbon Disulfide

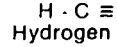


Sulfuryl Fluoride

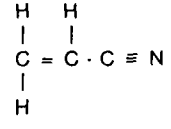


Phosphine (from $Al \equiv P + H_2O$)

CYANIDES



Hydrogen Cyanide



Acrylonitrile

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COMMON COMMERCIAL FUMIGANT PRODUCTS

Chloroform, carbon tetrachloride, methyl bromide (Brom-O-Gas, Fumigant-1, Kayafume, Me Br, Meth-O-Gas, Pestmaster, Profume); chloropicrin (Acquinite, Chlor-O-Pic, Pic-Clor, Picfume, Tri-Clor); ethylene dichloride (EDC), ethylene dibromide (EDB, Bromofume, Celmide, Dowfume W-85, Kop-Fume, Nephis, Pestmaster EDB-85, Soilbrom); dichloroprop-ene and -ane (Telone, D-D), sulfuryl fluoride (Vikane), dibromochloropropane (DBCP).

The Dowfume fumigants manufactured by the Dow Chemical Company are mixtures of halocarbons, mainly EDC, EDB, carbon tetrachloride, Me Br, and chloropicrin, formulated to meet specific needs.

Ethylene oxide (ETO, oxirane); propylene oxide (epoxypropane); formaldehyde (Formalin is a 40% aqueous solution), propenal (Acrolein, Aqualin, Acrylaldehyde); carbon di- (or bi-) sulfide; hydrogen cyanide (prussic acid, Cyclon); acrylonitrile (ingredient of fumigant mixtures Acrylofume, Acritet, Carbacryl); aluminum phosphide (Phostoxin).

TOXICOLOGY

Fumigants have extraordinary power to penetrate the lining membranes of the respiratory and gastrointestinal tracts, and the skin. They also penetrate the rubber and plastics used in protective garb and they are not efficiently taken up by conventional adsorbents used in ordinary respirators. These properties make the protection of applicator personnel very difficult, essentially mandating methods of use that do not require on-site operator handling.

Because these chemicals are either gases or volatile liquids at room temperature, inhalation is the most common route of absorption. Dermal injury does follow contact with some fumigants, ranging in severity from a mild chemical burn to vesiculation and ulceration. Fumigant gases irritate the eyes; liquid fumigant may cause blindness from corneal ulceration.

Respiratory tract irritation is the most common and serious injury caused by fumigants. Some agents such as sulfur dioxide, chloropicrin, formaldehyde and acrolein cause so much irritation of the upper respiratory tract that the exposed individual is unlikely to inhale a quantity of fumigant capable of damaging the lung. Rarely, laryngeal edema or bronchospasm results from inhalation of high concentrations.

Other gases, such as methyl bromide, phosphine, and ethylene oxide, are not so irritating to the nose, eyes, throat, and bronchi, but cause serious injury to the cells lining the fine air sacs of the lung. Thus, they are more likely than other fumigants to induce pulmonary edema, a major cause of death from fumigant exposure.

In varying degrees, these fumigants depress the central nervous system. As in the case of the anesthetic chloroform, adequate dosage may lead to unconsciousness. Depression or cessation of respiration is a major hazard of acute inhalation exposure to fumigants. Acute exposures to methyl bromide have induced convulsions. Absorbed in lower concentrations over several consecutive

days, methyl bromide has impaired basal ganglion function in humans, causing ataxia for weeks or months after exposure. Protracted exposure to carbon disulfide has caused peripheral neuropathy and changes in CNS function (chronic encephalopathy) of chronically exposed workers.

The halocarbon fumigants increase the irritability of the heart muscle. Intensive exposures may lead to sudden death as a result of ventricular fibrillation.

Liver and kidney damage occurs commonly following excessive exposure to fumigants. Liver injury may take the form of fatty infiltration, diffuse necrosis or massive necrosis. Elevated serum levels of GOT, LDH, alkaline phosphatase, and bilirubin reflect hepatocellular injury. The fumigants may inflict direct injury on glomerular and tubular elements of the kidney, leading to functional proteinuria and glycosuria, or to acute renal failure, depending on severity of toxicant exposure. In addition, hyperbilirubinemia resulting from liver damage may compound the tubular injury (hepatorenal syndrome).

Inhaled phosphine gas (PH_3) and ingested metal phosphides cause pulmonary edema, CNS depression, toxic myocarditis, and circulatory collapse. Victims who survive these immediate actions suffer liver injury (fatty degeneration and necrosis) and acute renal tubular necrosis. Unlike its analogue arsine, phosphine is not hemolytic. Enzymatic mechanisms of toxicity are not known. Ingested metal phosphide (from which phosphine is generated) causes intense gastrointestinal irritation, followed by degenerative and necrotizing lesions of the liver, kidney, and heart. Death is often due either to cardiogenic shock or pulmonary edema.

Hydrogen cyanide (HCN) and its salts poison by inactivating the cytochrome oxidase of cells in critical tissues, primarily the heart and brain. Acrylonitrile degrades slowly to HCN in the body, and therefore acts primarily by the same mechanism, although the slow release of free cyanide renders it somewhat less toxic than HCN itself. Both HCN and acrylonitrile are sufficiently absorbable across the skin to cause poisoning in the absence of inhalation exposure. Manifestations of poisoning are due mainly to intracellular anoxia of brain tissue (leading to respiratory failure), and to the circulatory insufficiency that results from myocardial weakness. The liver has substantial capacity for converting cyanide to the less toxic thiocyanate, a metabolic conversion that is accelerated by therapeutically administered thiosulfate.

Dibromochloropropane has reportedly caused sterility in manufacturing plant workers and reduced sperm counts in highly exposed applicators.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

HEADACHE, DIZZINESS, NAUSEA, and vomiting are prominent early symptoms of excessive exposure to these gases. Sulfur dioxide, formaldehyde, chloropicrin, and acrolein are strong irritants, causing **BURNING SENSATIONS** in the nose and throat, **TEARING, COUGH,** and sometimes hoarseness and wheezing. Exposures to methyl bromide, phosphine and ethylene oxide are more likely to produce prompt pulmonary edema: **COUGHING** of

copious amounts of **FROTHY FLUID,** associated with severe **SHORTNESS OF BREATH** and cyanosis. The remaining fumigants are less ly to cause respiratory tract injury.

DROWSINESS, TREMORS, double vision, and weakness are the common early manifestations of central nervous system impairment. Tremors may progress to myoclonic movements, then to generalized **SEIZURES, UNCONSCIOUSNESS,** and death. Protracted low level exposure to methyl bromide causes **ATAXIA** and impairment of manual coordination.

Injuries to the skin by liquid fumigants may be manifest as areas of redness or as **BLISTERS** which rupture, leaving raw skin or deep ulcers.

If ingested, the **LIQUID** forms of **HALOCARBONS** often cause pulmonary edema and **SHOCK** within a few moments. If victim survives, injuries to the brain, liver and kidney are life-threatening.

Longer-term low level inhalation of **CHLOROCARBONS** may cause liver damage, first manifest as **ANOREXIA,** then as **JAUNDICE.** Biochemical studies confirm hepatocellular injury.

Poisoning by excessive inhalation of **CARBON DISULFIDE** is characterized by **DIZZINESS,** headache, nausea, and sometimes disorientation, paresthesiae, hallucinations, and, rarely, convulsions. Protracted low level exposures produce **PAIN,** tingling, **WEAKNESS** of the extremities, and deterioration of mental functions.

Poisoning by **PHOSPHINE** gas is usually heralded by weakness, **TREMORS,** vomiting, a sense of pressure in the chest, **COUGH,** and dyspnea, sometimes progressing to **PULMONARY EDEMA.** Intense thirst results from hypotension and diarrhea. Severe poisonings lead to **CONVULSIONS,** coma, and death. Those who survive the acute phase suffer **LIVER INJURY** (elevation of serum GOT, LDH, and alkaline phosphatase, and sometimes, reduced prothrombin concentration, hemorrhage, and jaundice) and kidney damage (hematuria and sometimes anuria). Chronic exposures to lesser amounts have caused pain in the eyes and nose, nosebleeds, and abdominal pain.

Ingestion of **METAL PHOSPHIDES** leads promptly to **NAUSEA** and **VOMITING,** followed by injury to the lung, liver, kidney, heart and central nervous system. Hypocalcemic tetany (from hyperphosphatemia) and metabolic acidosis develop several hours after ingestion of solid phosphides.

Excessive inhalation of **SULFURYL FLUORIDE** may induce muscle twitching and convulsions. Persons repeatedly exposed risk injury to the lung (impaired pulmonary function) and kidney (proteinuria and azotemia).

Poisoning by **HYDROGEN CYANIDE** or **ACRYLONITRILE** may produce sudden **UNCONSCIOUSNESS** and respiratory arrest without warning symptoms. Lesser exposures cause **HEADACHE,** nausea, and a sense of constriction in the throat, followed by hyperpnea, dizziness, and apprehension. Pulse and respiratory movements then become weak, slow, and irregular as consciousness is lost. **CONVULSIONS,** either tonic or epileptiform, may supervene. Opisthotonus and trismus commonly appear, and sphincter control is usually lost. The heart often continues to beat after respiration has stopped. The skin generally remains pink.

CONFIRMATION OF DIAGNOSIS

Large industrial concerns monitor human absorption of halocarbons by analysis of expired air. Similar technology is available in many departments of anesthesiology. Such analyses are not often needed to identify the offending toxicant, because this is known from the exposure history. In managing difficult cases of poisoning, however, it may help to monitor breath concentrations of toxic gas.

Blood bromide concentrations† have some value in identifying poisonings by methyl bromide, and possibly ethylene dibromide, provided it can be established that the person exposed to the fumigant has not recently taken inorganic bromide medication. A level of organic bromide higher than 5 mg/100 ml indicates excessive absorption of fumigant. A blood concentration of more than 10 mg/100 ml of organic bromide represents a serious threat to health. A blood level of more than 15 mg/100 ml indicates an immediate threat to life.

Methods for detecting the organic oxides, aldehydes, sulfur dioxide, and phosphine are not generally available, but they are rarely needed. A simple method is available for detecting carbon disulfide in urine (Djuric et al. Brit. J. Indust. Med. 22:321-323. 1965). Cyanide can be detected and measured in blood and tissues, as can the thiocyanate metabolite in urine and saliva. Odors of gases on the victim's breath are sometimes helpful diagnostic clues: cyanide smells like bitter almonds, carbon disulfide like rotten cabbage, and phosphine somewhat like garlic or acetylene.

TREATMENT

1. **FLUSH** contaminating fumigant from the **SKIN** and **EYES** with copious amounts of water for at least 15 minutes. Contact with **LIQUID** fumigant can cause **BLINDNESS** or **DEATH.** Treat injuries **IMMEDIATELY.**
2. **REMOVE** victims of fumigant inhalation **TO FRESH AIR.** Even though initial symptoms and signs are mild, keep victim quiet, in a semireclining position. Reduction in physical activity reduces the likelihood of pulmonary edema.
3. If victim is not breathing, **RESUSCITATE** with positive pressure oxygen breathing apparatus, if available. If apparatus is not available, use mouth-to-mouth or mouth-to-nose methods. If victim is pulseless,use cardiac resuscitation.
4. If **PULMONARY EDEMA** is evident, there are several measures available to sustain life. Medical judgment must be relied upon, however, in the management of each case. The following procedures are generally recommended:

   A. Put the victim in a **SITTING** position with a backrest.

† Conway, E. J. Microdiffusion Analysis and Volumetric Error, 3rd edition. Crosby Lockwood, London 1950.

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B. Use intermittent and/or continuous positive pressure **OXYGEN** to relieve hypoxemia. (Do not give oxygen at greater c ntrations or longer periods than necessary, because it may exaggerate the fumigant injury to lung tissue. Monitor arterial p O_2).

C. Apply **TOURNIQUETS** in rotation to arms and legs to limit venous return.

D. Administer **AMINOPHYLLINE** (0.25-0.50 gm) slowly, intravenously.

E. Administer **MORPHINE** in small doses (5-10 mg), slowly, intravenously, to allay anxiety and promote deeper respiratory excursions. Children's dose, 0.1-0.2 mg/kg.

F. Digitalization may be considered, but be alert to the serious risk of arrhythmias in an anoxic mycardium.

G. Slowly administer **FUROSEMIDE,** 40 mg, or **SODIUM ETHACRYNATE,** 50 mg, to reduce venous load by inducing diuresis.

H. **TRACHEOSTOMY** may be necessary in some cases to facilitate aspiration of large amounts of edema fluid.

I. Epinephrine, atropine, and expectorants are generally **NOT HELPFUL** and may complicate treatment.

J. **STEROIDS** at high dosage are usually recommended, although their effectiveness is unproved.

K. If secondary pneumonitis occurs, administer **ANTIBIOTICS.**

L. Watch for **RECURRENT PULMONARY EDEMA,** even up to 2 weeks after the initial episode. Limit victim's physical activity for at least 4 weeks. Severe physical weakness usually indicates persistent pulmonary injury. Serial pulmonary function testing may be useful in assessing recovery.

5. Combat **SHOCK** by placing victim in the Trendelenburg position and administering blood plasma and/or electrolyte and glucose solutions intravenously, with great care, to avoid pulmonary edema. Central venous pressure should be monitored continuously. Vasopressor amines must be given with great caution, because of the irritability of the myocardium.

6. Control **CONVULSIONS.** Seizures are most likely to occur in poisonings by methyl bromide, carbon disulfide, phosphine, metal phosphide, cyanide, and acrylonitrile.

   A. Establish pulmonary gas exchange at the best possible level by administering 100% **OXYGEN** by IPPB.

   B. In poisoning by **CYANIDE** and acrylonitrile, proceed directly with **ANTIDOTAL** therapy (see below, paragraph 10C).

   C. Control convulsions caused by other agents with careful IV injection of **DIAZEPAM,** 5-10 mg in the adult, 0.1 mg/kg in children under 12 years. Repeat dosage in 4-6 hours if necessary.

      CAUTION: Be prepared to maintain pulmonary ventilation mechanically, and to manage hypotension and cardiac arrhythmias.

D. In methyl bromide poisoning, it may be necessary to give diazepam o rbiturates orally for some time after the acute poisoning to control involuntary motor activity.

7. If **FUMIGANT LIQUIDS** have been **INGESTED,** quantities remaining in the gut must be removed as effectively as possible by gastric **INTUBATION, ASPIRATION,** and **LAVAGE.**

   A. **IF** victim is **UNCONSCIOUS,** put in place a cuffed endotracheal tube prior to gastric intubation.
   B. Place conscious victim in a left lateral Trendelenburg position for intubation, and aspirate the pharynx as effectively as possible to minimize likelihood of tracheal aspiration.
   C. After aspirating stomach contents, **LAVAGE** the stomach with 2-3 liters 0.9% saline or 5% sodium bicarbonate, containing 30-50 gm **ACTIVATED CHARCOAL.** After lavage, leave 30-50 gm activated charcoal in stomach before withdrawing tube.
   D. If diarrhea does not develop spontaneously, give **SODIUM SULFATE** orally, 0.25 mg/kg, to induce catharsis.

8. Intravenous **INFUSIONS** of **GLUCOSE** are valuable in limiting the hepatotoxicity of fumigants. Monitor central venous pressure to avoid precipitating, or aggravating, pulmonary edema by fluid overload.
9. **MONITOR** fumigant poisoning victims closely for recurrent pulmonary edema and bronchopneumonia. Chart fluid balance and check urine sediment regularly to detect incipient tubular necrosis. Measure serum alkaline phosphatase, LDH, and bilirubin to assess liver injury.
10. Certain **SPECIFIC MEASURES** are recommended in poisonings by particular fumigants:

    A. If given very soon after exposure to **METHYL BROMIDE,** there may be some value in administering **DIMERCAPROL** (BAL) in vegetable oil intramuscularly. For adults, give 3-5 mg/kg q6h for 4 doses.

       CAUTION: **DIMERCAPROL** may cause troublesome side effects (hypertension, tachycardia, nausea, headache, paresthesiae, pain, lacrimation, sweating, anxiety, and restlessness). Although usually not so severe as to preclude treatment, these manifestation may require antihistamine therapy for adequate control.

    B. Mild poisonings by **CARBON DISULFIDE** inhalation may be managed best by no more than careful observation, even though sensory hallucinations, delirium, and behavioral aberrations can be alarming. Severe poisonings may require specific measures:

       1. **CAFFEINE** and sodium benzoate (0.5 gm subcutaneously) may help to relieve CNS depression.

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2. If manic behavior threatens the safety of the victim, **DIAZEPAM**, 5-10 mg, 0.1 mg/kg in chi ı, administered cautiously, intravenously, may be helpful as a tranquilizer. Do not give catecholamine-releasing agents such as reserpine and amphetamines.

C. Poisonings by **HYDROGEN CYANIDE** and **ACRYLONITRILE** gases are treated in essentially the same way as poisoning by cyanide salts. In addition to the general treatment described earlier, specific **ANTIDOTES** are required. (See line 6 for pediatric regimen).

1. Administer **AMYL NITRITE** (perles) by inhalation for 15-30 seconds of every minute, while a fresh solution of 3% sodium nitrite is being prepared.
2. As soon as solution is available, inject intravenously 10 ml of 3% **SODIUM NITRITE** solution over a 2-4 minute interval, keeping the **NEEDLE IN PLACE.**

   CAUTION: Monitor **PULSE** and **BLOOD PRESSURE** during administration of amyl nitrite and sodium nitrite. If systolic blood pressure falls below 80 mm Hg, slow or stop nitrite administration until blood pressure recovers.

3. Follow sodium nitrite injection with an infusion of 50 ml of 25% aqueous solution of **SODIUM THIOSULFATE** administered over 10-minute period. Initial adult dose should not exceed 12.5 gm.
4. If symptoms persist or recur, treatment by sodium nitrite and sodium thiosulfate should be **REPEATED AT HALF THE DOSAGES** listed in paragraphs 2 and 3.
5. Measure hemoglobin and methemoglobin in blood. If more than 50% of total hemoglobin has been converted to methemoglobin, **BLOOD TRANSFUSION** or exchange transfusion should be considered, because conversion back to normal hemoglobin proceeds slowly.
6. Dosage of **ANTIDOTES** in **CHILDREN:**

   C. M. Berlin (Pediatrics 46:793-796, 1970) has recommended the following procedures in case of cyanide poisoning in children:

   (a) Children over 25 kg body weight should receive adult dosages of sodium nitrite and sodium thiosulfate.
   (b) Children less than 25 kg body weight should first have two 3-4 ml samples of blood drawn and then, through the same needle, receive 10 mg/kg (0.33 ml/kg of 3% solution) of **SODIUM NITRITE** injected over a 2-4 minute interval. Following sodium nitrite, administer an infusion of

1.65 ml/kg of 25% **SODIUM THIOSULFATE** at rate of 3-5 ml per minute.

(c) At this point, determine the hemoglobin content of the original blood sample. If symptoms and signs of poisoning persist or return, give *supplemental* infusions of sodium nitrite and sodium thiosulfate based on hemoglobin level, as presented in TABLE 2. (These recommended quantities are calculated to avoid life-threatening methemoglobinemia in anemic children).

TABLE 2. *Recommended dosages of supplemental sodium nitrite and sodium thiosulfate based on hemoglobin level.*

Initial Hemoglobin Concentration, gm/100 ml	Supplemental Volume of 3% Sodium Nitrite, ml/kg	Supplemental Volume of 25% Sodium Thiosulfate, ml/kg
14.0	0.26	1.28
13.0	0.21	1.05
12.0	0.17	0.83
11.0	0.12	0.60
10.0	0.07	0.38
9.0	0.04	0.23
8.0	0	0
7.0	0	0

(d) When possible, monitor **BLOOD LEVELS** of **METHEMOGLOBIN** to achieve approximately 40% conversion of hemoglobin to methemoglobin.

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Chapter 13

MISCELLANEOUS PESTICIDES OF HIGH TOXICITY

Pesticides included in this chapter are not similar in chemical structure or toxicologic actions to the major classes of pesticidal toxicants (organophosphates, arsenicals, etc.) In general, they are not widely used and opportunities for serious human exposure are rare. However, those included here are characterized by either high toxicity or an important unique mechanism of toxic action. Occasional poisonings by these chemicals have occurred in humans and domestic animals.

4-aminopyridine (Avitrol, 4-AP)

This chemical, now used as a bird repellant, has caused severe poisoning in adult humans at dosages no greater than about 60 mg. This is only 2-3 times the dosage employed clinically in managing certain rare neuromuscular disorders. The principal pharmacologic action of 4-aminopyridine is to facilitate release of transmitter substances at neuroeffector junctions and at synapses throughout the nervous system.

Human poisonings have been characterized by thirst, nausea, dizziness, weakness, and intense diaphoresis, followed by toxic psychosis, ataxia, tremors, dyspnea, and tonic-clonic convulsions. Metabolic acidosis, leukocytosis, and elevations of serum GOT, LDH, and alkaline phosphatase were notable laboratory findings. EKG may show nonspecific ST-T wave changes.

Treatment

Promptly evacuate gut by intubation, lavage, activated charcoal administration, and saline catharsis. Control convulsions with diazepam. Initiate diuresis with intravenous infusions, including mannitol. To date, poisoning victims have recovered in 24-48 hours without severe sequelae.

Pancuronium is an antagonist of 4-aminopyridine, and can control seizures. It must be administered under the supervision of an anesthesiologist because of the likelihood of generalized paralysis. Propranolol may help to limit cardiac toxicity. Atropine controls the gastrointestinal symptoms.

Chlordimeform (Acaron, Fundal, Fundex, Galecron, Spanone)

Although the acute toxicity of this ovicidal agent is low (oral LD_{50} in the rat about 200 mg/kg), it is now known from an incident of excessive respiratory and dermal exposure to chlordimeform powder that it can cause acute illness and urinary bladder irritation. In all likelihood, the offending metabolite is 2-methyl-4-chloroaniline. Principal symptoms are dysuria, gross hematuria, urethral discharge, abdominal and back pain, and a hot sensation all over. Sleepiness, skin rash, anorexia, and a sweet taste in the mouth have also been

reported. Cystoscopic examination of victims of excessive exposure demonstrate ute hemorrhagic cystitis.

Methods are available for detecting the 2-methyl-4-chloroaniline metabolite in the urine.

Treatment

Flush contaminant from eyes and wash from skin. Symptoms resulting from undue occupational exposure resolve in a few days if exposure is terminated. If chlordimeform has been recently ingested, it should be removed from the gut either by administering Syrup of Ipecac, or by gastric intubation. aspiration, and lavage with 0.9% sodium chloride, followed by activated charcoal and sodium sulfate catharsis. Serial urinanalyses should be performed to assess injury to the urinary tract.

Copper salts and organic complexes (oxide, hydroxide, arsenite, carbonate, chloride, oxalate, phosphate, silicate, sulfate, zinc chromate, acetate, naphthenate, oleate, quinolinolate, and resinate).

These are commonly used as fungicides, either alone or in combination with other agents. There are several dozen proprietary products.

LD_{50} values vary from 6 to 1000 mg/kg, depending mainly on the solubility and degree of ionization of the copper compound.

Toxicity of copper-arsenite salts is due mainly to the arsenic content.

All of these salts irritate the skin and eyes and damage mucous membranes. When ingested, they are powerfully emetic: the stomach usually empties promptly and automatically in fully conscious individuals. When retained and absorbed, toxic injury affects the gastrointestinal lining, capillaries, brain, liver, kidney, and formed elements of the blood. Copper salts are hemolytic.

Manifestations of poisoning include burning pain in the chest and abdomen, intense nausea, vomiting, diarrhea, headache, sweating and shock. Later, the liver is enlarged. Jaundice may reflect hemolysis or liver damage or both. Anuria indicates kidney injury by copper and/or free hemoglobin. Death may occur from convulsions, coma, or hepatorenal failure. Elevated serum copper levels (maximum normal level is 125 μg per 100 ml) indicate severity of poisoning.

Treatment

Wash contaminated skin and flush eyes with copious amounts of water. If copper salts have been ingested, lavage the stomach with 0.1% potassium ferrocyanide, then instill a suspension of egg white. Intravenous fluids accelerate excretion. If signs of systemic poisoning develop, give dimercaprol (see Arsenical Pesticides for dosage) or penicillamine, 0.5 gm orally four times daily, if patient can retain oral medication. Shock may require blood transfusions and pain may require morphine. Exchange transfusions may be considered in severe poisonings. Renal failure may require protracted hemodialysis.

Cycloheximide (naramycin, Acti-dione, Actispray, Hizarocin)

This is an antibiotic fungicide of high toxicity: oral LD_{50} in rats is 2 mg/kg.

Dermal absorption is probably not efficient. When ingested, the agent causes excitement, tremors, salivation, diarrhea, and melena. Mechanisms of toxicity are not well defined, but probably include irritation of the gut, stimulation of sympathetic and parasympathetic nervous systems, renal injury, and damage to the adrenal cortex.

There are no chemical tests to confirm cycloheximide poisoning.

Treatment

Remove toxicant from gut by lavage. Instill activated charcoal, then a cathartic dose of sodium sulfate. Intravenous fluids accelerate excretion.

Hydrocortisone appears to be antidotal, particularly in combination with the adrenergic agent methoxyphenamine (Orthoxine®). Atropine relieves the cholinergic symptoms.

Endothall (Accelerate, Aquathol, Des-i-cate, Hydout, Hydrothol)

Acute oral LD_{50} of this herbicide is 51 mg/kg. Dermal absorption of the commonly used salts is probably slight. It is irritating to eyes, mucous membranes and skin, but it is not sensitizing. Mechanisms of systemic toxicity are not clear, but the central nervous system, heart, blood vessels, and gastrointestinal lining appear to be primary targets. Poisoned animals exhibit ataxia, convulsions, shock, and respiratory depression. Erosions and ulcers of the gastrointestinal tract follow ingestion.

There are no standard analytical methods for confirming poisoning.

Treatment

Wash contaminated skin and flush eyes with copious amounts of water. Instead of gastric evacuation following ingestion, administer cold milk or aluminum hydroxide gel. This may be followed by saline catharsis. There is no specific antidote. Shock may require blood transfusions. Use of adrenergic amines is probably hazardous in view of myocardial irritability.

Nicotine sulfate (Black Leaf 40)

This time-honored natural insecticide is still used in horticulture. Lethal dose in humans is about 60 mg. Nicotine preparations, especially those using the free alkaloid, are well absorbed across the gut wall, lung, and skin. Poisoning symptoms from excessive doses appear promptly. They are due to transient stimulation, then prolonged depression, of the central nervous system, autonomic ganglia, and motor end-plates of skeletal muscle. Central nervous system injury is manifest as headache, dizziness, incoordination, tremors, then clonic convulsions leading to tonic-extensor convulsions which are often fatal. In some instances, convulsive activity is minimal and death by respiratory arrest occurs within a few minutes. Effects on autonomic ganglia give rise to sweating, salivation, nausea, abdominal pain, diarrhea, and hypertension. The heart is usually slow, and often arrhythmic. Block of skeletal muscle motor end-plates causes profound weakness, then paralysis. Death may occur from respiratory depression or from shock.

Nicotine can be measured in blood and urine to confirm poisoning.

Treatment

Promptly wash contaminated skin and flush eyes with water. Ingestion of nicotine requires immediate gastric intubation, aspiration, and lavage, the latter preferably with 1.5% tannic acid solution, or 1:5000 potassium permanganate solution. Before withdrawing the lavage tube, instill 3-4 ounces of activated charcoal in a slurry of water. Diazepam and/or barbiturates may be required to control convulsions. Atropine and phenoxybenzamine (Dibenzaline®) may help to control the autonomic manifestations. Positive pressure ventilation of the lungs with oxygen may be necessary to sustain life when respiration is arrested.

Phenylmercuric salts. Most commonly used is phenylmercuric acetate (PMA, Agrosan, Cekusil, Gallotox, Hong Nien, Luquiphene, Mersolite, Phenmad, Phix, PMAS, Shimmer-ex)

Phenylmercuric acetate is a widely used fungicide. Acute oral LD_{50} in the rat is 22 mg/kg. Other salts are also highly toxic. They probably undergo some dermal absorption. Because of lower volatility and less penetration of the brain, they are somewhat less toxic than alkyl mercury compounds.

Early manifestations reflect injury to the central nervous system: ataxia, muscle weakness, visual impairment, and delirium. After a single moderate exposure, these symptoms usually resolve promptly. Repeated intensive exposures cause symptoms and signs resembling amyotrophic lateral sclerosis: weakness and incoordination of the arms, difficulty in swallowing and talking, weakness and spasticity of the legs. Concurrent or later manifestations of excessive absorption reflect renal injury: albuminuria, hematuria, azotemia, and sometimes acute tubular necrosis. Induction of nephrotic syndrome has been reported. This is characterized by massive albuminuria, generalized edema, and hypercholesterolemia.

Methods are available at specialized toxicology laboratories for measuring phenylmercuric compounds in urine.

Treatment

Wash contaminated skin and flush eyes with water. If ingested, remove the chemical from the gut by prompt gastric intubation, aspiration, and lavage with 5% sodium bicarbonate solution and instillation of activated charcoal, followed by catharsis with sodium or magnesium sulfate. Intravenous infusions of fluids accelerate excretion of mercurials and limit kidney damage. There is no specific antidote; dimercaprol is not very effective in limiting toxicity.

Sodium chlorate (De-Fol-Ate, Drexel Defol, Drop-Leaf, Fall, Grain Sorghum Harvest-Aid, Klorex, Kusatol, Tumbleaf)

Although the oral LD_{50} in the rat is high (1200 mg/kg), there have been several deaths from this herbicide-defoliant in the past decade. The principal mechanisms of toxicity are irritation of the gastrointestinal lining, central nervous system depression, hemolysis, oxidation of free hemoglobin to methemoglobin, and renal tubular injury. Dermal absorption is minimal. If ingested,

chlorate causes swelling of the oral and pharyngeal membranes and pain in the chest and abdomen. The victim is first restless, then apatheti n the third or fourth day after ingestion, lumbar pain, albuminuria, hematuria, then anuria with azotemia, reflect renal injury. Death may be due to hyperkalemia (hemolysis), tissue anoxia (methemoglobinemia), or renal failure.

Although chlorate itself is not readily measured in the blood, free hemoglobin and methemoglobin in the plasma point to poisoning by an oxidizing agent.

Treatment

Remove from gut by prompt gastric intubation, aspiration, and lavage using 3 gm sodium thiosulfate in 300 ml 5% sodium bicarbonate. Instill 30-50 gm activated charcoal in a slurry. Pain may require narcotics. Both hemodialysis and exchange transfusions have been used successfully in treating poisonings. Methylene blue is of no value in reducing the extracellular methemoglobin. Intravenous infusions of 1% sodium thiosulfate (100-500 ml) limit the concentration of circulating chlorate. Monitor serum electrolytes. Hemodialysis may be needed to sustain life in the event of extensive renal tubular necrosis.

Sodium cyanide (Cymag)

Occasionally, this is used as a rodenticide. Toxicity is extreme, similar to that of hydrogen cyanide gas used as a fumigant. **CONSULT** Chapter 12 on **FUMIGANTS** (hydrogen cyanide) for toxicology, poisoning manifestations, diagnosis, and management. Cyanide salts are not adsorbed on activated charcoal.

Chapter 14

MISCELLANEOUS PESTICIDES OF LOW OR MODERATE TOXICITY

These compounds are included in the manual because their wide use generates inquiries as to their potential for causing adverse effects.

Description of the toxic potential of these chemicals as low or moderate does not preclude the need for cautious handling. Many agents have irritant properties, and individuals vary widely in their reactions to them. Certain predisposed persons may suffer dermal and respiratory illness from substances that have no effect on other persons or experimental animals. It is also true that the sum total of potential effects of a chemical, and by-products formed in synthesis and storage, plus the metabolites formed into vivo is never fully known. Reasonable precautions to avoid contact with pesticides are always recommended regardless of the reported toxicity of the principal active ingredient.

Lowest reported acute oral LD_{50} in the rat is cited in this listing as an indication of overall toxicity, manifest as killing power. The LD_{50} rating says nothing of dosages necessary to produce symptoms or signs, disease conditions characterized by long latency, subclinical biochemical effects, or other nonlethal effects on health. It is essential that high LD_{50} ratings not be interpreted as indications that the subject chemicals are innocuous.

Knowledge of use is sometimes helpful in identifying chemicals. Agents on this list are used as herbicides (H), fungicides (F), or insecticides (I).

There are many proprietary **MIXTURES** of these chemicals and it is common to tank mix many of them according to the grower's requirements. Intelligent management of exposures requires that the full list of active ingredients in mixtures be ascertained from the producer or applicator. In general, management is aimed at the most toxic ingredient.

Chemical Class	Generic Name	Use	LD_{50}	Proprietary Name	Known or Suspected Adverse Effects
Acetamides	allidochlor	H	750	Randox, CDAA	Moderately irritating to skin and eyes.
	metolachlor	H	2,780	Dual, Bicep, Primagram, Primextra	
Acetanilides	alachlor	H	1,800	Lasso, Lazo, Alanex	Mild irritant
	propachlor	H	710	Ramrod, Bexton	Dermal irritant and sensitizer
	propanil	H	1,384	DPA, Propanex, Riselect, Rosanil, Stam F34, Strel, Supernox, Surcopur, Surpur, Vertac	Mild irritant

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Chemical Class	Generic Name	Use	LD_{50}	Proprietary Name	wn or Suspected iverse Effects
Aliphatic Acids	dichloro-propionic acid	H	970	Dalapon, Dowpon, Crisapon, Basfapon	Skin and eye irritants
	trichloro-acetic acid	H	5,000	TCA	
Aluminofluoride salt	sodium fluoro-aluminate	I	>10,000	Cryolite, Kryocide	Slight irritant
Benzenes	hexachloro-benzene (perchloroben-zene)	F	10,000	HCB, No Bunt, Anticarie	Chronic ingestion causes porphyria cutanea tarda
	paradichloro-benzene	I	500	PDB, Paracide	Mild respiratory irritant and hepatotoxin
	pentachloro-nitrobenzene	F	1,700	PCNB, Terrachlor	Skin irritant
Benzoic and Benzilic Acid Derivatives	benzyl benzoate	I	1,700	Benzyl benzoate	Irritating to skin and eyes.
	chlorobenzilate	I	980	Acaraben, Akar, Benzilan, Kop-Mite, Benz-O-Chlor	
	trichloro-benzoic acid	H	1,370	Benzac, TBA, TCBA, Tribac	
Benzonitriles	chlorothalonil	F	10,000	Bravo, Daconil 2787	Moderately irritating to skin and respiratory tract
	dichlobenil	H	3,160	Casoron, Du-Sprex	
Carbamates	asulam	H	5,000	Asulox 40, Asulox F	Mild irritants. These carbamates do not inhibit cholinesterase enzyme.
	benomyl	F	10,000	Benlate, Tersan 1991	
	chlorpropham	H	3,600	Furloe, Chloro IPC, CIPC, Sprout Nip, Taterpex, Unicrop CIPC	
	terbucarb	H	34,000	Azak, Azac, Azar	
Carbanilate	barban	H	600	Carbyne, Neoban, Caryne	Irritant and dermal sensitizer
Dicarboximides	captafol	F	6,200	Difolatan	Skin irritant
	captan	F	10,000	Captan, Merpan, Orthocide	Skin irritant
	folpet (thiophal)	F	10,000	Phaltan, Folpan	Skin irritant
Dinitrotoluidine Compounds	benefin	H	10,000	Benfluralin, Bethrodine, Balfin, Benefex, Quilan	Slightly to moderately irritating to skin, eyes, and *mucous membranes*. These agents do not uncouple oxidative phosphorylation.
	butralin	H	12,600	Amex	
	dinitroamine	H	3,700	Dinitramine, Cobex	
	fluchloralin	H	1,550	Basalin	
	isopropalin	H	5,000	Paarlan	
	oryzalin	H	10,000	Surflan, Rycelan, Ryzelan	
	pendimethalin	H	1,250	Prowl, Herbadox, Stomp	
	profluralin	H	1,808	Tolban, Pregard	

Chemical Class	Generic Name	Use	LD_{50}	Proprietary Name	Known or Suspected Adverse Effects
	trifluralin	H	>10,000	Treflan, Crisalina, Digermin, Elancolan, Ipersan	Slightly to to moderately irritating to skin, eyes, and mucous membranes. These agents do not *uncouple oxidative* phosphorylation.
Oxadiazolinone	oxadiazon	H	3,500	Ronstar	Irritating to skin and eyes
Phthalate	chlorthal-dimethyl	H	3,000	Dacthal, DCPA	Mild irritant
Picolinic acid Derivative	picloram	H	8,200	Tordon, Amdon	Irritating to skin, eyes, and respiratory tract
Pyridazinone	maleic hydrazide	Growth retardant	6,950	Burtolin, Chemform, De-Cut, De-Sprout, Regulox, KMH, Maintain, Stunt-Man	Slightly irritating
Phosphonomethyl glycine	glyphosate	H	4,300	Roundup	Irritant to eyes and respiratory tract
Thiadiazin (ol)	*bentazon*	H	2,063	*Basagran*	Moderately irritating to skin, eyes, respiratory tract. On ingestion, has caused vomiting, diarrhea, dyspnea, tremors, weakness.
	terrazole	F	1,077	*Terrazole*	Moderately irritating to skin, eyes, and respiratory tract.
Triazines	*ametryn*	H	1,750	Evik, Ametrex, Gesapax	*Some triazines are* mildly irritating to skin, eyes, and upper respiratory tract. Systemic toxicity is unlikely unless very large amounts have been ingested.
	anilazine	H	5,000	Dyrene, Direz, Kemate, Triasyn	
	atraton	H	1,465	Atratone, Gesatamin	
	atrazine	H	3,080	AAtrex, Atranex, Gesaprim, Primatol A, Atred, Crisazine, Vectal SC	
	cyanazine	H	334	Bladex, SD 15418	
	desmetryn	H	1,390	Semeron	
	isomethiozin	H	10,000	Tantizon	
	metribuzin	H	1,100	Sencor, Lexone, Sencorex, Sencoral	
	prometone	H	2,980	Pramitol, Gesafram-50, Prometon, Primatol 25E	
	prometryn	H	5,235	Caparol, Gesagard, Primatol Q, Prometrex	
	propazine	H	>5,000	Milogard, Gesamil, Primatol P, Prozinex	
	Simazine	H	>10,000	Princep, Gasatop, Simadex, Simanex	

Chemical Class	Generic Name	Use	LD_{50}	Proprietary Name	Known or Suspected Adverse Effects
Triazines	terbuthylazine	H	2,610	Primatol-M, Gardoprim, GS 13529	Some triazines are mildly irritating to skin, eyes, and upper respiratory tract. Systemic toxicity is unlikely unless very large amounts have been ingested.
	terbutryn	H	2,500	Igran, Terbutrex	
Uracils	bromacil	H	5,200	Hyvar X, Uragan, Urox B, Urox HX	Irritant to skin, eyes, and respiratory tract.
	lenacil	H	11,000	Venzar	Moderately irritating
	terbacil	H	5,000	Sinbar	
Urea Derivatives	chloroxuron	H	3,700	Tenoran, Chloroxifenidim	Many substituted ureas are moderately irritating to skin, eyes, and mucous membranes.
	chlortoluron	H	10,000	Dicuran, Tolurex, Clortokem	
	difenoxuron	H	7,750	Lironion	
	diflubenzuron	I	4,640	Dimilin	
	diuron	H	3,400	Cekiuron, Crisuron, Dailon, Diater, Di-on, Diurex, Dirurol Dynex, Karmex, Unidron, Urox D, Vonduron	
	fluometuron	H	6,416	Cotoran, Lanex, Cottonex	
	isoproturon	H	1,826	Arelon, Belgran, Graminon, Tolkan	
	linuron	H	1,500	Afalon, Hoe 2810, Linurex, Lorox, Premalin, Sarclex	
	methabenzthiazuron	H	2,500	Tribunil	
	metobromuron	H	3,000	Patoran, Pattonex	
	metoxuron	H	3,200	Deftor, Dosanex, Dosaflo, Purivel	
	monolinuron	H	1,800	Aresin, Afesin, Arresin, Premalin	
	monuron	H	3,600	Monurex	
	neburon	H	11,000	Granurex, Kloben, Neburex	
	siduron	H	7,500	Tupersan	
	tebuthiuron	H	644	Spike	
	tetrafluoron	H	1,265	Tomilon	

Many of these compounds are primary irritants to skin, eyes, and respiratory tract. The ureas and uracils are perhaps the most common offenders, although captafol and chlorothalonil have apparently caused contact dermatitis in some agricultural workers. Propachlor is a dermal sensitizer in predisposed individuals.

Although hexachlorobenzene has low acute toxicity, long-term ingestion of HCB-treated seed grain caused an epidemic of porphyria cutanea tarda among Turkish farm families in the 1950's. No such effect has been found in HCB handlers in the United States.

Given to cattle in extreme dosage, some triazines have caused neuromuscular abnormalities and damage to internal organs. It is unlikely that domestic animals would consume these amounts voluntarily, and still less likely that humans would be exposed to such extreme dosage.

CONFIRMATION OF ABSORPTION

The benzene derivatives and benzonitriles can be identified in plasma by gas-liquid chromatography. Methods for benzoic acid and triazine metabolites in urine have been developed. Analytical methods used for agricultural residues of the remaining compounds might be adapted to analysis of gastric contents or skin wipings. Samples must be collected within hours of exposure, because most of these chemicals are promptly excreted.

It is unlikely that such analyses will be required in cases of human exposure to these agents. In the event that workers experiencing protracted heavy exposure develop suspicious manifestations of injury or toxicity, urine or blood analyses may help to confirm chemical absorption. Tests may be conducted in private or university laboratories, or laboratories supported by the state or federal government, i.e., the United States Environmental Protection Agency or Occupational Safety and Health Administration.

TREATMENT

1. **WASH** contaminated **SKIN** with soap and water.
2. **FLUSH** contaminated **EYES** with copious amounts of fresh water for 15 minutes.
3. **INGESTIONS** of **SMALL** amounts (less than 10 mg/kg body weight) occurring less than an hour before treatment, are probably best treated by:
   A. **SYRUP OF IPECAC,** followed by 1-2 glasses of water. Dose for adults and children over 12 years: 30 ml. Dose for children under 12 years: 15 ml.
   B. **ACTIVATED CHARCOAL**
      Administer 30-50 gm as a slurry in tap water, after vomiting stops.
   C. **SODIUM OR MAGNESIUM SULFATE,** 0.25 gm/kg in tap water, as a cathartic.

4. **INGESTIONS** of **LARGE** amounts (more than 10 mg/kg) occurring less than an hour before treatment, should probably be treated by gastric lavage:

   A. **INTUBATE** stomach and **ASPIRATE** contents.
   B. **LAVAGE** stomach with slurry of **ACTIVATED CHARCOAL** in 0.9% saline. Leave 30-50 gm activated charcoal in the stomach before withdrawing tube.
   C. **SODIUM SULFATE,** 0.25 gm/kg in tap water, as a cathartic.

   CAUTION: Hydrocarbons (kerosene, petroleum distillates) are included in some formulations of these chemicals. Ingestion of very **LARGE AMOUNTS** may cause CNS depression. In this case, **IPECAC IS CONTRAINDICATED.** Also, gastric intubation incurs a risk of **HYDROCARBON PNEUMONITIS.** For this reason observe the following precautions:

   (1) If the victim is unconscious or obtunded and facilities are at hand, insert an **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.
   (2) Keep victim's **HEAD BELOW LEVEL OF STOMACH** during intubation and lavage (Trendelenburg, or left lateral decubitus, with head of table tipped downward). Keep victim's head turned to the left.
   (3) **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.

5. **INGESTIONS** occurring **MORE THAN** an **HOUR** before treatment are probably best treated only by **ACTIVATED CHARCOAL,** 30-50 gm, and **SODIUM** or **MAGNESIUM SULFATE,** 0.25 gm/kg, as described above.
6. There are no specific antidotes for these chemicals. Because manifestations of toxicity do occasionally occur in peculiarly predisposed individuals, **MAINTAIN CONTACT** with victim for at least 72 hours so that unexpected adverse effects can be treated promptly.

INDEX TO PESTICIDE POISONINGS BY SYMPTOMS AND SIGNS

A listing of pesticides capable of causing specific symptoms and signs may be of some help to professionals confronted with illnesses possibly caused by pesticides. However, the limitations of this kind of index should be clearly understood. Rarely are particular manifestations *always* present in poisonings by a given chemical, and many poisonings are characterized by unexpected symptoms. Furthermore, there are usually many causes of particular symptoms and signs.

The purpose of these lists is, therefore, only to direct the professional's attention to a series of chemicals possibly responsible for various symptoms and signs, based on past experience. Starting from the major presenting feature of the illness, the interviewer can inquire closely into possible exposures to the principal causative toxicants, and then, if appropriate, assemble more substantive evidence for or against a poisoning diagnosis, e.g., concurrence of multiple manifestations of specific poisonings, and laboratory test findings.

Not all manifestations of illness are included. Some symptoms, such as dizziness and weakness, are caused by so many chemicals by either direct or indirect mechanisms that they have little value diagnostically.

This approach to clinical toxicology has been developed by Alan K. Done, M.D., of Wayne State School of Medicine. His general format of classification (Solving the Poison Puzzle, *Emergency Medicine*, February 1979) is used in the following tables. Chemicals appearing in the lists headed "Characteristic of These Poisonings" have been substantially consistent in producing the symptoms or signs identified in the left column. Agents listed in the column headed "Occurs in These Poisonings" are found with sufficient frequency to deserve mention, but the association is not highly consistent.

MANIFESTATIONS	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
General		
Breath odor of:		
Garlic	Arsenic Phosphorus Phosphides Phosphine	
Bitter almonds	Cyanide	
Rotten cabbage	Carbon disulfide	
Fever	Nitro-, chloro- phenols	Chlorophenoxy compounds
Hypothermia	Vacor	
Myalgia		Chlorophenoxy compounds
Chills	Arsine Vacor	

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MANIFESTATIONS	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
Thirst	Nitro-, chloro-, phenols Aminopyridine Phosphine	
Anorexia	Organophosphates Carbamate insecticides Nicotine	Fumigants Nitro-, chloro-, phenols Arsenicals
Hot sensations	Chlordimeform Arsine	
Skin and Mucous Membranes		
Dry, cracked skin of hands	Paraquat Petroleum distillates Weed oil	
Loss of nails	Paraquat	
Brittle nails	Inorganic arsenicals	
Loss of hair	Thallium Inorganic arsenicals	
Sweating	Organosphates Carbamate insecticides Nitro-, chloro- phenols Nicotine Aminopyridine	
Pallor	Organchlorines	Anticoagulant rodenticides
Cyanosis	Paraquat Strychnine Crimidine Nicotine Sodium fluoroacetate	Organophosphates Carbamate insecticides Organochlorines
Scratchy throat and irritated eyes	*Sulfur dioxide* Acrolein Chloropicrin Nitro-, chloro- phenols Formaldehyde Pyrethrins Copper compounds Endothall Sodium chlorate Methyl bromide	*Paraquat* Bisdithiocarbamates Ethylene bisdithiocarbamates Chloroaliphatic acids
Blisters or burns	Phosphorus	Liquid methyl bromide or ethylene oxide
Rash	Sulfur Thiram Propachlor Barban	Picloram Difolatan Captan Chlorothalonil Nitro-, chloro- phenols Many other herbicides and fungicides
Yellow stain	Nitrophenols	
Ecchymoses	Anticoagulant rodenticides *Phosphorus* Phosphides	
Keratoses	Inorganic arsenicals	

MANIFESTATIONS	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
Jaundice	Phosphorus Phosphides Phosphine Halocarbon fumigants	Paraquat Inorganic arsenicals
Central Nervous System		
Headache	Organophosphates Carbamate insecticides Organochlorines Fumigants Nicotine Inorganic arsenicals	Nitrophenols Chlorophenols
Ataxia	Organophosphates Carbamate insecticides Endothall Nicotine *Phenyl mercuric acetate*	Fumigants Inorganic arsenicals Organochlorines
Convulsions	Organochlorines Strychnine Crimidine Phosphorus Cyanide Sodium fluoroacetate Nicotine Aminopyridine Endothall	Nitro-, chloro- phenols Organophosphates Carbamate insecticides Sulfuryl fluoride
Muscle twitching	Organophosphates Carbamate insecticides Sulfuryl fluoride	Chlorophenoxy compounds
Tremors	Organophosphates Carbamates insecticides Phosphine Aminopyridine Cycloheximide Nicotine	Pyrethrins Nitro-, chloro- phenols Bentazon Sulfuryl fluoride
Mental confusion	Organophosphates Carbamate insecticides Nitrophenols Chlorophenols Cyanide Organochlorines Vacor Sodium fluoroacetate Carbon disulfide Aminopyridine Cycloheximide	Strychnine Crimidine Nicotine Inorganic arsenicals
Sudden unconsciousness	Cyanide	Organophosphates Diquat Carbamate insecticides Halocarbon fumigants
Central Nervous System		
Tingling and numbness in the extremities	Carbon disulfide Vacor Sodium fluoroacetate	Inorganic arsenicals
Tetany	Phosphorus Phosphides	
Myotonia		Chlorophenoxy compounds

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MANIFESTATIONS	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
Miosis	Organophosphates Carbamate insecticides	
Gastrointestinal Tract		
Nausea, vomiting, abdominal cramps, diarrhea	Organophosphates Carbamate insecticides Diquat Phosphorus Phosphides Phosphine Inorganic arsenicals Arsine Fumigants Red squill Cycloheximide Endothall Nicotine Chlorates Copper Compounds	Organochlorines Chloro-, nitro- phenols Bisdithiocarbamates Ethylene bisdithiocarbamates Chlorophenoxy compounds Organic arsenicals Paraquat Bentazon Chloroaliphatic acids
Salivation	Organophosphates Carbamate insecticides Cycloheximide Nicotine	
Respiratory System		
Stuffy nose, wheezing	Pyrethrum Bisdithiocarbamates plus alcohol	
Nosebleed		Paraquat
Coughing frothy sputum (pulmonary edema)	Methyl bromide Phosphine Phosphorus Phosphides Ethylene oxide	Organophosphates Carbamate insecticides ANTU
Rhinorrhea	Organophosphates Carbamate insecticides Fumigants	
Tachypnea	Nitro-, chloro- phenols	
Respiratory depression	Organophosphates Carbamate insecticides Fumigants Cyanide Acrylonitrile Nicotine Endothall Sodium chlorate	Organochlorines
Labored breathing	Methyl bromide Organophosphates Carbamate insecticides Phosphine Phosphides Phosphorus	Sulfuryl fluoride
Chest pain	Fumigants Sodium chlorate	Organophosphates Carbamate insecticides Chlorophenoxy herbicides Nitro-, chloro- phenols Chloroaliphatic acids

MANIFESTATIONS	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
Cardiovascular System		
Bradycardia	Organophosphates Carbamate insecticides Cyanide	
Tachycardia	Nitrophenols Chlorophenols	Organochlorines
Hypotension, shock	Phosphorus Phosphides Phosphine Vacor Endothall Cyanide	Bisdithiocarbamates plus alcohol Inorganic arsenicals Anticoagulant rodenticides
Irregular heart beat	Sodium fluoroacetate Halocarbon fumigants Endothall	Organochlorines Red squill
Hypertension	Nicotine	
Renal System		
Renal failure	Arsine Fumigants Cycloheximide Chlorates	Paraquat Diquat Inorganic arsenicals Copper compounds
Urinary frequency, dysuria	Chlordimeform Vacor	
Renal colic	Anticoagulant rodenticides Chlorates	
Blood		
Anemia	Naphthalene Anticoagulant rodenticides	Inorganic arsenicals
Leukopenia		Nitrophenols Inorganic arsenicals
Hypoprothrombinemia	Anticoagulant rodenticides	
Depressed cholinesterase enzyme activities	Organophosphates	Carbamate insecticides (large dosage)
Methemoglobinemia	Chlorates	
Free hemoglobin in plasma	Naphthalene Arsine Copper compounds Sodium chlorate	
Elevated alkaline phosphatase, GOT, LDH	Halocarbon fumigants Inorganic arsenicals Diquat Paraquat Aminopyridine	Endrin
Elevated blood bromide	Methyl bromide	
Hyperbilirubinemia	Paraquat Diquat Phosphine Phosphorus Phosphides Copper compounds Inorganic arsenicals	Halocarbon fumigants

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MANIFESTATIONS	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN POISONINGS
Elevated BUN, creatinine	Paraquat Diquat Fumigants Chlorates Inorganic arsenicals	Sulfuryl fluoride Nitro-, chloro-, phenols
Hyperkalemia	Naphthalene Chlorates Copper compounds	
Urine		
Proteinuria	Diquat Paraquat Nitro-, chloro-, phenols Fumigants Cycloheximide Copper compounds Phenyl mercuric acetate Sodium chlorate	Endothall Sulfuryl fluoride
Hematuria	Anticoagulant rodenticides Sodium chlorate Cycloheximide Chlordimeform	Chlordimeform Fumigants Paraquat Diquat
Ketonuria	Vacor Aminopyridine	Phosphorus Phosphides
Hemoglobinuria	Naphthalene Arsine Sodium chlorate	
Myoglobinuria		Chlorophenoxy compounds
Porphyrinuria	Hexachlorobenzene	
Bilirubinuria	Halocarbon fumigants Phosphorus Phosphides Phosphine	
Glycosuria	Vacor	
Feces		
Blood present (melena)	Diquat Sodium chlorate Anticoagulant rodenticides Phosphorus Phosphides Endothall Cycloheximide	Paraquat
Luminescence	Phosphorus	
Semen		
Low sperm count		Dibromochloropropane Kepone

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Special Article

Dioxin Effects on Human Health

By
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Columbia

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DIOXIN, and its possible effects on health, have received an enormous amount of exposure in the popular media. Concerns were initially raised by the controversial use of the herbicide, Agent Orange, in Vietnam. The alleged harmful effects of this spray were attributed to contamination of the herbicide with small quantities of dioxin. The issue was heightened by controversies over toxic waste disposal and accidental spills, which have resulted in many lawsuits. Michael Brown, probably the best known popular writer about toxic wastes and the reporter who "exposed" the Love Canal story, has said that Missouri is the "Dioxin capital of the world."[1]

In conversations with local physicians and in second hand reports from patients of comments by their doctors, the view is often expressed that nothing much is known about dioxin. *Actually, there is a great deal of information about the effect of dioxin on health in both animals and humans. The problem is that these studies are scattered in a wide variety of publications, usually toxicology or occupational medicine journals that have a small circulation.*

Only a few attempts have been made to consolidate and summarize the information.[2-4] This article is a brief review of some of the highlights of what is currently known so that physicians can respond to inquiries from their patients.

EXPOSURE

Dioxin has been called the most toxic chemical known to man.[5] This statement refers to a specific chlorinated derivative, 2,3,7,8-tetrachlorodibenzodioxin, usually abbreviated as TCDD. In a strict chemical sense, the plain dioxin molecule without chlorine is relatively harmless. The addition of chlorine makes a more toxic molecule, with four chlorines being the worst, TCDD (Fig. 1). In the remainder of the paper, I will use the terms dioxin and TCDD interchangeably because this is the standard practice in the news media.

On a weight-for-weight basis, TCDD is one of the most toxic synthetic chemicals in terms of LD_{50} for some species of laboratory animals.[6] This fact is the basis for the claim that dioxin is one of the most toxic chemicals known. On a practical level, however, it is very unlikely for anyone to come in contact with large amounts of dioxin. It is ordinarily found in quantities described as parts per million or parts per billion. There is no industrial use for dioxin. Outside of a few research laboratories, no one intends to directly synthesize the harmful chlorinated isomers of dioxin.

The problem is that dioxin is often an unwanted by-product in small quantities of the manufacture of chlorinated phenols[7] — a group of chemicals that do have a wide variety of important uses. Small quantities of dioxin (and the equally toxic dibenzofurans) are present in the fly ash of municipal and industrial incinerators.[8] Dioxin has even been found in the mufflers of trucks and cars from combustion in diesel engines. Millions of people in industrial regions of the world are exposed to minute traces of dioxin in ordinary house dust.[8] Very small quantities of dioxin have been found in beef fat from cattle that grazed on rangeland sprayed with herbicides contaminated with low levels of dioxin.[9] Most likely, such low exposures are harmless.

The best information about human exposure to dioxin has been obtained by studying the results of several industrial accidents in which workers are exposed to chemicals. The best example in the United States was a plant in Nitro, West Virginia that produced trichlorophenol. On March 8, 1949, a violent reaction caused a relief valve to open, releasing fumes and residue from an autoclave into the interior of the building. Two hundred and eighty-eight employees and clean up workers were exposed to the material which included 2,3,7,8-tetrachlorodibenzodioxin

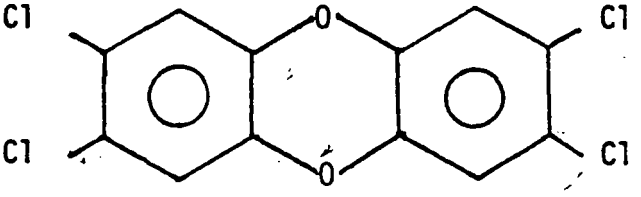

Fig. 1 Chemical structure of 2,3,7,8-tetrachlorodibenzodioxin (TCDD). The term dioxin is commonly used for this substance.

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Much information about dioxin has been published recently and several definite cases of dioxin toxicity have occurred in Missouri. However, many other people who may be worried about possible exposure actually have very low absorbed doses and show no harmful effects. Dioxin toxicity has a fairly consistent pattern and is dose-related. A patient who has only subjective symptoms without any objective signs should not be considered as having true adverse effects of dioxin.

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(TCDD).[10] Similar accidents involving plants that produce trichlorophenol have occurred at Ludwigshafen, West Germany in 1953;[11] Amsterdam, Netherlands in 1963; Grenoble, France in 1966; Czechoslovakia from 1965 to 1969;[2, 12] and Bolsover, United Kingdom on April 23, 1968.[13] Health effects from all these accidents have been reported in foreign medical journals. On July 10, 1976, an explosion in a trichlorophenol plant at Seveso, Italy, 20 miles north of Milan, resulted in the spread of products including TCDD over an area of 700 acres and exposing about 28,000 people. Seven hundred thirty-three people were in the most heavily contaminated area. A large epidemiologic screening program was established by the Lombardy regional government, and the results of the acute effects of exposure have been published.[2, 3, 14, 15]

In 1970 and 1971, a company in Verona, Mo. used trichlorophenol in the manufacture of hexachlorophene. In 1972, the company went out of business after the FDA restricted the use of hexachlorophene to prescription only. Through a round-about sequence of events, oily wastes contaminated with high levels of TCDD, which had been stored at the site, ended up being sprayed on several horse arenas throughout Missouri for the purpose of dust control. The effects on animals and humans at one horse arena were published in 1975.[16] Soil from this site has shown the highest level of TCDD of all the environmental contamination areas tested to date, about 30 parts per million.[17] The full extent of the unauthorized disposal of dioxin in Missouri is unknown.

Millions of people in industrial regions of the world are exposed to minute traces of dioxin in ordinary house dust.

The average soldier in Vietnam was probably exposed to extremely low concentrations of TCDD, if any, compared to the preceding categories. A total of 11 million gallons of Agent Orange was sprayed on 3½ million acres in South Vietnam between 1965 and 1971. The average concentration of TCDD in the spray was 2 parts per million. The estimated seven-year total amount of TCDD for all of South Vietnam was 170 pounds,[18] compared to the estimate of 20 pounds for one horse arena in Moscow Mills, Mo.[3] Spraying missions almost always occurred when allied troops were not present; in fact, fighter aircraft usually strafed the ground preceding the spraying aircraft.

Most veterans claim exposure by walking through vegetation. TCDD is degraded by ultraviolet light, and studies show that it cannot be detected on vegetation after one day of sunlight.[19] Dioxin, in low concentrations, can also be degraded by soil bacteria.[20] The actual dose that would penetrate through human skin by brushing against vegetation is conjectural.

The personnel actually involved in the spraying program, Operation Ranch Hand, would likely be exposed to much higher levels than other soldiers. The armed services are conducting an epidemiologic study of personnel involved with Operation Ranch Hand. The preliminary results should be available in May, 1983. If no adverse effects are noted in this group who worked with the chemical daily, then it would be very unlikely for the average soldier who had much less exposure to have any effects.

Health Effects in Humans

Thousands of people with known definite exposure to dioxin have been observed; some have been followed for 30 years after industrial accidents at Nitro, West Virginia and Ludwigshafen, West Germany. The only disease which unequivocally follows exposure is a rare skin condition known as chloracne. Many other reported conditions must be examined in detail from one report to another. Using the accident at Nitro as an example, one can separate immediate, delayed and long-term effects.

Immediate Effects

Immediate symptoms at Nitro were irritation of the skin, eyes and respiratory tract and

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headache, dizziness and nausea.[10] These symptoms were probably due to other chemicals, such as chlorinated phenols, present in the reaction mixture in much higher concentrations. The accident at Bolsover, England, resulted in different symptoms. In this case, workers were not exposed to vapors from the explosion. The explosion occurred at night and the plant was closed for ten days. When work was resumed, no immediate effects were noted. The first abnormality detected was chloracne, mostly in fitters, plumbers and electricians. Subsequently, it was shown that TCDD was present in greasy deposits on the walls, roof and other surfaces of the plant. The 79 workers who developed chloracne were the ones most likely to come into direct contact with such surfaces.[13, 21] Some other cases in which there were no immediate effects of dioxin exposure include two laboratory scientists in Britain[22] and large numbers of people at Seveso, Italy. Apparently, exposure to low or moderate amounts of dioxin does not produce immediate symptoms.

The Italian medical commission which thoroughly studied a large number of people at Seveso concluded that chloracne was the most frequent and reliable indicator of TCDD exposure.

Delayed Effects

Chloracne usually begins four to eight weeks after exposure. This is the most consistent finding and has been reported in all the studies of known dioxin exposure. The Italian medical commission, which thoroughly studied a large number of people at Seveso, concluded that chloracne was the most frequent and reliable indicator of TCDD exposure, and its incidence was proportional to the level of exposure.[3] Chloracne is a persistent condition that may last for a year or two after exposure. Some cases last longer, and one has been noted 15 years after an industrial accident.[13] Chloracne consists primarily of open comedones with a low proportion of inflammatory lesions versus acne vulgaris. In addition, chloracne occurs in many skin locations such as the pinna where acne vulgaris is unusual.[23]

Chloracne appeared in 122 of 288 workers at Nitro after a delay of a few weeks. Other delayed symptoms were muscle pains, fatigue, nervousness, decrease in libido, dyspnea, vertigo and cold intolerance.[10] Some of these symptoms may have been due to phenols and other chemicals in the reaction mixture. Some symptoms are common everyday complaints, are difficult to quantify and are not consistently present in other studies. Very few objective findings were reported. At Bolsover, England, even though many of the chloracne cases were severe and persisted up to four years, no other ailment that could reasonably be attributed to dioxin were found.[13] In particular, monitoring of results of liver function tests and urinalyses were normal.

After the accident at Ludwigshafen, 66 of 74 workers developed chloracne. Twenty-one of the most severely affected had other complaints related to polyneuritis, sensory impairment or liver damage. Again, there were many other chemicals beside TCDD in the reaction mixture. Signs of porphyria cutanea tarda were noted in several workers.[11] PCT was also noted after industrial exposure in Czeckoslovakia[2] and an unspecified plant in the USA.[24, 25] Most of the signs of PCT are cutaneous: fragility of the skin, blisters, hirsutism and hyperpigmentation. Hirsutism and hyperpigmentation were also noted in two laboratory scientists doing research on TCDD in Great Britain.[22] Although no porphyrins were detected in the urine, the descriptions are compatible with PCT and, perhaps, the diagnostic tests were not as accurate as current ones.

After the accident in Seveso, Italy, no clinically evident PCT was found, but subtle changes in urinary porphyrin ratios were detected in some patients.[26] TCDD is a potent inducer of the enzyme delta-aminolevulinic acid synthetase, which is the first step in the formation of porphyrins.[27] So, there is a good theoretical explanation for the occurrence of PCT after dioxin exposure.

Dioxin toxicity has a fairly consistent pattern and is dose-related.

Symptoms of neuresthenia (lack of vigor, sleep disorder, etc.) have been reported in several studies. Although these symptoms are subjective and difficult to quantify, they do seem to be significant in persons likely to have large exposure to the chemical as shown by chloracne. There have been some reports of objective neurologic signs such as weakness of the lower extremities and nerve conduction deficits of the demyelinization type. However, at Seveso, most people who had these changes were over 55 years old and had other possible predisposing conditions, such as

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More About the Author

A Topeka, Kan. native who graduated summa cum laude from the University of Kansas, Dr. Dunagin finished his medical schooling at the same institution in 1975 and his dermatology residency at the University of Missouri-Columbia School of Medicine. Dr. Dunagin became a Diplomate of the American Board of Dermatology in 1979 and his professional society affiliations include Fellow, American Academy of Dermatology and membership in the Society for Investigative Dermatology, American Dermatologic Society for Allergy and Immunology and the Missouri State Dermatological Society. Among his other published articles are "Drug Eruptions" (with co-author L. E. Millikan, M.D.) in the Journal of the Medical Clinics of North America *in 1980 and "Clinical Toxicity of Chemotherapeutic Agents: Dermatologic Toxicity" in* Seminars in Oncology *in 1982.*

diabetes or nutritional impairment.[3] Two people who operated one of the horse arenas in Missouri developed symptoms of headache and nausea four days after the arena was sprayed with waste oils containing dioxin. Later, they developed chloracne. Two children who played in the area had headaches, diarrhea, epistaxis and chloracne. One developed an acute hemorrhagic cystitis, which required hospitalization but resolved in three days.[3, 16, 17, 28]

An extensive epidemiologic study was conducted after the release of dioxin at Seveso, Italy. One hundred eighty-seven cases of chloracne were discovered, mostly in the zone with the highest levels of dioxin. There was some question about neurologic findings discussed above, but few other significant problems were found. The Seveso Medical Commission looked extensively but found no evidence for hepatotoxicity, congenital malformations, spontaneous abortions, chromosome aberrations, immunosuppression, susceptibility to infection or overall death rate.[3, 14, 15]

Other delayed effects that have been reported occasionally after dioxin exposure include muscular pain, hypercholesterolemia, hepatic enzyme elevation, conjunctival irritation, prolonged prothrombin time and blurred vision. These effects are not reported frequently and may be due to incidental disease, dioxin or other chemicals and irritants in the industrial setting.

The subjective and objective findings that have been reported consistently in patients with known dioxin exposure are listed in Table 1. There are very few cases of high level exposure. The problems listed for the high category should not be taken as firm or exhaustive. Some are based on only one or two cases in humans and analogies to animal toxicity.

Long-Term Effects

Another major concern about dioxin is the possibility of inducing cancer. The evidence from animal studies is conflicting. The Ames test is positive in some strains of bacteria but not in others.[4] Cultured mammalian cells have not shown mutagenic responses.[4] Some strains of laboratory animals develop cancers after continuous dioxin feeding, but the dosage level required is so high that multiple organ toxicities are produced.[2] The thymus is particularly susceptible, and the problem may be decreased immune surveillance. No particular type of malignancy has been found consistently.

In long-term follow-up of human exposure, no increase has been noted in overall mortality. Thirty-year follow-up of 122 workers at Nitro, W. V. showed no excess over the expected rate of malignancy.[10] Follow-up of 74 workers exposed to dioxin at Ludwigshafen, West Germany showed three deaths due to stomach cancer, with less than one expected statistically.[11] No other

TABLE 1
DIOXIN TOXICITY

Amount of Exposure	*Subjective Symptoms*	*Objective Signs*
Low	Headache Fatigue	Chloracne
Moderate	The above plus Neuresthenia —depression —lack of vigor —sleep disorder —loss of libido —profound weakness Nausea Muscle pains Lack of concentration Anorexia	The above plus Porphyria cutanea tarda —blisters —fragility of skin —hyperpigmentation —hirsutism Sensory peripheral nerve impairments Nerve conduction abnormalities
High	The above plus Abdominal pain	The above plus Hepatic necrosis T cell depression Bleeding tendency Diarrhea Prolonged prothrombin time

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disease or type of malignancy was increased compared to control populations. No increase in stomach cancer has been found in any other study.

The other question about human cancer concerns soft-tissue sarcomas. This question was initially raised by a study of Swedish forestry workers exposed to phenoxy herbicides. An increase in soft tissue sarcomas was noted in workers using herbicides contaminated with dioxin. However, a similar increase was also noted in workers using herbicides that were not contaminated with dioxin.[29] Furthermore, studies of Swedish agricultural and railroad workers and studies of forestry workers in Finland and New Zealand who used the same herbicides did not show any increase in malignancy. One patient who developed chloracne after the accident at Nitro died 29 years later of malignant fibrous histiocytoma.[10] Two people who worked at other plants producing phenoxy herbicides have died of fibrosarcoma and liposarcoma. Some people have suggested that these three soft-tissue sarcomas are more than expected by chance.[29] However, no soft-tissue sarcomas have been detected after any of the industrial accidents in Europe.

Suggested Evaluation for Dioxin Exposure

Many patients who claim exposure to dioxin have been exposed to such low quantities, and even lower absorbed doses, that they do not have any real toxicity. It is important to separate those people who have only psychosomatic complaints from those who have true toxicity. Every patient should have a dermatological evaluation for chloracne and porphyria cutanea tarda. Serum chemistry profiles and prothrombin time should rule out hepatocellular damage. A 24-hour urine collection for uroporphyrins should be done. A spot check of urine for uroporphyrins is not reliable. Muscle weakness or neuritis symptoms should be evaluated by electromyography and motor conduction velocity. Immunologic evaluation may be considered in someone with other organic disease and high exposure.

Summary

A large number of people with definite exposure to dioxin have been reported in the medical literature. The consistent effects which can reasonably be attributed to dioxin are listed in the table. Chloracne is the most significant of the objective signs, occurring in most cases of true toxicity. Chloracne is a distinctive entity which may occur from topical or systemic absorption, and differs from acne vulgaris and from acneiform eruptions secondary to topical tar or oil.[23] It may occur in pre-pubertal children and the elderly. The amount and tone of news coverage of dioxin may have a significant power of suggestion, and many patients attribute psychosomatic complaints to dioxin. However, a patient with no objective signs of dioxin toxicity should not be considered as having true adverse effects of dioxin.

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THE AGENT ORANGE CASE
An Overview

B. History Of The Case ~~I. The Beginnings~~

Much has been written concerning how the Rudersham case was brought to Victor Yannacone who, by 1978 had developed a reputation as an environmental lawyer in the DDT cases, and how Yannacone subsequently formed a consortium of Long Island lawyers under the name and style of Yannacone & Associates to process the case.

The reality that this group of lawyers had to face was that, armed with only their own personal resources, they were being called upon to prosecute what was at best an arguable case against some of the largest, wealthiest and best-connected corporations in the world. Their clients, at first just a few veterans and their families, were in no position to assist in the financing of the effort.

From the outset, strategies were attempted that would minimize or eliminate the advantage that the defendants' unlimited financial and professional resources would give them. The first plan to short-circuit the case was to move for a preliminary injunction under FIFRA and whatever other grounds were available to stop the manufacture and use of 2,4,5-T. A hearing on a preliminary injunction would force the defendants into a trial without any discovery and before they could get prepared to conduct a war of attrition.

Unfortunately, Judge Pratt could not be made to go along with this strategy. Instead, he deferred the claims to the EPA proceedings then pending without prejudice to renewal in the event the EPA proceeding should prove defective.

There were numerous motions directed to the Second and Third Amended Complaints which led to some serious litigation. Before considering those, however, it should be noted that Yannacone, in an effort to reduce some of the apparent disproportion between the parties, was travelling around the country publicizing the case and trying to drum up interest in the crusade. In this he was successful, but his activities drove the defendants to attempt to obtain a "gag" order against him. This was a high-powered effort for the defendants who spent a lot of time developing favorable law and facts. Judge Pratt denied the motion without opinion.

Returning to the motions directed to the Complaints, the defendants questioned federal jurisdiction and also pushed statute of limitations as a defense. In his famous "Claiming to be the harbinger" opinion (506 F. Supp. 737), Judge Pratt denied the former grounds and found federal question jurisdiction. The latter he sidestepped by (1) not deciding the question while the jurisdiction matter was pending, and (2) conditionally certifying a class to toll the statute of limitations so as not to exacerbate any problems while the matter was sub judice. Indeed, he asked that no further complaints be filed to avoid burying the court clerk with paper. For a while merely the names and addresses of new plaintiffs were filed; then he dispensed with even that formality.

* Federal question jurisdiction was important because (1) there was no diversity between defendants and large numbers of plaintiffs, and (2) federal question jurisdiction would be a big help in ultimately overcoming Statute of Limitations problems. It was not too surprising, therefore, that Judge Pratt elected to certify the question to the Court of Appeals for interlocutory consideration on November 21, 1979. That certification put the case somewhat in limbo for nearly a year.

After certification, the focus of the litigation shifted

temporarily from the district court to the appeals courts. The matter was briefed and argued to the Court of Appeals on May 1, 1980. For some reason, the Court did not issue its opinion until November 24, 1980, at which time it reversed Judge Pratt and held that there was no federal question jurisdiction. Immediately thereafter, plaintiffs were obliged to seek a stay of the mandate (without bond) and also to seek a Writ of Certiorari under the caption "Chapman v. Dow." This was denied on December 14, 1981 (454 U.S. 1128).

While the appeal from the jurisdictional question was pending, the parties sought to exchange first wave interrogatories. At first the Court appeared to encourage discovery (there were some diversity actions that were clearly valid in any event). A few days later, however, the Judge decided that the benefits of continuing discovery were outweighed by the possible difficulties inherent in the circumstancews and he effectively stayed all discovery until the appellate courts should have spoken. Also, noting the various defenses asserted in the Answers, Judge Pratt ordered the defendants to bring motions for summary judgment on their defenses. The object was to simplify the pleadings, but it was clear that Judge Pratt was looking for one or possibly two key issues that would be dispositive of the case.

In line with a general briefing of the issues, Judge Pratt directed a conference in July of 1980 to consider solely the Australian cases. He found that they were generally bound by all the same Feres-type rules applicable to the suits by american servicemen.

The period waiting for the Court of Appeals to decide jurisidiction was also used to some extent to work out an outline for in extremis depositions and to promote plaintiffs' plan for serial trials. Basically, plaintiffs sought in the latter to convince the Court that it would be desirable to break the case

up into a series of trials on critical issues, such as generic causation, or product use and abuse, rather than to attempt to resolve the entire case at one confused, incomprehensable trial. While Judge Pratt ultimately rejected plaintiffs' precise formulation, the concept finally governed the case in another guise for a considerable period.

The Government Contract Defense

The efforts to simplify the pleadings led Judge Pratt to begin to concentrate on the so-called "Government Contract Defense" as a possible descrete, simplified issue that might turn the whole case. After the initial motions for summary judgment had been decided (506 F. Supp. 762), he called for further briefs refining this particular defense. These briefings led to his first opinion on the Government Contract Defense in 1982. 534 F. Supp. 1046.

The opinion was a disappointment to the plaintiffs. In what Judge Pratt probably saw as an effort to streamline the defense, he eliminated numerous subtleties that plaintiffs believed were important considerations in the defense, such as indirect responsibility for the specifications, coercion and consciousness of choice on the part of the government. Instead, he reduced the effort into a showing of what the government knew, what the defendants knew, and what the defendants told the government.

Having determined that those were the central issues to be considered, Judge Pratt directed discovery to begin on those issues. It might be noted that by far the greatest part of this discovery was at the "expense" of the government, in terms of time and effort, as well as money. Thus the plaintiffs were temporarily freed from crushing demands for discovery against themselves. The demands of keeping pace with the discovery against the government, however, was considerable. Some limited

discovery was also had against the defendants on their knowledge and activities.

The government's posture in the case at that point was somewhat ambiguous. In late 1981 and early 1982, Yannacone & Associates had attempted to file large numbers of Federal Form 95, the Administrative Claim Form under the Federal Tort Claims Act, on behalf of their clients. The project was, in mnay ways, doomed from the outset. First of all, each form had to be prepared individually for each client and signed by him. Because of sheer numbers, that was a virtual impossibility. Secondly, administrative regulations made it mandatory to file the form at different places for different categories of claims or different kinds of individuals. A full staff would have taken months to accomplish the task, and Yannacone & Associates did not have the staff to devote to the cause nor the months to spare. A couple of applications were made to the Court to try and bend the rules. Judge Pratt was asked to authorize the filing of a single administrative claim on behalf of all the class members, and he was also asked to at least get the government to accept service of all claims by class members at a centralized location. Judge Pratt, however, ruled that he had power to do neither. A further ploy was attempted in the guise of Ryan v. Clelland, a case that attempted to avoid the requirements of the Federal Tort Claims Act by seeking injunction, etc., without demanding a money judgment. Again, Judge Pratt ruled the Complaint could not prevail against the government. 531 F. Supp. 724.

While Judge Pratt could not be convinced to evade the requirements of the Tort Claims Act or to simplify the administrative requirements under the Act, he declined to enter a final order dismissing either plaintiffs' direct claims or the defendants' third-party claims against it. As a practical matter, this meant that the government was available to cooperate in discovery requests like those pressed in pursuit of the Government Contract Defense, whether it agreed to cooperate with

such discovery or not.

With the completion of appellate review of the Jurisdictional Question on December 14, 1981, Judge Pratt decreed that the case would go to trial on the single issue of the government contract defense in June of 1983. He also appointed Sol Schreiber to act as Special Master to supervise discovery.

It would not be appropriate in an "over view" to discuss the minutiae that were brought before the Special Master during this time. In addition to the details of discovery, the defendants kept before the Master and the plaintiffs their position that the case was essentially non-justiciable, at least before a jury, and that they did not accept the procedures being employed to advance the case.

In March of 1983 the Court and the Special Master believed discovery was sufficiently advanced (and the trial sufficiently near) to authorize a further set of motions for summary judgment. These motions, now based on discovered facts, were governed by the November, 1982 decision. The marshalling of the facts and the law for and against these motions constituted one of the principal landmarks in the case up to that point in time. The motions were submitted in April, 1983. Shortly after the papers were in, the Court announced it would issue its decision on May 20, 1983, but that all discovery was to halt until then.

Judge Pratt's decision was, again, a disappointment for the plaintiffs because he disregarded, at least for purposes of the motion, a series of factors that plaintiffs regarded as critical for the government contractor defense. Specifically, he disregarded the concept of "level of responsibility" and held that the knowledge of the lowest private was equivalent, for purposes of the government contractor defense, with the knowledge of the President of the United States. He disregarded any

concept of vicarious liability based on conspiracy to withhold from the government information about the toxicity of dioxin. Such a conspiracy had emerged from discovery, but Judge Pratt was prepared to dismiss from the case any defendant against whom nothing more could be shown. On the other hand, Judge Pratt appeared to accept the idea that a defendant could prevail on the defense no matter what his other conduct if he could show that he produced a "clean" product for the government, which Judge Pratt accepted to be a product containing no more than 1 part per million of dioxin.

Given these criteria, Judge Pratt dismissed Riverdale Chemical and Hooker Chemical (as to whom no real argument had been raised) but he also dismissed Hercules Chemical Company, a primary actor in the conspiracy to conceal from the government, but a producer of what Judge Pratt considered to be a "clean" product. 565 F.Supp. 1263.

The Summer of 1983 and the Breakdown of Control under Yannacone & Associates

The exercise with the motions for summary judgment on the government contractor defense convinced Judge Pratt that it would not be possible to segregate that issue as a discrete one for separate trial. On the contrary, it convinced him that the trial would have to be broadened to include issues of liability and causality. Accordingly, he cancelled the June, 1983 deadline and opened discovery up as to matters of causality and fault between plaintiffs and defendants.

The summer of 1983 was largely consumed with the discovery thus directed. Roughly depositions were held in days. Even before the institution of that discovery schedule, however, Yannacone & Associates had begun to crumble under the pressures of the case. In the spring of 1983, just before the motions for summary judgment, they had agreed to accept what they had heretofore resisted, the formation of a plaintiffs'

management committee including other counsel. Indeed, such new attorneys made a valuable contribution to the resistance to the motions. With the accelerated discovery schedule, however, even greater deficiencies appeared in the Yannacone organization. Certainly ability and dedication remained, but the discipline necessary to get the job done in an orderly fashion seemed lacking. Depositions were missed or nearly missed and commitments were not kept. Plaintiffs' attorneys were obliged to expend their efforts reacting to the demands of the defendants and did little by way of seizing the initiative. Most importantly, though, the financial demands of the case were beginning to get ahead of plaintiffs' counsel. Bills from court reporters, for example, mounted to upwards of $50,000. Such failings did not bode well for a group that proposed to put on a major case against some of the most seasoned and best equipped defense organizations in the not-too-distant future. Various solutions were proposed. One organization offered to work with the existing counsel group provided they agreed to subordinate their management prerogatives to that organization. While it was not questioned that the offer was well-intentioned, it was rejected. Instead, Yannacone & Associates moved to be relieved as counsel altogether, giving assurances to any successor that they would cooperate in the further management of the case, but that they could not cope with the financial burdens of the case as it was developing.

It was in this context that the present Management Committee, as augmented from time to time thereafter, accepted the challenge and took over management of the case with the approval of Judge Pratt. Composed of seasoned trial lawyers with experience in mass tort personal injury cases, its members also brought with them the financial capabilities of seeing the case to its conclusion.

Shortly after the new management committee took over the case, Judge Pratt made it known he could no longer supervise the

case (he had, in the meantime, been appointed to the United States Court of Appeals for the Second Circuit) and the matter was turned over to Chief Judge Jack B. Weinstein.

A New Judge and a New Management Committee

Judge Weinstein made it plain from the outset that he had a different view of the case than Judge Pratt. In the first place, whereas Judge Pratt had largely accepted in concept plaintiffs' idea of limited subtrials, Judge Weinstein saw the case as involving just one major trial encompassing all issues. Where Judge Pratt had accepted the idea of 'generic causation' as a trial issue, Judge Weinstein, while acknowledging that something like generic causation would have to be tried, also wanted the case pinned down the case of specified individuals. Lastly, while Judge Pratt had dismissed those whom he felt did not belong in the case, Judge Weinstein made public his feeling that no one should be dismissed from the case before trial. Within weeks of his comments, plaintiffs had moved to bring Hercules and Thompson back into the case and had succeeded. Even more dramatically, the defendants moved to reinstitute their third-party complaints against the government, and were rewarded with success.

For their part, the new Management Committee moved in the direction of taking control of the case. Armed with a depth of personnel and resources not available to Yannacone & Associates, the new Management Committee organized itself into groups with specific responsabilities and began to take the initiative. A comprehensive approach to the management of the causality trial was planned and carried into execution, and much groundwork was done to bring the legal considerations of the trial into a line advantageous to the plaintiffs. New looks were suggested at the interplay between the doctrines of negligence, strict liability and failure to warn; and wholly new formulations of the government contractor defense were suggested.

Ar. Democrat Wed. July 6, 1983

Associated Press

scene of slayings

harge laying amily

lled to hide in an upstairs
t and shot Mrs. Candelaro
n she came home from work
6:30 p.m., police said.
Authorities said Nasta was
ested at 10 p.m. Sunday after
ey noticed inconsistencies
his version of events.
Nassau County Homicide In-
ctor Kenneth Carey said five
ells recovered at the home
e fired from a .38-caliber pis-
Police said the weapon had
en recovered.
he Candelaros' home, be-
th and a life-insurance
y would have given Nasta,
assistant supervisor for fore-
with the Town of Hemp-
Highway Department, and
ut between $150,000 and
0. Nassau County homi-
commander Lt. Shaun Spill-
said at a news conference
y that he said the Nastas had
arried four years, had no
ren and had the normal
s of young married couple.
[illegible] said, "I think she doesn't
w he did it."
her arraignment Tuesday,
ad District Attorney Dan-
Fee said he would present
e case to a grand jury and
ks the high bail, $1 mil-
each count of murder,
of the "serious nature
crime and the relation-
ip involved."
Nasta's lawyer, Ira Jul-
ed for a "pre-parole risk
the first step to a bail
, Judge Eli Mellan re-
Absolutely not."
ine said the arrest was
de public until Tuesday
police at first were not
ither someone else was

Firms knew dioxin effect, memos show

The Associated Press

UNIONDALE, N.Y. – Chemical companies making dioxin-contaminated Agent Orange secretly discussed the extreme toxicity of the Vietnam War defoliant many times before its ban in 1970, according to court documents released Tuesday.

The documents show that company officials discussed "known health problems" and described dioxin as "exceptionally toxic" and that they wanted to solve the contamination problem before outsiders "cause us no end of grief."

Details of the internal industry communications, which date back to 1965, are contained in thousands of pages of documents released Tuesday in a class-action federal court suit filed by Vietnam veterans against major chemical manufacturers. The documents previously had been sealed.

Attorneys for the veterans contend that "silence and confidentiality were the code words utilized to conceal the knowledge which these defendants had amassed concerning the potential health hazards" associated with Agent Orange contaminated with the unwanted chemical byproduct called dioxin.

The veterans blame the herbicide for a wide range of ailments, including a severe skin disorder called chloracne, liver disease and birth defects in offspring.

The five defendants – Dow Chemical, Monsanto, Diamond-Shamrock, Uniroyal and Thompson-Hayward Chemical – say that if dioxin caused illnesses, they didn't know it, claiming that the government knew more about it at that time than they did.

The plaintiffs contend that the companies knew of the health hazards and did not tell the government.

Dioxin is short for tetrachlorodibenzo-p-dioxin, also known as TCDD, composed of chlorine and hydrocarbons. It has been linked to skin disorders, birth defects and cancer in laboratory animals.

While there is no proof that [illegible] 1980 federal Environmental Protection Agency report said exposure to the most toxic form of dioxin had been associated with liver damage, emotional disorders, sensitivity to light, risk of artery degeneration, chloracne, involuntary rapid movement of the eye, hormone imbalances, deterioration of immune systems and pains in the joints.

According to the federal Centers for Disease Control at Atlanta, a maximum safe exposure to humans is just one part per billion.

High levels of dioxin have been found at former chemical plant sites in New Jersey, and dioxin-contaminated oil was ouri, including the town of Times Beach.

One of the documents, a Feb. 22, 1965, Dow memo, summarized a meeting at which 13 executives discussed dioxin contamination of 2,4,5-T, one of the two ingredients of Agent Orange. It also contained the herbicide 2,4-D.

The Dow officials decided to contact other makers of 2,4,5-T, short for 2,4,5-trichlorophenol.

Another Dow report indicates that the company was aware in 1957 of an incident two years earlier in West Germany where there were "severe cases (of chloracne), including some suspected fatalities."

That document includes among the entries for effects in humans: "Usually not disabling, but may be fatal," "liver injury" and "long-term – two to five years to recover."

In March 1965, Dow official V.K. Rowe called a meeting of executives of Monsanto; Hooker Chemical, which operated the Love Canal dump; Diamond Alkali, a predecessor of Diamond-Shamrock; and the Hercules Powder Co., now Hercules Inc.

The meeting's purpose, according to the documents, was "to discuss the toxicological problems caused by the presence of certain highly toxic impurities" in samples of 2,4,5-T.

Dow officials distributed a memo dated Nov. 30, 1964, which called dioxin a "causative factor in the known health problems."

Later, E.L. Chandler of Diamond-Shamrock wrote a memo that said the meeting "was obviously designed to help us solve this problem before outsiders confuse the issue and cause us no end of grief."

C.L. Dunn of Hercules, dismissed as a defendant in the Agent Orange case, said in a memo for his company that Dow said "their examination of their own and competitors' 2,4,5-T products shows that some may contain what they term 'surprisingly high' amounts of the toxic impurities."

"In addition to the skin effect, liver damage is severe ... even vigorous washing of the skin [illegible] after application will not prevent damage and may possibly enhance absorption of the material," Dunn wrote on March 26, 1965.

Three months after the meeting, Rowe told Ross Mathieson, a manager with Dow Chemical of Canada, in a memo that dioxin "is exceptionally toxic; it has a tremendous potential for producing chloracne and systemic injury."

Rowe also warned that dioxin could form in products sold to the public and could lead to chloracne cases among consumers.

The letter carried a postscript: "Under no circumstances may this letter be reproduced, shown or sent to anyone

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Westinghouse retrenches on synfuels

Westinghouse is moving to unload its synfuels division, which includes a coal-gasification pilot plant at Waltz Mill, Pa. The plant, with a capacity of 35 tons/day, has logged over 10,000 hours of operation since 1975 on a wide variety of coals. Westinghouse claims that it has had "serious discussions" about the synfuels division with several potential buyers but has not disclosed their identity or the asking price. Westinghouse adds that it has not decided whether the division will be liquidated if a sale cannot be arranged. The apparent indecision is related to diverse trends in the synfuels business. Although the decline in world oil prices favors the division's divestment, Westinghouse still hopes that the U. S. Synthetic Fuels Corp. will support Westinghouse's Keystone Project in Pennsylvania, a venture that would burn 2,000 tons/day of coal to produce 120 million cu ft/day of medium-Btu gas for local utilities.

Foremost-McKesson is now McKesson

At the annual meeting last week, Foremost-McKesson shareholders approved a corporate name change to McKesson. The move stems from the $62 million sale last fall of its Foremost Dairies. The switch also signals a broader change of direction. "Over the past decade, we have divested ourselves of some $225 million of assets and reinvested $650 million in new growth businesses," emphasizes Thomas E. Drohan, president and chief executive officer. For the next several years, the $4 billion distributor of health care products, chemicals, and spirits will invest $100 million/year in new businesses and acquisitions.

Esmark prevails in its takeover battle

Another pair of corporate giants were united last week as Esmark won its takeover battle for Norton Simon. The Chicago-based maker of food, personal-care products and fertilizers succeeded in gaining 89% of Norton Simon's 24.8 million shares outstanding before the $35.50/share tender offer expired last Monday night. In addition, Norton Simon directors elected Donald P. Kelly, Esmark chairman, as chief executive officer of the New York-based company. Norton Simon's businesses include Avis car rental, Max Factor cosmetics, and Hunt-Wesson foods.

Vertac beefs up in herbicides

Vertac Chemical (Memphis, Tenn.) has taken another step toward strengthening its position as a herbicides producer (*CW, Apr. 6, p. 9*). Last week, the privately-held firm acquired the U. S. rights to Dow Chemical's 2,4-D trademarks. Included are rights to Formula 40 weed killer, Esteron weed and brush killer, DMA herbicide, and 99 herbicide. Vertac, a $100 million company, also gets the registration rights, inventories, formulation recipes and marketing data for the phenoxy herbicides. In addition, Dow will assign Vertac the exclusive U. S. rights to market and use the Dowpon grass killer trademark. A. Charles Fischer, herbicide business manager for Dow's U. S. Ag Dept., says that the sale will allow Dow "to utilize more of our resources on newer, growth-oriented products," including Lorsban insecticide, N-Serve nitrogen stabilizer, and four herbicides.

A split for Mobil Chemical's plastics segment

Mobil Chemical has split the operations of its Plastics Div. into two new units. The restructuring "reflects projected growth for both our established and newly-introduced plastic products," says Arthur E. Biggs, president. Mobil Chemical's new Consumer Products Div. will govern the company's Hefty, Kordite and Baggies brandname product lines, which primarily include trash bags, sandwich bags, and disposable plates and cups. The Plastic Packaging Div. will consist of stretch films, plastic grocery sacks, industrial waste bags, and plastic foam products such as egg cartons, meat trays and fast-food containers. Croft C. Hangartner, formerly head of the Plastics Div., is the general manager of the Plastics Packaging Div., and William C. Seanor, formerly manager of planning coordinations for petrochemicals and plastics, is the general manager of the Consumer Products Div.

Grace acquires a lubricants maker . . .

W.R. Grace has acquired privately-held S. H. Mack, of St. Charles, Ill., a producer of synthetic lubricants used in making two-piece cans. "S. H. Mack will complement our existing can-related specialty chemicals," says Jack Rimmer, Grace executive vice-president and head of the company's Industrial Chemicals Group. Grace will operate Mack as a unit of its Dewey and Almy Chemical Div.

. . . and forms two research ventures

W. R. Grace has formed 50/50 joint ventures with two German companies. One partnership, with Feldmuehle, of Dusseldorf, will study the world market for ceramic materials in internal combustion engines. The other venture, with Dynamit Nobel, of Troisdorf, will study the North American market for high-purity silicon. Both partnerships will be based in New York. Feldmuehle is a leading European paper producer and a maker of technical ceramics. Dynamit supplies specialty chemicals and high-purity silicons.

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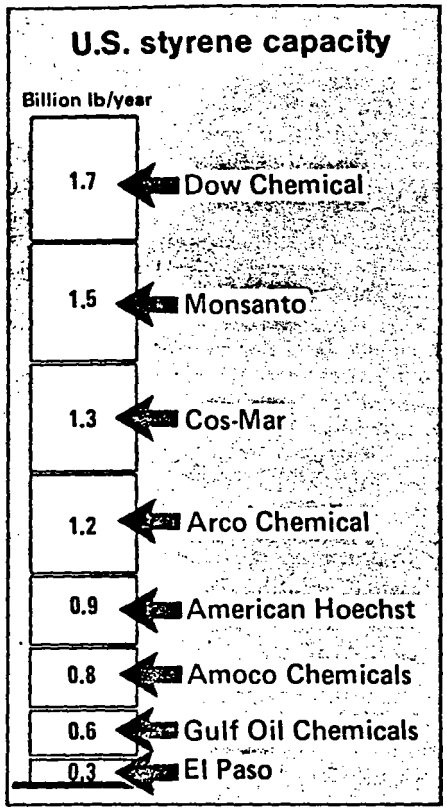

Warner, which shares ownership of Cos-Mar 50/50 with Cosden, Thomas Caltrider, business manager for petrochemicals, says, "We have a substantial commitment to the merchant market, and we intend to keep it that way." And Caltrider adds, "We have contractual positions with our customers, and we see no reason at all why we can't honor our commitments."

Why the sudden squeeze. The tightness was brought about by a second-quarter surge in demand for styrenic plastics and a spate of temporary shutdowns for maintenance and debottlenecking in July. In addition, El Paso had to put its customers on allocation when its small plant in Odessa, Tex., was closed down because of fouling in the purification system. Moreover, says Caltrider, inventories were low when the upturn started.

There's plenty of active capacity for styrene—over 8 billion lb/year, counting the expansion of Amoco's Texas City unit to 790 million lb/year from 615 million lb/year. And American Hoechst has an idle 600-million-lb/year unit in Baton Rouge, La., that could be reactivated, though it's not considered likely to start up soon.

Producers turned the material out at the rate of 5.7 billion lb/year in the first quarter and actually cut back production slightly in April. But, says the U. S. International Trade Commission, styrene production in May was 585 million lb, equal to 7.1 billion lb/year and more than 85% of capacity. Marketing managers for styrene producers say that much of their planned output in the third and fourth quarters is already committed, either to supply customers or to repay material borrowed during recent shutdowns.

Restarting. The result, according to one Gulf Coast observer, is "a powerful incentive to restart plants." Domestic demand seems sure to continue strong because of the accelerating pace of the economic recovery. And a Gulf Coast trader points to "vibrant Far East interest in soaking up any excess styrene supplies," even at higher prices.

Prices of both styrene and polystyrene have been a sore point with producers for a long time. Styrene marketers have been trying to get prices up above 30¢/lb and recently posted prices of 33¢/lb. But the spot market is now 30-31¢/lb, and the European price is 1810 deutschemark/metric ton, a little over 30¢/lb at recent foreign-exchange rates.

Some of the idled plants started up recently, and most of the rest will soon be back onstream. But a New York-based trader says that even with the shutdown capacity starting up again, "it will be weeks before the market sees any slack." Others say that the snugness in the market will last much longer, and Hoechst has delayed its scheduled three-week maintenance shutdown from October to November, when the market is expected to be easier.

How tight the market will be through the rest of this year will also depend on demand for downstream resins such as polystyrene and ABS. All the styrene producers but El Paso make either polystyrene or other styrenic resins, and they will keep substantial quantities of styrene to supply their downstream operations if necessary. And demand for those materials has heated up.

The key factor is strength in the markets for polystyrene, the biggest use for the intermediate. Sales and captive use of polystyrene rose to 1.39 billion lb in the first five months of this year, compared with 1.28 billion lb in the same period of 1982. But that rise follows three straight years of decline, and it leaves movement for the five-month period about 18% below that of the same period of 1979, when polystyrene markets hit their peak.

Styrene makers thus need continuing improvement in polystyrene demand. It looks, say marketers, as though they will get that improvement, despite reports of a sluggish PS market in June. Still, it may take more time for styrene buyers to fully accept that prognosis. Meanwhile, says one observer, styrene output will be limited by available capacity, but prices are more likely to respond to the strength of demand. □

Dow sells its 2,4-D trademarks

One company's commodity may be another firm's premium product. In Dow Chemical's eyes, 2,4-dichlorophenoxy herbicides are too common to warrant the expense of marketing Dow's own 2,4-D trademarks. So Dow has sold most of its 2,4-D trademarks to Vertac, a privately held Memphis firm with both a position as a 2,4-D maker and an appetite for product acquisition.

Dow has made 2,4-D since the late 1940s. The company has been both a purveyor of 2,4-D "technical" material—the basic ingredient used to formulate 2,4-D herbicides—and its own trademark products. The problem, Dow says, is that marketing the trademark products was too demanding for what the company deems a commodity. So Dow is selling off its trademarks but will still supply technical 2,4-D to herbicide formulators, including Vertac.

"We are not reducing our capacity to produce 2,4-D," insists A. Charles Fischer, herbicide business manager for Dow Chemical's domestic Agriculture Dept. "We have decided not to take it all the way to the distributor."

Dow's deal with Vertac includes the sale of several 2,4-D trademarks: Formula 40 weed killer, Esteron weed and brush killer, DMA herbicide, and 99 herbicide. Vertac is also buying Dow's DMA-6 trademark for Dow's technical 2,4-D, but Dow will keep the right to use it. Dow is throwing in several non-2,4-D product lines, including Dowpon, a dalapon product that Vertac will sell under a trademark license, since Dow won't sell a trademark bearing its name. Vertac is also buying Veon, a 2,4,5-T product.

Dow's sales of technical 2,4-D to formulators—especially to Vertac—could actually increase because of the sale, says Fischer. "Vertac will put more ef-

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fort into it than we were able to," he explains. The only other remaining U. S. maker of 2,4-D is SDS-BioTech, a 50-50 joint venture of Diamond Shamrock and Japan's Showa Denko that has taken over Diamond's 2,4-D production and marketing. A spokesman says the firm is "surprised at Dow's move."

But the sale is readily understood by others. Lacking strong patent protection, 2,4-D has had commodity status for three decades. Two others, Monsanto and Du Pont, have already ceased production, choosing to stress proprietary herbicides instead. Dow, too, wants to focus on proprietary products.

Overall trends in the 2,4-D market are not encouraging, since growth has been rather flat in recent years. "It's probably held fairly steady" over the last decade, says the purchasing manager for a Midwestern agricultural products distribution firm, since 2,4-D has "found its niche" in corn and small grains. But he thinks the advent of DuPont's Glean herbicide may spell diminished sales for 2,4-D, since Glean covers many of the same crops as 2,4-D.

Jack P. Taylor, Union Carbide's product manager for phenoxy herbicides, concedes that Glean "could impact the consumption of 2,4-D considerably." Taylor estimates that the U. S. market for 2,4-D is now 40-45 million lb/year.

Vertac president C. P. Bomar, Jr., says he is undaunted by such trends. He hopes to convince farmers that 2,4-D is as effective as newer herbicide products, even though applying 2,4-D products may take more work. Bomar says Vertac will continue to sell its own 2,4-D label goods along with the Dow trademarks, which he says it will sell "more or less as a premium line."

Beefing up. And Bomar thinks Dow's trademarks will strengthen Vertac in the Midwest and the Pacific Northwest, where its position is weak. To maximize the value of the trademark and some other acquisitions, he says, Vertac will expand its marketing force by 25%.

Vertac's purchases of Dow's 2,4-D is the latest in a string of recent herbicide acquisitions by the company. In 1981, Vertac bought Dow's Dinoseb weed killer. As with the 2,4-D sale, Vertac already manufactured that type of herbicide. Last year, the company bought a line of monosodium methanarcyanate herbicides from now-defunct Crystal Chemical. And this February the firm bought Rhone-Poulenc's 2,4-DB herbicides for soybeans and peanuts.

Herbicides represent about 60% of Vertac's business. The company, which projects $70 million in total sales for 1983, is the only U. S. producer of potassium nitrate, and it makes related industrial products. It is also a custom synthesizer of herbicides for others.

Now, Bomar says, Vertac wants to expand into fungicides and insecticides, but his strategy is to minimize research costs by acquiring rather than developing new products. "They are never going to invent a new molecule," observes Dow's Fischer. "They aren't even trying to invent a new molecule. They are gearing up to be profitable marketers of commodity products." □

Textile-import accord—maybe

The U. S. and China have been haggling since last summer over replacing the three-year-old textile trade agreement that expired Dec. 31, 1982. Now, after much maneuvering, stalling, and bargaining, the two countries have reached a new bilateral accord that specifies allowable growth rates for textile imports from China for the next five years. But even though the pact's details haven't yet been made public, textile producers are voicing their disapproval.

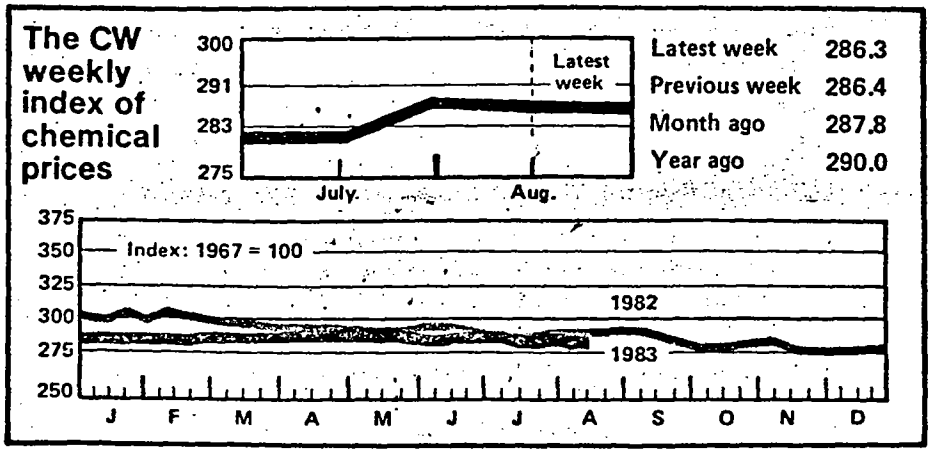
Industry officials walked out of negotiation talks held two weeks ago in Geneva, Switzerland, because the agreement was more generous to China than the manufacturers had wanted. Industry had been pushing to hold yearly growth of certain textile imports from China—the fastest-developing exporter of such goods—to 1%/year, considerably below the 4.3% rate permitted under the earlier three-year contract. China had been bargaining for 6%/yr. According to some government reports, the new agreement, which is retroactive to Jan. 1, places a 2-3%/year growth ceiling on the imports.

Skeptics. U. S. trade officials, muzzled until the formal exchange is signed in Beijing at the end of this month, hesitate to confirm the 2-3% figure, and this has led to industry skepticism. "I wouldn't be surprised if it were more [than 3%]," says Larry K. Martin, vice-president of the Man-Made Fiber Producers Assn. (MMFPA). Industry contends that any import limit surpassing the current annual growth rate—1.0-1.5%—of the domestic market for textiles and apparel is punishing to U. S. producers.

Since 1979, China has positioned itself as a major textile exporter to the U. S., tagging behind only the Big Three—South Korea, Hong Kong and Taiwan. Commerce Dept. figures show that U. S. textile imports from China advanced about 15% in 1979, 41% in 1980, 73% in 1981, and 19% in 1982, when they reached 671 million sq yd (*chart*). On a dollar basis, that volume—an 11% share of all U. S. textile imports—was worth $800 million. The Big Three accounted for about 60% of U. S. textile imports.

But the impact the proposed agreement will have on import volumes will be difficult to calculate, says Ann R. Berry, a textile negotiator for the U. S. Trade Representative's Office. That's because the ceiling does not affect all textile and apparel imports even-handedly. The original agreement restricted only 17 of the more than 100 categories of textiles and apparel established by Commerce, and the new proposal expands that coverage to only 33 categories, Berry explains.

And though the U. S. has restricted those textiles with the highest import



International Study Is Urged Of Agent Orange in Vietnam

1/21/84

By PHILIP M. BOFFEY
Special to The New York Times

WASHINGTON, Jan. 20 — The senior member of the House Veterans Affairs Committee today called for an international study of whether Agent Orange, a herbicide used to defoliate trees and kill crops in the Vietnam War, had caused harm to the Vietnamese who were exposed to it.

Representative Don Edwards, Democrat of California, who recently returned from a week in Vietnam, said an objective study conducted there could help resolve the dispute over whether the herbicide caused long-term harm to American troops. It was used to destroy vegetation that provided cover for the Vietcong.

"We can't resolve the problem here, apparently," Mr. Edwards said in a telephone interview. "I concluded that a study of what happened over there would assist greatly in the American studies of our veteran population. It just doesn't make sense not to go where the living laboratory is."

Vietnamese See a Link

Mr. Edwards said Vietnamese hospital administrators, scientists and doctors had told of health damage to women who had apparently been exposed to the herbicide as girls in jungle villages. He said he had been told there was a high rate of cancer of the uterus and of abnormal births among these women.

"Maybe Agent Orange had nothing to do with it," Mr. Edwards said, "but that should be established. An investigation should be done."

Vietnamese scientists have conducted studies concluding that birth defects and cancer appear related to Agent Orange. One group of scientists from Western and Communist bloc countries that visited Vietnam a year ago said it found the studies "suggestive" but not conclusive.

The group, of which Arthur H. Westing, an ecologist at Hampshire College in Amherst, Mass., was the co-leader, called for cooperation between Vietnamese and other scientists on the question.

Itching Skin and Sleeplessness

The Federal Government is sponsoring more than 50 studies of Agent Orange in this country. The key studies require accurate records of where people were at the time the herbicide was sprayed and of subsequent health problems. Some American scientists doubt that adequate records for such a study exist in Vietnam.

Mr. Edwards said that in visiting hospitals in both Ho Chi Minh City and Hanoi he heard far fewer complaints of suffering among male Vietnamese veterans than he had expected, based on complaints by American veterans.

Some Vietnamese officials said male veterans were suffering from itchy skin, inability to sleep and other health problems, he reported, and one doctor said he was convinced that male veterans had chromosome damage. But Mr. Edwards said that Vietnam was such a primitive country that it had made no real effort to keep track of its veterans and determine their health problems.

Mr. Edwards said he would issue a report next week calling for an international study. He said it should be conducted by a respected international organization, perhaps the World Health Organization or the Food and Agricultural Organization, both of which are specialized United Nations agencies, because studies begun by either the United States or Vietnam alone would lack credibility.

He said he did not know if Agent Orange was connected with the genuine health problems experienced by Vietnam veterans, but added, "We have an obligation to get an answer to this conundrum."

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BULLETIN

U S Committee for Scientific Cooperation with Viet Nam

Mobil Hoan Khiem

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REPORT

Edward L Cooperman

Organizational Structure

Due to the rapidly expanding activities of our Committee, we are now in the process of constituting a "National Board". Listed below are those Committee members who have agreed to join. Other members are invited to participate. National Board members are expected to participate actively in formulating the exchange program, organize intineraries of visitors, etc. and assist in formulating future activities of the Commmittee, especially in their professional areas of interest. This may entail one or more visits to Vietnam.

The National Board members are grouped by their areas of interest:

- Social Sciences

  Professor JAYNE WERNER (1)
  Southern Asia Institute
  Columbia University

  Professor STEVE O'HARROW, Chair
  Dept of Indo-Pacific Languages
  University of Hawaii

- Mathematics and Computer Sciences

  Professor NEAL KOBLITZ (1)
  Dept of Mathematics
  University of Washington

- Agriculture and Biological Sciences

  Professor ARTHUR GALSTON (2)
  Dept of Biology
  Yale University

  Professor ALAN HOOPER (1)
  Dept of Cell Biology & Genetics
  University of Minnesota

- Health Sciences

  Professor JUDITH LADINSKY (1)
  Dept of Preventive Medicine
  University of Wisconson

  Dr GLENN GORDON, MD, FACS
  Eugene, OR

  Professor JOHN LEVAN
  Chicago Medical School

  Professor JAMES DWYER
  Dept of Paychology
  State University of New York
  Stony Brook

  Dr WILLIAM EISMAN, DDS
  San Francisco, CA

- Physical Sciences

  Professor E L COOPERMAN (1,2)
  Dept of Physics
  California State University
  Fullerton

(1) Subcommittee coordinator
(2) Executive Board member

Activities

At the beginning of next year, Professor HOANG THUY NGUYEN, Director, Institute of Epeidemiology and Hygiene (Pasteur Institute) and President, Medical Research Council of Vietnam will be our guest. One of his goals is to set up an ongoing exchange program in the medical sciences. Also, we expect two delegations of agricultural/microbiological experts, the Dean of the Ho Chi Minh City Dental School, the President of the Chemical Society of Vietnam, two journalists, and one mathematician.

Our Committee is cooperating with two International Conferences to be held in Viet Nam in January 1983.

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1. "International Symposium on the Long-Term Ecological and Human Consequences of Chemical Warfare in Vietnam", Ho Chi Minh City, 12-19 January. A copy of the preliminary program is available upon request. Participation is by invitation only. Currently there are 40 international participants and observers from eleven countries with an equal number of Vietnamese participants.

2. "IFIP Working Conference on Recent Advances in System Modeling and Optimization", Hanoi, 10-14 January. Details in the first issue of the "Bulletin".

The Committee now has established working relations with five Vietnamese organizations: Vietnam Science Center, Vietnamese State Committee for Science and Technology, Social Sciences Commission, Ministry of Health, and the Ministry of Higher Education (university professors exchange program).

The exchange program with the Social Sciences Commission has developed rapidly this year with the visit to the U S of Professor PHAM HUY THONG, Vice-Chair of this Committee.

Other activities include the continual sending of scientific and technical books, and medical journals and supplies to various Vietnamese libraries and hospitals. A fully furnished ambulance was delivered to St Paul Hospital in Hanoi (jointly with the U S-Vietnam Friendship Association of Northern California). St Paul is the main hospital for Hanoi, and had only one ambulance available.

In addition to on-going research programs on the effects of Agent Orange, our Committee is involved in a program to improve the heath-care delivery system, and in setting up prototype village-level solar energy-operated grain and vegetable dryers.

We are assiting in the design and construction of solar energy hot-water heaters in several Ho Chi Minh City hospitals, as well as participating in improving agricultural production in the Mekong Delta (Can Tho University). Where possible, Committee members are assisting in United Nations-sponsored projects.

Inquiries about this Committee may be made to:

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Articles for submission to this "Bulletin" as well as comments should be sent to "Bulletin" editor:

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Box 4617
Berkeley, CA 94704.

TELEGRAM ON TYPHOON NANCY

We regret to inform that typhoon #7 (Nancy) on 18 October 1962, with windspeeds up to 140 km/hr, heavily destroyed Nghe Tinh province, causing torrential rains and big flood there and provinces: Thanh Hoa, Ha Nam Ninh, Thai Binh.

(1) Great losses caused by the typhoon are focused on Nghe Tinh where seven districts -- Nghi Loc, Nghi Xuan, Dien Chau, Nam Dan, Thanh Chuong, Hung Nguyen and Vinh (in Diên Chau) -- are heavily destroyed; saltwater intruded into an area 15 km long and 3 km wide; another eight districts are variously affected; all the above districts mainly produce food.

1,335,000 people in 255,000 households were affected; with 70 dead, 290 injured and 194,200 homeless. 68,894 were broken down with roofs torn off another 125,930.

Thirteen district/provincial hospitals were destroyed; 194 commune health centres completely broken down.

4,233 classrooms were broken down, 1,353 heavily damaged, 100,000 books soaked; 185,000 pupils out of school, 585 kindergartens down, roofs torn off another 104. 47 barges and 449 fishing boats sunk.

A number of main and supportive dikes and irrigation constructions were crushed: 661,000 cubic meters of earth and 13,160 cubic meters of stones.

(2) Crop losses were: in Nghe Tinh, 43,000 hectares of rice were inundated, 28,100 completely lost and 15,000 partially destroyed. In other provinces, the respective figures were: for Thanh Hoa, 66,800, 4,000, 57,000; Ha Nam Ninh, 57,100, 9,000, 47,300; Thai Binh, 40,000, 7,000, 33,000. Output losses were about 300,000 tons of food.

Facing the above natural calamity, AIDRECEP urgently appeals to you for active emergency aids of materials to the affected areas out of your traditional charity, friendship and solidarity with the Vietnamese people.

The needs are for: FOOD, FERTILIZERS, PESTICIDES, ANTIBIOTICS, CLOTH, PAPER and ROOFING MATERIALS. Please send any relief goods to the address: AIDRECEP/VTKC 82, so that we can easily distribute them to the affected areas and report to you.

Anxious to receive your active response.

Best regards,

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O THI TAI President of AIDRECEP

NOTE: TAX-DEDUCTIBLE contributions for the benefit of the victims of this typhoon may be made to the "FOUNDATION FOR SCIENTIFIC COOPERATION WITH VIET NAM" and sent to the Committee, c/o Department of Physics, California State University Fullerton CA 92634.

IN MEMORIAM: PROFESSOR TON THAT TUNG (1912-1982)

Edward L Cooperman

Professor Ton That Tung died on 7 May 1982, three days before his seventieth birthday, from heart failure at his home in Hanoi.

To many of us who knew him his dynamic personality, his exuberance, his desire to help his people, strongly affected and touched us. His shock of pure white hair, his spontaneous smile, and to those who knew him well, his caustic wit and criticism, will make him hard to forget.

Professor Tung was among the first "native" medical doctors to graduate from the Hanoi Medical College in 1939. He became well known internationally as an acclaimed liver cancer surgeon, but this short memoriam is not to emphasize his professional qualities, but rather his human qualities.

Tung's first choice was made early during the Vietnamese resistance. The Emperor asked him to be his personal physician at the Court in Hue. Tung told this writer that at this time he met Ho Chi Minh. Ho Chi Minh never asked him to go with him to the jungles, but Tung said he knew in his heart what he had to do. Tung was Vice-Minister of Public Health in 1947, but resigned to return to his Viet-Duc Hospital where he served as Chief of Surgery. He fostered many health-related programs during his life, and most recently was the chairman of the coordinating committee which was planning the "International Symposium on the the Long-Term Ecological and Human Consequences of Chemical Warfare in Vietnam" (12-19 January 1983, Ho Chi Minh City). Tung worked long and hard to try to determine the lasting effects of dioxin impurities in the herbicides used in Vietnam.

Tung was one of the major supporters of the U S Committee. In a letter to this writer shortly before he died, he again reitereated the need to develop scientific and medical exchanges between our two peoples, but said that this would be "a long term project".

By persevering we will succeed in Tung's goal, which, as Prime Minister Pham Van Dong said to us, "scientific exchange leads to mutual respect, then to trust, and eventually is important toward establishing peace between nations".

VIET NAM, SEEN FROM AMERICA

Ton That Tung

This April (1979), when I was about to leave for my visit to the United States, I was quite anxious. This was my first trip to America, I didn't speak English well, and for the most part I had never my scientist friends there, but only knew them through our correspondence. Besides, the United States is regarded as the most scientifically advanced country in the world. What would they think of the work I was doing in our severely limited conditions? What would they think of Vietnamese medicine? But I also realized that this was an unprecedented opportunity for me to make objective observations and comparisons, and at the same time to see how Americans regard our country, our work, our people and our science.

Many American scenes left deep impressions: the tall skyscrappers, the broad highways sometimes on two levels, packed with countless vehicles yet so very orderly, the bright green countryside with wheat silos scattered here and there like white towers, a broad carpet of flowers and grass surrounding clusters of charming wooden houses. When I went to visit universities in the cities of New York, New Haven, Boston, Amherst, Chicago, Philadelphia, Madison, Washington and San Francisco, I usually stayed in the homes of professors or doctors, living with their families. This gave me the chance to talk frankly with them, to get to know Americans, and to gain a clear sense of their attitudes toward our people and our work.

One curious thing was that whenever I met American intellectuals, their first sentence would be, "I was against the Viet Nam war". There was only one exception -- Professor Allen at the University of Wisconsin, Madison. He admitted to me, "I was one of those who supported the American government in the Viet Nam war, but since I met you I've changed ranks". This shows the characteristic spontaneity and flexibility of the Americans; they will readily change their opinions if their perceptions change.

In the past the universities were strongly opposed to the aggressive war in Viet Nam. They set up scientific groups which still want to help Viet Nam. These groups at Columbia University in New York, at the universities in Chicago, Portland and Irvine, and researchers at biological and environmental laboratories all across America offered to cooperate with me in work in environmental sciences and genetics.

The image etched most deeply in my memory is that of an American youth in the beautiful city of Portland. He stood waiting for me at the door of the lecture hall after I had given my lecture and discussed the dioxin problem. With a distressed expression, he came up to me and said, "I used to be in the Air Force. I'm very sorry to have spread such suffering in your country. I want to apologize to you". I took his hand and said, "From now on we must look toward the future".

American veterans of Viet Nam have realized they are victims of the U.S government because of the effects -- they compare them to the explosion of a delayed-action bomb -- caused by various defoliants, especially by Agent Orange which carries an extremely dangerous contaminant called dioxin.

Ten years ago, I had been the first to describe those effects, and had presented my findings to two international conferences, in Paris and Copenhagen, and had written many articles for the Paris press. At that time one segment of public opinion had criticized my ideas as anti-scientific and as anti-American propaganda. But afterwards experiments and observations supported these findings. Two years ago, some people in Oregon mounted a struggle calling on American scientists to recognize the terrible effects of Agent Orange. Thousands of American veterans of Viet Nam stood shoulder to shoulder with the people of Oregon in that struggle calling for a special category of "Viet Nam veterans" who could be observed for effects of the chemicals and calling for large payments as compensation under American law. These veterans followed me and guarded me carefully. Thanks to that I was never harassed or attacked, even though some of my activities were in areas like California where a great many Saigon soldiers have taken refuge.

In America there is a widespread loss of confidence in surgeons and everyone talks about "malpractice". So Americans are very interested in the organization of medicine in other countries, especially in Viet Nam, a country which has had to endure 30 years of war with a backward economic infrastructure.

In talking with American friends we brought out two characteristics of Vietnamese medicine. First, our medicine is combat medicine which took shape beginning in the years of the resistance against the French. At that time Vietnamese doctors were fighters in action with the guerillas or the regular army on the battlefield, and those were the best schools for our medical cadres. Very early on we used Vietnamese as our language of instruction, in constrast to other countries of Southeast Asia where English is still used, and thanks to that we wiped out the roots of the class monopoly on medicine which still exists in other former colonies. Thanks to our use of the Vietnamese language and to our expandion of secondary education, we were quickly able to build a large corps of assistant doctors and doctors for the north. We had one assistant doctor or doctor for every 800 people, a ratio not yet achieved in any other Third World country.

The second point is that Vietnamese medicine set itself the goal of serving patients no matter what the circumstances. If we were short of medicines or other resources, we would invent replacements, we would rely on traditional medicine, and thanks to that we were able to solve such problems as carrying on surgery in wartime, preventing common epidemic diseases, and taking health care directly to the countryside.

I have to say that one weak point in American science is that it relies too much on machinery and animal experiments and conducts too little observation of people. Take the problem of cancer. Despite years of research costing millions of dollars, and although American science has discovered viruses which cause cancer in animals, it has not been successful in discovering viruses in human cancer. Thus American researchers have now made a 90-degree turn and have proposed epidemiological studies of various cancers in an effort to trace the causes.

Vietnamese doctors took an overall apporach to the problem of harmful effects of defoliants begin-

ning in 1970. But in other countries no one was willing to follow the effects in people even though Agent Orange was in use in America, France, England and Sweden. So far only France has banned the use of 2,4,5-T.

Carrying a bell to ring it abroad, I was happy to find that thanks to our people's just and victorious struggle, thanks to our people's great accomplishments in many areas despite our very difficult situation, and thanks to our government's correct course in foreign policy, when the Vietnamese bell sounds in America it still echoes clearly and in tune. And that fact makes me feel extremely proud of our people and of the great task we have taken on.

Note: The above excerpts from a lengthy article by Professor Ton That Tung were translated by JOHN SPRAGENS, a staff associate at the Center for International Policy, Washington, DC.

THE QUESTION OF DIOXIN LEVELS IN VIET NAM, THEN AND NOW

Arthur Westing

Large numbers of individuals in Indochina, both military and civilian, were inadvertently exposed to dioxin (TCDD: 2,3,7,8-tetrachlorodibenzo-para-dioxin) as a result of U S actions during the second Indochina war. This continues to be a matter of grave concern owing to the toxic, teratogenic, carcinogenic, and mutagenic properties of this substance. I provide the following information on dioxin levels in Viet Nam owing to the widely divergent views that keep appearing especially in the popular and semi-popular literature, often incorrectly attributed to me.

Dioxin was disseminated as impurity of the 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) component of the now notorious anti-plant chemical weapon code-named Agent Orange; and also of its much more modestly used close relatives (Agents Orange II, Pink, Purple, and Green), all subsumed here under Agent Orange [2]. The Agent Orange was dispensed by the U S between 1962 and 1970 (although primarily between 1966 and 1970) in attacking inland and coastal forests and some crop lands. Although Kampuchea [1], Laos [4] and north Viet Nam were all thus attacked, it was south Viet Nam (and especially its former Military Region III, a large area centered around Ho Chi Minh City) that was the major recipient [3].

Approximately 44.3 thousand cubic meters (57.0 million kg) of Agent Orange was expended by the U S during the war, containing about 24.1 million kg of 2,4,5-T per se [2, p 26]. It is difficult to make a reliable estimate of the actual amounts of dioxin contained in the Agent Orange used in Indochina owing to the untimely destruction by the U S Air Force and the Dow Chemical Company of the reference samples of most of the lots that had been expended. An estimate based on Dow determinations released by the U S Air Force in 1974 is that the Agent Orange had an average dioxin content of 2.5 grams per cubic meters, ie, 1.9 mg/kg [2, p 44-45]. This concentration suggests that a total of at least 110 kg of dioxin was disseminated. Some new information released by

the U S Air Force in 1980 indicates that the total was somewhat higher than this, perhaps 170 kg [5, p 368]. As dubitable as these Dow/Air Force dgta are, I am aware of no others from which to make better estimates (and would welcome being referred to any reliable new information). It should also be noted here that the total amount of dioxin in Viet Nam, whatever it was, was probably augmented to a slight extent as a result of the burning of wood that had been sprayed with 2,4,5-T.

It appears that on the order of half the amount of aerially applied dioxin decomposes within a few days, with the remainder becoming more permanently incorporated into the soil and biota. Here it can work its way food chains, including those culminating in humans, becoming concentrated in the process. The dioxin thus incorporated into the ecosystem appears to disappear following first-order kinetics, having an environmental half-life of perhaps 3.5 years [3, p 290; 5, p 368]. In the case of Viet Nam, if one makes the simplifying assumptions that the amount of dioxin introduced was, indeed, 170 kg and that it had been all introduced in 1968, then perhaps 8 kg remained at large in 1980, 3 kg will be present in 1985, and 1 kg in 1990. Its legacy, on the other hand, could persist far longer.

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THE PRESENT STATE OF NUTRITION IN VIET NAM

Tu Giay

Forty consecutive years of war, profound consequences of chemical war, repeated floods accompanied by severe droughts of recent years have left their trace of devastation with respect to the nourishment of the Vietnamese people.

The National Institute of Nutrition of the Socialist Republic of Viet Nam, founded in 1980, has begun work initially in establishing the concrete state of nutrition of the country.

The first surveys have given us significant preliminary results. The average diet of a Vietnamese peasant suffers a calorie deficit of 10-15% and amounts to only 1,800-2,000 kcal a day. Calories from protein sources constitute only 9-10% of the energy value of the diet. There is very little protein of animal origin (only 10-15% of total protein in the diet). Energy from lipids is only 6-8%.

Data already gathered are summarized in the table below:

AVERAGE DAILY DIET FOR A PEASANT AGED 18-40 YEARS
(The family's main breadwinner)

REGION OF THE COUNTRY:	Northern	Central	Southern
VILLAGE NAME:	Co Bi	Van Thien	Binh Trung
NEAREST CITY OR PROVINCE:	Hanoi	Thanh Hoa	Ho Chi Minh City
SURVEY DATE:	September 1980	March 1981	November 1981
FOOD ITEMS			
Rice	504 g	94 g	493 g
Wheat		42 g	
Meat	5 g		19 g
Fish, fresh-water crab, prawns	33 g	21 g	56 g
Fat			13 g
Eggs			13 g
Beans, peas, peanuts	10 g		6 g
Vegetables, fruit	175 g	825 g	64 g
Sugar			1 g
Soybean cake			12 g
Soy, fish sauce	30 g		22 g
TOTAL KILOCALORIES	2021	1410	2013
PROTEINS	53 g (10.8%)	28.4 g (8 %)	60 g (11.2%)
LIPIDS	10 g (4.7%)	5.3 g (3.5%)	11 g (5.1%)
MEAT PROTEINS	(11 %)	3 g	(22 %)

The above table shows that the peasants in southern Viet Nam have a much more varied diet. The region of Thanh Hoa was hit by a typhoon in October 1980 (and more recently by typhoon Nancy in October 1982). Fifteen-year old children in this frequently flooded region weigh on the average six to eight kilograms less than those in other parts of the country.

Investigations on the nutritional status of younger children (one to three years of age) yield more alarming results. The average diet is about 700 to 800 kcal, less than the norm fixed in Viet Nam (1,100 kcal), much less that the norm in developed countries (1,300 kcal). The protein proportion is very low and attains less than 20 g, barely half the ration of youngers of the same age in developed countries (normally higher than 40 g). Animal proteins constitute only 20% of all proteins (required norm is more than 50%). Lipid proportion is even lower: only 5 g and barely 10% of the norm; the established norm in developed countries is 50 g.

The consequences of shortage of energy, proteins and lipids, and the lack of attention to vitamins and minerals are the development of malnutrition, kwashiorkor, anemia, children less than three years old ranges from 12 to 18%.

This percentage is even higher if international norms are taken into account. The average weight and height of two-year-old children in Viet Nam are only 80% and 90% of the Harvard norms, respectively.

The percentage of malnourished children in flooded regions reaches 24%; and this number climbs to 40% in those regions, like Binh Tri Thien provice, which has been devastated by chemical war.

It is regrettable that we have

not been able to get more detailed studies on the influence of malnutrition on the child growth, on health, development of infectious diseases and deficiency-induced sicknesses. But it is clear that the present state of the country's nutrition poses urgent problems which must be solved on a scientific basis with multi-disciplinary means.

It is in this spirit that our Government has posed the problem of nutrition for the people as a State problem of utmost urgency. We know that our daily meals are the results of a long process of work and collaboration between many different branches of the economy and science.

Meanwhile, the first duty of the physician is to study the nutritional needs of the organism, establish different diet requirements for each age group and profession, indicate how to economically fulfill one's needs with alimentary products, demonstrate the efficacy of a rational nutrition on physical development and work ability, control the nutritional value of a meal and hygienic conditions of food enterprises, carry out mass work for rational nutrition.

In this direction, the Government has chosen a physician to head the State program to search for rational nutrition for the popula tion. He has three vice-ministers as assistants: vice-minister of agriculture, of food industry and of internal commerce. The active members of the program are experts of agriculture, husbandry, food technology, organization of collective nutrition; economists, specialists of culinary art, of mechanization of food preparation; doctors (physiologists, biochemists, hygienists,...). These specialists in different branches of the economy, science and agriculture show the scope and variety of the program.

The national food program for 1981-1985 encompasses these six major problems:

1. The study of nutritional needs and establishment of special diets for each ecological region of the country, based on local foodstuffs;
2. The nutritional value of local foodstuffs;
3. The exploitation of a closed ecological system (gardening - husbandry - pisciculture) for families and small collectives to contribute a supplementary source of proteins, lipids and vitamins;
4. Applied nutrition in organization and food technology in solving energy problems in the countryside;
5. Child nutrition; and
6. Nutritional diets in hospitals.

Cadre training and nutritional education play a special role in the program. The creation of 12 pilot villages in different ecoregions (delta, normal, mountainous, plateau, coastal, new economic zone) from north to south Viet Nam, as well as the creation of models of nutrition collectives in the cities and factories are places where the program promoters will concentrate their attention.

The experience of these pilot programs will be disseminated throughout the country for development and for the final goal of intensifying agricultural production, reducing the rate of population growth, increasing the consumption of foodstuffs for each person and ameliorate the nutritional situation of the Vietnamese people in its entirety.

The author is Director of the Institute of Nutrition and the State Program for Popular Nutrition.

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REPORT ON THE VISIT BY DR HA HUY KHOAI (April-May 1982)

Neal Koblitz

In Seattle, Dr Ha Huy Khoai gave two seminar talks during his two weeks at the University of Washington: (1) p-adic meromorphic functions; (2) a new construction related to the Kuzin problem in several complex variables. The work described in the first of these talks is the first major attempt to work systematically with interpolation by p-adic meromorphic functions. The work arose partly in response to a problem posed by Professor B Mazur of Harvard, and partly because of the natural desire to carry over some very basic facts from complex analysis to the p-adic domain. This work interests me and other algebraic number theorists (especially R Greenberg) because much of our own work has been related to problems in p-adic interpolation and Gauss sums. The University of Washington happens to have active groups of researchers in both of Khoai's major interests (number theory and several complex variables). The second seminar talk, on the Kuzin problem, was very well received by the group working in several complex variables (L Stout, J Morrow, J King). Even though this work had been done by Khoai about nine years ago, it was only published in Vietnamese, was unknown in the West, and had not been superceded since that time. Stout and King suggested that he publish it in a European language.

At Harvard, a special seminar was scheduled, so that Khoai could present his work on p-adic Nevanlinna theory to the Harvard mathematicians. I have since spoken with Prof Mazur, who told me that the talk went very well. He and Prof Tate (the two leading number theorists at Harvard) had numerous discussions with Khoai during his visit. In particular, Mazur gave him some advice on further directions of research that he might want to pursue. Here, Khoai wrote the first draft of a short article on his construction of the inverse Mellin-Mazur transform, and also started work on a major article on p-adic Nevanlinna theory. The latter article has since been completed, and will be submitted to the "Duke Mathematical Journal". Prof Mazur commented to me that it would be good for Khoai to publish in American or European journals so that Western colleagues are in touch with what he is doing. Khoai did extensive library research, taking advantage of his five-week stay in a math department office at Harvard right near library facilities which in many respects are even better that what's available in Moscow. In addition, he attended several seminars, and reacted very favorably to the mathematical atmosphere at Harvard. Besides Moscow, the main centers of research in his field are Harvard, Princeton and Paris. Khoai was struck by the international environment at Harvard, in particular, in the Mathematics Department. The graduate students and other mathematicians come from many countries, including Thailand, China and India.

Khoai gave a talk at Princeton's weekly algebra seminar on his p-adic Nevanlinna theory. The talk was very well attended, and I have heard several favorable reactions from my acquaintances who were there. Khoai met many mathematicians both at the Institute for Advanced Study and at Princeton University, including key people in his field, such as B Dwork, P Robba and N Katz. Most of Khoai's week-long visit to Princeton was hosted

by the Bulgarian mathematician Andrei Todorov (probably the leading mathematician of his generation in Bulgaria), who was at that time visiting the Institute for Advanced Study. Todorov was helpful in introducing him around. Over the years, Todorov has served as a bridge between East and West in certain fields of mathematics, and he has now become interested in mathematics in Viet Nam. For a few days, Khoai stayed with the Slaby family, and much enjoyed their hospitality.

It is clear from the above discussion that Dr Khoai's visit to the U S was highly successful both in relation to his own research program and from the standpoint of developing relations between the Vietnamese and American mathematical communities.

I was able to have extensive informal discussions with Khoai about the situation in Vietnamese mathematics. I also have a better idea of what books and supplies are needed. I understand that the earlier problem in administration of the Hanoi Mathematics Institute library is now cleared up, so that I can feel more confident that books donated will be well used. In addition, it is clear that books should only be shipped in the Committee's shipments, if possible personally accompanied to Hanoi. There are still great problems in shipping things to Viet Nam by the ordinary postal routes.

Quite correctly, Viet Nam's primary emphasis is in applied areas of science. But it shows impressive foresight on their part that they give support and encouragement to someone who works in a highly abstract area of research. Even though Khoai's work, and the specific fields he studied while in the U S, have no bearing on Viet Nam's practical problems, his scientific success brings prestige to Viet Nam, and his visit has led to increasing interest in Viet Nam on the part of an influential group of American intellectuals. Moreover, applied mathematics can only flourish in an environment in which basic research and "pure" mathematics are also emphasized. The interrelation and interaction between various branches of mathematics, and between pure and applied mathematics, is so extensive that no particular branch of mathematics is likely to develop in isolation from the mainstream of pure mathematics. In addition, it should be noted that pure mathematics, unlike most applied sciences, does not require a large capital investment. Thus, Viet Nam can relatively "cheaply" attain a high level of development and a good international reputation in mathematics, especially in view of the already high calibre of the specialists in the field and the mathematical traditions that have been established in Viet Nam. It would be much harder for Viet Nam to develop international prominence in, for example, DNA research or particle physics. Thus, it is in Viet Nam's long-range interest to continue to support and encourage researchers in both pure and applied mathematics. Perhaps this is obvious and unnecessary to state; however, it is interesting to note that among the developing countries only India, China and Viet Nam support mathematical development at a high level (as far as I am aware). Mathematicians I have talked with about Viet Nam are always surprised and impressed to learn of the high level of mathematical activity that Viet Nam has been able to sustain despite all the years of war and hardship.

The author is with the Department of Mathematics, University of Washington, Seattle, and coordinates Committee activities in mathematics and computer science.

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Excerpts from: Second Notice of the I F I P WORKING CONFERENCE ON ADVANCES IN SYSTEM MODELING & OPTIMIZATION Hanoi, 10-14 Jan 1982

The following have been confirmed to present invited lectures: J P Aubin (France), A V Balakhrishman (USA), K H Elster (GDR), Yu G Evtushenko (USSR), D Hinrichsen (FRG), Huynh H T (Canada), Hoang Tuy (Viet Nam), S E Jacobsen (USA), R Kluge (GDR), N Levan (USA), J L Lions (France), N N Moiseev (USSR), P Nepomiastchy (France), M Peschel (GDR), Phan Dinh Dieu (Viet Nam), O F Vasiliev (USSR).

A limited number of contributed papers will be presented in afternoon sessions, following the invited lectures. The time limit for each contributed paper is 30 minutes (including discussion).

All participants and companions are kindly invited to a welcome party on Monday evening (Opening day, 10 January). A Conference dinner will be held on Thursday evening (13 January).

Sightseeing tours will be arranged by the Viet Nam Travel Agency. A trip to the famous Bay of Ha Long will be organized on Saturday, 15 and Sunday, 16 January.

Immediately following the Conference, a short Winter School on "Systems Analysis and Optimization" will be held in Hue, the old capital of Viet Nam, from 17 to 24 January. This Winter School, sponsored by the Viet Nam Center for Scientific Research in conjunction with the Academy of Sciences of the GDR, is intended to introduce young research workers to the current state of the art in Systems Analysis and Optimization.

AMERICAN UNIVERSITIES AND VIET NAM

Pham Huy Thong

I had just arrived in Honolulu, just set foot on American soil, when I had the opportunity to glance through a catalog of more than 200 books of research on Asia, distributed by the University of California Press. In among the listings for art, history, political science, business and economics, literature and language, philosophy and religion, sociology and humanities was a listing headed "Viet Nam". In contrast to the books on Japan, China, India, Thailand and Indonesia, which were scattered through the various categories, the books on Viet Nam were set apart in a section of their own.

It was a real pleasure to see that the topic of Viet Nam received such special attention, with each project introduced quite attractively. Here was one on the roots of the Vietnamese nation through the 10th Century; another dealt with the upheavals in traditional Vietnamese society during the years of the resistance against French colonialism, then the momentous period of the August 1945 Revolution; yet another contained the animated recollections of American special representative Archimedes Patti about the Viet Minh, about President Ho Chi Minh, and about the days which gave birth to the Democratic Republic of Viet Nam.

Professors Solheim and O'Harrow, who met our delegation of Vietnamese social scientists at the Honolulu airport, on the Hawaiian islands, said that the study of Viet Nam is making remarkable progress, not just in California, but throughout the United States.

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Honolulu, for example, is also a center of research on Viet Nam.

Here, American archeologists are prepared to coordinate their work with Vietnamese scientists to shed light on the ancient Hoa Binh culture which, some 10,000 years ago, left its traces in what is now Viet Nam -- a definite advance in the human race. That culture, known to French researchers for 50 years, needs to be reconsidered and reevaluated in light of recent discoveries we have made in Viet Nam and discoveries made by Americans and others in Thailand. There are also American documents on the Kalanay culture in the Philippines, which may be comparable to documents we have on the Sa Huynh culture in our own country. And the remains of ancient people which Americans have collected in the Pacific and Southeast Asia may be comparable to remains discovered in our country.

One area in which there is close agreement between American scholars in Honolulu and Vietnamese researchers in history and literature is in recognizing and analyzing the attachment of the Vietnamese people to their national territory through the ages. In researching exemplary patriots in each patriots, discussing Shih Naieh or Nguyen Trai, discussing "nom" characters or the "quoc ngu" alphabet, both sides consider that the awakening of various successive generations in Viet Nam as they created a culture was also a process of fortifying the foundations of a national identity. Another point worth noting about Vietnamese studies in Honolulu is its wide-ranging nature. Alongside history they study literature and language. There have been initial efforts to translate and introduce Vietnamese poetry. There is research into the structure of the Vietnamese language and other languages of Viet Nam such as Muong and Hmong, through the prism of modern theories of semantics and grammar.

Hawaii and California -- universities in America's West, looking out towards Asia -- are developing Vietnamese studies. At the same time the development of Vietnamese studies in America is not determined by geography; it has its roots in history.

At one time, now long past, a number of American universities carried out psychological warfare research for the benefit of the American expeditionary forces in Viet Nam. That effort led to results which are clear to everyone: American social scientists did not wait until 1973 or 1975 to change their orientation, to begin research into the history and culture, the people and society of Viet Nam in the "post-Viet Nam" spirit of today.

The military defeat, the total defeat of American imperialism in Viet Nam jolted the American public and American intellectuals into an awareness of the reality of Viet Nam. A small nation, restrained for many years by poverty, backwardness and oppression, and yet it dared stand up to the United States, one of the great powers, and had the strength to keep up the battle until it fought its way free -- such a nation deserved consideration and careful research. That conclusion, that attitude, is shared by many American social scientists, even some who once confronted us on the battlefield. Research and teaching on the history, psychology, culture and arts of Viet Nam, seeking out Vietnamese studies of history and culture and other achievements of Vietnamese social scientists -- these are not limited to universities in the

West, nor are they only the concerns of small research centers or individual scholars. A movement for Vietnamese studies is spreading through many American universities.

Is it possible to consider another step forward? At the scholarly conference which the American Association for Asian Studies recently organized in Chicago, scholars from the Soviet Union, China and a number of other Asian countries participated. Viet Nam was invited to present a paper and defend its archeological principles and arguments. Only archeology this time. But after that, in meetings with the Coordinating Committee for Vietnamese Studies in America, and in visiting many American universities and social science research centers, our Vietnamese delegation had the opportunity to explain to large numbers of our American colleagues how we organize, teach and carry out research in the social sciences in Viet Nam. We were also able to gain an understanding of the basic characteristics of the development of social sciences -- especially Vietnamese studies -- when we met American scholars in Chicago, New York, Boston, Cambridge, Philadelphia, Los Angeles, Honolulu and many other places.

History is given first importance. Ancient history, and modern history. John Withmore, Keith Taylor, Holmgren, O'Harrow, Wolters -- from the Asiatic mode of production in the Red River delta and the Dong Son culture to Chinese characters, "nom" characters, Tran literature, and the writing of Nguyen Trai, the field of Vietnamese studies in America, with the scholars mentioned above, is demonstrating the distinctive cultural and artistic accomplishments of the various generations of ancient Vietnamese who, step by step, created our unique national characteristics, our capacity as a nation to stand resolute. Likewise, David Marr and Gary Porter, Jayne Werner and Karl Thayer, William Duiker and George Kahin, Tice and Jeffrey Race are presenting the history of Viet Nam in recent decades -- the history of the Vietnamese revolution, from the fight against the French to that against the United States, in all its sweep, its excitement, its wonder. History is the greatest strength, especially at such major universities as Cornell, Yale and Berkeley. The famous univerasity Harvard has emphasized literature. After efforts spanning many years, this June they organized a conference of scholars on Vietnamese literature prior to the August (1945) Revolution. The organizers realized that, even though it was a week-long conference, with very serious debates, these sessions could only give an overview, a "kindergarten" view. But they hoped that once the issues were unearthed and spread around -- from the affirmation of the "quoc ngu" alphabet in the journal "Nam Phong" and the Self-Reliance Literature Group to the Communist Party's thesis on literature -- and with a number of Vietnamese scholars participating, the conference could perform a certain useful function: opening the way to seeking a deeper understanding of Viet Nam through Vietnamese perceptions of themselves.

Enthusiastic research on Viet Nam, which first began to bloom in the antiwar movement, did not decline after the end of the war. Instead it has spread and grown more enthusiastic in recent times, with the discovery of a number of unique characteristics of the civilization and the national traditions of Viet Nam. In Vietnamese social sciences the "human sciences", literature and history, are

now the most attractive to Americans. In the recent past, because of the preasure of public opinion, more than a hundred centers of teaching or research on Viet Nam received government support. Now, the Reagan administration, in order to fuel the arms race, has a policy of decreasing the budget for culture, science and education, which has hit budgets for Vietnamese studies hard. They have agreed to fund fewer than 40 centers. Researchers and teachers in the Vietnamese studies field have reacted sharply.

What has sparked this spirit of struggle? After nearly a month in the United States, talking with hundreds of American scholars, I can affirm: it is a heartfelt respect for our people, a deep enthusiasm for trying to understand our people, our society and our civilization. It is not true that Americans, who do not have a long-lived culture of their own, do not know how to appreciate old cultures. For Americans, the Hoa Binh and Dong Son cultures and the literature of the Ly-Tran period are marvels.

But this is not all there is to it.

There are some progressive Americans who are grateful to Viet Nam for, by their struggle, awakening Americans to the issue of morality in foreign policy. To them, honor for the United States does not mean using its strength to put obstacles in the way of other peoples, but respecting every nation, whether large or small, guaranteeing a life of peace and equality among the peoples of all countries. The lesson to be drawn from the aggressive war in Viet Nam is that America acted contrary to morality, and for that reason was defeated and lost credibility in the world. Now those very circles in America who are eager to intervene in other countries, like El Salvador, are insisting, "El Salvador is not Viet Nam", at the very time when, more than ever, it is impossible to disregard the lessons of Viet Nam. Recognizing that, it is very commendable that two history professors in New York, who have taught about Asian history but not about Viet Nam because it is outside their specialization, have had discussions about revising their program beginning next year to teach about Viet Nam.

Other well-informed Americans think that, whether or not Americans like Viet Nam's course of development, still Viet Nam -- with its past civilization, with its role in recent history, with its current population -- holds an important position in an Asia on the threshold of the 21st Century. Immediately, is it possible to continue forever the current situation with Southeast Asia divided into two opposing blocs without endangering the common security? Or to put it the other way round, if people want Southeast Asia to become a peaceful region and -- along with Southeast Asia -- want all of East Asia, South Asia and the Pacific to enjoy quiet under the stars and across the waves, then how can they belittle Viet Nam and not make an effort to gain a deep understanding of the reality of Viet Nam?

Then there are some Americans -- teachers and researches, and even a considerable number of young people -- who are heatedly demanding a continuation of university teaching and research on Viet Nam, because Viet Nam has become linked with their personal interests. Every research center which is shut down or which had to reduce its activities means a number of people

ut of work, a number of books which cannot be written or printed. Yet there are Americans, and their number is not small -- scholars, intellectuals, entrepreneurs or social activists -- who have linked their interests and their future with Viet Nam, an inseparable part of the Asian continent and of tomorrow's world.

Faced with the danger of being pushed back a step, the area of Vietnamese studies is defending itself with determination -- because of the personal interests of the scholars, because of the long-term interest of the United States, or for reasons of morality, of scholarship or of personal attraction. If it cannot yet develop, cannot yet expand, then so be it, but don't narrow it, don't decrease it.

So in discussions with us, their Vietnamese colleagues, both sides were looking forward, not back. We must strengthen our relations, that is a point of clear determination: exchange publications, exchange documents; exchange researches to present papers, lead seminars, participate in symposia, train and give refreshers for young cadre, organize exhibits and performances. There is no lack of difficulties, and the numbers are not small: language, travel and material resources. All the same, in our discussions the determination and enthusiasm were central.

But the enthusiasm was there already. We saw that clearly when we arrived. I will risk saying that when we left, the enthusiasm was turning into determination. Our American friends were thinking: if we have the cooperation of Viet Nam, Vietnamese studies in America will not stop with projects of simple, superficial description, but can be precise, looking beneath the surface in a truly scientific fashion.

The desire of many American intellectuals who are actively building the field of Vietnamese studies is thus linked closely to scholarly cooperation with their colleagues in the social sciences in Viet Nam. The U S Committee for Scientific Cooperation with Viet Nam will be able to make practical contributions to putting this principle into practice.

The current struggle to develop the field of Vietnamese studies in America is to our country's advantage, to the advantage of the American people, and to the advantage of the progressive world. Scholars of the two countries want to join hands and work together. The national leadership of the Association for Asian Studies respectfully received our gifts from Viet Nam -- two artifacts representative of the products of the Dong Son culture -- and announced that they were "a very gracious gesture", "evidence of the friendly spirit of the Socialist Republic of Viet Nam". People at the Museum of the University of Pennsylvania were deeply moved when I came to visit the place where Chester Gorman, the famous American archeologist, struggled to work during the last years of his life, after he was taken dangerously ill, so I could write a few lines to express the friendship and the high regard for his scholarship felt by his Vietnamese colleagues. Experiences like these from the short period of my recent visit to America are surely a fine opening toward a promising cooperation.

The author is Vice-Director of the Viet Nam Social Sciences Commission. He visited the U S in April 1982 with his colleague DINH GIA KHANH, Director of the Folklore Institute. Translation is by JOHN SPRAGENS.

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REPORT ON THE CONFERENCE 'A CRITICAL EXAMINATION OF THE VIET NAM EXPERIENCE SINCE 1975' Amsterdam, 4-6 Jun 82

Jayne Werner

The purpose of the Conference was to bring together aid organizations working in Viet Nam, "solidarity organizations", academic specialists concerned with Viet Nam, and officials from Viet Nam, to discuss Western aid to Viet Nam and contemporary economic issues. The conference was organized by the Transnational Institute, the European affiliate of the Institute for Policy Studies in Washington, DC. The representatives from Viet Nam were Hoang Nguyen, editor of the "Viet Nam Courier", and Dao Van Tap, Director of the Economics Institute of the Social Sciences Commission. oth are from Hanoi. There were 40 to 50 Western participants, from aid organizations, universities, and the press. They came from several European countries and the United States.

The conference opened with a public session discussing Western aid to Viet Nam. The speakers were Hoang Nguyen, who made general remarks on Viet Nam's aid needs. Eric Wulff, a long-time activist from Germany, Lennart Klackenberg, a former member of the Swedish Parliament, and Charles Fourniau, Chairperson of the French-Vietnamese Friendship Association, talked about aid programs from their respective countries to Viet Nam. Nayan Chanda, the diplomatic correspondent for the "Far Eastern Economic Review", discussed the economic problems faced by Viet Nam. There was a brief exchange between Hoang Nguyen and anda on journalists obtaining frank and accurate information from Vietnamese officials, which led to a discussion on the relationship between accurate reportage and assistance to Viet Nam. This theme came up again in the conference and, given the diversity of the participants, was not ultimately resolved. The conference's theme was criticized by some of the participants. Others suggested that one cannot be a "friend" of Viet Nam (since Viet Nam is a state, with which it is anomalous for individuals and groups to be "friends"), although there can be sympathy toward Viet Nam. Dao Van Tap said that "we accept criticism which helps understanding". It was agreed, however, that all the participants shared the objective of working toward breaking the U S economic blockade and diplomatic isolation of Viet Nam.

The working sessions led to a detailed discussion of the current difficulties, the food situation and the nature of the new economic reforms that have been instituted. The resolutions of the Fifth Party Congress were analyzed. The role of the market in the economy and the process and problems of industrialization were brought up.

The seriousness of the current economic difficulties came out most forcefully. Viet Nam will have difficulty moving forward, or even staying in the same place, without foreign assistance. Foreign aid is critical to a solution of the food problem. Internal domestic conditions were particularly highlighted, giving us a greater understanding of the obstacles Viet Nam faces. The conference also brought out that Viet Nam is currently facing a "war of sabotage" by the U S and its northern neighbor, and is suffering greatly for it. International events pose the greatest problems for economic development.

The point was brought out that

there is a strong relationship between development and national defense. The resolutions of the Fifth Party Congress decided Viet Nam should devote its resources equally to national defense and socialist construction. It also made decisions relating to the relationship between agriculture and industry, the inclusion of the south in the socialist revolution, policies on consumer goods, and technical/scientific aspects of economic development. These resolutions continue to stress industry as the central task, but in the 1980's, the Party will concentrate on agriculture. This will be accompanied by the production of consumer goods and the selective building of some sectors of heavy industry. Viet Nam will continue the three-fold revolution in ideology, culture and science/technology. "Socialism" in Viet Nam still means wide-scale industrialization.

In response to a paper on the Fifth Party Congress, Hoang Nguyen said that the Congress looked into the mistakes made by its leadership. The "subjective" reasons for the failure of economic policies were publicly recognized. These mistakes were attributed to inadequate knowledge of conditions and inexperience in economic management. In 1979, at the sixth plenum of the Fourth Party Congress, new methods of economic management were introduced and were developed further at the recent Congress. Hoang Nguyen said, "we recognize the failures we've made, but we count on making less and less". He also said that Viet Nam has much less outside aid than before.

Other presentations pointed out that the main economic problem is the crisis in food production. As a result, a new contracting system has been introduced in the agricultural cooperatives. Quotas and piece-work have been instituted. In some places, these new methods have been in operation for two years. The idea is to link the self-interest of individual peasants to production, or rather to the volume of food produced. Hoang Nguyen mentioned that the objective of these changes is to increase agricultural production so that the import of grains can be terminated.

Viet Nam's leaders have admitted that there is a serious economic crisis. There has been a recovery since 1978, but the level of production in that year was still lower that in 1966. Imports will be needed at least until 1985. This means continued overseas aid, given the problem of balance of payments. 1981 was a good year for rice production, but overall yield was still low, which was 180 kilograms of paddy per person.

As to the potential of the new contracting system to get Viet Nam out of its agricultural production difficulties, a Vietnamese residing in the West expressed pessimism that this would be a long-term solution.

An interesting presentation was given by Fethi Benammer during a discussion of the industrialization process. Benammer is an engineer who spent three years in Viet Nam on a German-funded project. A spinning plant was built in Hanoi, which officials admitted to Benammer was meant to be a showcase both for foreigners and for the local population. But the plant construction faced numerous difficulties. It took several authorizations to move small quantities of supplies, since the officials with whom the crew worked seemed to try to avoid responsibility for making decisions. There were also great diff[illegible] with the work force which lacked the necessary respect for the machinery in the plant. It was not a matter

United States
Environmental Protection
Agency

Office of Water
Regulations and Standards
Washington, DC 20460

EPA 440/5-84-007
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Water

EPA

Ambient Water Quality Criteria for 2, 3, 7, 8 - Tetrachloro-dibenzo - p - dioxin

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AMBIENT WATER QUALITY CRITERIA FOR

2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

Office of Water Regulations and Standards
Criteria and Standards Division
Washington, D.C.

Office of Research and Development
Environmental Criteria and Assessment Office
Cincinnati, Ohio

Carcinogen Assessment Group
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Reproductive Effects Assessment Group
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Environmental Research Laboratories
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Gulf Breeze, Florida
Narragansett, Rhode Island

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INTRODUCTION

The major source of 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) (CAS Number 1746-01-6) appears to be as a contaminant formed during the production of 2,4,5-trichlorophenol (2,4,5-TCP) from 1,2,4,5-tetrachlorobenzene (Milnes, 1971; Kimmig and Schulz, 1957; Firestone et al., 1972). 2,4,5-TCP is the major chemical feedstock in the production of several herbicides including 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 2,4,5-T esters and Silvex. Each of these chemicals may contain 2,3,7,8-TCDD as a contaminant (Buser and Bosshardt, 1974; Courtney et al., 1970; Edmunds et al., 1973; Zitko and Choi, 1971). It has also been reported that 2,3,7,8-TCDD may be formed during the pyrolysis of chlorinated phenols (Buu-Hoi et al., 1971a,b), chlorinated benzenes (Buser, 1979) and polychlorinated diphenyl ethers (Lindahl et al., 1980), and thus can also be emitted by municipal incinerators (Rappe et al., 1983a; Lustenhouwer et al., 1980; Olie et al., 1982, 1983). There is no clear evidence that 2,3,7,8-TCDD is a typical contaminant in the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) (Woolson et al., 1972; Henshaw et al., 1975; Cochrane et al., 1981).

Physical Properties

2,3,7,8-TCDD is a symmetrical, nearly planar molecule with the empirical formula $C_{12}H_4Cl_4O_2$. The four chlorine atoms are indistinguishable from one another (Poland and Glover, 1973). 2,3,7,8-TCDD is a white crystalline solid with a melting point range of 302-305°C (Sparschu et al., 1971; Elvidge, 1971) and has a molecular weight of 321.9. The vapor pressure of this compound is estimated to be 10^{-6} mm of Hg (0.1 mPa) at 1 atmosphere and 25°C (Mabey et al., 1981). The Henry's constant has been estimated to be 2.1×10^{-3} atmosphere $m^3 \cdot mol^{-1}$ (Mabey et al., 1981). 2,3,7,8-TCDD is lipophilic, exhibiting some solubility in fats, oils and

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other relatively nonpolar solvents, and is only slightly soluble in water (0.2 µg/ℓ) (Crummet and Stehl, 1973; Norris, 1981). The solubility of 2,3,7,8-TCDD in various organic solvents is given below (Crummet and Stehl, 1973):

Solvent	Solubility (ppm)
lard oil	44
benzene	570
o-dichlorobenzene	1400
chloroform	370
acetone	110
n-octanol	50
methanol	10

The partition coefficient of 2,3,7,8-TCDD in a water:hexane system has been reported to be 1000 (Matsumura and Benezet, 1973). The octanol/water partition coefficient (K_{ow}) has been calculated by the methods of Hansch and Leo (1979) and has been experimentally measured. Calculated values for log K_{ow} range from 6.84-7.28, and a measured value of 6.15 has been reported (see Section B, Bioaccumulation).

Cocontaminants of 2,3,7,8-TCDD in Chlorinated Products

2,3,7,8-TCDD is only one of many trace contaminants found in some chlorinated industrial products including a few chlorinated phenols, a few chlorinated phenoxy acids (especially the herbicides 2,4,5-T and Silvex) and hexachlorophene. Among the other trace contaminants found in these products are members of the polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), polychlorinated diphenylethers (PCDPEs), polychlorinated phenoxyphenols (PCPPs), polychlorinated biphenyls (PCBs) and polychlorinated benzenes (PCBz). Of these, some possess properties that make them difficult to separate analytically from the 2,3,7,8-TCDD isomer (Kimbrough, 1974; U.S. EPA, 1980; Bumb et al., 1980; Rappe et al., 1983b).

Synthesis

2,3,7,8-TCDD has been synthesized by several methods in moderate yield (e.g., reaction of dichlorocatechol salts with o-chlorobenzene by refluxing in alkaline dimethylsulfoxide; chlorination of dibenzo-p-dioxin in the presence of ferric chloride and iodine; UV irradiation of PCDDs of high chlorine content; Ullman reaction of chlorinated phenolates at 180-400°C; pyrolysis of chlorinated phenolates and chlorinated phenols; heating 1,2,4-trichloro-5-nitrobenzene and 4,5-dichlorocatechol in the presence of base). These processes have been reviewed in U.S. EPA (1980).

Chemistry

2,3,7,8-TCDD is considered to be relatively stable toward heat, acids and alkalies. It begins to decompose at 500°C, and at a temperature of 800°C, virtually complete degradation occurs within 21 seconds (Stehl et al., 1973). From a theoretical equation for thermal dissociation constant

$$K = 10^{15.5} \exp(-80{,}000/RT) \text{ sec}^{-1}$$

K = dissociation constant, R = universal gas constant, T = temperature for tetrachlorodibenzo-p-dioxins formulated by Staub and Tsang (1983), the 99.99% gas phase dioxin dissociation at 727°C will require about 15.4 minutes. The same equation predicts a 99.99% decomposition of tetrachlorodibenzo-p-dioxins in 0.3 seconds at 977°C. Gamma radiation degrades the molecule (Fanelli et al., 1978). 2,3,7,8-TCDD can be perchlorinated (Hutzinger et al., 1972).

2,3,7,8-TCDD is transformed very slowly in aquatic systems. Of the four transformation processes (photoreaction, biotransformation, hydrolysis and radical oxidation) that control the fate of a chemical in aquatic media only the first two processes are throught to effect the transformation of 2,3,7,8-TCDD (Matsumura et al., 1983). In organic solvents, 2,3,7,8-TCDD undergoes reductive photodechlorination at wavelengths <320 nm (Crosby et

al., 1971; Liberti et al., 1978). In aqueous solution hydroxylative dechlorination probably occurs, although this has not been seen. Liberti et al. (1978) showed that 2,3,7,8-TCDD spread over silica gel, aluminum, glass, ceramic tile and marble in the absence of an organic solvent showed various decomposition rates on UV irradiation. Little decomposition occurred on glass or marble, but substantial degradation occurred on silica gel and aluminum. Also, 1:1 ethyl oleate/xylene was found to be a satisfactory H donor. Plimmer et al. (1973) reported that a 2,3,7,8-TCDD suspension in distilled water remained unchanged when irradiated with a sunlamp. Similarly, a thin dry film of 2,3,7,8-TCDD on a glass plate or 2,3,7,8-TCDD on dry and wet soils showed negligible photodegradation after irradiation with sunlamps (Crosby et al., 1971). In contrast, 2,3,7,8-TCDD in methanol solution, or a benzene solution of 2,3,7,8TCDD in water in the presence of a surfactant underwent substantial photodegradation under sunlamp or sunlight irradiation (Plimmer et al., 1973; Crosby et al., 1971). Nestrick et al. (1980) experimentally determined the photolytic half-life of 2,3,7,8-TCDD in n-hexa-decane under sunlamp irradiation to be ~57 minutes. The surfactant, 1-hexyldecylpyridinium chloride, sensitized the photodecomposition in aqueous solution (Botre et al., 1978). The evolution of 2,3,7,8-TCDD from more highly chlorinated PCDDs on UV irradiation from sunlight is unlikely since dechlorination in organic solvents and in the presence of artificial UV sources occurs preferentially at the 2,3,7,8-positions (Buser and Rappe, 1978; Nestrick et al., 1980).

Analytical Methods for TCDD

Most of the current analytical methods used for the identification and quantitation of 2,3,7,8-TCDD are based upon gas chromatography/mass spectrometry (GC/MS). This method provides both high sensitivity (detection at

February 27, 1984

Steve or Ed,

Enclosed please find your copy of 1) additional expanded summaries as requested by Shindlin, and Ed, since our copies were (originals) were missing pages

I have sent the court a copy, you must have enough copies to send to Service List (all Defendants and Plaintiffs Mgmt Committee

2) Plaintiffs' Government Causation Witnesses and Compliance with US Guideline page 34, as order ed by Judge Weinstein, including copies of the EPA Documents 1983 - these must be copied and hand delivered to all Defendants and our committee no later than 2pm February 27, 1984

3) A copy of Alistair Hay expanded Summary for Benton along with a portion of the transcript from Nov. 21, 1984 regarding Thompson Request for Summary Judgement, and its denial for Benton.

Please have these xeroxed Monday and passed out. We have sent a copy to Ms. Gretchen Witt, US Dept of Justice, Washington DC and to the Court so we could begin the deposition on Thursday, March 1, 1984 and have complied with his Honor's ruling.

Thanks, Alison

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37.

DEBORAH A. BARSOTTI, Ph.D.

I. QUALIFICATIONS

Dr. Barsotti is an Assistant Professor of Tocicology in the Department of Pharmacology and Toxicology of the Philadelphia College of Pharmacy and Science in Philadelphia, Pennsylvania. Her curriculum vitae is attached.

II. SUBJECT MATTER

Dr. Barsotti is a toxicologist who has done substantial personal investigative work with halogenated aromatic hydrocarbons. This category of chemicals includes various biphenyls and dioxins, and specifically includes tetrachlorodibenzo-p-dioxin (TCDD). She will testify as to the relative chemical stability and lipophilicity of these chemicals as well as their resistance to degradation, and will testify that these qualities are what account for the perceived and documented bioaccumulation of the chemicals in the human system. Dr. Barsotti will emphasize the difference in results between chronic and acute exposures to these chemicals, testifying as to the varying types of responses to acute and chronic exposures.

Dr. Barsotti will discuss her own work as well as review the literature in these areas, noting differences in routes of

administration, and in the species and genetic strain of the animals involved. She will explain these variations and where they permit extrapolation of results from animals to humans. In particular, Dr. Barsotti will also testify as to the similarities in response to these chemicals by rhesus monkeys and by humans, and will explain how the similarities permit extrapolation in this instance.

Dr. Barsotti will also discuss reproductive toxicity, teratology and post-natal toxicity, including instances where no gross or clinical signs of maternal toxicity could be detected.

III. SCIENTIFIC PRINCIPLES

See General Statement of Scientific Principles and Assumed Facts attached.

IV. SUBSTANCE OF OPINIONS

A. That dioxins are toxic, and in particular TCDD is exceptionally toxic.

B. That dioxins bioaccumulate because of their chemical stability, lepophilicity, and resistance to degradation.

C. That chronic low level exposure to dioxins is significantly toxic.

D. That TCDD accumulates and persists in the lipid stores.

E. That TCDD, in chronic doses, is toxic, is particularly toxic to reproductive system, is teratogenic, and is fetotoxic.

F. There are ample scientific bases, for extrapolating animal experimental data to man, in the case of TCDD, for example, as demonstrated by Dr. Barsotti's work on rhesus monkeys.

V. GROUNDS FOR EACH OPINION

A. General

Review of applicable medical and scientific literature; education and training; personal research. The work on the chronic toxicity of HAHs in rhesus monkeys has culminated in numerous publications as presented in Dr. Barsotti's curriculum vitae. In addition, she has been invited to speak or present her work in various atmospheres including community meetings and scientific symposia.

B. Specific

1. With respect to opinion IV A, see generally references attached.

2. With respect to Opinion IV B, note the following:

In the course of Dr. Barsotti's graduate and post-graduate studies, she has had the opportunity to conduct research and evaluate others' work on members of the class of chemicals called halogenated aromatic hydrocarbons (HAHs). She will discuss the fact that this class of chemicals includes the chlorinated dibenzo-p-dioxins and the halogenated biphenyls (polychlorinated and polybrominated biphenyls) and that HAHs are similar in chemical structure, in the pattern of toxic responses that they produce and in the mechanism by which they are believed to act (Allen et al., 1979; Poland and Knutson, 1982). Although individual HAHs vary in potency, their chemical stability and lipophilicity, as well as their resistance to degradation results in bioaccumulation (Isensee and Jones, 1975; Meselson et al., 1978; Marinucci and Bartha, 1982; Mes et al., 1982).

3. With respect to opinion IV C, note the following:

Thesis work performed by Dr. Barsotti at the University of Wisconsin with polychlorinated biphenyls indicated that evaluation of the toxic effects of HAHs in the Rhesus monkeys was valuable to the understanding of the potential hazards of HAHs in the environment (i.e. chronic exposure). In addition, this work indicated, unlike rodent models, that there were similarities in the response of humans and rhesus monkeys to these chemical toxicants (Barsotti, 1980). Like man, the rhesus monkey is genetically diverse and responded to PCB exposure on an individual basis.

Dr. Barsotti will contrast the acute toxicity that one observes in accidental or intentional ingestion of toxic or lethal doses of chemicals with the effects of chronic or lower levels of exposure to chemicals such as HAHs.

4. With respect to Opinion IV D, note the following:

Dr. Barsotti will comment on the state of the literature on the fate of TCDD once in the body, i.e. TCDD metabolism (Vinopal and Cassida, 1973; Ramsey et al., 1979; Schlatter, 1979). Efforts to identify metabolites in tissues and excreta from various studies have been unsuccessful. Recent advances in detection methodology indicate elevated levels of TCDD in Vietnam veterans and other exposed persons. Generally, however, the data indicate that if metabolism does occur the rate is slow (Guenthner et al., 1979). The ramification of this finding is that the body would be incapable of or slow in ridding itself of TCDD and TCDD would accumulate and persist in the lipid stores. In Dr. Barsotti's work, as well as others', this appears to be the case with rhesus monkeys and man (Montagna et al., 1979; Van Miller, 1981; McNulty et al., 1983).

5. With respect to opinion IV E, note the following:

Not only did the rhesus monkey appear a good model for HAH toxicity but established, as had been in other animal species, that the reproductive system was extremely sensitive to PCBs at intake levels below that required for the manifestation of toxic signs in the adult (Barsotti et al., 1976). In addition to PCB induced reproductive toxicity, PCBs were found to be fetotoxic

three months in animals receiving TCDD in the diets at levels of 500 parts per trillion (ppt) and in animals consuming diets containing 50 ppt TCDD these same symptoms occurred after consuming the diets for 30 months (Allen et al., 1977; Schantz et al., 1979). This indicates cumulative toxicity associated with ingestion of TCDD. Thus, there is evidence for bioaccumulation and associated chronic toxicity at lower doses than that required for acute toxicity in rhesus monkeys and presumably man (Pazderova et al, 1981; Ideo et al., 1982.)

6. With respect to Opinion IV F, see generally references attached and V A above.

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ALASTAIR W. M. HAY, Ph.D.

I. QUALIFICATIONS

Dr. Hay is a lecturer on Chemical Pathology, Department of Chemical Pathology, Old Medical School, University of Leeds, Leeds, England. His Curriculum Vitae is attached. A list of seminars, meetings and awards is also attached.

II. SUBJECT MATTER

Dr. Hay will provide background testimony on a broad range of matters relating to Agent Orange, phenoxy herbicides, and their contaminants, including 2, 3, 7, 8-TCDD.

Dr. Hay will discuss in detail his knowledge of the various phenoxy herbicides and their contaminants, including but not limited to the various aspects of: chemistry; biochemistry; manufacture and/or production; fate in the environment, animals, and humans; modes of exposure, i.e. absorption, ingestion and inhalation, specifically by the veterans who served in Vietnam; toxicity; and the state of the medical and scientific literature at various times since at least 1957 forward.

Dr. Hay's testimony regarding the medical and scientific literature will include an exposition of the definitions and explanations, and their applicability to the troops exposed in Vietnam, of the phenoxy herbicides and their contaminants, in

the following areas: plant physiology; toxicology; neuro-toxicology, both neurological and psychological; epidemiology; immunology; mutagenicity; teratology; embryotoxicity; reproductive toxicology; and carcinogenicity.

III. SCIENTIFIC PRINCIPLES

See General Statement of Scientific Principles and Assumed Facts attached.

IV. SUBSTANCE OF OPINION

Dr. Hay will testify to the following opinions:

A. That phenoxy herbicides, including Agent Orange, and 2, 4, 5-T, and their contaminants, especially TCDD, are:

1. Highly toxic
2. Neurotoxic
3. Immunosuppressive
4. Teratogenic and Embryotoxic
5. Potentially Mutagenic
6. Carcinogenic.

B. That there is no "minimum effect" level for 2, 3, 7, 8-TCDD and all other dioxins or, in other words, there is no known "safe level" for any human intake of 2, 3, 7, 8-TCDD and all other dioxins.

V. GROUNDS FOR EACH OPINION

A. General

The medical and scientific literature, attendance and participation in various symposia, review of various documents of certain defendants, personal research, and experience form the bases of whatever facts and opinions to which Dr. Hay will testify.

B. More specifically, the phenoxy herbicides, including Agent Orange, 2,4,-D and 2,4,5-T and their contaminants, including dioxin, especially TCDD, are:

1. Highly toxic	McConnell, E.E., et al. Toxicology & Applied Pharmacology 44, 355-356 (1978); Schwetz, B.A., et al. Advances in Chemistry Series, ed. E. H. Blair, 120 55-69 (1973); Greig, J.B., et al. Food & Cosmetics Toxicology, 11,585-595 (1973);
2. Neurotoxic	Kimmig, J. & Schultz, K. H. Dermatologica 115, 540-546 (1957); Bauer, et al. Archiv. Fuer Gewerbepathology un Gewerbehygin, 18,538-555 (1961)
3. Immunosuppressive	Vos, J.G., & Moore, J.A. Internal Archives of Allergy and Applied Immunology 47,777-794 (1974); Faith, R.E., and Luster, M.I. Annals of The N.Y. Acad. of Sciences, 320, 564-571 (1979)

4.	Teratogenic and Embryotoxic	Neubert, D., and Dillmann, I. Naunym Schmiedebergs Archives and Pharmacology (Berlin) 272 (3), 243-264 (1972) Neubert, D. Environmental Health Perspectives 5, 67-79 (1973); Courtney, K.D., and Moore, J.A. Toxicology and Applied Pharmacology, 20, 396-403 (1971); Courtney, K.D. Bulletin of Environmental Contamination and Toxicology, 16, 674-681 (1976); Smith, F.A., et al. Toxicology and Applied Pharmacology 38, 517-523 (1976); Moore, J.A., et al. Environmental Health Perspectives 5, 81-85 (1973); Sparschu, G.L., et al. Food and Cosmetic Toxicology, 9, 405-412 (1971); Roll, R. Food and Cosmetic Toxicology, 9,671-676 (1971)
5.	Potentially Mutagenic	Rogers, A.M., et al., Mutation Research 105, 445-449 (1982); Bronzetti, G., et al. in Chlorinated Dioxins and Related Compounds: Impact on the Environment (pergamon Press, Oxford, NY (1982) pp 429-436; Hay, A. in The Chemical Scythe (Plenum Press, 1982) pp. 43
6.	Carcinogenic	Allen, et al., Chemosphere, 9,537-544 (1977); Kociba, R.J., et al. Toxicology and Applied Pharmacology. 46, 279-303 (1978); Anonymous. Bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin for possible carcinogenicity (gavage study), National Cancer Institute DHHS Publication No. (NIH) 80-1757 (1980); Toth, K.S., et al. Nature (London) 278,548-549 (1979); Anonymous. National Cancer Institute Technical Report Series No. 123 (1979); Anonymous. Bioassay of a mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin for possible carcinogenicity (gavage study), National Cancer Institute, Technical Report Series No. 198 (1980); Anonymous. Bioassay of a mixture of 1/2/3/6/7/8- and 1/2/3/7/8/9-hexachlorodibenzo-p-dioxin for possible carcinogenicity (dermal study), National Cancer Institute, Technical Report Series No. 202 (1980)

Dr. Hay will testify to examples of the grounds which support the above, including: knowledge of spraying Agent Orange, especially its effect on the Vietnamese countryside; the purpose and historical tracing of the animal studies; historical tracing of the human data, including the various industrial incidents since 1949 (Hay, A. The Chemical Scythe, Plenum, N.Y. (1982) pp 95-146); references to specific documents such as the EPA Dioxin document (presently in draft form); various cancer epidemiology; (Hardell, L. & Sandstrom, A. British Journal of Cancer, 39, 711-717 (1979); Hardell, et al. British Journal of Cancer, 43, 169-176 (1981); Honchor, P.A. and Halperin, W.E. Lancet, I. 268-269 (1981); and Cook, R.R., Lancet, I. 618-619 (1981); pertinent teratology epidemiology (Hanity, J.A., et al., Science, 212, 349-351 (1981); Field, B., and Kerr, C. Lancet I. 1341-1342 (1979)); various studies of the Vietnamese (Tung, T.T., LaRevue de Medicine, 14, 653-657 (1977)); especially reproduction toxicology (Constable, J. Report of the Workshop on Reproductive epidemiology. International Symposium on Herbicides and Defoliants in War: The long term effects on Man and Nature. Ho Chi Minh City 13-20 January 1983; to be published in Herbicides in War. Ed. A.H. Westing, SIPRI); and those reports of the symptoms and diagnoses of the U. S. Vietnam veterans.

C. The above will be relied upon to show that there is no "minimum effect" level for 2,3,7,8-TCDD or other dioxins.

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Degrees:	B.Sc.(Hons), Chemistry IIA - London 1969 Ph.D., Biochemistry, London 1973
Home Address:	School House, Arthington Lane, Arthington, Leeds LS21 1PE England.
Work Address:	Department of Chemical Pathology, Old Medical School, University of Leeds, Leeds LS2 9NL England.
Place of Secondary Education:	Gifford Technical High School, Bulowayo, Zimbabwe (formerly Rhodesia)
Present Appointment:	University lecturer in Chemical Pathology since April 1979 (University of Leeds) Leeds, England.
Former Appointments:	Research Fellow - Zoological Soc. of London September 1972 - November 1977 Research Fellow - University of Leeds, Department of Animal Physiology and Nutrition December 1977 - March 1979
Societies:	Biochemical Society Nutrition Society
Expert Committees:	1983 EPA Review Panel on Dioxins for Environmental Criteria and Assessment Office.

PUBLICATIONS:

Books

1. Alastair Hay. The Chemical Scythe: Lessons of 2,4,5-T and Dioxin. Plenum Press. 265 pp. August 1982.

2. Sean Murphy, Alastair Hay and Steven Rose. No Fire: No Thunder. The threat of chemical and biological warfare. Pluto Press. (To be published in January 1984). 135pp.

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HAY, Alastair W.M.

Additional Papers

1. Paper: "Relationship between Sex Hormones and Fructose Metabolisms in Rat Liver"; Presented at Nutrition Society, London, December 7, 1972.

2. Participant: International Agency for Research on Cancer, NIEHS/IARC Working Group on the Coordination of Epidemiological Studies on the Long-Term Hazards of Chlorinated Dibenzo Dioxins-Chlorinated Dibenzo Phurons; Lyon, Lyon, France, January 10-11, 1978.

3. Member: Panel on Human Observation of the Consequences of Dioxon Exposure; Meeting: International Symposium on Chlorinated Dioxins and Related Compounds, Arlington, Virginia, October, 1981.

4. Paper: "The Role of Membrane Lipids in the Expression of Vitamin D Function in the Intestinal Nucosal Cell"; Presented at the Biochemical Society, London, December, 1981.

5. Paper: "The Manufacture of 2,4,5-Trichlorophenol and its Social Consequences"; Presented at the Royal Society of Chemistry, Education Division Meeting, Leeds, England, September, 1981.

6. Presentation: "Renal Toxicity to the Yorkshire Regional Health Authority Meeting on Aspects of Pathology:; Harigat, January, 1980.

7. Paper: "TCDD Mutagenic Property"; Presented at the International Symposium on Herbicides and Defoliants in War; Long-Term Effects on Man and Nature; held in Ho Chi Minh City, Vietnam; Also, repertoire of working group on experimental toxicology and cytogentics at this Conference.

HERBERT KAYE, Ph.D.

I. QUALIFICATIONS

Dr. Herbert Kaye, Ph.D., is a psychologist in the Department of Psychology at the State University of New York at Stoneybrook, Long Island and a visiting Associate Professor in the Department of Psychiatry at New York University Medical Center. See attached curriculum vitae.

II. SUBJECT MATTER OF TESTIMONY

Dr. Kaye will testify concerning the significance of a battery of quantitative neurophysiological tests called neurometrics which will be performed on various plaintiffs. The procedures were developed in part by Dr. Kaye in conjunction with medical and psychological researchers from this and other countries. He will testify that neurometrics, on which he has written extensively, is a sophisticated battery of electrical tests in use for about fifty years, which are highly efficient in the determining cortical EEG and evoked responses.

Dr. Kaye will explain the model used in the computerization against which the test results are compared and will explain how deviations from normal produce certain effects.

Dr. Kaye will also discuss the mechanism by which toxins produce these altered responses, and what effect those altered responses have upon the individual veterans at present, and the prognosis for any additional changes or deterioration in the future based upon an assumed bioaccumulation of the toxic materials in the system. In doing so, he will rely on his experience in diagnosing many Vietnam veterans exposed to Agent Orange.

III. GENERAL SCIENTIFIC PRINCIPLES RELEVANT TO AREA:

The scientific principles arise from three general disciplines: neurophysiology, mathematics, and neuropsychology.

The area of neurophysiology includes the work on neuro-anatomy, neurochemistry, neuropharmacology, and applied or clinical electrophysiology. The work in mathematics represents multivariate statistics. The work in neuropsychology includes direct and indirect brain-behavior research and clinical diagnostics.

The neurophysiological basis of the development of neurometrics is presented in Volumes I and II of Functional Neurosciences, published in 1977 by Lawrence Erlbaum Associates, publishers, Hillside, New Jersey. However, this work represents an integration of research and applications in the neurosciences over a period four decades, initiated with the seminal EEG work of Gibbs (see, for example, Atlas of Electroencephalography, Cambridge, Massachusetts, Addison-Wesley) W. Gray Walter (see, for example, Electronic Engineering, 1943, 16, pp. 9-13) and going through the specific and extensive quantitative work of Matousek and Peterson (Automation of Clinical Electroencephalography, New York, Raven Press, 1973, pp. 75-102) and current work by quantitative electrophysiologists such as A. S. Gevins, C. Shagass, Theodore Gasser, Enoch Calloway, T. M. Itil, L. Goldstein, and others. (See, for example, Neuro-psychopharmacology, Proceedings of the Tenth Congress of the Collegium Internationale Neuro-psycho-psychopharmacologicum,

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Quebec, July 4-9, 1976, edited by P. Deniker, C. Radouco-Thomas and A. Villeneuvg, Volume II; and P. Kelloway and Ingemar Peterson, editors, Quantitative Analytic Studies in Epilepsy, Raven Press, New York, 1975).

The clinical description and original validating studies were published by E. R. John, et al., in Science, Volume 196, 1977. Several additional studies utilizing the neurometrics technology have been published and referred in invited article, presentation, chapters, reviews, etc.

In essence, the work inquantitative electrophysiology provides a much more reliable numerical indexing of variables previously and currently considered to be of clinical significance to the neurologist and neuropsychiatrist, than may be obtained from conventional EEG tracings that are visually inspected and interpreted. This latter technique is currently the only other means for assessing the dynamic functioning brain from an electrophysiological prospective.

The mathematical principles employed are those pertaining to inferential statistics, probability theory and multivariate vector construction. The mathematics developed for neurometrics were done in conjunction with work and assistance from Professor John Pukey, Ph.D., one of the country's outstanding statisticians, and with the assistance of Dr. Paul Easton, a mathematician. The mathematical strategies employed to reduce the huge amount of data to the variables employed in the neurometrics battery are standard. However, these data, for any individual, are further transformed in a manner identical to the transformations used in making the original set conformed to a Gaussian distribution, and this, then, provides the comparison to the

eighth relevant norm. (See John, et al., Science, Volume 210, 1980).

Neuropsychological literature represents the third strand. This represents the melding of brain electrophysiology and other neurophysiological techniques with those of psychology, or the study of mental and behavioral processes. There is a huge literature in the area, and recent work by such researchers as Gevins, Galin, Tucker, Thatcher, Needleman, and others, as well as those studies of Dr. Kaye and his students and colleagues indicate that quantitative electrophysiology is valuable in diagnosing underlying cortical processes serving certain behaviors.

IV. SUBSTANCE OF OPINION

1. Agent Orange represents a neurotoxic agent that works indirectly by affecting liver function and the liver's production of heme; and in doing so makes an individual, so affected, vulnerable to neurohypoxia.

2. Agent Orange may also work at a local level on enzymes relevant to the production and mobilizations of neurotransmitters.

3. Agent Orange, which is lipid, soluable, is likely to be stored in myelin and other fatty material and is collectively "time released" under "stress".

4. Storage is likely to be greater in the long fiber tracts, such as the major pathways from spinal cord to peripheral cutaneous receptors, pathways from frontal cortical regions to the thalimus and in spinal cortical motor pathways.

5. Changes in cortical functioning, represented by each EEG's slowing, represent breakdown of neural metabolic function occurring as a result of progressive neurotoxic assault.

6. Changes in cortical functioning represented by inter-hemispheric asymmetries and wave-shape incoherence represent the disruption of neural

timing either through the breakdown of cortical pacers, or through the failure of transcortical communication via the corpus collosum.

7. The occurrence of sharp-wave activity is caused by disruption of inhibitory neurotransmitters and represents a mechanism that can partially account for mood lability, which along with selective suppression of frontal lobe function would provide the basis for behavioral discontrol.

V. GROUNDS FOR MY OPINION

A recent study by Needleman (Acta Psychiatrica-Scandinavica, 1983, Supplement No. 303, pp. 26-37) indicates the ability to utilize simple quantitative EEG spectral measures along with the psychological measures to classify children from the "normal" population to have high and low lead levels (using dentyne lead levels). The disrciminating variables for the EEG were the variables associated in our and inconventional EEG work with abnormalities; that is, excessive slow wave energy.

Recent work in our evaluation unit has examined the abnormality profiles of thirty-two Vietnam veterans. In summary, approximately fifty percent showed spectral abnormalities, fifty percent showed power asymmetries, fifty percent showed wave-shape incoherence, and fifty percent showed sharp wave activity. In all, eighty-four percent showed some significant degree of abnormality. Correlation of these patients' neurometrics profiles with other behavioral and physiological data is progressing. Specific correlation of neurometrics profiles and behavioral reports of individual patients who were exposed to herbicides while engaged in non-military activities is also proceeding.

Finally, there is a growing body of data relating research with people who were exposed to low levels of toxic material and who show the range of effects present in the Vietnam veterans exposed to Agent Orange. In particular,

research on the mechanisms underlying heavy metal toxicity (such as with lead and with methyl mercury) suggests possible mechanisms for both neurotoxic and genetic effects. (See, for example, Chang, L.W. "Pathogenetic Mechanisms of the Neurotoxicity of Methyl Mercury" in Mechanism of Actions of Neurotoxic Substances, edited by K.N. Prasad and A. Vernagakis, Raven Press, New York, 1982; and, Egan, et al., "Experimental Design for Animal Toxicity Studies" in Experimental and Clinical Neurotoxicology, edited by P.S. Spenser and H.H. Schaumberg, Williams and Wilkins, Baltimore, 1980.

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ALAN SCOTT LEVIN, M.D.

I. QUALIFICATIONS

Dr. Levin is engaged in the practice of medicine in San Franciso. His Curriculum Vitae and Addendum, listing Professional Societies and Awards, are attached.

II. SUBJECT MATTER

Dr. Levin will discuss the following in his testimony: the immune system, with its organic, cellular, and humoral components - most especially with regard to the latter, T-helper cells, B-cells, plasma cells and immunoglobulin production; immune response, both beneficial and harmful; the various experimental studies, particularly those demonstrating atrophy of the thymus, weight loss, depletion of lymphoid organs, lymphopenia, cutaneous type delayed hypersensitivity (skin thickness) and altered bacterial immunity.

In addition, Dr. Levin will discuss the following and their significance: immunology as molecular biology; chemical-induced immune disregulation; T-cells (lymphocytes from thymus) acting as immune modulators (for which there is "no effect" level); immune surveillance; the similarity of the immune, neurologic, and endocrine systems and their significance in the area of immuno-toxicity; the relationship of immune disregulation caused by chemicals and carcinogenicity, including cancer and the oncogene theory.

Also, Dr. Levin will discuss clinical uses of the epidemologic approach, i.e., clinical epidemiology.

And, Dr. Levin will discuss the problems of diagnosing "psychiatric disease" and the misdiagnosis which frequently occurs.

III. SCIENTIFIC PRINCIPLES

See General Statement of Scientific Principles and Assumed Facts attached.

IV. SUBSTANCE OF OPINIONS

A. That phenoxy herbicides and their contaminants, specifically dioxin, most especially 2,3,7,8-TCDD, cause an assortment of immunological responses, i.e. immuno-toxicity, which predispose persons exposed, by absorption and/or ingestion and/or inhalation, to such chemicals to a whole host of adverse health effects, such as: chloracne or other skin rashes; liver and other organ damage; various neuro-toxic effects; reproductive effects; and neoplasm.

B. That, in connection with the carcinogenic effect, there is no safe level for TCDD or any other carcinogen, and that a single exposure several years earlier can result in human cancer many years later.

C. Dr. Levin will then testify to the causal relationship of the various Agent Orange/dioxin related adverse health effects of the representative plaintiffs, including: chloracne; liver damage; neuro-toxic effects, both neurological and psychological; reproductive toxic effects, both miscarriages and birth defects; and such neoplastic processes as soft tissue sarcoma, as here a

rhabdomyosarcoma, lymphocytic lymphoma and basal cell carcinoma.

V. GROUNDS FOR EACH OPINION

A. General

The bases for such facts and opinions expressed herein by Dr. Levin include: review of the medical and scientific literature, including both animal and human data; his personal researches; his clinical experiences; and his personal knowledge of the defoliation of Vietnam by such phenoxy herbicides and dioxins, with such chemicals in the presence of the veterans and their presumed exposure thereby; and review of all pertinent medical data of the representative plaintiffs, particularly with respect to Opinion IV C.

B. With respect to Opinion IV A, note the following:

The basic discussion on the immune response will be drawn from a series of articles in a variety of immunology texts and journal articles. In addition to the articles in Dr. Levin's bibliography, the references are outlined in the enclosed copy of "A Plea For Thoughtful Consideration" which was presented to the Medical Board of the State of California.

Dr. Levin will also refer to articles on the effect of dioxin on the immune system and refer to the articles in the list entitled "Dioxin and the Immune System".

Dr. Levin will also reply upon the findings of William Rea, M.D., whose bibliography is attached. Additionally, he will rely upon an article Dr. Rea has written with Dr. Lassiter in the Archives of Clinical Ecology in 1983 on pestacide and herbicide detoxicification.

ALAN SCOTT LEVIN, M.D.

ADDENDUM

Professional Societies

1. Alpha Omega Alpha Honor Medical Society
2. Certified Diplomate-American Board of Allergy and Immunology
3. Certified Diplomate-American Board of Pathology-Clinical Pathology
4. Member-Medical Quality Review Committee #4, Board of Medical Quality Assurance, State of California
5. Fellow-American College of Emergency Physicians
6. Fellow-College of American Pathologists
7. Fellow-American Society of Clinical Pathologists
8. Member-American Academy of Allergy
9. Member-American Association of Clinical Chemists
10. Member-Americal Medical Association
11. Member-California Medical Association
12. Member-San Francisco Medical Society
13. Member-Society for Clinical Ecology

Awards

1. American Cancer Society Faculty Research Award

Dr. Levin will also rely on the following articles:

Gallo, R.C. The Virus-Cancer Story: Hospital Practice pp. 79-89, June 1983.

Leder, P. Genetic Control of Immunoglobulin Production: Hospital Practice pp 73-82, February 1983.

Bishop, J.M. Oncogenes and Proto-Oncogenes: Hospital Practice pp. 67-74, August 1983.

Biological Relevance of Immune Suppression as Induced by Genetic, Therapeutic and Environmental Factors: J. H. Dean and M. L. Padarathsingh Editors, Litton Bionetics, Van Nostrand Reinhold Co. New York, Cincinanti, London, 1981.

Inadvertent Modification of the Immune Response: The Effects of Foods, Drugs and Environmental Contaminantsl Proceedings of the 4th FDA Science Symposium August 28-30, 1978.

Immunologic Considerations in Toxicology Vol 1 & 2, Raghubir P. Sharma, CRC Press, Inc. Boca Raton, Fla. 1981.

Pathology of Drug-Induced and Toxic Diseases: R.H. Riddell editor. Churchill Livingstone, New York and London, 1983.

Goldberg, R.J. Clinical Uses of the Epidemiologic Approach: Hospital Practice pp. 177-188, August 1983.

C. With respect to Opinion IV B, note the following

IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans.

EPA Criteria Documents, Publications and Assorted References Re: TCDD

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MARVIN A. SCHNEIDERMAN, Ph.D.

I. QUALIFICATIONS

Marvin A. Schneiderman of Bethesda, Maryland is a statistician and epidemiologist who is the former Chief of Statistics and Epidemiology and the former Director for Science Policy of the National Cancer Institute. He is currently a consultant. His curriculum vitae is attached.

II. SUBJECT MATTER

Dr. Schneiderman will testify in areas concerning mathematical models, statistics, and epidemiology particularly in the area of the determination of cancer causation. He will also discuss the epidemiology of dioxins and their contaminants specifically as that relates to cancer in humans specifically soft tissue sarcoma, stomach cancers and lymphomas. He will further testify to the relationship of exposure to the time of manifestation of disease, i.e. the "latency period" for the development of neoplasms.

Included within his testimony will be a discussion of the multiplication of base rates in the production of cancers; the presentation of a multi-stage model for cancer induction; the age relationships and the role age plays in the various stages of cancer development as they are effected by dioxins and/or their contaminates. He will also discuss and present the pertinent animal data and the fact that the animal data in the reputable and respected medical and scientific literature is consistent with the epidemiological

studies pertaining to dioxin effects in humans and that the animal data is an accurate and appropriate method for the extrapolation and prediction of disease in humans.

His presentation will include a discussion of a mathematical model for the association of the multi-faceted presentation of signs and symptoms in the veteran who was exposed to Agent Orange and the correlation between those signs and symptoms and said exposure and the causal relations between those two elements. Dr. Schneiderman will, of necessity, discuss the incidence of these rare cancers in the general population for a comparison of the onset ages in the general population as compared to the ages of onset for these cancers observed in the Vietnam veterans.

His testimony shall also include a discussion of the relationship of cancer induction to immune deficiencies or deficits as brought about by the immuno-suppressive effects of exposure to dioxin and will rely upon the experience with organ transplant patients and the development of lymphomas and soft tissue sarcomas which he will testify validates his opinions as to the cancer induction in the representative veterans.

Finally, his testimony shall include a discussion of the question of a threshold exposure to a known carcinogen for the induction of cancer. This will include testimony to the effect that there is no "safe" level for exposure to a carcinogen, that a single exposure may cause cancer, and that there is no "no effect" level to a known carcinogen. In his testimony he will present his opinion that TCDD is the most toxic and potent carcinogen ever synthesized by man. And, finally, his testimony shall cover the widely held belief in the respected medical and scientific community that an

entity known to be carcinogenic of one organ will, in all probability, be carcinogen at multiple sights within the human body dependant upon dose, durration of dose, and latency periods.

III. SCIENTIFIC PRINCIPLES

See General Statement of Scientific Principles and assumed facts attached.

IV. SUBSTANCE OF OPINIONS

1. Epidemiology and Biostatistics are the sciences and methods through which "cause and effect" relationships are developed.

2. The research work and resultant epidemiology on animals establishes that TCDD is carcinogenic.

3. The epidemiology developed in human cohorts is consistent with that developed in the animal studies.

4. Epidemiology has established a cause and effect relationship between exposure to TCDD and soft-tissue sarcomas.

5. Epidemiology has established a cause and effect relationship between exposure to TCDD and lymphomas.

6. TCDD is the most toxic substance synthesized by man.

7. TCDD is a complete carcinogen.

8. There is no safe level for exposure to a carcinogen.

9. There is no "no effect" level for exposure to TCDD.

10. TCDD is carcinogenic at extremely low levels of exposure.

11. TCDD effects the immune system so as to make the body more susceptible to carcinogenesis, including but not limited to, soft-tissue

sarcomas, lymphomas and skin cancers.

12. A carcinogen capable of causing cancer in one organ or system is more probably than not capable of causing cancer in a variety of organs or systems.

13. The cancers present in representative plaintiffs Lambiotte and Ford are consistent with TCDD exposure.

14. It is more probable than not that the cancers present in Plaintiffs Ford and Lambiotte were caused by their exposure to Agent Orange.

V. BASES FOR OPINIONS

A. General

Dr. Schneiderman's opinion will be based upon his education, training, experiences, participation in on-going scientific research and investigations, a review of the medical and scientific research, and a review of the medical records of the plaintiffs.

B. Specific

1. Epidemiology of Cancer

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7. Olsson, H. and L. Brandt, 1981, Non-Hodgkins Lymphoma of the Skin and Occupational Exposure to Herbicides, Lancet, 12 September 1981, p. 579.

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12. Barthel, E., 1981, Increased Risk of Lung Cancer in Pesticide Exposed Male Agricultural Workers, Journal of Tox. and Environmental Health, 8:1027-1040.

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15. Hardell, L., B. Johansson, and O. Axelsson, 1982, Epidemiologic Study of Nasal and Nasal Pharyngeal Cancer and Their Relation to Phenoxy Acid or Chlorophenol Exposure, Am. Journal of Ind. Medicine, 3: 247-257.

16. Maclennan, R., J. Ford and M. Coates, 1982, Cancer in the Blue Mountains of New South Wales, Medical Journal of Australia, 2:319-323.

17. Moses, M., and I.J. Selikoff, 1981, Soft-tissue Sarcoma, Phenoxy Herbicides and Chlorinated Phenols, Lancet (1): 1370.

18. Riihimaki, Z., S. Asp, and S. Hernberg, 1982, Mortality of 2,4-D and 2,4,5-T Herbicide Applicators in Finland: First Report of an Ongoing Prospective Cohort Study, Scan. J. of Work, Env. and Health, 8:37-42.

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TELEPHONE 205-345-3441

March 16, 1984

Mr. Tom Henderson
1612 Frick Building
Pittsburgh, PA 15219

Dear Tom:

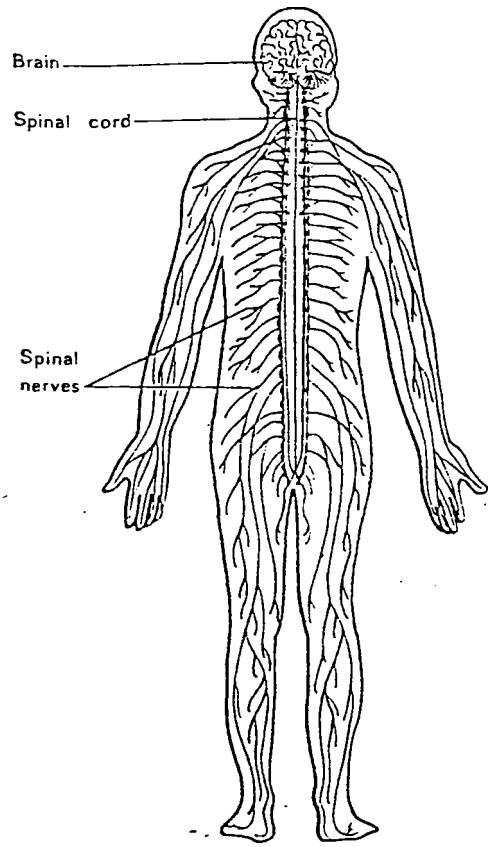
Attached are some ideas that I have had or collected for posters regarding scientific causation for the agent orange case. For each veteran/test case, I think we should have a poster showing that veteran's different weights over the years, as well as, another poster for each vetern showing the medical problems that veteran has had that we attribute to agent orange.

Yours truly,

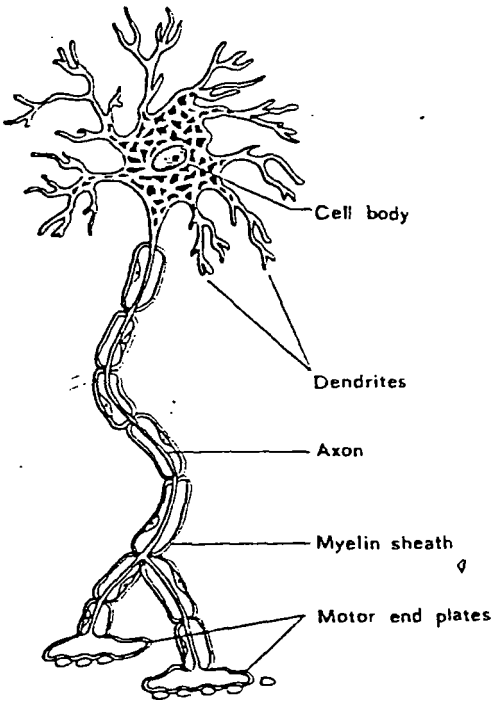
Margie T. Searcy

MTS/mlv
Enclosures
cc: Mr. Phillip Brown
Mr. Stanley Chesley
Mr. David Dean
Ms. Jan Levin
Mr. Gene Locks
Mr. Benton Musslewhite
Mr. Neil Peterson
Ms. Alison Pettiette
Mr. Newton Schwartz

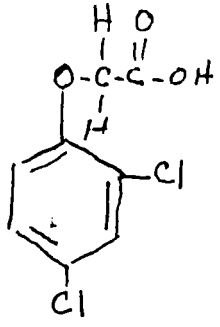
NERVOUS SYSTEM



NERVE CELL

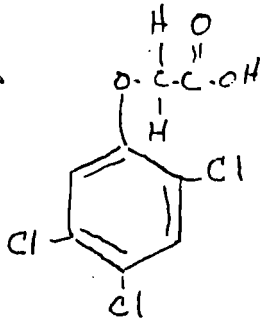


HOW DIOXIN IS FORMED:

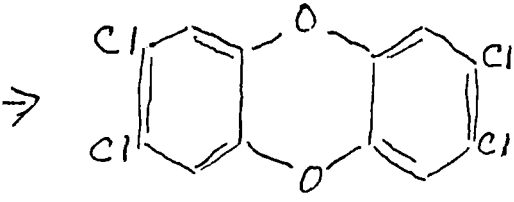


2,4-D

+



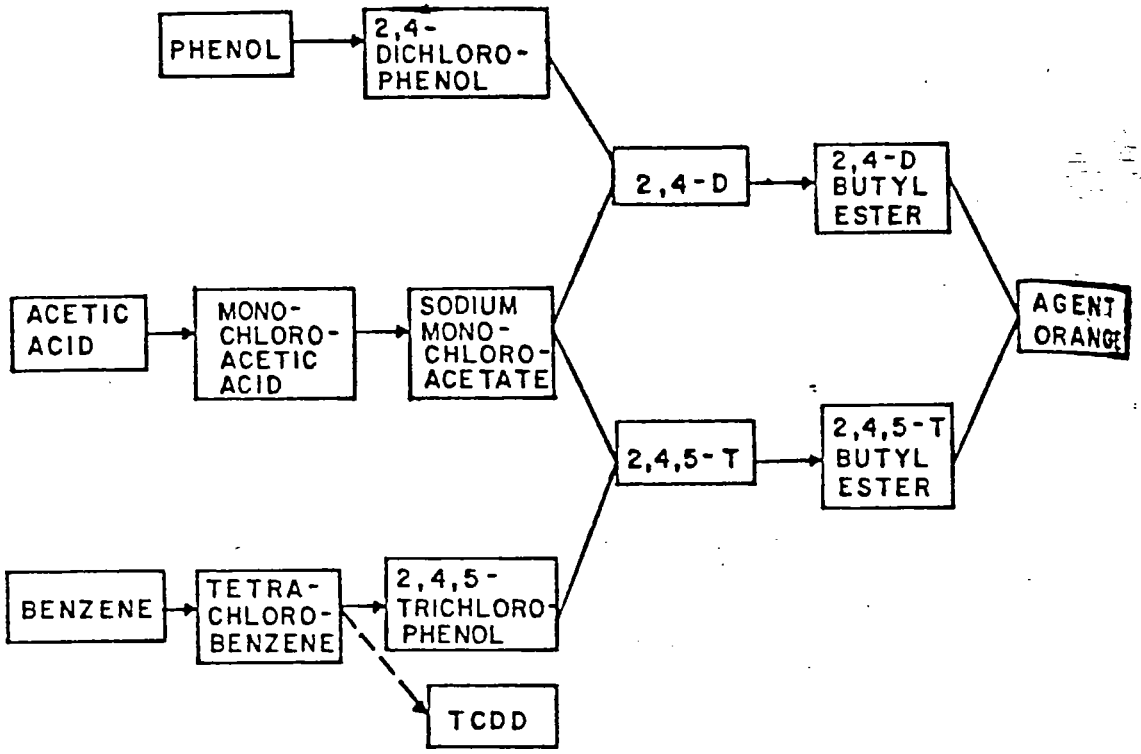
2,4,5-T



2,3,7,8 TCDD

DIOXIN (TCDD) + HUMAN LIVER → ENZYMES THAT ARE HARMFUL TO THE BODY

THE MAJOR STEPS IN MANUFACTURING AGENT ORANGE:



WAYS VETERANS WERE EXPOSED TO DIOXIN (TCDD):

1. Breathing
2. Eating
3. Drinking
4. Touching

HOW DIOXIN TRAVELED IN THE ENVIRONMENT:

1. Direct Spray
2. Drift
3. Volitization
4. Evaporation
5. Leaching
6. Movement by Animal, Machines, and Plants, etc.

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK
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In re:

"AGENT ORANGE" MDL #381

Product Liability Litigation
----------x

PLAINTIFFS' MEMORANDUM ON CAUSATION

PLAINTIFFS' MANAGEMENT COMMITTEE

By Thomas W Henderson
Thomas W. Henderson, Esquire

I. Introduction

II. Pertinent Litigation History

III. Medical Causation

A. Background

B. Causation in Fact

C. Expert Opinion

D. Disease Litigation

E. Application to Agent Orange Case

1. Agent Orange/dioxin is highly toxic and carcinogenic.

2. Agent Orange/dioxin has no safe level of exposure.

3. Plaintiffs were exposed to Agent Orange/dioxin.

4. Agent Orange/dioxin did cause an array of adverse health effects in the 9 representative Plaintiffs.

a. Dermatological

b. Systemic

i. liver
ii. immuno-suppressive

c. Neuro-toxic

i. neurological
ii. neuro-behavioral

d. Cancer

e. Birth defects

IV. Conclusion

I. INTRODUCTION

This memorandum is submitted on behalf of all members of the class by the Plaintiffs' Management Committee. The request for leave to submit it was occasioned by virtue of comments made on various occasions by the Court concerning the strengths, or, we respectfully submit, as the Court has erroneously indicated, the great weaknesses in the Plaintiffs' cases on medical causation issues. The Management Committee has been concerned for some time now that the Court misperceives the requirements of proof on causation issues, especially the proper use and weight to be afforded statistics, and more recently, from comments made by the Court at the first hearing regarding fee and expense applications, concerning the relationship between proofs on causation issues and whether this case should have been brought at all.

In its Preliminary Memorandum and Order on Settlement dated September 25, 1984, this Court touched on problems it perceives in Plaintiffs' cases on causation issues, i.e. "III. Factual Problems with Claims", pp. 96-150. These problems were known and would have been handled in the presentation of Plaintiffs' proofs. The Committee nonetheless acknowledges that there were several factors, most of which were included in said Memorandum of the Court, which led to its evaluation and conclusion that the proposed settlement of this litigation is in the best interests of the class members as a whole (See, generally, Plaintiffs' Fairness Brief dated August 7, 1984). However, the Committee believes the Court's suggestions that Plaintiffs' counsel (both Committee members and other counsel representing certain Plaintiffs) were unable to prove causation

by a preponderance of the evidence of adverse health effects other than chloracne, are misplaced. The Court misperceives the strengths of the proofs adduced with respect to the individual representative Plaintiffs. Indeed, the Court places an inappropriate burden upon Plaintiffs in disease litigation generally in suggesting a "statistical requirement" as a form of "litmus paper test" in order to proceed.

The Committee strongly believes the Court's view is erroneous, because, if adopted, it would discourage the prosecution of many types of valid occupational and environmental disease claims. To support our belief, we shall set forth the pertinent history of this litigation, an exposition of the legal sufficiency of the proof on causation in disease litigation, and specific relevant Court documents, especially those pertaining to experts' opinions. The Committee therefore submits that it can adduce legally sufficient and clear evidence of CAUSE.

II. PERTINENT LITIGATION HISTORY

In its Preliminary Memorandum and Order on Settlement dated September 25, 1984, this Court gives an accurate chronology of the institution and early procedural history of this litigation, and the transfer and consolidation of actions pursuant to 28 U.S.C. §1407 (See, Opinion at pp. 20-31). What is lacking there, but pertinent here, is a brief working history of the litigation.

Early in the litigation Judge Pratt, in fundamental agreement with the procedural aspects of the motion of the Plaintiffs to conduct serial trials of various issues common to class members' claims, ordered that the government contractor defense be tried first and separately, and permitted discovery to proceed on issues pertaining to that defense (See, 506 F.Supp. at 762). This was done under the supervision primarily of Special Master Sol Schreiber. The then lead counsel group accomplished the discovery necessary to prepare for Judge Pratt's "Phase One" trial through the taking of numerous depositions and the review of voluminous documents produced. In addition, they briefed the early legal positions on various issues and responded successfully to the Defendants' motions for summary judgment based upon the government contractor defense.

Judge Pratt dismissed the veterans' complaints against two of the Defendants, Hercules and Thompson Chemical, which were subsequently brought back into the litigation. Another significant aspect of his opinion was that issues regarding liability, general medical causation, and government contractor defense were interrelated. Therefore, he determined that the "Phase One" trial was no longer appropriate in his "Case Management"

of the litigation. Judge Pratt instructed Special Master Schreiber to continue in his role, and to recommend an appropriate timetable for remaining discovery (on the vastly enlarged issues) "with the objective being a trial at the earliest reasonable date." (See, 565 F.Supp. at 1277, June 22, 1983).

Following this order, Special Master Schreiber began to supervise and schedule remaining discovery pertaining to government witnesses requested by the Defendants and, soon thereafter, discovery of liability issue witnesses, including employees and former employees of Defendants.

The transfer of the litigation to Chief Judge Weinstein and his Order in October of 1983 to further expand the issues through the device of choosing representative individual cases that were to be tried to verdict, placed immense burdens on Plaintiffs' counsel. That occurred within just 3 weeks of the motion of Yannacone & Associates to be relieved of their duties as lead counsel, primarily for financial reasons, and the appointment of Messrs. Henderson, Schlegel and Musslewhite to the position of the Management Committee or lead counsel, which appointment was filed with the Court on October 5, 1983.

At that time Special Master Schreiber was supervising a discovery schedule of depositions of liability witnesses which was proceeding on a multiple track basis, with as many as 15 depositions scheduled each week all over the country. Judge Weinstein's direction to choose individual representative cases from the thousands that were on file required a phenomenal amount of work on the part of Henderson's causation "team" and the expanded Management Committee.

A determination as to the location and content of medical records pertaining to individual Plaintiffs from all over the country had to be

made. (This is but one example of the tremendous burdens placed upon the Committee to comply with an almost unbelievable timetable. Further examples are contained in Appendix 1 attached hereto). Where records were not complete, they had to be obtained. Plaintiffs with diagnosed diseases which could be related to Agent Orange had to be found. Their local counsel had to be consulted. Interviews with prospective representatives and their families were held. Experts from a variety of scientific disciplines had to be consulted and retained. The importance of making the right choices, and the consequences to the individual Plaintiffs involved were monumental. All of this work was accomplished in the space of just a few months.

The Committee believes that the consequence of the choices of the representative Plaintiffs and of the testimony adduced from the highly qualified experts, Defendants' protestations notwithstanding, resulted in the Defendants' presumed conclusion that causation issues would be submitted to the jury. In our view, that was the primary reason why the Defendants agreed to settle this litigation.

The type and quantity of discovery taken is important to note. No significant prior discovery had been taken on causation issues prior to October 5, 1983, the date when the Management Committee was appointed by Judge Pratt. Counsel's first meeting with Judge Weinstein took place on October 21, 1983, and it was only thereafter that causation issues became the subject of any substantial legal effort.

Records on file with the Court indicate that 157 depositions were taken between the outset of the litigation in 1979 and June 22, 1983, virtually all of which had to do with government contractor defense issues, and many of which were quite short in duration.

After expansion of the issues, however, the pace quickened dramatically. Between June 22, 1983 and May 7, 1984, over 216 depositions were completed. During the first four months of 1984, over 100 depositions were taken and of these, more than 60 pertained to causation issues, both general and specific. The depositions during this period of expert witnesses and representative Plaintiffs were not only technical and complex in nature, but were two days (or longer) in most instances.

During the post October 21, 1983 period it was obviously necessary to interview and prepare experts and Plaintiffs for their testimony. The appointment of Magistrate Scheindlin to supervise discovery, both as to scheduling, progress and claimed abuses was another factor which, although very helpful to all (and we congratulate her on a job magnificently performed) added still more demands on the causation "team". Rule 26(b)(4) summaries, in extraordinary detail, were ordered to be submitted, requiring extensive review of source materials by lawyers and experts as well.

We believe the talents and efforts of defense counsel deserve some mention. In terms of causation issues there simply has never been a litigation in which Plaintiffs' efforts were so strongly defended, not just in spirit, but with resources and efforts that were unparalleled. For example, nearly every opinion given by Plaintiffs' witnesses was attacked from a wide variety of perspectives. No cost or effort was spared.

Despite the defense effort, and as is chronicled hereafter, the Plaintiffs' causation case was ready for trial on May 7, 1984. There was substantial probability of success on those issues as they relate to the representative Plaintiffs. We could prove that each was exposed to Agent Orange/dioxin and suffered from one or more adverse health effects as a result of such exposure.

III. MEDICAL CAUSATION

A. Background

The relationship between Agent Orange and disease, i.e. cause, while not as easily perceived as, for example, physical trauma and a broken bone, is by no means as perplexing and complicated as has been suggested. The legal standard of establishing cause is identical, whether the adverse health effect results from a single event producing trauma, a single acute exposure to a toxic substance, or a chronic low level exposure to one or more toxic substances; that standard of legal sufficiency is whether the particular toxic substance more likely than not caused, or contributed to, or aggravated the disease (adverse health effect).

While the "actual" exposure to any toxic substance, specifically here Agent Orange, perforce must be decided on an individual basis, and otherwise be convincing to the fact-finder on the "more probably than not" standard, for purposes of the expert's opinion on cause, the exposure is always hypothetically assumed by the expert. There are several reasons for this: 1) the expert is almost never present when the alleged exposures take place; 2) testing to determine the levels of contamination of a particular toxin, e.g. air sampling, rarely can be performed, even after the fact; and 3) even if such testing were possible, the difficulties in establishing admissible testimony, i.e. by reproducing identical, even substantially similar conditions as were prevalent at the time of exposure, often several years later, are manifest.

The arguments advanced by the defendants - that the Plaintiffs' inability to scientifically establish a "toxic dose" in any particular

Plaintiff, that any exposure to Agent Orange/dioxin in Vietnam cannot be distinguished from an etiologic standpoint from other sources of dioxin contamination in the environment, and even that no exposure to Agent Orange/dioxin can be established, are inappropriate and/or simply have no merit. In the last analysis, all of these defense positions are to be decided by the fact-finder, based upon the various forms of admissible evidence.

Exposure is determined by the fact-finder, taking into account such admissible evidence as oral testimony of the Plaintiff or the individual allegedly exposed, co-workers or, in this case, other military personnel having relevant knowledge of that individual's alleged exposure to Agent Orange, and such documentary evidence, i.e. relevant military records, which would be helpful to the fact-finder, and even certain opinion testimony of probable or greater exposure, as, for example, from Richard Christian. Specifically, in those areas of toxic tort litigation wherein trial and/or appellate courts have addressed this matter in both general and specific terms, e.g. asbestos, silica, benzene and radiation, the requirement of a plaintiff having to prove his particular "toxic dose" has been thoroughly rejected. Indeed, an overwhelming majority of such cases rely exclusively on the oral testimony of a plaintiff and/or co-workers for legally sufficient exposure evidence. Where exposure to a toxin is "established", i.e. to the satisfaction of the fact-finder, the inquiry turns to that which exists in the scientific literature in the areas of toxicology, epidemiology, and clinicial medicine, and even the impressions and expressions of qualified clinicians who have performed the appropriate battery of tests and have interpreted the medical data resulting therefrom.

There is no requirement that statistical evidence be adduced to a probability of 50+% to submit to a jury or to persuade any other fact-finder that the exposure is a cause, or contributed to, or aggravated, the disease or adverse health effect. This error is a judicial construct under which the epidemiologic term "statistical significance" has been expropriated inappropriately into a judicial setting, the effect of which is to predetermine a matter adversely to a plaintiff when courts do not routinely consider such burdens to be properly on a plaintiff. For example, where a given plaintiff has 4 separate lung conditions - silicosis, bronchitis, emphysema, and asbestosis - all of which contribute to a total disability, it cannot logically be said that any one of the 4 disease processes is the cause of the disability, even from the perspective of a 50+% probability. However, in such cases, courts routinely permit an expert to testify that asbestos exposure was, to a level of reasonable medical probability or certainty, a substantial contributing factor in the disability.

That is not to say that where statistical evidence is available, it is not useful. To the contrary, the existence of such statistics is very helpful. Those statistical analyses are present in all 3 relevant areas of medical science, i.e. toxicology, epidemiology and clinical medicine. Indeed, those disciplines require the use of statistics in their respective evaluations of the pertinent data.

Specifically, Defendants advanced arguments in support of their position on causation during the course of the pretrial discovery in two of those disciplines, i.e. toxicology and epidemiology.

With respect to toxicology, the Defendants postulated that, since all substances can cause harm or even death if taken in high enough doses,

and since Plaintiffs were unable to prove a specific dosage of dioxin which may have been absorbed, the Plaintiffs' proof therefore fails. The circularity of this argument is manifest. Since there is no known safe level to dioxin, and the fact that exposure at some level may be assumed by the experts, as set forth above, an appropriate opinion as to the relationship between the "fact" of exposure and the particular adverse health effect may be admitted.

In animal toxicology, the scientific discipline of statistics is an essential component in the utilization of control groups of the species under observation, and in the analyses of whether the toxin or carcinogen under study is indeed toxic or carcinogenic. The suggestion by the Defendants, therefore, that the evaluation of animal data cannot be extrapolated to the human experience in an evaluation of cause in humans in this context is outrageous. No one suggests that human experimentation is proper; indeed it is immoral and illegal. The Defendants' position in this regard is thus reduced to the absurd claim that a requirement which is proscribed must be satisfied, i.e. that only epidemiological data from a human can establish cause and effect in humans. From a policy standpoint, that is, in a word, unacceptable; from a scientific standpoint it is ridiculous.

Nevertheless, the Defendants argue (1) that there are insufficient human data to establish "cause and effect" relationships; (2) that there are no data to support the claims of Plaintiffs with respect to exposure to Agent Orange/dioxin while in Vietnam; and (3) that, in any event, epidemiology is designed to assess risks in the regulatory sense, but cannot be used to prove individual causation.

The first and second aspects of these contentions are, to put it bluntly, not so. To the contrary, there is an abundance of human studies

regarding dioxin, including specifically 2,3,7,8-TCDD. Moreover, the Vietnamese studies on male-mediated birth defects as reviewed by Hatch and Constable, Ranch Hand II, and the Center for Disease Control (CDC) study of birth defects in relation to a father's service in Vietnam all demonstrate the presumed causal association between Agent Orange/dioxin exposure in Vietnam and various adverse health effects including male-mediated birth defects.

Moreover, epidemiology can certainly be used on an individual basis. Where exposure is established, that individual becomes part of the exposed group, and the relative risk otherwise ascertained by relevant epidemiology studies is applicable to that individual, i.e. in this case any one or more of the representative Plaintiffs who were exposed in Vietnam. Otherwise, it (the discipline of epidemiology) would be useless except on a theoretical level. By definition, epidemiology deals with human experience, and perforce therefore includes individuals in its statistical analyses.

Certainly, epidemiology relies very heavily on statistics and statistical techniques. The important relevant distinction is between the respective levels of scientific and legal proof in the demonstration of cause, i.e. why epidemiology is not essential in this consideration and determination of cause. Scientific proof in the context of epidemiology and its application of statistics often is expressed in terms of 95% or 99% probability, (i.e. where $P < 0.05$ and $P < 0.01$, respectively), that the event considered is not due solely to chance; this translates into a conclusion that the event (adverse health effect) results from chance alone less than 5% or less than 1%, as the case may be. Such "statistical significance" concepts are far different from the legal standard of "more probably than not".

Lastly, the question of whether a given Plaintiff was exposed to one or more variables (chlordane, DDT, malathion, lindane, aflatoxin, etc.) is simply a "red herring". The concern of an expert in sorting out possible competing causes is manifest in toxic tort litigation; the expert testimony would have been presented with consideration of all such possible competing causes. The issue is no different conceptually in Agent Orange than in any other toxic substance litigation, e.g. lung disease and smoking. The presence of such confounders in a given case does not prevent expert testimony but only mandates a restructuring thereof if it is to have any weight.

Likewise, the analyses by a clinician of various objective tests and their resultant data necessarily imply the use of statistics, in that statistical techniques already have been employed and statistical analyses already have been made to establish the "normal" range of responses for each of those tests. The evaluations and diagnoses by clinicians, together with clear expressions of cause of such diagnoses, are performed every day. In the context of a toxic substance, clinicians frequently make diagnoses and at the same time ascribe cause and prescribe treatment based upon the patient's history of exposure. For example, a patient may exhibit an asthma condition of recent origin after having been exposed to a particular toxin known to cause asthma during the same time period. In this case, a clinician's recommendation that the patient should not be further exposed to such substance impliedly concludes that the substance caused or contributed to the asthma. Furthermore, that situation has nothing to do with ascribing cause in the medico-legal sense. Yet, the clinician could certainly, and should be permitted to, testify to cause, in this context.

In the Agent Orange case, the Plaintiffs can amply demonstrate exposure to Agent Orange/dioxin. The scientific literature is replete with both toxicological and epidemiological data regarding dioxin, especially 2,3,7,8-TCDD. Moreover, one or more clinicians and other scientists were and are prepared to tie in the various objective medical criteria to formulate diagnoses and "cause" resulting from such exposure. The case of each representative Plaintiff would be analyzed accordingly, specifically with respect to the pertinent testimony of the various "world-class scientists".

The Plaintiffs were and are prepared, in the legal sense, to prove CAUSE.

B. Causation in Fact

Causation is a key issue in all personal injury litigation. As a threshold matter in any tort action, the plaintiff must establish a reasonable connection between the conduct of the defendant(s) and the damage suffered. Conceptually, the causation issue is framed in terms of "causation in fact". (See, Prosser and Keeton on The Law of Torts, 5th ed., 1984, §41). The inquiry surrounds whether the identifiable incident (such as an accident, exposure to a toxic substance, or medical treatment) is a proximate cause of the injury, either totally, as a substantial factor, or as an aggravating and underlying disorder, resulting in death or impairment sooner than would have occurred otherwise.

A detailed analysis of Prosser and Keeton, §41, Causation in Fact is appropriate. As described therein:

> the term "cause in fact" embraces all things which have so far contributed to the result that without them it would not have occurred.

§41 at 265.

Certain "rules" with modifications come into play in this analysis. The so-called "but for" rule is defined as:

> The defendant's conduct is a cause of the event if the event would not have occurred but for that conduct; conversely, the defendant's conduct is not a cause of the event, if the event would have occurred without it.

§41 at 266.

The authors, however, recognize that the "but for" rule cannot be applied universally, specifically where more than one variable may "cause"

the event.

In recognition of such inadequacy of the "but for" rule, various courts have fashioned the so-called "substantial factor" rule as follows:

> The defendant's conduct is a cause of the event if it was a material element and a substantial factor in bringing it about.
>
> It has been considered that "substantial factor" is a phrase sufficiently intelligible to furnish an adequate guide in instruction to the jury, and that is neither possible nor desirable to reduce it to any lower terms.

§41 at 267 (Footnotes and citations omitted).

In particular, the "substantial factor" test has been adopted by the New York Court of Appeals. Dunham v. Village of Canisteo, 303 N.Y. 498, 104 N.E.2d 872 (1952); see also Restatement (Second) of Torts, §§430-433 (1965).

At least one commentator seems to couch "substantial factor" in the form of "causal linkage". See Calabresi, "Concerning Cause and the Law of Torts", 43 U. Chi. L.Rev. 69 (1975). Specifically, "causal linkage" is defined in part as when ". . . the occurrence of activity A will increase the chances of injury B." (at 71, footnote 4).

The "substantial factor" test also has been described by another commentator as the "material and contributing factor" test in cases of mixed causation; this requires only that plaintiff show defendant's conduct contributed to the injury. See, Delgado, "Beyond Sindell: Relaxation of Cause-In-Fact Rules for Indeterminite Plaintiffs", 70 Cal. L.Rev. 881, 887 (1983). (The lack of pertinence of the so-called "indeterminate plaintiff problem" will be discussed hereinafter)

Insofar as proof on the issue of causation, Prosser and Keeton indicate clearly that expert testimony may provide a sufficient basis for it (see, §41 at 269); see also Pritchard v. Liggett & Myers Tobacco Co., 3d Cir.

1961, 295 F.2d 292 (1961); Grinnell v. Charles Pfizer Co., 274 Cal. App. 2d 424, 79 Cal. Rptr. 369 (1969). In addition, it is noted there that ". . . fact of causation is incapable of mathematical proof."

Plaintiffs' proof in the Agent Orange case was sufficient under either "rule" to establish "causation in fact." However, we submit that the "but for" rule is singularly inappropriate in the general context of "disease litigation." The "substantial factor" rule is conceptually more akin to the medical and scientific realities in the qualitative and quantitative assessment of cause in a possible multi-factorial context, e.g. Agent Orange disease. This will be discussed and developed more fully hereinafter.

Medical causation is vitally important to a physician in treating his patient. Indeed, "diagnosis" has been defined as "a medical term, meaning the source of a patient's illness or the determination of the nature of his disease from a study of its symptoms." Black's Law Dictionary, 408 (rev. 5th ed. 1979) (Emphasis supplied).

Medical causation, although related to "causation in fact", is nonetheless analytically distinct. See, Olson v. St. Croix Valley Memorial Hospital, Inc., 55 Wis. 2d 628, 201 N.W.2d 63, 65-66 (1972). Thus, a patient may be advised of the source or nature of his disease, and yet have insufficient medical evidence as a plaintiff to prove that any particular defendant was the proximate cause of his injuries.

The difference between causation in fact and medical causation has been well-described in the following terms:

> The physician who testifies in proceedings aimed at answering the basic question of legal causation is placed in a professionally uncomfortable position, because the legal approach to causation differs markedly from the medical approach to which the

> physician is accustomed through his specialized training and experience. For example, in viewing a patient's current medical problems, physicians more or less instinctively search for the basic cause or causes of the disorder that underlies those problems. Judges and attorneys, in contrast, seek to determine whether one particular event precipitated, hastened, or aggravated the patient's current condition. Furthermore, physicians, oriented toward treating the entire patient, strive to identify and to understand all aspects of the patient's condition, whereas judges and attorneys tend to limit their concern to only that aspect of the patient's condition that allegedly was precipitated, hastened, or aggravated by the event in question.

Danner, Douglas, "Medicolegal Causation: A Source of Professional Mis-Understanding", 3 Am. J. Law & Med., 303, 304 (1977).

The plaintiff in a tort case is required only to introduce evidence which establishes that the acts of the defendants "more probably than not" caused, contributed to or aggravated the injury (disease), taking into consideration all admissible evidence, including experts' opinions.

C. Expert Opinion

An "expert" is a witness who is permitted to testify as to matters about which the trier of fact has insufficient knowledge to make the necessary inferences to arrive at a decision on the ultimate issues in dispute. Similarly, "expert testimony" is that class of matters as to which a person acquires knowledge only by means of some experience, knowledge or training not shared by the general population.

Expert testimony is even required in certain types of cases. For example, in a medical malpractice case, a plaintiff must normally establish through a medical expert the appropriate standard of care in the locality. The expert must also prove that defendant was negligent in light of that standard and that his lack of skill or care proximately caused plaintiff's injury. See, Walski v. Tiesenga, 72 Ill, 2d 249 (1978) and Borowski v. Von Solbrig, 60 Ill. 2d 418 (1975).

Traditionally, the expert has derived his facts and data to support his opinions from two sources. First, the expert could render an opinion based on his firsthand knowledge of the facts, as, for example, a treating physician. Second, the expert could render an opinion based upon facts given to him in a hypothetical question.

A treating physician, for example, could testify as to his observations, treatment, and diagnosis of a patient based on his firsthand knowledge of those facts. If the treating physician was not qualified to read x-rays, then the radiologist could testify to the radiological findings and those findings could be incorporated in a hypothetical question as

additional facts to be considered by the physician in forming his opinion.

If further corroborating testimony of the treating physician's opinions was deemed necessary, a non-treating physician could be called as an expert witness. He could then be asked a hypothetical question, incorporating the treating physician's findings and opinions, the radiologist's findings and opinions, and the plaintiff's account of the incident, as bases for his opinion.

The use of expert testimony was streamlined and simplified in 1975 by the adoption of the Federal Rules of Evidence, and thereafter by the many states which have incorporated them in whole or in part.

Rule 702 states:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise.

Rule 702 speaks for itself.

Rule 703 states:

> The facts or data in the particular case upon which an expert bases an opinion or inference may be those perceived by or made known to him at or before the hearing. If of a type reasonably relied upon by experts in the particular field in forming opinions or inferences upon the subject, the facts or data need not be admissible in evidence.

The purpose of Federal Rule 703 is to eliminate the expenditure of substantial time and effort in producing and examining various authenticating witnesses. As long as the requirement is met that the facts or data "be of a type reasonably relied upon by experts in the particular field", the rule is satisfied. The assumption is that the

expert himself is fully competent to assess the reliability of information received from others.

Rule 704 states:

> Testimony in the form of an opinion or inference otherwise admissible is not objectionable because it embraces an ultimate issue to be decided by the trier of fact.

As in Rule 702, Rule 704 is clear on its face.

Rule 705 states:

> The expert may testify in terms of opinion or inference and give his reasons therefor without prior disclosure of the underlying facts or data, unless the court requires otherwise. The expert may in any event be required to disclose the underlying facts or data on cross-examination.

The purpose of Rule 705 is to eliminate the necessity of the hypothetical question during trial. As the Advisory Committee has noted, "[t]he hypothetical question has been the target of a great deal of criticism as encouraging partisan bias, affording an opportunity for summing up in the middle of the case, and as complex and time consuming . . . While the rule allows counsel to make disclosure of the underlying facts or data as a preliminary to the giving of an expert opinion, if he chooses, the instances in which he is required to do so are reduced." Fed. R. Evid. 705, Advisory Committee Note.

A key element in applying Rules 703 and 705 is whether the information upon which the expert bases his opinion is of a type which is "reliable". Federal courts have allowed expert opinion testimony based upon a wide variety of informational sources since 1975. A trial court's discretionary supervision in determining what information is "reasonably relied upon" by an expert can lead to admission of expert opinion testimony based on an

expanding variety of inadmissible facts and data. While the facts or data that the Federal courts have determined to be "reasonably reliable" can be challenged, the burden is placed on the cross-examiner to do so.

The general rule on opinion testimony as it relates to causation-in-fact is whether the injury is "more probably than not" related to the event, in this case, the exposure to Agent Orange. Various courts have couched the standard of legal sufficiency in this regard to "reasonable degree of medical certainty", "reasonable medical probability", even "might have caused" or "could have caused". In the last analysis, however, the differences are essentially semantic. See, e.g., Miller v. National Cabinet Co., 8 N.Y.2d 277, 168 N.E.2d 811, 204 N.Y.S.2d 129 (1969). What the courts actually require, as noted above, is that evidence transcends "conjecture or speculation" to that which a jury may reasonably conclude that the event (exposure) resulted in the condition (adverse health effect). This Court had already concluded that the standard of "more probably than not" was to be employed, presumably in accordance with the prevailing view and New York law. See, e.g. Matott v. Ward,423 N.Y.S.2d 645, 47 N.Y.2d 455, 399 N.E.2d 532 (1979); Sentilles v. Inter-Carribean Shipping Corp., 361 U.S. 107, 80 S.Ct. 173, 4 L.Ed.2d 142 (1959).

In Sentilles, supra, the Supreme Court reinstated plaintiff's District Court jury verdict. The Court held that the failure of medical experts to testify that plaintiff's tubercular condition had in fact been caused by a work-related accident did not preclude the jury from drawing a legal conclusion of causation, which was specifically noted to be its (the jury's) duty:

> The jury's power to draw the inference that the aggravation of petitioner's tubercular condition, evident so shortly after the accident, was in fact

> caused by that accident, was not impaired by the failure of any medical witness to testify that it was in fact the cause. Neither can it be impaired by the lack of medical unanimity as to the respective likelihood of the potential causes of the aggravation, or by the fact that other potential causes existed and were not conclusively negated by the proofs. . . . The members of the jury, not the medical witnesses, were sworn to make a legal determination of the question of causation. They were entitled to take all the circumstances, including the medical testimony, into consideration.

361 U.S. at 109-110 (Emphasis supplied).

In short, the Federal Rules of Evidence specifically provide for opinion testimony by qualified experts (Plaintiffs' experts were eminently qualified). See, Fed. R. Evid. 702. Opinion evidence may include expressions of causation in fact, negligence, "outrageous conduct", or any other "ultimate issue". See, Fed. R. Evid. 704. Most importantly, the decisional law, i.e. Sentilles, etc. mandates that the fact-finder, here the jury, ". . . make a legal determination of the question of causation."

D. Disease Litigation

With this background on causation, and the modern use of experts under the Federal Rules of Evidence, it is appropriate to examine specific cases involving personal injuries, with specific causation problems, especially in the area of disease and related litigation. While the cases fall into different categories, the vast majority of Courts have held that there is sufficient evidence to go to the fact-finder, even where there are conflicts between expert testimony. The Courts hold that the conflict is for the fact-finder to resolve.

The general standard of opinion testimony as to whether the disease resulted from the exposure is on a "more probably than not" basis. Most Courts have agreed that this standard is sufficient to raise a jury question, recognizing that some uncertainty exists in every issue of fact.

As well summarized by one commentator:

> There is universal recognition that some uncertainty must attach to all human affairs. So the general quantum of civil proof required is recognizably not perfection ("absolute") but "reasonable certainty" or "reasonable probability" which may be established by the preponderance of the evidence.
>
> "Preponderance of the evidence" is generally recognized as the "greater weight" of evidence which tips the scales of justice in favor of the prevailing party. It need not "satisfy the minds" of the jury to the establishment of the facts, but need only allow reasonable men conclude that the greater probability lies with the plaintiff.

Belli, Modern Trials, §5.2 (2d ed. 1982) (Citations omitted).

In American Life Ins. Co. v. Moore, 216 Ark. 44, 223 S.W.2d 1019 (1949), the doctor for the plaintiff stated that in his opinion the fracture of the decedent's leg, which he had received while cutting timber, was the probable cause of the pulmonary embolism and subsequent death of the decedent. Plaintiff's expert did not preclude all other causes. The defendant's doctor denied any causal relation and stated that the time lapse between the accident and the pulmonary embolism was too great to justify such a relation.

The court said:

> This conflicting expert testimony presented a question for the jury . . . when medical men differ about the matter the verdict is not contrary to natural or scientific principles, nor is it based on what is not and could not be true.

216 Ark. at 45.

In Smith v. Humboldt Dye Works, Inc., 34 A.D. 2d 1041, 312 N.Y.S.2d 612 (1970), a worker allegedly contracted cancer of the bladder after exposure to aniline dyes. He had been an assistant dyer, dyer and foreman in charge of dyeing wool yarn for a period of about twenty-five years.

Claimant's two medical expert witnesses concluded that the cancer was caused by exposure to finished dyes containing anilines, beta naphthylamines and alpha naphthylamines. The employer sought review of a disability award. The court affirmed, explaining:

> Appellants' two medical experts testified that, in their opinion, there was no causal relation between claimant's work and the disease. The issue of causal relation thus presents the usual conflict of medical testimony which is a question of fact for the board to determine * * * The record contains substantial evidence to support the board's finding of causal relationship.

312 N.Y.S.2d at 614 (Citations omitted).

In Fink, Appel., v. Sheldon Axle & Spring Co., 270 Pa. 476, 113 Atl. 666, 667 (1921), the plaintiff sought workers' compensation for a paralysis which he claimed was caused by being struck in his employer's establishment. The court said:

> It must be understood, however, that when, in cases of this class, expert testimony is relied on to show the connection between an alleged cause and a certain result, it is not enough for the doctors to say simply that the ailment in question might have resulted from the assigned cause, or that the one could have brought about the other; they must go further and testify at least that, taking into consideration all the attending data, it is their professional opinion the result in question most probably came from the cause alleged.

270 Pa. at 479 (Emphasis supplied).

In Kling v. Central Lumber & Millwork Co., 3 N.J. Super. 151 (1949), the plaintiff fell from a platform while on duty. It was held that the trauma probably aggravated a brain tumor was sufficient.

Similarly, in Sundquist v. Madison Rys. Co., 197 Wis. 83, 221 N.W. 392 (1928), a plaintiff claimed hysterical paralysis as the result of a collision with a streetcar two months earlier. The court allowed recovery on testimony of two doctors that such a result may probably follow, or is likely, liable or apt to follow an accident.

At least one Federal Court has criticized the use of the terms "probable" and "possible" as frequently converting the trial into a "semantic ritual or hassle." Norland v. Washington General Hospital, 461 F.2d 694, (8th Cir. 1972). The court then stated that regardless of the term used in a doctor's testimony:

> . . . if his testimony is such in nature and basis of hypothesis as to judicially impress that the opinion expressed represents his professional judgment as to the most likely one among the possible causes of the

conditions involved, the court is entitled to admit the opinion and leave its weight to the jury.

461 F.2d at 697.

In Dzurik v. Tamura, 44 Haw. 327, 359 P.2d 164 (1960), the court explained:

> When causation of the injury is a medical issue, as it is here, "the matter does not turn on the use of a particular form of words by the physicians in giving their testimony," since it is for the trier of facts, not the medical witnesses, to make a legal determination of the question of causation. Hence, the failure of a medical witness to testify positively as to what was the cause of the injury, or his statement that the accident "might" be or "probably" was the cause of the injury, is merely a circumstance to be taken into consideration by the trier of facts.

359 P.2d at 165-66.

In Eli Witt Cigar and Tobacco Company v. Matatics, 55 So.2d 549 (Fla. 1951), the Supreme Court of Florida held that the time sequence of the accident and the symptoms of the condition, plus expert testimony that the condition "could have" been caused by the accident were sufficient to create a jury question on the issue of causation. The court explained:

> The plaintiff testified that he had never suffered dizzy spells prior to the first accident, that he began to suffer such spells immediately thereafter, and that he had such a spell only three or four days prior to the second accident. It was also shown by the expert testimony of a physician that a loss of equilibrium could result from a brain concussion. We think that such evidence fairly warranted an inference of proximate cause and effect between the brain concussion and the dizzy spells, under the authority of Southern States Power Company v. Clark, 181 Fla. 521, 159 So. 881.

55 So.2d at 551 (Emphasis supplied).

In Ideal Food Products Co. v. Rupe, 76 Ariz. 175, 261 P.2d 992 (1953), plaintiff claimed that she contracted traumatic arthritis from a

fall caused by the defendant's negligence. The court stated:

> . . . [W]e held that where there was expert testimony that the injury possibly was or could have been the cause, together with other evidentiary circumstances indicating the verity of the causal relationship, same could legitimately be found.

76 Ariz. at 178 (Emphasis in original).

Two recent cases which are most analogous to the specific causation issues addressed herein are Ferebee v. Chevron Chemical Co., 552 F.Supp. 1293 (D.C. 1982); aff'd 736 F.2d 1529 (D.C. Cir. 1984), cert. denied (See Appendix 3) and Allen v. United States, 588 F.Supp. 247 (D. Utah 1984).

In Ferebee, supra,an agricultural worker was exposed to the herbicide paraquat. He ordinarily sprayed it six or seven times a month for between one and three hours during the outdoor growing seasons of 1977-1979 in Maryland. He allegedly developed pulmonary fibrosis, which caused his death.

Decedent's estate offered both of plaintiff's treating physicians as expert witnesses. They testified that, in their opinion, paraquat had caused plaintiff's illness. This was based not only on their own observations of plaintiff and medical tests that they performed on him, but also on medical studies which they asserted suggested that dermal absorption of paraquat could lead to chronic lung abnormalities.

The defendant urged that there was insufficient medical evidence to support this theory of causation. The jury resolved the issue in favor of the plaintiff. In seeking judgment n.o.v., the defendant again attacked the scientific methodology of the plaintiff:

> Defendants [sic] also argue, based upon the evidence of Dr. Carrington, that plaintiff's experts did not base their conclusions upon proper scientific methodology, as

> is required of a medical expert. * * * Dr. Carrington stated that the only proper way to establish a medical hypothesis scientifically would be either to do a number of animal studies on the subject or to conduct a population study, surveying a large number of cases. Since cases of dermal paraquat poisoning of any kind are so rare, a population study is impossible, and, according to Dr. Carrington, animal studies have not yet been done in sufficient numbers to support the hypothesis that dermal exposure can cause this kind of disease.

552 F.Supp. at 1301 (Citations omitted).

The District Court rejected the argument of the defendant in no uncertain terms:

> It is true that medical expert testimony must be grounded in proper scientific methodology, but the extremely stringent standard that defendant suggests is beyond reason. Product liability law, especially as it relates to relatively new products or those with a relatively rare yet significant danger, would be rendered next to meaningless if a plaintiff could prove he was injured by a product only after a "statistically significant" number of other people were also injured. A civilized legal system does not require that much human sacrifice before it can intervene. The fact that this is the first case of this exact type--or at least the first of its exact type in which the involvement of paraquat was discovered by alert doctors--cannot be enough by itself to shield defendant from liability. Defendant's experts were not able to fault Dr. Crystal for his basic diagnostic methodology; in fact, they used the same kinds of test results, consultations, and other tools that he did. What they disagreed with chiefly were his conclusions.

552 F.Supp. at 1301 (Emphasis supplied).

On appeal, Chevron again attacked the jury's verdict. It urged that there had never been any scientific evidence nor suggestion that paraquat could cause chronic lung injury, and, in any event, decedent could not have been exposed to enough paraquat to injure him as claimed.

The Court of Appeals for the District of Columbia Circuit affirmed, explaining:

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> The short answer to Chevron's argument is that two expert witnesses refuted it and that the jury was entitled to believe those experts. Both Drs. Crystal and Yusuf, who are eminent specialists in pulmonary medicine and who were Ferebee's treating physicians, testified that paraquat poisoning was the cause of Ferebee's illness and death. Both admitted that cases like Ferebee's were rare, but Dr. Crystal identified three other cases he felt were similar to that of Mr. Ferebee. Chevron argues that these cases can be distinguished from Mr. Ferebee's, but it is not our role to decide the merits of Chevron's attempted distinctions; Dr. Crystal thought the cases were similar, and the jury was entitled to believe him. Chevron of course introduced its own experts who were of the view that Ferebee's illness was not caused by paraquat, but the testimony of those witnesses, who did not treat Mr. Ferebee or examine him, can hardly be deemed so substantial that the jury had no choice but to accept it. The experts on both sides relied on essentially the same diagnostic methodology; they differed solely on the conclusions they drew from the test results and other information. The case was thus a classic battle of the experts, a battle which the jury must decide the victor. * * *

736 F.2d 1529 at 1535 (D.C. Cir. 1984) (Citation omitted)(Emphasis supplied).

The Court of Appeals rejected the argument of Chevron that the approach of plaintiff's expert witnesses was not sufficiently reliable:

> Chevron seeks to avoid this conclusion by asserting that expert opinion testimony must be generally accepted in the scientific community before it can be introduced as evidence and that the views of Drs. Crystal and Yusuf, while not rejected by the medical community, are sufficiently novel at this point as to be inadmissible. As support for this proposition, Chevron cites the Maryland Court of Appeal's statement in the criminal case of Reed v. State, 283 Md. 374, 381, 391 A.2d 364, 368 (1978): "before a scientific opinion will be received in evidence at trial, the basis of that opinion must be shown to be generally accepted as reliable within the expert's particular scientific field." The court in Reed, however, was referring to the introduction of evidence based on novel scientific techniques or methodologies, see, id. 391 A.2d at 367-68, and carefully distinguished the test applied to such evidence from that involved in the admission of scientific opinion testimony that, while

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> controversial in its conclusions, is based on well-founded methodologies. ("The question of the reliability of a scientific technique or process is unlike the question, for example, of the helpfulness of particular expert testimony to the trier of facts in a specific case.") Id.

736 F.2d at 1535 (Emphasis in original).

The Court of Appeals also rejected Chevron's assertion that a cause-and-effect relationship had to be clearly established by animal or epidemiological studies before plaintiffs' expert testimony could be given any weight:

> . . . a cause-effect relationship need not be clearly established by animal or epidemiological studies before a doctor can testify that, in his opinion, such a relationship exists. As long as the basic methodology employed to reach such a conclusion is sound, such as use of tissue samples, standard tests, and patient examination, products liability law does not preclude recovery until a "statistically significant" number of people have been injured or until science has had the time and resources to complete sophisticated laboratory studies of the chemical. In a courtroom, the test for allowing a plaintiff to recover in a tort suit of this type is not scientific certainty but legal sufficiency if reasonable jurors could conclude from the expert testimony that paraquat more likely than not caused Ferebee's injury, the fact that another jury might reach the opposite conclusion or that science would require more evidence before conclusively considering the causation question resolved is irrelevant. That Ferebee's case may have been the first of its exact type, or that his doctors may have been the first alert enough to recognize such a case, does not mean that the testimony of those doctors, who are concededly well qualified in their fields, should not have been admitted.

736 F.2d at 1535-1536 (Emphasis in original).

The policy enunciated by both Ferebee Courts is clearly appropriate, and we urge its adoption by this Court.

On the substantive level, the facts in the Agent Orange case are even more compelling. Here, both toxicological and epidemiological

studies have been conducted as well as the "standard tests, and patient examination" included in Ferebee. Clearly, those studies are relevant in demonstrating a probable relationship between exposure to Agent Orange and the various adverse health effects. See, e.g., Hall and Silbergeld, "Reappraising Epidemiology: A Response to Mr. Dore." 7 Harv. Envtl. L.Rev. 441, 445 (1983).

Finally, in Ferebee, the Court of Appeals refused to hold, as a matter of law, that a low level of exposure to a toxic chemical, such as paraquat, could have no adverse health effects on plaintiff:

> Finally, Chevron argues that its expert, Dr. Fisher, proved that it was physically impossible for Ferebee to have been exposed to enough paraquat to cause him any injury. Dr. Fisher's testimony, however, went only to the amount of paraquat necessary to cause the short-term illnesses that have long been recognized to follow from paraquat exposure. Accepting Dr. Fisher's testimony as true, as plaintiff's did not at trial, it still would not necessarily follow that the same amount is needed to trigger a chronic case like that which Ferebee allegedly contracted. The jury could therefore have concluded that Ferebee had been exposed to sufficient amounts of paraquat to cause the chronic disease from which he suffered--even if that exposure was not substantial enough to produce acute symptoms. The dose-response relationship at low levels of exposure for admittedly toxic chemicals like paraquat is one of the most sharply contested questions currently being debated in the medical community, see generally Leape, Quantitative Risk Assessment in Regulation of Environmental Carcinogens, 4 HARVARD ENVT'L L. REV. 86, 100-103 (1980); surely it would be rash for a court to declare as a matter of law that, below a certain threshold level of exposure, dermal absorption of paraquat has no detrimental effect. We therefore conclude that there was sufficient evidence of causation to justify submission of that issue to the jury.

736 F.2d at 1536.

The language in Ferebee is particularly pertinent, in that the factual setting in Agent Orange is remarkably similar to that which confronted the District of Columbia Court of Appeals!

The effort to fashion a fair and just "rule of law" often involves an analysis of appropriate policy considerations. As one commentator, see, Malone, "Ruminations on Cause-in-Fact", 9 Stanford L.Rev. 60 (1956), puts it:

> . . . Whenever it can be said with fair certainty that the rule of conduct relied upon by the plaintiff was designed to protect against the very type of risk to which the plaintiff was exposed, courts have shown very little patience with the efforts of defendant to question the sufficiency of the proof on cause. Such cases nearly always reach the jury if the plaintiff's contention on the issue has the slightest factual possibility . . ..

9 Stanford L.Rev. at 73 (Emphasis supplied).

A similar functional approach to "causation in fact" is described by another commentator, see, Calabresi, "Concerning Cause and the Law of Torts", 43 U. Chi. L.Rev. 69 (1975), where it is stated:

> Causal requirements, like all other legal requirements, must ultimately justify themselves in functional terms. Law is a human construct designed to accomplish certain goals . . . object of law is to serve human needs, and thus legal terms . . . must sooner or later be linked to the service of human needs.

43 U. Chi. L.Rev. at 105.

As demonstrated, even to the highly emotional level, at the Fairness Hearings conducted in 5 cities by this Court, the magnitude of the suffering of these veterans and their families should be, to the extent possible, "linked to the service of human needs." The "causal requirements" therefore should, as a policy matter, serve those needs.

Clearly, in the Agent Orange cases, we were prepared to prove ". . . that the rule of conduct relied upon by the plaintiff was designed to protect against the very type of risk to which the plaintiff was exposed . . . ". Recently, the District of Utah spoke to that concept.

In Allen v. United States, 588 F.Supp. 247 (D. Utah 1984), plaintiffs sought to recover for cancer or leukemia allegedly caused by United States testing of atomic devices prior to 1953. The court first explained that the issue of causation was very difficult:

> In this case, the factual connection singling out the defendant as the source of the plaintiffs' injuries and deaths is very much in genuine dispute. Determination of the cause-in-fact, or factual connection, issue is complicated by the nature of the injuries suffered (various forms of cancer and leukemia), the nature of the causation mechanism alleged (ionizing radiation from nuclear fallout, as opposed to ionizing radiation from other sources, or other carcinogenic mechanisms), the extraordinary time factors and other variables involved in tracing any causal relationship between the two.

588 F.Supp. at 405.

The court also noted that the issue of causation was further complicated by the long delay between the exposure to radiation and the observed cancer or leukemia. 588 F.Supp. at 405.

Nonetheless, the court said that a remedial framework could still be fashioned to fairly compensate a plaintiff's injuries. 588 F.Supp. at 414-415.

The Allen court is to be commended for grappling so well with such a complex problem. The real value is that the Allen "causation solution" is at the same time scientifically sound, judicially workable because of its relative simplicity, and most importantly, fair and just from a policy standpoint.

The court had extensively discussed a series of cases dealing with the problem of indeterminate causation in which a plaintiff was able to rely on a series of factual connections which established a rational, reasonably exclusive relationship between a defendant's conduct in releasing lethally hazardous chemicals into the environment and each claimant's injuries. 588 F.Supp. at 407-414. In these cases, the burden then shifted to the defendant to show that his conduct had not played a substantial factor in causing the harm. In Allen, the court then held:

> Where a defendant who negligently creates a radiological hazard which puts an identifiable population group at increased risk, and a member of that group at risk develops a biological condition which is consistent with having been caused by the hazard to which he has been negligently subjected, such consistency having been demonstrated by substantial, appropriate, persuasive and connecting factors, a fact finder may reasonably conclude that the hazard caused the condition absent persuasive proof to the contrary offered by the defendant.
>
> In this case, such factors shall include, among others: (1) the probability that plaintiff was exposed to ionizing radiation due to nuclear fallout from atmospheric testing at the Nevada Test Site at rates in excess of natural background radiation; (2) that plaintiff's injury is of a type consistent with those known to be caused by exposure to radiation; and (3) that plaintiff resided in geographical proximity to the Nevada Test Site for some time between 1951 and 1962. Other factual connections may include but are not limited to such things as time and extent of exposure to fallout, radiation sensitivity factors such as age or special sensitivities of the afflicted organ or tissue, retroactive internal or external dose estimation by current researchers, a latency period consistent with a radiation etiology, or an observed statistical incidence of the alleged injury greater than the expected incidence in the same population.

588 F.Supp. at 415.

The striking similarity to the types of disease associated with Agent Orange, especially various forms of cancer, is manifest, and we submit, compelling. Also it is consistent with the approach taken by 2 commentators, i.e. Hall and Silbergeld, "Reappraising Epidemiology: A Response to Mr. Dore", 7 Harv. Envtl. L.Rev. 441, 445 (1983).

Finally, the court noted that the government's own negligence at the time of the incidence in this case was an additional persuasive factor warranting a shift in the burden of causation, given the other connecting factors:

> . . . the Government's negligent failure to adequately monitor and record the actual external and internal radiation exposures of off-site residents on a person-specific basis has yielded many glaring deficiencies in the evidentiary record as it relates directly to the question of causation. The current multi-million dollar effort to reconstruct the radiation dosages received by plaintiffs or their decedents is constantly hampered by the failure of the off-site radiation safety personnel to gather whole categories of exposure data at the time that the exposures actually took place. Furthermore, had Government personnel provided adequate warnings of risk and information as to precautions minimizing the amount of exposure, a materially different picture as to appropriate inferences about factual connection and cause-in-fact might now be presented. Accurate monitoring of persons largely was not undertaken; adequate warnings and information were almost entirely omitted from the operational radiation safety activities. A strong additional reason for shifting the burden of proof on the cause-in-fact question is thus readily apparent from the record.

588 F.Supp. at 412-413.

As to the burden-shifting aspect, in particular its applicability to the case against the chemical companies, please see Plaintiffs' Memorandum of Points and Authorities in Opposition to the United States' Motion to Dismiss filed October 10, 1984, specifically "9. Burden Shifting", pp. 131-191, inclusive.

This Court, in its Preliminary Memorandum and Order on Settlement dated September 25, 1984, strongly indicates approval of the burden-shifting concept in these circumstances when it states:

> The solution that would most readily suggest itself is a burden shifting approach, analogous to that used in the indeterminate defendant situation already discussed. Allen v. United States provides a good example of how burden-shifting would be applied in an indeterminate plaintiff case. A plaintiff must show that the co-defendant, in that case the United States, negligently put "an identifiable population group" of which he was a member at "increased risk" and that his injury is "consistent with having been caused by the hazard to which he has been negligently subjected, such consistency having been demonstrated by substantial, appropriate, persuasive and connecting factors, a fact finder may reasonably conclude that the hazard caused the condition". Allen, slip op at 343. At that point, the burden shifts to the defendant who will be held liable unless it can offer "persuasive proof" of noncausation. Id. at 344.

The argument applies with equal force to the chemical companies. The introduction of similar pertinent evidence would have laid the factual predicate for this "burden shifting approach" as to the defendants (chemical companies).

Plaintiffs however take strong issue with the Court when it says that "it would be impossible in most cases to identify the individual class members who were injured by Agent Orange". (Prel. Memo., pp. 296-297). While the class device was appropriate for reasons expressed at length and often, each individual's case in terms of causation in fact,

proximate cause and damages must be handled "on a case-by-case basis using the preponderance-of-the evidence rule". This is the essential reason why the "indeterminate plaintiff" problem is not relevant to this case, Delgado's hypothesis notwithstanding. See, 70 Cal. L.Rev. supra at 887 (footnote 27). (Prelim. Memo. at 273 citing Santosky v. Kramer, 455 U.S. 745, 755, 102 S.Ct. 1388, 1395 (1982); W. Prosser, Handbook of the Law of Torts, §38 at 208-09 (1971); [Keeton and Prosser, The Law of Torts, §38 at 239 (1984)]; Kaplan, Decision Theory and the Fact Finding Process, 20 Stan. L. Rev. 1065, 1072 (1968)).

With respect to the statistical evidence in Allen v. United States, supra (see, Prel. Memo. at 273), we submit that there are stronger positive associations in certain Agent Orange/dioxin-related cancers, e.g. soft-tissue sarcoma and lymphoma, than exist with low-level ionizing radiation and leukemia. As noted a few pages later (see, Prel. Memo. at 278), the fact-finder (the Court in Allen) noted significant variation in experts' interpretations of statistical evidence, but notwithstanding such variation, found in favor of those plaintiffs based upon the analyses set forth earlier.

In the last analysis, what the Courts did in Allen and Ferebee were to let the fact-finder resolve issues of credibility, giving appropriate weight to conflicting testimony - whether analyses and/or conclusions of expert witnesses. Nothing is as fundamental and so deep-seated in our system of American jurisprudence. We ask for no more!

E. Application to Agent Orange Case

1. Agent Orange/Dioxin is highly toxic and carcinogenic.

The most toxic of the several dioxin isomers is 2,3,7,8-Tetrachlorodibenzo-para-dioxin (TCDD) - commonly referred to as "the most toxic substance ever synthesized by man." TCDD has also been shown to be the most potent of all known carcinogens. These facts have been forcefully confirmed in agency reports, medical and scientific literature, and in testimony from Plaintiff, defense and government expert witnesses.

The United States Environmental Protection Agency effectively characterized the extreme toxicity of TCDD in their "Ambient Water Criteria Document for 2,3,7,8-Tetrachlorodibenzo-p-dioxin" of February, 1984 stating:

> 2,3,7,8-TCDD is one of the most toxic substances known. It exhibits a delayed biological response in many species and is highly lethal at low doses to aquatic organisms, birds and mammals. It has been shown to be acnegenic, fetotoxic, teratogenic, mutagenic (in a limited number of mutagenicity tests) and carcinogenic, and affects the immune responses in mammals.
>
> These findings, in conjunction with the wide distribution of contaminated products and its extreme stability in the environment, lead to the conclusion that 2,3,7,8-TCDD represents a potential hazard to both aquatic and terrestrial life, and makes 2,3,7,8-TCDD one of the major concerns for public health.

(Ambient Water Criteria Document for 2,3,7,8-TCDD, p. A-8)

When Plaintiffs' government causation witness, K. Diane Courtney, Ph.D., was questioned "Is there any man-made substance that is any more toxic, to your knowledge, than TCDD?", she replied, "Based on my knowledge, I do not know of any man-made compound that is more toxic." (Courtney depo., 347:18-22) Government witness Philip Landrigan of the National Institute for Occupational Safety and Health (NIOSH) described the extreme toxicity of TCDD differently, claiming that he did not know "of any other man-made toxin that

produces lethal results in any animal species at doses less than TCDD." (Landrigan depo., 251:6-8) Additionally, Plaintiffs' expert witness, Deborah Barsotti, Ph.D., testified "that dioxins are toxic, and in particular TCDD is exceptionally toxic", and, "that chronic low level exposure to dioxins is significantly toxic." (Barsotti 26(b)(4) Statement).

Several Plaintiff, defense and government witnesses were prepared to further express both the extreme toxicity as well as the exceptional carcinogenicity of 2,3,7,8-TCDD. Dr. Donald Barnes, the Senior Science Advisor to the Assistant for Pesticides and Toxic Substances for the EPA claimed that:

> Certainly in terms of traditional measures of toxicity, it (2,3,7,8-TCDD) is in my opinion clearly demonstrated to be a particularly toxic chemical . . .

(Barnes depo., 12:7-11)

Dr. Barnes later added, "I would certainly characterize 2,3,7,8-TCDD as exquisitely or a uniquely toxic chemical . . .". (Barnes depo., 262:3-5) In addition, Dr. Barnes claimed:

> . . . that in animal studies 2,3,7,8-TCDD . . . can elicit a carcinogenic response. There are some data to suggest . . . that 2,3,7,8-TCDD may be -- exposure to 2,3,7,8-TCDD may be associated with the incidence of cancer in humans.

(Barnes depo., 77:12-17)

Elaborating on the carcinogenicity of TCDD, six scientists involved in the peer review of the previously cited EPA Criteria study stated that:

> 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is probably carcinogenic for humans on the basis of animal carcinogenicity studies which were positive in multiple species and organs. Epidemiological studies of workers exposed to chemicals contaminated with TCDD such as 2,4,5-T (trichlorophenoxyacetic acid) and 2,4,5-trichlorophenol are consistent with the position that TCDD is

> carcinogenic for humans; the available evidence indicates an excess incidence of soft tissue sarcomas.

(Consensus Statement of July 29, 1983).

Similarly, Plaintiffs' expert witness, Theodor D. Sterling, Ph.D., was prepared to testify:

> That there exists a considerable body of medical and scientific evidence which demonstrates that the preparations of 2,4,5-T and 2,4-D are toxic, teratogenic and carcinogenic . . based on the reviews of the literature and critical evaluation of data pertaining to the health effects of 2,4,5-T and 2,4-D on animals and humans and is contained in documents of which Dr. Sterling is the sole author.

(Sterling 26(b)(4) Statement).

Defendants' expert witness, Dr. Vernon Houk, agreed with these findings, claiming that:

> TCDD is carcinogenic in several species of animals, produces cancer in those animals in at least three different routes of exposure . . . (and) [i]t is very likely that it is a carcinogen in man.

(Houk depo., 113:7-12)

Defendants' government causation witness, Dr. Han Kang, also affirmed the toxicity and carcinogenicity of TCDD. (See, Kang depo., 97-98, 141).

Plaintiffs' expert witnesses, Drs. Codario, Legator, Orris, Hay and Silbergeld each intended to testify that Agent Orange and its contaminant TCDD is (1) highly toxic and (2) carcinogenic. (See generally, the 26(b)(4) Statements and supplements of Plaintiffs' expert witnesses).

Specifically, Dr. Peter Orris is and was prepared to testify that:

> Dioxins are extremely toxic particularly 2,3,7,8-TCDD . . . That TCDD is extremely toxic at extremely low levels . . . That TCDD is carcinogenic, specifically causing soft tissue sarcomas and lymphomas . . . That TCDD as a carcinegen [sic] does not affect one organ,

> but many . . . (and) . . . That additional sites of cancer may be caused by exposure to TCDD.

(Orris 26(b)(4) Statement).

Certain witnesses elaborated specifically on the strength of TCDD as a carcinogen. Drs. Ellen Silbergeld, Marvin Legator and Marvin Schneiderman testified that dioxin is a complete carcinogen. (See, Legator depo., 118, 147-148; Schneiderman depo., 357:4-19; Silbergeld depo., 221: 12-22, as well as subsection (d) infra). Stated differently:

> Dioxin is capable of contributing to all of the stages necessary to produce cancer and can enormously increase the incidence of cancer when prior carcinogenic exposure has occurred.

(Schneiderman depo., 283:16-25, 284:1-8)

Furthermore, Dr. Lennart Hardell is prepared to testify to the causal relationship between exposure to phenoxy herbicides and human cancer, particularly soft-tissue sarcoma and malignant lymphoma. (Hardell 26(b)(4) Statement).

Finally, several expert witnesses testified to the overwhelming potency of TCDD relative to other carcinogens. Dr. Steven Bayard, a member of the Carcinogen Assessment Group (CAG), stated that 2,3,7,8-TCDD was "the most potent of the 54 chemicals which the CAG evaluated as potential carcinogens . . .". (Bayard depo., 80:1-11) and that,

> With respect to relative potency, we (CAG) found that it (2,3,7,8-TCDD) was 100 times more potent than the next most potent chemical, which is benzidene, and 100 million times more potent than vinyl chloride.

(Bayard depo., 80:19-22).

Moreover, Plaintiffs' government causation witness, Dr. Janet Springer, and Dr. Marvin Schneiderman and the Environmental Protection Agency

each reiterated these relative potencies. (See, Springer depo., 41-42; Schneiderman 26(b)(4) Statement; Ambient Water Criteria Document).

It is obviously clear that Agent Orange, with its contaminant 2,3,7,8-TCDD is the most toxic substance known to man. Testimony from both Plaintiffs and defendants agree on this point. These witnesses also acknowledge that TCDD is not only a proven carcinogen, but the most potent of all known carcinogens. Due to the extremely toxic and carcinogenic nature of TCDD, no "no effect" or "safe level" of exposure can be determined. (See the following section 2).

2. Agent Orange/dioxin has no safe level of exposure.

Due to its extreme toxicity, as detailed in subsection (1) supra, experts cannot determine what, if any, safe level or "no effect" level of dioxin exposure exists. In fact, Plaintiff and defense expert witnesses have testified (1) that there is no "safe level" of dioxin exposure, and (2) specifically, that as a carcinogen, there is no known "no effect" or "minimum effect" level.

Addressing the exposure level of TCDD in general, Dr. Ronald Codario stated:

> . . . I think it's very important for us to understand that since scientists throughout the world can never agree on a safe limit for dioxin, we certainly must assume until proven otherwise that any exposure to TCDD, regardless of the amount, cannot be considered safe as of this time.

(Codario depo., 427:2-7)

Dr. Donald Barnes' deposition emphasized the uncertainty surrounding the levels of dioxin exposure. The testimony followed:

> Q. As it relates to 2,3,7,8-TCDD in toxicological terms, at what level do you believe there is a no effect, a minimum level?
>
> A. I don't think that's been established . . .
>
> Q. . . . What do you mean when you say it has not been established?
>
> A. I don't know what that level might be.

(Barnes depo., 103:10-25, 104:1)

The questioning continued:

> Q. In the case specifically of 2,3,7,8-TCDD, is there any known level which is acceptable? Is there any known level today that is acceptable for risk for human beings being exposed to this chemical?

A. There's nothing established on the books of any agency or Government or so on that I'm aware of.

(Barnes depo., 104:13-16, 20-21)

Stated differently, Dr. Schneiderman explained:

. . . that dioxin has the steepest dose-response curve of any material that EPA has reported on, and that there's no material . . . that has a dose-response curve within that range . . .

(Schneiderman depo., 185:10-16)

Dr. Schneiderman concluded "I believe, and I think most people who are working in this field believe that there is no threshold, i.e. any level of exposure has some finite probability of causing the disease . . .".

(Schneiderman depo., 236:20-24)

Dr. Legator supplemented Dr. Schneiderman's statement in his deposition claiming:

. . . TCDD is unique in every way . . . I am saying that TCDD is a unique chemical, and then by that I mean because it is so much more active than these other chemicals, that, indeed, you may get a greater blurring of a dose response curve than you would with a chemical that is less active in terms of inducibility.

(Legator depo., 108:25, 109:1-7)

As a known carcinogen, experts further contend that there is no known "no effect" level below which there is no increased risk of cancer. Dr. Ellen Silbergeld effectively capsulized in her deposition testimony:

. . . that once you have a known carcinogen . . . that is a substance which is known to produce carcinogenic effects within a range of doses below a lethal dose, there is no level below which that substance will not produce an increased risk . . .

(Silbergeld depo., 196:5-11)

In the Annals of the New York Academy of Sciences (NYAS), Volume on "Occupational Carcinogenesis", Dr. William J. Nicholson wrote, "In spite of considerable research on the effects of carcinogenic substances, no data exist that would define a threshold for any carcinogen. (Annals of the NYAS, Vol. 271, "Occupational Carcinogenesis", 155: 1976). In a subsequent volume of the NYAS on "Public Control of Environmental Health Hazards", Plaintiffs' expert, Dr. Marvin Schneiderman, summarized:

> We see little or no evidence for the existence of thresholds in human cancer. There is much conjecture, some of it high quality and there are some scattered data, but convincing evidence for threshold is not at hand either from animals or from man.
>
> Dose-response studies in the laboratory are consistent with there being no threshold for a carcinogen.

(Annals of the NYAS, Vol. 329, 126: 1979).

Defendants' expert witness, James G. Wilson, revealed that he did not know the dose relationship of cancer or the level of TCDD which does not cause cancer. (Wilson depo., 194:1-8). Dr. Marvin Legator further stated that:

> . . . with carcinogens, it's . . . difficult to establish a threshold if one does even theoretically exist, and TCDD is in particular, by the very nature of response we're seeing with it, I would venture to say that any amount of exposure could be detrimental.

(Legator depo., 105:5-10)

In addition, Plaintiffs' expert witnesses, Drs. Schneiderman, Levin, Legator and Orris are and were prepared to testify that no safe level exists for the highly potent carcinogen TCDD. Dr. Theodor Sterling planned to testify that:

> . . . There is no credible scientific evidence of a no effect level, said another way, as a carcinogen, there is no safe level and therefore, a single exposure years

ago may be responsible for human cancer which develops today.

(Sterling 26(b)(4) Statement)

Similarly, Dr. Alan Levin was prepared to state:

That, in connection with the carcinogenic effect, there is no safe level for TCDD or any other carcinogen, and that a single exposure several years earlier can result in human cnacer many years later.

(Levin 26(b)(4) Statement)

Lastly, Drs. Schneiderman and Orris affirmed that there is no known safe level for TCDD - a known carcinogen. (See, Schneiderman depo., 239-240; Orris 26(b)(4) Statement).

In summary, dioxin is highly toxic and carcinogenic at extremely low levels. For this reason, neither defense nor Plaintiffs' expert witnesses can state that a "safe level" of dioxin exposure exists. These witnesses instead hold that, in fact, no "minimum effect" or "no effect", or "threshold" level of dioxin exists. Furthermore, due to its extraordinary carcinogenicity, no safe level exists below which no increased risk of cancer occurs.

It is clearly evident from the testimony and literature described herein that dioxin is uniquely toxic, rendering it virtually impossible to determine a "no effect" or "safe level" of exposure.

3. Plaintiffs were exposed to Agent Orange/dioxin.

Proving direct or proximate exposure of an individual Plaintiff to Agent Orange can be approached in different ways. Exposure to Agent Orange can be verified through testimony of the Plaintiff or his military co-personnel. This testimony can certify direct spraying, undocumented missions in sprayed areas, and the ingestion and inhalation of Agent Orange through eating, drinking, and living in defoliated areas. See, generally, depositions of representative Plaintiffs, e.g., depositions of George Ewalt taken 2/20/84 and 2/21/84, pp. 37-38; 72-96; 146-169; 264; 275-378; depositions of Dan Ford Taken 2/20/84 and 2/21/84, pp. 108-190; 222-292; 322-323; 376-422; 425-426; 430-439; 443-450; 464-482; depositions of Dan Jordan taken 2/22/84, 2/23/84 and 4/30/84, pp. 114-116; 120-121; 248-252; 281-490; 504-664; deposition of David Lambiotte taken 2/24/84, pp. 142-326; depositions of Mike Ryan taken 2/13/84 and 3/6/84, pp. 38-41; 121-127; 164; 223-408.

Furthermore, Plaintiffs' expert witnesses were and are prepared to testify to the various methods of exposure as well as to the specific individual exposure of the representative Plaintiffs. (See the depositions and 26(b)(4) Statements and supplements of Plaintiffs' expert witnesses in general, and specifically: Codario depo., 109, 222-225, 562-563 and 26(b)(4) statement and supplements; Schneiderman depo., 190; Levin depo, 17-20).

A second method of verifying individual exposure is through specific military documents. These documents can potentially prove exposure in and of themselves, or strengthen the Plaintiff or co-personnel testimony described above. In fact, the Army Agent Orange Task Force used these records along with the spray mission tapes and general military knowledge

to determine levels of exposure in the individual representative Plaintiffs. See, results of the Army Agent Orange Task Force Study attached as Appendix 2.

Presumably, through determining the movement of a Plaintiff's military unit and correlating these movements with the spray mission tapes, individual exposure can be assessed. However, the documents used by the Task Force in their study and subsequently, a large portion of the military documents produced in discovery, were written on the Division or Batallion levels. Written on such high levels, these documents often excluded mention of any individual soldier's or their respective company's and unit's movements. Therefore, to construe the Army Agent Orange Task Force Study as complete in including all relevant exposure information would be inaccurate. For example, the Task Force determined that Plaintiff David Lambiotte was "not exposed". (See, Appendix 2 at p. A2-4) However, deposition testimony of the Plaintiff and/or his co-personnel would reveal that he frequently went on convoys in or near defoliated areas.

The methods of proving individual Plaintiff exposure to Agent Orange described above can be further supplemented through testimony of specific military personnel, for example, Richard Christian. Such testimony could add to the validity or highlight the limitations of the military documents in addition to verifying and possibly supplementing individual Plaintiff or co-personnel testimony.

4. Agent Orange/dioxin did cause an array of adverse health affects in the 9 representative Plaintiffs.

The proof of Plaintiffs' causation case was premised upon a two-tier approach as the case was to be presented to the jury as a class action utilizing representative plaintiffs. One level of proof was to be an exhaustive explanation of the incredible toxicity of 2,3,7,8-TCDD (dioxin) and the many bodily systems which dioxin can affect. This testimony was to describe the animal studies, retrospective human studies, and the current epidemiological studies which all confirm that dioxin is capable of causing a multitude of pathologies, i.e. dermatological problems, liver and other systemic disorders, immunological disorders, neuro-toxic effects, cancers, and reproductive problems, including birth defects. Specifically, this proof would have established that dioxin is a "complete" carcinogen, i.e. both as an "initiator" and potent "promoter"; that therefore there is no safe level of exposure, and conversely, that any level of exposure is capable of causing disease.

Plaintiffs' witnesses on causation would have testified within the scope of this level of proof, as well as the other aspect of causation proof, i.e. "cause-in-fact" which would have dealt with the specific problems presented on behalf of the class through the representative Plaintiffs. More particularly, some of the expert witnesses would have testified as to the cause in fact, i.e. exposure of Agent Orange in relationship to the adverse health conditions in the representative Plaintiffs.

This dual level of proof was necessary to form the proper foundation for damages on behalf of the entire class as well as for the jury to fully comprehend the individual causation in the representative Plaintiffs. Without the overview of toxicity, methods of testing for toxicity and carcinogenicity,

and methodology of epidemiology as it relates to presumptive conclusions of causation, the testimony of exposure and "cause and effect" would have been received in a vacuum and would have been difficult for the jury to understand.

When reviewing the current presentation of Plaintiffs' causation witnesses in this capsule summary, it must be remembered that the majority of the testimony was developed by counsel for the defendants through the discovery process. Had this matter proceeded to trial the same subject matter would have been structured and articulated in a positive and direct fashion rather than in an adversarial setting. Regardless of these limitations, the testimony and evidence presented herein will show that the Plaintiffs' causation case was complete and comprehensive and fully capable of establishing causation on behalf of the class, and for the representative Plaintiffs, within a reasonable degree of medical and scientific probability.

A summary of each of the major areas of injury will be discussed below and will be followed by specific references to testimony as to the diseases present in each representative Plaintiff, together with factual support from the Record of the relationship of such diseases to the particular veteran-Plaintiffs' exposure to Agent Orange.

a. Dermatological

On this issue there can be no real dispute; TCDD can cause chloracne. As clearly stated by the United States Environmental Protection Agenty ("EPA"):

> The most commonly reported symptom related to 2,3,7,8-TCDD exposure in man has been chloracne (Bauer et al., 1961; Kimmig and Schulz, 1957; Schulz, 1957; Firestone, 1977; Dugois and Colomb, 1956, 1957; Dugois et al., 1958; Bleiberg et al., 1964; Oliver, 1975; Poland et al., 1971; Kimbrough, 1980).

(Ambient Water Quality Criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin, U.S. EPA Office of Water Regulations and Standards, February, 1984, p. C-62)

The fact that TCDD can cause chloracne was also repeated by Defense, Plaintiff and Government causation witnesses. Dr. Donald Barnes, a Ph.D. in chemistry and physics, called as a "government causation" witness, stated that TCDD has "clearly been demonstrated to be a particularly toxic chemical". (Barnes depo., 12:8-9) Dr. Barnes was the Science Advisor to the Assistant Administrator for Pesticide and Toxic Substances for the EPA and had participated in preparing the peer review documents of the EPA pertaining to TCDD. He was clearly of the scientific opinion that TCDD affects the skin and is acnegenic, i.e. it causes chloracne. (Barnes depo., 126:13-18) Dr. Barnes further acknowledged that all possible routes of exposure, i.e. inhalation, dermal absorption and ingestion, can result in adverse health effects. (Barnes depo., 157:4-13)

Dr. Debdas Mukerjee, a Ph.D. in genetics and cytogenetics, while testifying primarily as to carcinogenicity and reproductive problems, stated that "TCDD at acute or subchronic exposures had demonstrated adverse health effects on the skin . . ." (Mukerjee depo., 98:6) and specifically, that

"TCDD is acnegenic." (Mukerjee depo., 100:25) Furthermore, among Plaintiffs' witnesses, Dr. Deborah Barsotti, a toxicologist having done a substantial amount of research in halogenated aromatic hydrocarbons, including TCDD, stated:

> I have an opinion that on an individual basis, the halogenated aromatic hyrdocarbons, members of that class of compounds will induce chloracne in those species which are susceptible to chloracne.

(Barsotti depo., 91:19-22)

She supported her statement further, noting: "There are at this time indications that chloracne is a TCDD symptom in exposed animals and this is also certainly in the literature for humans." (Barsotti depo., 193:17-19)

Plaintiffs' two primary expert witnesses, Dr. Ronald Codario and Dr. Peter Orris, stated clearly that the existence of chloracne is a significant sign of TCDD exposure and that, ". . . there is no question . . . chloracne has been found in humans so exposed to trichlorophenol and TCDD." (Codario depo., 576:15-18) The strength of dioxin to cause skin eruptions was expressed as:

> Chloracne may develop anywhere, especially with systemic exposure to these chemicals, but it has predominance in the exposed areas of the skin that may have been exposed to higher quantities of these chemicals than other areas. With respect to dioxin from herbicides or others, you may find it in . . . areas other than exposed because clothes get soaked and various parts of the body were exposed, close relationship to the skin and that area of clothing.

(Orris depo., 147:19-25, 148:1-3)

More specifically, Dr. Codario indicated the significance of the location and cause of chloracne in representative Plaintiff Mike Ryan's case. In his examination and subsequent report on Mike Ryan (February 15, 1984), Dr. Codario noted:

> . . . and most significantly of all he developed a scarring acne-like eruption around the temples, cheeks and groin which still persist today . . . This gentleman has marked peripheral neuropathy along with an acne-like eruption in his groin. This combination of physical findings is highly consistent with TCDD poisoning and should be considered so unless proven otherwise. Young points out that when the acne eruption occurs in the groin, the diagnosis of chloracne is highly likely!

(Codario report dated February 15, 1984)

Dr. Ronald Codario affirmed Mike Ryan's diagnosis of chloracne in his deposition and attributed this condition to Ryan's dioxin exposure in Vietnam.

Furthermore, Dr. Peter Orris recognized Plaintiff Dan Ford's "acneform lesions" as a condition confirming his exposure and thereby strengthening the association between his exposure and subsequent development of soft-tissue sarcoma. Dr. Orris stated these factors after his examination of Dan Ford's medical records in his report of April 9, 1984, stating:

> In light of Mr. Ford's exposure to TCDD containing herbicides in Vietnam; the development of acneform lesions at that time, and the absence of any confounding exposures, it is likely in my opinion that his soft tissue sarcoma, that was diagnosed in 1980, was caused by his TCDD exposure in Vietnam.

(Orris report to Thomas W. Henderson, Esq. dated April 9, 1984)

The defendants recognized the causal relationship between TCDD exposure and chloracne. The defendants argued that absent chloracne, a specific individual could not associate other adverse health effects with their dioxin exposure. In other words, without having a diagnosis of chloracne, an individual plaintiff could not consider dioxin exposure a "cause" of any of his subsequent medical conditions.

Nevertheless, Plaintiffs were and are prepared to prove causation on a variety of adverse health effects (as outlined previously in subsection 4) without chloracne as a necessary precursor. Plaintiffs' are of the opinion that chloracne is by no means a necessary presequisite for other Agent Orange/dioxin-related adverse health effects. Dr. Peter Orris elaborated on this, stating:

> The soft tissue sarcomas were not associated [with chloracne] to my knowledge, The patients that developed porphyria cutanea tarda did not necessarily have chloracne. The patients with acute and chronic neuropsychiatric problems did not necessarily have chloracne. I believe the patients with peripheral neuropathy as well did not have chloracne and case reports of hepatitis I don't think were associated 100 percent to chloracne. It is my reading of the literature that chloracne cannot be used as an index of exposure.

(Orris depo., 152:25, 153:1-11)

Nevertheless, it is clear that chloracne is a significant indicator of dioxin exposure. Plaintiffs hold, however, that chloracne is only one sign of exposure; more specifically, of acute, as opposed to chronic, exposure. Plaintiffs will set out in subparts b through e to prove specific individual causation on a variety of health problems which are not predicated on the presence of chloracne.

b. Systemic

Exposure to dioxin can cause systemic effects, that is, conditions or diseases involving the entire body as opposed to a localized condition. The primary systemic effects involve (1) the liver and (2) the immunosuppressive responses.

i. liver

The liver is the primary site of several metabolic activities. The liver's metabolism of TCDD, however, is not normal. TCDD is chemically stable, lipophilic and resists degradation, thus attributing to its bioaccumulation (Barsotti 26(b)(4) Statement). Because TCDD is not water but fat soluble, it cannot be eliminated by the kidneys, "unless it is converted to a water soluble substance which does not appear to occur in humans." (Codario 26(b)(4) Statement, Section III)

Plaintiffs' expert witness, Dr. Deborah Barsotti, described this further, stating:

> Generally, however, the data indicate that if metabolism does occur the rate is slow (Guenther et al., 1979). The ramification of this finding is that the body would be incapable of or slow in ridding itself of TCDD and TCDD would accumulate and persist in the lipid stores. In Dr. Barsotti's work, as well as others', this appears to be the case with rhesus monkeys and man (Montagna et al., 1979; Van Miller, 1981; McNulty et al., 1983).

(Barsotti 26(b)(4) Statement, Section V, subsection 2)

TCDD, therefore, can be stored in the fat, furnishing a constant or chronic source of exposure. Plaintiffs' experts were and are prepared to testify that, "The literature and . . . research documents that chronic exposure to TCDD exhibits many more deleterious effects than single or acute exposures," (Codario 26(b)(4) statement, Section IV, subpart 5) and that,

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"stored in the lipid compartment . . . it can cause problems that continue on beyond the point that detectable dioxin can be found in the adipose tissue." (Levin depo., 136:10-13)

By storing in fat, TCDD affects lipid profiles, causing increases in blood cholesterol and triglyceride levels; the increased blood cholesterol levels being a significant risk factor for cardiovascular disease. When asked whether TCDD affects lipid profiles, Dr. Hay responded:

> Yes, it does. The men in industry who have been exposed to TCDD have high blood cholesterol and high triglyceride levels.

(Hay depo., 279:6-10)

In addition, Dr. Hay testified that dioxin will cause blood cholesterol levels to rise. (Hay depo., 337:3-5) The EPA cited in its Ambient Water Quality Criteria Study several studies on TCDD-exposed workers noting significant liver disorders including raised levels of blood cholesterol and total lipids. (US EPA Ambient Water Quality Criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin, C-62 to C-70, February, 1984)

Exposure to TCDD also initiates enzyme induction, specifically upsetting the porphyrin metabolism which occurs in the liver. Drs. Hay, Silbergeld and Codario were prepared to testify on the effects of TCDD on porphyrins as well as to the porphyrin disturbances of specific representative cases. In his report on George Ewalt, Dr. Codario stated:

> In addition, Mr. Ewalt has a porphyrin disturbance, confirmed by special testing at Abbott-Northwestern Hospital- world renowned for porphyrin research. The TCDD contaminant of the herbicides is known to cause this type of disturbance. 3/
>
> 3/ Strik, J. (1979) "Porphyrins in Urine as an Indication of Exposure to Chlorinated Hydrocarbons." Ann. N.Y. Acad. Sci. 320:308-310.

(Codario report to Gene Locks, Esq., 1984)

Additionally, Dr. Herbert Kaye was prepared to testify that:

> Agent Orange represents a neurotoxic agent that works indirectly be affecting liver function and the liver's production of heme (an iron compound of protoporphyrin); and in doing so makes an individual, so affected, vulnerable to neurohypoxia.

(Kaye 26(b)(4) Statement, Section IV. subpart A)

Because the liver performs several metabolic functions, TCDD affects these functions in several different ways, examples of which have been discussed herein. Plaintiffs' expert witnesses were and are prepared to testify to the various toxic effects of TCDD on the liver's functions, based on their research, experience, the medical and scientific literature, as well as on their clinical data and observations on the individual representative Plaintiffs.

ii. immune system

A second major area of systemic concern is the effect of TCDD on immuno-suppressive responses. Both animal and human data indicate that dioxin is an immune suppressant. (Schneiderman depo., 316:1-6) Dr. Ronald Kerman, a Ph.D. in immunology, was to testify on immuno-toxicology, "which has been defined as 'the undesirable effects of an inappropriate response of the immune system.'" The substance of his opinions, and the significant areas of concern, are:

> A. That TCDD is immunosuppressive.
> B. That a person exposed to TCDD might have increased predisposition to increased infection, neoplasm (cancer), and other diseases

(Kerman 26(b)(4) Statement, Section II).

In addressing the first concern, Dr. Alastair Hay testified that TCDD is immunosuppressive in humans based on "the substantial body of animal evidence that TCDD affects the immune system . . " (Hay depo., 73:9-11) Plaintiffs' expert witness, Alan Scott Levin, M.D., testified that "After

having read a large number of studies, including the Ranch Hand Study, "(He) had formulated an opinion that Agent Orange can be the cause of chemically-induced immune disregulation." (C.I.I.D. (Levin depo., 244:22-25, 245:1) Dr. Levin also planned on using the clinical data he had gathered after testing the representative Plaintiffs to support his opinion on the causal relationship between dioxin exposure and immune dysfunction.

Plaintiffs underwent immunological testing from Plaintiffs' expert witnesses Drs. Alan Levin and Ronald Kerman. Both found significantly abnormal results. In discussing the findings from his testing, Dr. Levin revealed that:

> Generally it [the testing] indicated that the individuals that we studied had immune disregulation.

The questioning continued:

> In those individuals in which you found immune disregulation, what did that tell you about the ability of their immune systems to actually function properly . . .
>
> . . . It was an indicator that there was some alteration in their capacity to respond appropriately to the demands placed on the normal immune system.

(Levin depo., 63-64: 22-23, 1-15)

Dr. Levin summarized his findings in his affidavit to Thomas W. Henderson dated 11/18/84. Of significant part, Dr. Levin stated:

> 11. I have obtained and reviewed the medical records and detailed medical histories of the plaintiffs. The histories and physical findings in these plaintiffs are totally consistant [sic] with immune dysregulation caused by exposure to 2,3,7,8-TCDD.
>
> 12. We have performed immunologic tests on the plaintiffs. These tests are totally consistant [sic] with immune dysregulation caused by exposure to 2,3,7,8-TCDD.

13. The cause of the damage to cells in the immune system is biochemically similar to damage to germ line cells.

(A. Levin Affidavit dated 11/18/84)

Dr. Kerman substantiated these results, finding abnormal values for the representative Plaintiffs including Plaintiff Michael Jordan.

As previously stated, the second area of major concern is that TCDD may cause an increased predisposition to infection, cancer and other diseases in exposed individuals. The substance of Dr. Alan Levin's testimony is and was:

> That phenoxy herbicides and their contaminants, specifically dioxin, most especially 2,3,7,8-TCDD, cause an assortment of immunological responses, i.e. immuno-toxicity, which predispose persons exposed, by absorption and/or ingestion and/or inhalation, to such chemicals to a whole host of adverse health effects, such as: chloracne or other skin rashes; liver and other organ damage; various neuro-toxic effects; reproductive effects; and neoplasm.

(Levin 26(b)(4) Statement, Section IV, subpart A)

Specifically, Dr. Levin testified that "each of the plaintiffs in this case have evidence of chemically-induced immune disregulation (C.I.I.D.)" (Levin depo., 177:14-16) C.I.I.D. is "a state when an individual has an increased propensity to developing diseases associated with exposures to other chemicals, virus, bacterium, and also natural malignant degeneration of cells within the individual's own body." (Levin depo., 180:2-6)

Dr. Kerman expressed significant concern of this immuno-toxic effect, emphasizing:

> What is most distressing and of greatest concern is the data reflecting decreased immunocompetence following TCDD exposure leading to increased susceptibility to infection and/or possible tumor challenge in experimental animals. It indicates a fundamental inbalance [sic] in immunoregulation.

(Kerman 26(b)(4) statement, Section V)

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Plaintiffs' witness, John Garofalo, M.D., an immunologist, explained that Agent Orange "can affect the immune system by producing changes in the number of distribution of T cells, T helper cells, and T suppressor cells . . ." and that, "the effect on helper T cells may result in a heightened immune response, leading to the formation of auto-immune diseases. These in turn may lead to excess cancer formation . . . and nerve damage . . .". (Garofalo 26(b)(4) Statement, Section IV).

In summary, it is clear that TCDD is immuno-suppressive. Medical and scientific research and literature as well as clinical data indicate that the representative Plaintiffs suffer from TCDD-induced immune dysregulation. More significantly, the TCDD exposure is capable of causing these Plaintiffs' susceptibility to a wide variety of diseases, including cancer. In conclusion, as stated by Dr. Levin, "Dioxin has a long-term detrimental effect on the immune response." (Levin depo., 337:25, 338-1)

c. Neurological

The neurological effects of TCDD exposure can be both physiological and psychological - range from peripheral and central nervous system disorders to neurasthenia and neurohypoxia. Medical and scientific research and literature, as well as clinical tests, observations and data all indicate these neurological effects.

Plaintiffs' expert witnesses, specifically Drs. Raymond Singer, Ernest Baran, Ellen Silbergeld and Herbert Kaye were and are prepared to testify to the several neuro-toxic effects of TCDD as specified in their respective 25(B)(4) Statements and supplements. Additionally, Plaintiffs' witnesses were and are prepared to testify to the specific neuro-toxic effects suffered by the representative Plaintiffs as a result of their exposure to Agent Orange and its dioxin contaminant.

As stated by Dr. Alastair Hay, a Ph.D. in biochemistry at the Chemical Pathology Department of the University of Leeds, England, the representative Plaintiff cases further substantiated his opinion that Agent Orange is neurotoxic to humans:

> I mean the specific [representative] cases that will form part of this case, the specific veterans who were in Vietnam and who have symptoms which are covered by neurotoxic. They have some peripheral neuropathy. A number of others have documented that, and the doctors examining them have documented that they have neurological problems. The basis for saying that I believe that Agent Orange is neurotoxic in humans is because if you look through the scientific literature on the effects of exposure to TCDD in industry, you will find that going back to 1957, even earlier than that, the accident at Monsanto in 1949, that people who were exposed in this accident and the people exposed in industrial accidents since then, neurotoxic problems are a common feature of the exposure to this chemical agent, TCDD.

(Hay depo., 60:16-25, 61:1-6)

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The representative Plaintiffs exhibited both peripheral and central nervous system disorders. Dr. Raymond Singer explained in his 26(B)(4) statement that:

> Agent Orange and its contaminant TCDD produce peripheral nervous system effect [sic], which include:
>
> a. Numbness
> b. Loss of feeling
> c. Weakness
> d. Pain

(Singer 26(B)(4) Statement, Section IV)

Prevalent among each of the representative Veteran Plaintiffs was and remains a condition diagnosed as "peripheral neuropathy". Neuropathy is defined as "any functional disturbances and/or pathological changes in the peripheral nervous system . . .". (Dorland's Pocket Medical Dictionary, 23rd Ed., 1982). Specifically, in 1980, Plaintiff George Ewalt had a nerve biopsy at the University of Pennsylvania, "which confirmed the presence of a demyelinating neuropathy." (Codario report to Gene Locks, Esq., 1984) Dr. Codario distinguished George Ewalt's condition stating:

> The peripheral neuropathy that this man has is definitely not an inherited one and has all the characteristics of a toxin induced neuropathy. The only toxic substance that Mr. Ewalt was exposed [to] was herbicides (with their TCDD contaminant). TCDD and the herbicides can cause this type of neuropathy. There is no question to me that this man has this neuropathy due to herbicides and TCDD exposure.

(Codario report to Gene Locks, Esq., 1984) (References omitted)

Dr. Hay also confirmed that Agent Orange was the cause of George Ewalt's peripheral neuropathy. (Hay depo., 164:19-22) Dr. Codario further found that Mike Ryan's "marked peripheral neuropathy along with an acne-like eruption in the groin" was a combination of effects, "highly consistent with TCDD poisoning." (Codario report to Gene Locks, Esq., 1984). As stated differently, "Michael Ryan has a severe peripheral neuropathy, that in my medical opinion is re-

lated to herbicide exposure." (Codario depo. 166: 20-22).

After examining and testing representative Plaintiff Dan Jordan, Dr. Codario indicated that, "Mr. Jordan's constellation of symptoms and clinical signs of peripheral neuropathy . . . are most consistent with TCDD exposure." (Codario report to Gene Locks, Esq., 2/18/84) Drs. Codario and Orris also associated Dan Ford's and David Lambiotte's peripheral neuropathies to their Agent Orange exposure. (See, Codario 26(b)(4) Statement and Orris report to Thomas W. Henderson, Esq., 4/9/84).

In addition to the peripheral neurological effects, TCDD has been associated with central nervous system disorders. (See, Hay depo., 160) Central nervous system disorders include "a. Irritability. b. Nervousness. c. Sleep Disorders. d. Memory Problems" and "e. Other Mental Dysfunctions." (Dr. Raymond Singer, 26(b)(4) Statement, Section IV). The "Ranch Hand II" Study revealed that "a variety of subjective defects (fatigue, anger, fear, etc.) were significantly more common in the high school educated Ranch Handers." (Ranch Hand II, 2/24/84, p. ii) These "defects" can also include: lack of drive, insomnia and loss of libido . . .". (Codario depo., 63:1-12)

Dr. Peter Orris diagnosed representative Plaintiff George Ewalt as having a "central nervous system neuropsychiatric disorder." (Orris report to Thomas W. Henderson, Esq., 4/9/84) Dr. Codario, having treated Mr. Ewalt since 1981, stated that George Ewalt ". . . came to the office complaining of personality problems, fatigue . . . episodes of violent rages, difficulty concentrating, memory lapses . . . headaches . . .". (Codario report to Gene Locks, Esq., 1984). After also examining George Ewalt's medical records and history, Dr. Orris claimed that the association between TCDD and George Ewalt's neurological disprders are well documented in the literature, and in his opinion, likely caused by his exposure to TCDD. (Orris report to Thomas W. Henderson, Esq. 4/9/84)

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In representative Plaintiff David Lambiotte's case, Dr. Peter Orris stated:

> Neuropsychiatric disorders associated with exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin are a recurrent theme in the literature from as early as initial case reports in 1958 4/ to a most recent publication from Pazderova-Vejupkova, et al. in 1981 5/. Peripheral neuropathic abnormalities as well are frequently noted in conjunction with this exposure. 6/
>
> In light of this patient's [David Lambiotte] history of exposure; development of neuropsychiatric and peripheral neuropathic disorders; malignant lymphoma as well as neoplastic skin changes; it is my opinion that it is probable that these conditions were caused by this patient's contact with herbicides in Vietnam containing the contaminant 2,3,7,8-Tetrachlorodibenzo-p-dioxin.
>
> 4/ Oliver, R.M. - Toxic Effects of 2,3,7,8-Tetrachlorodibenzo-1, 4, Dioxin in Laboratory Workers, British Journal of Industrial Medicine, 32 (1) 49-53, 1975.
>
> 5/ Pazderova-Vejupkova, J.M., et al. - The Development and Prognosis of Chronic Intoxication by Tetrachlorodibenzo-p-dioxin in Men. Archives of Environmental Health.
>
> 6/ Ambient Water Quality Criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin, prepared by the U. S. Environmental Protection Agency, 1984.

(Report of Peter Orris to Thomas W. Henderson, April 9, 1984)

Dr. Orris also claimed that neuropsychiatric disturbances can result from exposure to TCDD without evidence of chloracne. (Orris depo., 163:19-25, 164:1-4)

Furthermore, representative Plaintiff Mike Ryan "complains of anxiety, nervousness . . . headaches . . ." and "easy fatigability." (Codario report to Gene Locks, 4/15/84) Dan Jordan "complains of temper problems, nervousness, memory lapses" and "depression." (Codario report to Gene Locks, 2/18/84) It should be noted also that a great proportion of the Veterans interviewed nationally in the selection of the representative Plaintiffs indicated suffering

from one and often several of these "subjective defects."

In summary, TCDD can affect the nervous system in several ways. Clearly, the representative Veteran Plaintiffs suffer a cross-section of neuro-toxic effects associated with their TCDD exposure. As documented herein, Plaintiffs' expert witnesses were and are prepared to testify as to the causal relationship between these neurological conditions and their respective TCDD exposure. Plaintiffs' witnesses were also prepared to testify to: the additional neuro-toxic effects of TCDD, including the effects of TCDD on specific nervous system functions; the methods for assessing these functions; and the "interrelationships between effects on other organ systems and the nervous system." (Silbergeld 26(b)(4) Statement, Section II). (See also, 26(b)(4) Statements of Drs. Baran, Kaye, and Singer). The above stated testimony was to be supported by a vast body of literature, experience, research, clinical data and observations as cited in Plaintiffs' expert witness 26(b)(4)(A)(i) Statements.

d. Cancer

TCDD is a known animal and human carcinogen. This fact is supported by a substantial body of literature and research (See the affidavit of Dr. Bertram Warren Carnow dated October 16, 1984 and the 26(b)(4) statements and supplements of plaintiff's expert witnesses for references). Several of plaintiff's expert witnesses were and are prepared to testify to the extreme carcinogenicity of TCDD. Plaintiff's expert witnesses were further prepared to discuss the tremendous strength of TCDD as a carcinogen, not only in terms of its extreme potency relative to other carcinogens, but also to its "complete" carcinogenicity. In other words, dioxin acts as an early stage, promoter and late stage carcinogen.

Among plaintiff's witnesses, Drs. Legator, Schneiderman and Silbergeld were prepared to testify as to the complete carcinogenicity of TCDD. As stated by Dr. Legator:

> With TCDD, not only are we talking about promotion, but we're also talking about induction . . . With TCDD, we are talking about a complete carcinogen versus just one that has promotional activity. (Legator depo. 110-111:23-25, 6-9)

Dr. Ellen Silbergeld elaborated on this, explaining:

> The animal bioassays clearly indicate that dioxin is a complete carcinogen. That is without pre-exposure of an initiator or concomitant exposure with a promoter, it can produce cancer in experimental animals.
>
> In addition, I accept as a matter of reasonable scientific certainty the work of PITOT and others that dioxin is also the most powerful promoter which has ever been studied in mammalian systems. (Silbergeld depo. 221:13-22)

Several of Plaintiffs' expert witnesses also were prepared to testify on individual causation in the representative Plaintiff cases. Plaintiffs George Ewalt, Dan Ford and David Lambiotte each suffered from different types of dioxin-related cancer.

Plaintiff George Ewalt developed basal cell carcinoma, a condition, "likely . . . caused by his exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)." (Orris report to Thomas W. Henderson dated 4/9/84) Plaintiffs' expert witness as well as George Ewalt's treating physician, Dr. Ronald Codario, claimed "George Ewalt has basal cell carcinoma . . . related to his exposure to phenoxy acids in Vietnam . . .". (Codario depo., 260:22-25) Plaintiffs' experts pointed out that the location of George Ewalt's basal cell carcinoma was atypical as well as not usually related to sun exposure, as argued by defendants. (Codario depo., 205:19-20; Hardell depo., 56:8-18, 277:20, 278:13) In addition, Dr. Marvin Schneiderman, a statistician, epidemiologist and former Chief of Policy for the National Cancer Institute, noted that George Ewalt's basal cell carcinoma is consistent with existing data relating basal cell carcionma with Agent Orange. (Schneiderman depo., 159:8-10, 160:6-10) Plaintiffs' witness, Dr. Alastair Hay also associated George Ewalt's carcinoma with his prior TCDD exposure. (Hay depo, 164:19-22)

Representative Plaintiff, David Lambiotte, also has had basal cell carcinoma. In discussing David Lambiotte's carcinoma, Dr. Marvin Schneiderman claimed:

> . . . basal cell carcinoma is consistent with the preliminary findings of the Ranch Hand Study in which the exposed persons apparently had a substantial increase in the relative risk of basal cell carcinoma.

(Schneiderman depo., 158:9-13)

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More devastating from a medical standpoint, Plaintiff David Lambiotte was also diagnosed as suffering from lymphocytic lymphoma. Dr. Lennart Hardell planned to testify with a reasonable degree of medical certainty that David Lambiotte's lymphoma was caused by Agent Orange. Hardell explained:

> . . . I base that upon his [Lambiotte's] service in Vietnam, during the period when the area was heavily exposed, sprayed on with Agent Orange and I base it upon my experience in this field.

(Hardell depo., 78:1-4)

Dr. Hay shared this opinion noting that "lymphoma is documented as one tumor that is increased in people who have been exposed to similar agents or chemicals." (Hay depo., 481:22-25) Dr. Ellen Silbergeld associated David Lambiotte's lymphocytic lymphoma with his Agent Orange exposure based on human and animal data regarding "the carcinogenicity of TCDD in Agent Orange." (Silbergeld depo., 321:8-9) Dr. Schneiderman further stated the relationship of Agent Orange exposure and lymphocytic lymphoma indicating that:

> . . . The proportion of these cases (lymphocytic lymphomas) occurring in persons of his (Lambiotte's) age group is relatively low, it's two percent of all cases, and under these circumstances, in the absence of information or evidence to the contrary, this would have to be my primary suspect.

(Schneiderman depo., 144:17-25)

In conclusion, Dr. Peter Orris in his report of April 9, 1984 wrote:

> In light of this patient's [David Lambiotte's] history of exposure; development of neuropsychiatric and

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> peripheral neuropathic disorders; malignant lymphoma as well as neoplastic skin changes; it is my opinion that it is probable that these conditions were caused by this patient's contact with herbicides in Vietnam containing the contaminant 2,3,7,8-Tetrachlorodibenzo-p-dioxin.

(Orris report to Thomas W. Henderson, Esq., 4/9/84)

Representative Plaintiff Dan Ford suffers from a different dioxin-related cancer known as rhabdomyosarcoma, one of the forms of soft-tissue sarcoma. Dr. Lennart Hardell, an M.D. and Ph.D. at the Department of Oncology, University Hospital, Umeå, Sweden, has performed extensive personal research on the exposure to phenoxy herbicides and chlorophenol and the risk of developing different types of cancer. After reviewing Dan Ford's case, Dr. Hardell stated:

> Regarding the [Dan Ford's] rhabdomyosarcoma, it is a soft tissue sarcoma and in reference to our studies about soft tissue sarcomas and exposure to phenoxy herbicides it's highly probable that exposure to Agent Orange has caused so much [sic] tissue sarcoma in Dan Ford.

(Hardell depo., 61:6-12)

After examining Dan Ford, Dr. Ronald Codario stated:

> . . . it is my medical opinion that this gentleman [Dan Ford] has developed this soft tissue sarcoma as a result of his exposure to phenoxy acids and/or tetrachlorodibenzo-para-dioxin.

(Codario depo., 301:16-24)

Dr. Codario based this statement on the related body of literature as well as on the following:

> The fact that he has peripheral neuropathy, the fact that this individual was in an area where herbicides were used, the clinical symptomatology that is consistent with the clinical symptomatology that I've seen described in the literature and the clinical

> symptomatology that I have observed in evaluating 500 individuals that have been exposed to herbicides.

(Codario depo., 302:7-14)

Drs. Peter Orris, Alastair Hay, Alan Levin, Marvin Schneiderman, and Ellen Silbergeld also attributed Dan Ford's rhabdomyosarcoma to his TCDD exposure. (See generally, Plaintiffs' expert witnesses' depositions and 26(b)(4) Statements.

Dr. Alan Levin testified that Dan Ford's soft tissue sarcoma developed as a result of his C.I.I.D., or, chemically-induced immune disregulation. (Levin depo., 493:22-25) He further stated:

> I'm testifying that the pattern that Mr. Ford presents, that being rhabdomyosarcoma, and a benign growth of the right kidney, is consistent with disease caused by exposures to high concentration of 2,3,7,8-TCDD.

(Levin depo., 491:17-21)

Dr. Marvin Schneiderman noted that embryonal rhabdomyosarcoma like Dan Ford's generally appears in the 8-15 age group. (Schneiderman depo., 72:6-15) Dr. Schneiderman also dispelled defendants' claim that Dan Ford's prior trauma in the cancerous site led to his subsequent development of rhabdomyosarcoma. On the contrary, Dr. Schneiderman claimed:

> Dan Ford's rhabdomyosarcoma has been related to human and animal defoliant exposure. The fact of his broken leg and metal exposure [the insertion of a metal plate] would seem to add to the probability that the additional exposure to dioxin led to this rhabdomyosarcoma.

(Schneiderman depo., 203:4-23)

Dr. Schneiderman concluded:

> I would say that the appearance of rhabdomyosarcoma in a person who has been exposed, and in the absence of any other knowledge of the cause of rhabdomyosarcoma in that individual is more likely, in my opinion, to have been related to that exposure than to some other not known ill-defined set of causes.

(Schneiderman depo., 49:12-25, 50:1-6)

It is a proven fact that TCDD is an extremely powerful carcinogen, as previously detailed in Section E, subpart 1. TCDD has further been shown to be a "complete" carcinogen. Specifically, Plaintiffs' expert witnesses have testified that the basal cell carcinoma, lymphocytic lymphoma and rhabdomyosarcoma suffered by the three (3) representative Plaintiffs were caused by their exposure to Agent Orange/dioxin. The testimony of these several witnesses, coupled with their supporting literature and experience is strong. Plaintiffs were and are prepared to show individual causation.

e. Birth Defects

Reproductive studies on both animals and humans indicate that dioxin can be teratogenic, mutagenic, fetotoxic, embryotoxic and gonadotoxic. As stated by Dr. Deborah Barsotti:

> Reproductive dysfunction has been associated with exposure to TCDD in experimental animals and man as well.

(Barsotti depo., 194:24-25, 195:1)

Plaintiffs' government causation witness, Dr. K. Diane Courtney, a research scientist for the Environmental Protection Agency, claimed that no recent studies have changed her conclusions that:

> It is evident that all species of pregnant animals treated or exposed to TCDD responded with abortions, fetal death, fetal toxicities or malformations. The routes of exposure were oral, diet or dermal. Since all species have responded adversely to TCDD in micrograms per kilogram or nanograms dose range, it could be expected that the human being would also respond adversely to these doses of TCDD. At this time, there is insufficient data to establish a no effect dose level.

(Courtney depo., 353:6-16)

Among Plaintiffs' expert witnesses, Dr. Maureen Hatch, Assistant Professor of the Division of Epidemiology at Columbia University, testified that there is positive evidence between Agent Orange exposure and birth defects. (Hatch depo., 55:19-22) In addition, Dr. Alastair Hay felt that the evidence "would suggest that it is probable that TCDD is involved in causing untoward pregnancy outcomes and birth defects." (Hay depo., 513: 9-12)

Dr. Alastair Hay testified with a reasonable degree of scientific certainty that TCDD is teratogenic in humans. Dr. Hay based this opinion on:

> . . . the substantial body of animal evidence which shows that TCDD is teratogenic, and in evidence on the human side, . . . the recent Ranch Hand Study that's been published, the morbidity study, . . . evidence from the conference . . .[he] attended in Vietnam, in particular an article by Hatch and Constable which reviews evidence from Vietnam on the effects of Vietnam veterans, Vietnamese Vietnam Veterans exposed to Agent Orange who reported an increased incidence of birth related problems.

(Hay depo., 83:14-25)

This article Dr. Hay refers to, co-authored by Plaintiffs' expert Maureen Hatch, finds that the reproductive studies in North Vietnam report an association between paternal exposure to herbicides, prior to or at conception, and congenital defects in subsequent offspring, particularly certain anomalies, e.g., anencephaly and orofacial defects. (Constable, J.D. and Hatch, M., Reproductive Effects of Herbicide Exposure in Vietnam: Recent Studies by the Vietnamese and Others, 1984).

Plaintiffs' expert witnesses also explained that the AH Locus of the chromosome in man is the target site for TCDD (Legator depo., 82:4-6) and that gonadotoxicity and hormonal dysfunction involve the TCDD receptor (or AH Locus) as a mechanism of action. (See, Silbergeld depo., 209:14-20) Dr. Legator associated reproductive problems, "such as cleft palate . . . and other toxic effects . . . to the interaction between TCDD, the genetically controlled AH Locus." (Legator depo., 81:22-25, 82:1-2)

Dr. Levin explained additional mechanisms of action in his Affidavit of November 18, 1984. Therein he described three mechanisms by which a toxic chemical can damage particular proteins thus leading to birth defects in the progeny of the host. (Levin Affidavit, Section 9)

Included in the body of research, literature and testimony on the reproductive toxicity of TCDD are studies indicating male-mediated

reproductive effects. Although significantly more difficult to prove, Plaintiffs were and are prepared to testify to the various mechanisms of male-mediated toxicity, as well as to the resulting male-mediated genetic effects, including birth defects, miscarriages and untoward pregnancy outcomes.

In discussing the reproductive toxicity of TCDD, specifically male-mediated reproductive toxicity, Dr. Maureen Hatch stated:

> It is my opinion based on the weight of evidence to date that exposure to the male human from Agent Orange is associated with an increased risk of birth defects, a modest to moderate increased risk of birth defects among his offspring.

(Hatch depo., 139:4-8)

Dr. Hatch went on to state:

> It's my professional judgment at this point that the data are sufficient to, with reasonable certainty, say that Agent Orange exposure appears to have a causal association with congenital malformation in offspring of exposed fathers.

(Hatch depo., 418:21-25, 419:1)

Dr. Alan Levin supported the above claim in his Affidavit dated November 18, 1984, writing:

> I have reviewed, in detail, the "Ranch Hand Study" performed by the United States Air Force on Agent Orange Exposed personnel. This study proved that Agent Orange Exposure of the father is associated with birth defects in the children. Although the population studied is quite different from the plaintiff group (they are significantly older and the nature of their exposure was entirely different) the increased incidence of birth defects in the plaintiff population can also be positively associated with Agent Orange exposure.

(Levin Affidavit of November 18, 1984)

Dr. Levin also revealed that:

> It's known that dioxin will promote the development of birth defects in humans and in animals, and the mechanism by which they do is some transmissible defect that is male mediated.

(Levin depo., 614:1-3)

Dr. Ellen Silbergeld claimed that TCDD and 2,4,5-T can cause "male-mediated transmittable damage." (Silbergeld depo., 222:9-12) The substance of Dr. Silbergeld's testimony is and was that:

> TCDD and 2,4,5-T can cause male mediated transmittable damage manifested by birth defects, miscarriages, and other untoward pregnancy outcomes when certain circumstances occur. These circumstances are when the amount of exposure to TCDD and to 2,4,5-T, either alone or together (this amount being measured by intensity and duration) is appropriately paired with the timing of that exposure in relationship to spermatogenesis and the participation of the male in reproduction.

(Silbergeld 26(b)(4) Supplement)

Specifically, Dr. Marvin Legator explained that male-mediated toxicological effects:

> . . . i.e. birth defects and miscarriages, of Agent Orange and/or TCDD . . . can occur through one or more of the following biological mechanisms: (1) decreased quality of sperm resulting from gonadal lesion during spermatogenesis, altered hormonal regulation, or transmittable defects in heritable characteristics of sperm; (2) potentiation of xenobiotic metabolism in gonadal tissue; (3) secretion of chemicals in Agent Orange or their metabolites into seminal fluid and subsequent transfer to the womb. These mechanisms can result from either the long-term effects of past exposure to Agent Orange or from the continuing presence of biologically active concentration of Agent Orange and metabolites of its constituent chemicals within the bodies of exposed persons.

(Legator 26(b)(4) Statement)

Moreover, Defendants' expert witness, Dr. James G. Wilson, testified that he agreed "that TCDD in the male's body can move into his body fluids, in general, including seminal fluids . . .". (Wilson depo., 69:12-14)

Plaintiffs' expert witnesses were also prepared to testify specifically that the birth defects and untoward pregnancy outcomes suffered by the Jordan and Ryan families were a result of Plaintiffs Dan Jordan and Michael Ryan's respective TCDD exposure.

In the Jordan family, both Mrs. Donna Jordan and her children, Michael and Chad, suffered the male-mediated toxic effects associated with Plaintiff Dan Jordan's TCDD exposure. Donna Jordan endured a miscarriage while several months pregnant. In discussing Mrs. Jordan's untoward pregnancy outome, Dr. Levin stated:

> I will tell you what I know about the (Jordan) miscarriage. It was caused by her husband's exposure to TCDD.

(Levin depo., 614:1-3)

Dr. Silbergeld further confirmed that Donna Jordan's miscarriage before term was consistent with and caused by her husband's exposure to Agent Orange in Vietnam. (See, Silbergeld depo., 282:7-12; 284:21-24). Dr. Silbergeld justified her opinion stating:

> First off is the fact that her husband was indeed in Vietnam prior to impregnating Donna Jordan, and that relying on the records I have, he was exposed to Agent Orange while in Vietnam.
>
> Second is the other reproductive history of this family, which includes two other untoward reproductive events. So that this miscarriage cannot be seen in isolation.
>
> Third, that all of these events, all of these reproductive events are consistent with the animal toxicology . . .

(Silbergeld depo., 285:1-13)

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Plaintiffs' witnesses also associated Chad and Michael Jordan's birth defects with their father Dan Jordan's Agent Orange/dioxin exposure. Dr. Alastair Hay was prepared to testify that Dan Jordan's "exposure to Agent Orange was the cause of his children having birth defects." (Hay depo., 164:7-10) When questioned as to what "was caused to Mr. Jordan and any of his family by his claimed exposure to Agent Orange?", Dr. Hay responded:

> That the birth defects, the limb deformities that his children had, particularly the thumb and the missing digits, and the absence of one bone in one of his children was caused by (Dan Jordan's) exposure to Agent Orange.

(Hay depo., 166:4-11)

In addition, Plaintiffs' experts Drs. Legator and Silbergeld testified that Chad and Michael Jordan's birth defects were consistent with and caused by Mr. Jordan's TCDD exposure.

Defendants argued that the Jordan's had a history of minor birth defects thus attributing to Chad and Michael Jordan's deformities. Dr. Levin challenged this defense claiming that this history strengthens the concept that TCDD initiated these children's defects. Dr. Levin explained:

> I believe that the individual possibility or probably [sic] carried a genetic propensity, which was then expressed by the 2,3,7,8-TCDD. This is commonly what happens, for instance in the development of cancer. The chemicals per se bring out the expression of the oncogene, the oncogene then is associated with the development of cancer.

(Levin depo., 623:22-25, 624:1-3)

Dr. Marvin Legator strengthened Plaintiffs' position regarding the Jordan's history of congenital malformations stating:

> . . . it is my view that whenever we have a genetic effect . . . that any further insult (e.g. TCDD exposure) can either accelerate, enlarge upon the affliction, or show us more diverse effects, and seeing that there was a history . . . then I would anticipate that exposure to dioxin, given what we know about dioxin, could, indeed, worsen the situation in terms of more effects.

(Legator depo., 288:20-25, 289:1-5)

Dr. Legator argued that given Dan Jordan's family history and his TCDD exposure, that "here . . . we have identified a chemical . . . which would substantially contribute to the adverse health outcome." (Legator depo., 289:18-21)

Dr. Legator further contended that Kerry Ryan's deformities were attributable to the father's (Plaintiff Michael Ryan) TCDD exposure. Dr. Legator asserted that:

> . . . the congenital malformations and birth defects of Kerry Ryan, daughter of Mr. and Mrs. Michael F. Ryan, are consistent with the presumed exposure of . . . Ryan to phenoxy herbicides and dioxins - specifically 2,3,7,8-TCDD - - while being in Vietnam.

(Legator 26(b)(4) Statement)

Plaintiffs' witness, Dr. Hay, stated that Michael Ryan's "exposure to Agent Orange was the cause of the birth defects in his child." (Hay depo., 164: 15-18) He further testified, "that the deformities in Kerry Ryan were attributable to Mr. Ryan's exposure to Agent Orange." (Hay depo., 166:16-20)

In summary, TCDD has been clearly implicated in causing reproductive toxic effects in animals and humans. Additionally, research and literature as well as expert testimony have described several mechanisms of male-mediated reproductive toxicity. Plaintiffs also specifically contend that the TCDD exposure of representative Plaintiffs Dan Jordan and Mike Ryan attributed to

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the reproductive toxic effects suffered by their children and Mrs. Jordan.

As stated by Dr. Marvin Legator:

> Based on the fact that we are dealing with an agent that has the properties we've already described to TCDD and that there was demonstrated exposure of the two veterans in point, Ryan and Jordan, that certainly the congenital malformations would be consistent with an adverse effect of this chemical.

(Legator depo., 287:15-25)

IV. CONCLUSION

The proof of "cause" between exposure to Agent Orange and the multitude of adverse health effects from which the 9 representative plaintiffs claimed damages very simply has been overwhelmingly demonstrated.

DIFFICULTIES/COMPLEXITIES IN AO DISCOVERY

RELATING TO CAUSATION

1. INTERVIEWING VETERANS

- Gathering names of potential representative plaintiffs from several sources.

- Briefing paralegals on interviewing veterans for pertinent exposure and medical information.

- Extensive telephone conversations with veterans and veterans' wives (evenings, weekends, every day), lasting approximately 2 hours in length for each initial "screening" telephone call.

- Asking veteran detailed questions on his medical condition(s) (including past and present symptoms and problems); his wife's history (including her medical condition and child bearing history); the veteran's military history (including information on his M.O.S. and exposure); potential variables such as the veteran's exposure to drugs and chemicals, as well as his family employment history, etc; and his children's history (including complete medical conditions).

- Summarizing all information to narrow down and screen the number of potential representative plaintiffs.

- Re-interviewing veterans for more detailed medical information, including all physicians and hospitalizations (of veterans, wives, and children), as well as additional descriptions and dates of occurrence of all symptoms and medical conditions.

2. MEDICAL RECORDS

(VA, Physician and Hospital)

- Searching for proper names and current addresses of past and often deceased physicians.

- Mailing hundreds of court orders for medical records of veterans, wives and children.

- Following-up mailings with extensive telephone calls to explain the urgency of our request; to justify expediting what is normally a several week-long request to days; to remedy simultaneous (dual) requests from defendants and plaintiffs.

- Payments required before receipt of records; inevitable delays.

- Organizing, separating and indexing all medical records consisting of thousands of pages of records for veterans, wives and children.

- Keeping track of medical records received and those never received; more telephone calls.

- Sending medical records to computer service for disbursement to defendants as they came in.

- Re-verification with veterans of all physicians and hospitals.

- Reorganizing and assessing final representative plaintiffs' medical records. (Travel to Pittsburgh, Philadelphia); shipping to Philadelphia for final indexing; copying for defendants.

- Trying to track down remaining medical records.

3. SELECTION OF REPRESENTATIVE PLAINTIFFS

- Medical record review.

- Summaries of veteran interviews.

- Consultations with treating physicians.

- Consultations with causation experts.

4. CONTINUOUS CONTACT WITH REPRESENTATIVE PLAINTIFFS AND DEFENDANTS

- Answering continuous defendant inquiries on representative plaintiffs.

- Addressing all representative plaintiffs' inquiries, problems, schedule conflicts; listening.

- Calling plaintiffs to explain aspects of litigation requiring their immediate assistance, e.g. - depositions; interrogatory answers; medical testing.

5. INTERROGATORIES ON INDIVIDUAL REPRESENTATIVE PLAINTIFFS

- Travel to New York.
- Numerous telephone calls to veterans, veterans' local attorneys (if applicable).
- Review of medical and military records.
- Coordinating, changing and adapting local counsels' interrogatory answers to individual plaintiffs' interrogatories.
- Time constraints; creating a uniform format to put information on the computer.
- Extensive telephone calls to plaintiffs to complete detailed interrogatories (nights, days, weekends, etc.).
- Adapting answers to rulings by Judge Weinstein and Magistrate Scheindlin.
- Completing interrogatories for Elmo Zumwalt.
- Supplementing answers in accordance with Magistrate Scheindlin's rulings.

6. EXPERT SUMMARIES

- Compiling and copying expert summaries; traveling to Philadelphia to merge with Neil Peterson's for filing the same day in New York.
- Supplementing - expanding.
- Adapting/expanding to confirm with modified rulings.

7. REPRESENTATIVE PLAINTIFFS' DEPOSITIONS

- Scheduling conflicts, illness; numerous telephone conversations.
- Time constraints.
- Preparation

8. PLAINTIFFS' EXPERTS' DEPOSITIONS

- Preparation.
- Scheduling, rescheduling.
- Time constraints.
- Handling (responding to) and making objections.

9. DEFENDANTS' EXPERTS' DEPOSITIONS

- Onerous schedule.
- Back-to-back time schedule/weekends/not enough attorneys.
- Researching defendants' experts' literature.
- Medline/Toxline searches.
- Hiring and supervising several students in Pittsburgh to gather and copy articles.
- Summarizing hundreds of articles for deposition preparation.
- Gathering more articles in New York.

10. MILITARY (EXPOSURE) DOCUMENTS

- Travel for document productions and briefings.
- Photocopying thousands of military documents.
- Researching method to utilize various types of records produced to determine exposure of representative plaintiffs.
- Analyzing the Agent Orange Army Task Force Study results, assessing alternative approaches to the Task Force Study protocol.
- Organizing and shipping thousands of records.

11. PRETRIAL ORDER

- Telephone calls to plaintiffs to determine Fact and Exposure witnesses and their (respective) testimony.
- Telephone calls to potential witnesses re: testimony, additional information; possible additional witnesses.
- Time constraints.
- Summarizing all witness testimony - directly plugging into computer.
- Listing all plaintiffs' treating physicians, addresses and summarizing testimony.
- Travel back and forth from Long Island.
- Citing medical and scientific literature.
- Summarizing Plaintiffs' expert witnesses' testimony.
- Listing and describing causation exhibits.
- Summarizing Plaintiffs' government causation witnesses' testimony.

NAME: EWALT, George

WID:

RANK:

SSN:

MSN:

VIETNAM SERVICE:

February 25, 1967 - February 24, 1968

UNIT OF ASSIGNMENT:

1st Battalion, 26th Infantry, 1st Brigade, 1st Infantry Division

POSITION:

Infantry man

___ EXPOSURE EXTREMELY LIKELY

_x_ MOST LIKELY EXPOSED

___ PROBABLY EXPOSED

___ PROBABLY NOT EXPOSED

___ NOT EXPOSED

REASON:

During Mr. Ewalt's tour in Vietnam, his unit moved around in the Phuoc Vinh, Quan Loi, Phu Loi, & Lai Khe area. When going through the Ranch Hand, on the first grid coordinate extracted, I had 9 8 km. hits, due to his job description as an infantryman, he would have many reasons for going outside of the perimeter. For this reason, and also for the amount of hits on the 1st grid coordinate, we have determined him as Mostly Likely Exposed

	Ranch Hand Orange	Services Orange	Services Unknown
2km/3day	0	0	9
8km/90day:	122	67	22

NAME: Danny L. Ford

WID:

RANK: E-4

SSAN: 365-52-1794

MSN: US 54-976-275

VIETNAM SERVICE: 27 September 1968- 16 September 1969

UNIT OF ASSIGNMENT: Battery C, 1st Battalion, 92nd Artillery, USArmy, Pacific

POSITION/MOS: 13A10- Cannoneer

____ EXPOSURE EXTREMELY LIKELY

____ MOST LIKELY EXPOSED

XX PROBABLY EXPOSED

____ PROBABLY NOT EXPOSED

____ EXPOSURE EXTREMELY UNLIKELY

REASON: Mr. Ford's unit was located in the II Corps area of Vietnam. It was a highly mobile unit which moved about in the Kontum and Pleiku Provinces. His unit was within 8km and 90 days of 11 sprays at two locations- Fire Support Base 12 (5 sprays) and Landing Zone Swinger (6 sprays). For the above reasons this individual is being classified as probably exposed.

	Ranch Hand Orange	Services Orange	Services Unknown
2km/3day	0	0	0
8km/90day	65	61	79

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T

NAME: JORDAN, DANNY G.

WID:

RANK: E-5

SSN: 443-70-2511

MSN: US1665959

VIETNAM SERVICE:

Company D, 1 Battalion, 5th Cavalry, 1 Cavalry Division: March 1 - Sept.
Company E, 1 Battalion, 5th Cavalry, 1 Cavalry Division: Sept. 2 - February 16, 1969

UNIT OF ASSIGNMENT: 1967

POSITION:

Mortar Gunner, Gunner, Crewman Squad Leader

X EXPOSURE EXTREMELY LIKELY

___ MOST LIKELY EXPOSED

___ PROBABLY EXPOSED

___ PROBABLY NOT EXPOSED

___ NOT EXPOSED

REASON:

During Mr. Jordan's Vietnam service, he was with the above units. These units were in several areas in I Corps and III Corps. I Corps places were such as Landing Zone Jane, Wonder Beach, LZ Barbara & Binh An. In III Corps, his units base camps were such as Katum, Landing Zone Eleanor, Dong Xoai, and Landing Zone Dolly.

While with these units, and only searching through the Ranch Hand Herbs Tape, we found 28 hits, 9 of which were 2 kilometer hits, or less. For this reason, we have determined him as exposure extremely likely.

	Ranch Hand Orange	Services Orange	Services Unknown
2km/3day:	9	3	0
8km/90day:	214	115	941

NAME: LAMBIOTTE, DAVID G.

WID:

RANK: E-4

SSN: 223-68-3895

MSN: US52913119

VIETNAM SERVICE:

May 26, 1967 - 15 May, 1968

UNIT OF ASSIGNMENT:

423rd Combat Support Repair Parts Company

POSITION:

Supply Clerk & Order Supply Clerk Specialist

___ EXPOSURE EXTREMELY LIKELY

___ MOST LIKELY EXPOSED

___ PROBABLY EXPOSED

___ PROBABLY NOT EXPOSED

X NOT EXPOSED

REASON:

While with the 423 Repair Parts Company during Mr. Lambiotte's Vietnam service, his unit's base camp was Cam Ranh Bay. We were unable to locate any perimeter hits during this time period, therefore we have determined him not exposed.

	Ranch Hand Orange	Services Orange	Services Unknown
2km/3day:	0	0	0
8km/90day:	0	0	38

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NAME: Michael F. Ryan

WID:

RANK: SP 4, E-4

SSN:

MSN: US 51 579 873

VIETNAM SERVICE: August 11, 1966 - August 20, 1967

UNIT OF ASSIGNMENT: Headquarters Troop, 3rd Squadron, 11th Armored Cavalry Regiment

POSITION: Court Martial Clerk

___ EXPOSURE EXTREMELY LIKELY

___ MOST LIKELY EXPOSED

X PROBABLY EXPOSED

___ PROBABLY NOT EXPOSED

___ NOT EXPOSED

REASON: Mr. Ryan's unit was highly mobile within the III Corps region in Vietnam. Unit records have placed his unit at Xuan Loc, Long Giao, Phu Hoi, and Ben Cat, and also his unit was providing security for the Long Binh - Bien Hoa area in the southern portion of the Iron Triangle. Some of these areas were heavily sprayed in 1967, but Mr. Ryan's position as a clerk would not put him in direct contact with the herbicides. Therefore, due to his mobility and the probability that he may have beeen put on guard duty, we have determined that Mr. Ryan is probably exposed.

	Ranch Hand Orange	Services Orange	Services Unknown
2km/3day:	0	0	0
8km/90day:	154	18	0

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SUPREME COURT OF THE UNITED STATES
OFFICE OF THE CLERK
WASHINGTON, D. C. 20543

November 26, 1984

Mr. Loren Kieve
Steptoe & Johnson
1250 Connecticut Avenue, N.W.
Washington, DC 20036

Re: Chevron Chemical Company,
v. Richard Leander Ferebee, Jr., et al.
No. 84-491

Dear Mr. Kieve:

The Court today entered the following order in the above entitled case:

The petition for a writ of certiorari is denied. Justice O'Connor took no part in the consideration or decision of this petition.

Very truly yours,

Alexander L. Stevas, Clerk

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LENNART HARDELL, M.D., Ph.D.

I. QUALIFICATIONS

Dr. Hardell is employed by the University Hospital in its Department of Oncology in Umea, Sweden, where he specializes in internal medicine and oncology. His work includes diagnosis, treatment, and evaluation of possible causes of cancer, and education of medical students. His Curriculum Vitae is attached. A list of seminars is also attached.

II. Subject Matter

Dr. Hardell will testify to several epidemiological studies which he and his colleagues have conducted in Sweden. This research includes investigations concerning the relationship between the risk for different types of cancer and exposure to phenoxy herbicides and chlorophenols. The research has been published in the medical and scientific literature.

These studies utilized the case-control study as the vehicle for investigation. Certain methodological aspects, such as selection of cases, selection of controls, assessment of exposure, and statistical methods, were considered; and then utilization was based upon thoroughly considered aspects of bias, all of which were well controlled.

Dr. Hardell has also seen in his clinical practice basal cell carcinoma of persons previously exposed to phenoxy herbicides, with no other known confounding variables.

III. Scientific Principles

See General Statement of Scientific Principles and Assumed Facts attached.

Dr. Hardell will use as a factual base for his testimony his hands-on diagnoses and treatment of various cancer victims as well as his review of the medical records and examinations of cases involved in his epidemiological studies. His additional clinical experiences also form a factual basis for his testimony, especially those patients with basal cell carcinoma.

Dr. Hardell will also review the medical records of George Ewalt, Danny Ford, and David Lambiotte for the opinions which he will express regarding the causation (in the legal sense) and their exposure to Agent Orange and basal cell carcinoma, rhabdomyosarcoma (form of soft tissue sarcoma) and malignant lymphocytic lymphoma.

IV. Substance of Opinions

A. Specifically, Dr. Hardell's studies, four in number, involved soft tissue sarcomas, malignant lymphomas, and colon cancer. Highly statistically significant risks of soft tissue sarcomas and malignant lymphoma were found, whereas no assiciation was found for colon cancer. In point of fact, the negative finding for colon cancer strongly supports the statistical significance of the increased risk demonstrated for soft tissue sarcomas and malignant lymphomas, and that there exists a presumed causal relationship between exposure to phenoxy herbicides and human cancer, particularly of soft tissue sarcoma and malignant lymphoma.

B. With respect to those cases with soft tissue sarcoma, malignant lymphoma, and basal cell carcinomas, Dr. Hardell will testify that the presumed exposure to Agent Orange caused, in significant part, such neoplastic processes.

V. Grounds for Each Opinion

A. General

The bases for Dr. Hardell's testimony as to various facts and opinions include: educational background, professional training, and experience; diagnosis and treatment of patients, review of the applicable medical and scientific literature; personal research; and a review of the pertinent medical data of the relevant representative plaintiffs.

B. Specific

1. Soft tissue sarcomas and malignant lymphoma

References:

Cook RR (1981): Dioxin, chloracne, and soft-tissue sarcoma. Lancet i. 618-619.

Eriksson M, Hardell L, Berg NO, Moller T, Axelson O (1981): Soft-tissue sarcomas and exposure to chemical substances; a case-reference study. Br J Ind Med 38: 27-33.

Hardell L (1979): Malignant lymphoma of histiocytic type and exposure to phenoxyacetic acids or chlorophenols. Lancet i: 55-56.

Hardell L (1981): Relation of soft-tissue sarcoma, malignant lymphoma and colon cancer to phenoxy acids, chlorophenols and other agents. Scand J Work Environ Health 7: 119-130.

Hardell, L, Sandstrom A (1979): Case-control study; soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. Br J Cancer 39: 711-717.

Hardell L, Eriksson J, Lenner P, Lundgren E (1981): Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids; a case-control study. Br J Cancer 43: 169-176

Honchar PA, Halperin WE (1981): 2,4,5-T trichlorophenol, and soft tissue sarcoma. Lancet i: 268-269.

Johnson FE, Kugler MA, Brown SM (1981): soft-tissue sarcomas and chlorinated phenols. Lancet I: 1370.

Moses M, Selikoff IJ (1981): soft-tissue sarcomas, phenoxy herbicides and chlorinated phenols. Lancet i: 1370

Pitot HC, Goldsworthy T, Poland H (1980): Promotion by 2,3, 7,8-tetrachlorodibenzo-p-dioxin of hepatocarcinogenesis from diethylnitrosamine. Cancer Res 40: 3616-3620.

Poland A, Palen D, Glover E (1982): Tumour promotion by TCDD in skin of HRS/J hairless mice. Nature 300: 271-273.

Sarma PR, Jacobs J (1982) Thoracic soft-tissue sarcoma in Vietnam veterans exposed to agent orange. N. Engl J. Med 306: 1109

2. Basal Cell Carcinoma

Case history:

Woman born in 1946. In 1964 operated for a cyst on one of her ovaries. No other diseases. In the end of the 1960's she developed a blister on her left shoulder and in the 1970's several ones on her back. In June 1977, two basal cell carcinomas were surgically removed from her back. In September 1977 nine more and in December 1977, two more basal cell carcinomas were excised from her back. In January 1983 one basal cell carcinoma on her shoulder and another on her back were cured by radiotherapy. In October 1983 five tumors were removed from her back; two basal cell carcinomas and three basal cell carcinomas in situ.

During summertime in 1959, 1960, and 1961 the patient afforested for one month each summer. The seedlings were treated with DDT. Moreover, she carried water for the dilution of phenoxy acids used by back pack sprayers. She walker in newly sprayed areas. In 1960 she used to basal bark spray for six weeks and in 1961 for two weeks. The chemical used was a combination of 2,4,5-T and 2,4,-D. She was thereby stripped to her waist but for a brassiere. She used no gloves.

The patient reported no heredity for basal cell carcinoma. She had not used any special drugs or been exposed to arsenic.

Curriculum Vitae

Lennart Hardell M.D.,Ph.D. Department of Oncology, University Hospital, S-901 85 UMEÅ, Sweden

Born in October 18, 1944.

Medical degree from University of Upsala, Sweden October 27, 1971.

Authorization to practice the medical profession, National Board of Health and Welfare, Stockholm, November 5, 1971.

Specialized in internal medicine October 18, 1976.

Specialized in oncology, June 20, 1979.

Medical dissertation University of Umeå, May 15, 1981.

Direct testimony before the United States Environmental Protection Agency in the matter of the hearing of 2,4,5-T and Silvex, Washington DC, September 29-30 1980 and February 9, 1981.

Receiver of the Fernström Award, University of Umeå, October 9, 1982. Delivered by the King Carl XVI Gustaf of Sweden.

Member of "Expert Panel on Dioxin Documents", United States Environmental Protection Agency, Cincinnati, Ohio, July 27-29, 1983.

Qualified for Associate Professor of oncology, University of Umeå, December 9, 1983.

Member of the Swedish Medical Association.
Member of Nordic Radiotherapy Club
Member of Swedish Association of Radiotherapy
Member of Swedish Association of Oncology
Member of Swedish Epidemiological Association

JOHN A. GAROFALO, M.D.

I. QUALIFICATIONS

See attached curriculum vitae.

II. SUBJECT MATTER

The subject matter of Dr. Garofalo's testimony will pertain to the field of immunology. He will elaborate on the effect that Agent Orange (dioxin) can have on the immune system.

III. GENERAL SCIENTIFIC PRINCIPLES

The field of immunology involves the study of how the body responds to antigenic (foreign) stimulation. Peripheral blood lymphocytes are made up of B-cells; T-cells; and T cell subsets (also referred to as the immunoregulatory cells of the immune system). During the past two decades, the field of immunology has recorded a number of dramatic advances. The most significant of which have been the recognition of the various classes of T and B lymphocytes, hybridoma technology (provides a reliable and consistent method for providing large quantities of monoclonal antibodies directed against specific cell surface antigens) and the technological advances in flow cytometry. T lymphocytes (65-85% of lymphocytes) are responsible for a spectrum of immune responses referred to as cell-mediated immunity which include delayed hypersensitivity; allograph rejection; tumor cytotoxicity, whereby they destroy host cells bearing foreign antigens; and cell-mediated resistance to infectious agents (fungi, viruses, and intracellular faculative bacteria). Two functionally

distinct subsets of T cells have been defined with monoclonal antibodies. T4+ cells represent the helper/inducer population 38-53%) whereas T8+ cells represent the suppressor/cytotoxic population (18-30%) (cytotoxic refers to the major effector functions of T cells, the capacity to kill specific cells to which they are sensitized). T4+ (helper/inducer) cells regulate the immune response by means of cell-cell interactions as well as by producing biologically potent regulatory molecules. T4+ cells provide inducer function in T-T cell (required for optimal development of cytotoxicity by the T8+ cells); T-B cell (induces B cells to proliferate and differentiateinto immunoglobulin containing plasma); and T-macrophage interactions. T4+ cells produce humoral factors such as lymphocyte mitogenic factor, which induces proliferation of all major lymphocyte subclasses. Antigen stimulated T4+ cells produce helper factors that modulate erythroid stem-cell production and are important in hematopietic differentiation. T8+ cells contain cells with suppressor/cytotoxic functions. This subset suppresses B cell immunoglobulin synthesis and has the capacity to kill cells to which they are sensitized. B lymphocytes are cells coded to product immunoglobulins, which are proteins found in blood and various secretions. B cells product Ig which belong to four major gorups: IgG - responsible for defense against bacterial infections i.e. pneumonia and strep throat; IgM - responsible for the defense against anerobic bacterial infections i.e. bowel pathogens; IgA - defends us against viral infections and is found in large quantities in our secretions; IgE - responsible for our defense against allergens.

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HYBRIDOMA TECHNOLOGY -- The advent of hybridome technology has provided a new approach to immunology research. With its application monoclonal antibodies capable of recognizing with precision the functional components of the immune system provide the medical community with highly specific reagents for the study of T lymphocyte maturation and for the identification of T lymphocyte syb-populations.

ORTHO SPECTRUM III utilizes the observation that human lymphocytes, monocytes and granulocytes posses different light scattering characteristics. Cells undergoing analysis travel in single file through a quartz cuvette where they intersect a narrowly focused 488nm wavelength beam of light from an argon-ion laser. The illuminated cells scatter the light in all directions. A solid-state sensor collects low angle forward scatter to discriminate size of cells, and a photomultiplier tube (PMT) set at 90°. These signals produce a histogram of cells counted based on intensity of green fluorescence. Analysis of peripheral blood samples is performed using whole blood. The cells are labeled by direct immunofluorescence, in which the monoclonal antibody directed against the desired cell surface antigen is conjugated with a flourescent dye, or by indirect immunofluorescence, in which the monoclonal antibody, having been found to the cell surface, is visualized with a second fluoresceinated antibody directed against the monoclonal immunoglobulin.

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In the evaluation of lymphocyte populations both percentages and absolute values are taken into consideration. The mechanism of how abnormal lymphocyte populations affects the im-

mune response will be set out. The basic theorem is that changes in lymphocyte populations are suggestive of disease processer and often but not universally relate to dysfunction. For the purposes of this litigation, it is important to distinguish between immune deficiencies and immuno-suppression. Suppression referring to an acquired immune deficiency that can be the result of exposure to chemical toxins.

Dr. Garofalo has had particular clinical experience relevant to this litigation. He has, since December, 1983, examined about thirty-five (35) Vietnam veterans for Agent Orange-related immune abberations. To the best of his knowledge, the published literature does not contain any reports of data comparable to that which he has acquired. A general review of his date indicates that the Vietnam veterans exposed to Agent Orange have slightly elevated levels of lymphocytes, with particular reference to T helper cells. There is even some elevation of suppressor T cells.

IV. SUBSTANCE OF OPINIONS

1. Agent Orange can affect the immune system by producing changes in the numbers and distribution of T cells, T helper cells, and T suppressors cells, though it is much more likely that it has its effect through changes in the latter two types of cells.

2. The effect on helper T cells may result in a heightened immune response, leading to the formation of auto-immune diseases. These in turn may lead to excess cancer formation, arthritis, and nerve damage, the latter including both central

nerve damage and peripheral neuropathy, of which the "dying back" variant is typical.

3. Agent Orange can cause an excess of T8+ cells (suppressor/cytotoxic). This may represent an increase in either the suppressor population which in turn can interfere with helper T cell and B cell function or the cytotoxic cell population which have the capacity to kill specific cells to which they are sensitized.

4. Agent Orange may act as an antigen bound to body tissues resulting in the formation of autoantibodies and cytotoxic cells directed against the sensitized tissue.

Auto Antibody: "Auto" refers to self; "Antibody" refers to a protein formed by the immune system in a response to antigen exposure. An autoantibody is thus an antibody that is formed within a person against their own tissues, i.e., red blood cells, platelers, nerve tissue, skin).

5. Individual opinions concerning the representative plaintiffs are contained in their individual reports.

V. GROUNDS FOR OPINIONS

Dr. Garofalo will rely upon his own experience in the evaluation of other veterans he has evaluated in the past or whom he will evaluate in the future, and upon the attached list of articles.

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Appointments by Dr Lennart Hardell

After authorization worked as:

General practitioner, Primary Health Centre, Haparanda, November 1 1971 - - August 31 1972.

Junior registrar, Department of Psychiatry, County Hospital, Kristinehamn, September 1-30, 1972.

Junior registrar, Department of Psychiatry, County Hospital, Boden, October 1 - December 31 1972.

From January 1 1973 to August 31 1976 various appointments as Junior registrar, Senior registrar and consultant at the Department of Internal Medicine, County Hospital, Boden.

From September 1 1976 various appointments as a Junior registrar, Senior registrar and consultant at the Department of Oncology, University Hospital, Umeå.

September 1 - December 31 1983 Head and consultant, Centre of Oncology, University Hospital, Umeå.

For the moment appointed as consultant at the Department of Oncology, University Hospital, Umeå, Sweden.

25. Seminar on Drugs and Pesticides; The Swedish Branch of Friends of Earth International ((nvited speaker)

Conference on Biological Mechanisms of Dioxin Action

Symposium on Toxicology; Swedish and Finnish Association of Toxicology
(Invited speaker - unable to attend)

Symposium on Leukemia and Related Diseases; International Association for Comparative Research
(Invited speaker - unable to attend)

Internation Symposium on Herbicides and Defoliants in War; The Long-Term Effects on Man and Nature
(Invited speaker - unable to attend)

Symposium on Public Health and Risks of Chlorinated Dioxins
(Invited speaker - unable to attend)

Congress on the Scientific and Social Response from Exposure to Dioxins and Related Material; Association of Occupational and Environmental Health
(Invited speaker - unable to attend)

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Biskopnarno, Sweden	November 26-27, 1983
Banbury Center, NY	April 1-4, 1984
Stockholm, Sweden	May 16, 1981
Los Angeles, CA	August 31-September 4, 1981
Ho Chi Minh City, Vietnam	January 13-20, 1983
Rockefeller University New York	October 19-20, 1983
Arlington, Virginia	December 6-7, 1983

9. Seminar on the Work with Pesticides and Associated Risk; The National Swedish Environmental Protection Board (Invited to participate)

10. Seminar on the Use of Phenoxy Acids in the Agriculture; Swedish National Board of Occupational Safety and Health (Invited to participate)

11. Conference on the Use of Pesticides in Forestries - Swedish Association of Churches (Invited speaker)

12. Conference by the Swedish Association of Pesticide Manufacturers; Phenoxy Acids and Cancer (Invited speaker)

13. Committee on the Use of Pesticides in Forestry and Agriculture - The Swedish Parliment (Invited speaker)

14. Conference on Use and Regulation of Pesticides - Nordic Counsel of Workers in Agriculture and Horticulture; Health Effects of Phenoxy Acids (Invited speaker)

15. Tenth Annual Meeting of European Environmental Mutagen; Society on Environmental Mutagenisis (Invited speaker)

16. Seminar on Demands Made by the Society for Registration and Use of Pesticides- Association of Nordic Agricultural Research (Invited speaker)

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Stockholm, Sweden	September 20, 1979
Stockholm, Sweden	October 3, 1979
Sodrahoka, Sweden	November 6, 1979
Stockholm, Sweden	November 27, 1979
Stockholm, Sweden	February 20, 1980
Istab, Sweden	September 1-5, 1980
Athens, Greece	September 14-19, 1980
Helleiud, Norway	November 12-13, 1980

HARDELL, Lennart

1. Conference organized by the Swedish Society of Medical Radiology (Invited speaker)

2. Conference by the Finnish Medical Association; Duodecim and Medical Faculty

3. Malignant Tumors and Chemical Risk Sectors in the Environment (Invited speaker)

4. Meeting on Phenoxy Acids; The Committee on Agriculture of Swedish Parliment (Invited speaker)

5. Soft-tissue Sarcoma and Exposure to Phenoxy Acids or Chlorophenols; Meeting by the Swedish Pharmaceptical Association in Umeå (Invited speaker)

6. Conference on Pesticides and Human Health - Society for Occupational and Environmental Health (Invited speaker)

7. Symposium by Nordic Counsel on Arctic Medical Research (Invited speaker)

8. Seminar by Umeå University Before The Swedish Work Environmental Fund; Chemical Substances in the Environment (Invited speaker)

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Umeå, Sweden	September 23-24, 1977
Oulu, Finland	
Oulu, Finland	February 22-23, 1978
Stockholm, Sweden	October 17, 1978
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EXECUTIVE DIRECTOR
DAVID B. WEISBAUM

Dear Friend:

The Illinois Agent Orange Study Commission is proud to have hosted the first national Agent Orange Medical Symposium. It is of major significance that 13 of the 20 states with Agent Orange Commissions or programs attended the Symposium.

The Symposium was the culmination of a great effort on the part of the Illinois Agent Orange Study Commission's staff and the leadership of other state commissions in promoting and organizing such a successful and productive event.

The panelists also deserve much appreciation for their gratis appearance. Without such waivers of honoraria the Illinois Agent Orange Study Commission would have been unable to hold such a program because of budgetary constraints.

It was the intention of the Illinois Agent Orange Study Commission to allow physicians and researchers familiar with herbicide exposure and its physiological ramifications to have a forum from which they could speak. They did so in an eloquent and comprehensive manner.

It is my hope that this publication of the Symposium's transcript will benefit those who have concerns regarding the Agent Orange issue. While questions still remain, we believe our efforts represent a positive step toward the ultimate resolution of this most complex and profound matter.

Sincerely,

Representative John T. O'Connell
Chairman

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MR. O'CONNELL: Good morning. My name is John O'Connell. I am a state representative from Illinois. And on behalf of Illinois, I'd like to welcome you to our state and the city of Chicago and our beautiful fall weather.

I am also the chairman of the Illinois Agent Orange Study Commission, which has been in existence in this state for a little over a year and a half. And in that year and a half, in addition to our public hearings that we have had throughout the state, we have had the opportunity to meet several other state commission representatives.

It occurred to us some time ago that it would be a very expenditious expenditure of money and time to have a symposium, wherein we could reach out and find an array of experts in the field of dioxin and the Agent Orange and present it for the record so that all of us could benefit.

In that regard, I think you will, upon review of our program today, agree that we have perhaps as comprehensive and prestigious a group of speakers on this issue as you will ever find in this country. We have twelve states that have indicated that they will be in attendance. And we have some distinguished guests in the audience. As an overview of today's meeting, I alluded earlier to the fact that all of us are looking for the same answers. In our own states, we have pursued an endeavor to find some answers for our citizens, the Vietnam veterans, and their families. This, we recognize as a state, is secondary to the overall federal probe of the Agent Orange issue. But, we at least in Illinois, and I suspect other states, felt that what was needed was involvement on behalf of the various states to puruse a third-party evaluation of this issue.

We, in Illinois, felt that in determining the answers to whether there is a causal factor of erious defects and diseases in exposure to Agent Orange, the federal government was in an adversarial posture. And in that adversarial posture, it was both the plaintiff and the defendant, if you will. And therefore, to make certain that the evidence was complete and whole, we as a state had a responsibility to submit testimony from our residents as to the symptoms that they have incurred.

In that regard, we have had eight public hearings throughout our state and developed a record of testimony.

A year ago, we had a hearing which featured medical practitioners in this area, as well as one or two out-of-town guests, including Dr. Codario who will speak again this morning. We felt that the testimony elicited at that hearing was so valuable in terms of an overall record that duplication of that, only on a broader spectrum, would be of extreme value to us in presenting this overall record of evidence on the issue. And in light of the controversy over the issue and the myriad of reports that are coming out, we felt indeed it was topical at this time that we should present to the various states and to the federal government a record of testimony from people who have made a career of studying this issue and, of course, evaluating the victims.

Today, if nothing more is gained than a transcript of a group of prestigious individuals—professionals offering their own experiences, it is indeed a success. I would like to commence this program by introducing our first speaker, who is Dr. Bertram Carnow.

Dr. Carnow is president and senior scientist for Carnow, Conibear & Associates, an environmental and occupational health consulting firm here in Chicago. This is the second time that the Illinois Agent Orange Commission has had the pleasure of introducing Dr. Carnow. He was a participant at our medical hearings last October. Dr. Carnow is a graduate of the University of Chicago School of Medicine. He is a veteran of the United States Air Force, and has been director of occupational and environmental medicine at the University of Illinois School of Public Health. And he is cur-

rently professor and director of Great Lakes Center for Occupational Safety and Health of the University of Illinois School of Medicine.

Dr. Carnow is also a much published and much-sought-after speaker. And he had the dubious distinction of appearing with me on a television show that aired at 6:00 o'clock in the morning.

So without further ado, I would like to introduce Dr. Bertram Carnow.

(Applause.)

DR. CARNOW: Thank you, Mr. Chairman.

It's a pleasure to be here to talk with you today. I expect or hope that by the end of the day, all of you will be able to answer the question or questions that seem to be plaguing many of us. Possibly the most asked question is "is dioxin really toxic?" Every time I hear that I cringe because a huge amount of scientific data has been gathered and reported including reviews by the Veterans Administration and the EPA, our studies, and the 2,000 or more scientific reports which have appeared in the scientific literature. There appears to be no question that dioxin is the most potent toxic agent ever produced by man The only substances more toxic are pure extracts of biological toxins including tentanus toxin, diptheria toxin, and botulinum toxin. It has also been shown that it will kill a young guinea pig at a concentration of approximately five parts per trillion.,

So the question of toxicity I don't think is at issue here. Another question is—"what damage does it do and how does it do it?" I won't discuss these in depth because there will be a lot of discussion about those questions this afternoon. Let me tell you only briefly what it does because it relates to our study. It moves into the body cells particularly in the liver and affects structures in these cells including one called endoplasmic reticulum and another called mitochondria. It causes the endoplasmic reticulum, a major regulator of production of enzymes, fats, and proteins, to go wild. As a result the body overproduces enzymes and accelerates the destruction and removal from the body of essential chemicals. The body in turn then keeps trying to manufacture more and more of these chemicals at an incredible rate. In doing so, it disrupts many essential activities of the body. The group of enzymes which are particularly affected, called mixed function oxidases are essential to body function.

It also destroys mitochondria. They are critical in energy transfer in muscle and other organs. Muscles, in order to work, use a great deal of energy. And the body has an energy transfer system which transforms food into energy which then provides fuel for muscle use. Dioxin, by destroying the mitochondria interfers with this energy transfer.

So we know a great deal even about dioxin's mechanisms of destruction, even at a molecular level. The next question is, given that this is true, "does it do very much clinically, from a disease standpoint?" Let me tell you that every single species of animal that has been examined following poisoning with dioxin has shown testicular damage, damage to the immune system, and damage to the liver. Every single species. This is extraordinary for a toxic agent. And there are innumerable examples of what it has done to humans in industrial accidents. Many of you know about those so I won't dwell on them. I believe that others will discuss them in greater detail this afternoon.

And finally, there has been another question which has been interjected, namely "what about chloracne, a particularly nasty form of acne found after some accidental plant explosions and other exposures?" "If you don't have chloracne, can you have dioxin intoxication?" Because chloracne involved the skin of the face, ears and trunk and was disfiguring, it received a great deal of attention. Those affected by dioxin with this condition were sent to skin specialists who treated it as a primary skin problem. And from this the fiction developed that chloracne was the sine qua non of dioxin in-

cation. It wasn't true of those exposed in Seveso and it wasn't true in the almost 400 people examined by us. In both groups approximately 10 to 15% of those affected had chloracne and these were younger people with a history of common adolescent acne. You do not have to have chloracne to have dioxin intoxication. Those are my answers to those four questions. Hopefully others will address these and other questions in more detail.

Now, let me then get on to our studies. We were asked to examine a group of workers who had been exposed while cleaning up a spill of dioxin, contaminated and chlorinated phenol and other phenols. And while the other chemicals present may lead to an acute clinical picture which is slightly different from that presented by veterans who were exposed, we belive the major effects, the long term effects were from the dioxin to which our study group was exposed. Since that time, we have studied many others who had other types of exposure to dioxin. We have also studied a small group of veterans, but they represent a very small percentage of our total. I am able only to discuss with you the 47 railroad workers.

Eventually we will discuss and publish all of our findings. However, let me assure you that in the examination of many of the others, the pattern that I will describe to you emerges over and over and over again. And I will show you what I believe to be a pattern or fingerprint of a disease which we call chronic chemical intoxication from dioxin. These examinations were carried out by our team of occupational medicine specialists at Carow, Conibear & Associates, incuding Dr. Shirley Conibear, Dr. George Benjamin and me.

How do you go about studying such an exposed group? How do you make a determination first, whether these people are ill? Secondly, if they are ill, what kind of illness do they have, what organs are involved and how serious is it? Third, is how do you then make a determination of whether or not the disease that they have is related to an external cause? Generally, most of us were trained to diagnose and treat disease; but except for bacterial diseases there is little emphasis on examining questions of causation. For those of you who may be interested, there will be published shortly, a paper that Dr. Conibear and I wrote on the probability of causation of chemical disease, which suggests ways of looking at diseases to make determinations of how they might relate to some type of external cause.

In order to do this, we first determined all of the things that others knew about what dioxin did. What organ systems, what mechanisms, what functions of the body were affected by this chemical. After knowning this, we then set up a protocol, a test protocol, which looked at all of these functions. If we found that people showed evidence of organ disease that fit what others have found and these were people who had been exposed to diosin, and the temporal relationship between exposure and disease was a reasonable one, we could say that they are causally related.

With some toxic agents, cause and effect are more easily determined. If someone inhales a large amount of cyanide gas and dies immediately afterward, the cause and effect relationship is fairly obvious. If somebody, however, is exposed to a chemical and five months later or two years later or three years later he becomes ill, it becomes a little more complex. One of the difficulties we have with dioxin is that it doesn't kill directly like cyanide. It affects enzyme systems which in turn affect many body activities so that the effects are very much delayed. This is true with animals as well as humans.

What I will be discussing with you now are the results that we found on administering these tests to this group of individual workers. The histograms show the percentage of exposed individuals with symptoms reflecting abnormalities of various organ systems. As can be seen, virtually every ma-

jor organ system was affected in someway, with a large majority complaining of headaches, depression and profound fatigue.

We believe the depression to be of the type called neurovegetative depression by some European scientists. It's described prominently in virtually every dioxin exposed group that has been studied; BASF in Germany, the group in Czechoslovakia, the group at Nitro, and many of the other groups and is the result of toxic depression of brain function. Some of our patients were potentially suicidal.

The genitourinary system also was affected as noted. Some of you may have heard of the young children in Missouri exposed in 1972 when a number of horse arenas were sprayed with a waste oil containing dioxin. The children became ill and some 85 horses wasted and died. Genitourinary symptoms and kidney destruction were prominently present in the horses and in some of the children.

Urgency and burning on urination, getting up at night to urinate, frequency of urination, decreased libido (decreased desire for sexual activity) also were noted. And in some cases decreased ability to have sexual activity.

In regard to the lungs, half of the people complained of shortness of breath. Some of those were acute symptoms present immediately after the exposure. Since there was phenol present, it may have been that this was the problem because we did not find that chronic lung disease was a very prominent factor in our examinations.

In regard to other systems, 10% or more complained of benign fatty tumors developing under the skin. One man deveoped 50 or 60 of them.

Weight loss was prominent in some and seemed to be an early phenomenon which went away after about three or four months.

In animals the weight loss was even more severe. Many of them died of a wasting disease. These included monkeys and the horses from the Missouri arenas. Some of the horses weighted only 90 or 100 pounds when they died.

Weakness was also prominent but not as much as general fatigue. Weakness and fatigue are sometimes difficult to separate. Fatigue is a general feeling of not being rested. You get up in the morning, you are tired. You are tired all day. It doesn't matter what you do. The tiredness remains. Weakness is somewhat different in that you may feel well after a good night's sleep but when you begin a task you run out of steam. For example, we found with some that if they lifted their arms to do a task, their arms would tire very rapidly. You have to understand that these people were maintenance and way people. It's physically one of the most demanding jobs on the railroad. Many of the men had worked for the railroad for 20 or 30 years. Most of them were hunters and sportsmen and many had small farms that they would operate after they finished their day's work on the railroad. Some hadn't missed a day of work in 10 years because of illnesses.

The average age was only 33 in this group, thus many were quite young and previously very healthy.

Headache and fatigue were the most common of the symptoms. The headaches were generally characteristic. They were frontal or bitemporal; that is, they would start in the front of the head or across the temples. Many complained of throbbing in the head made worse if they bent over, although not all of them had throbbing headaches. And they were often very severe. In other groups we have studied since then, a similar headache pattern is present.

The symptoms are critical and probably the most important component of the medical

evaluation, but other examinations contribute to understanding and defining the disease process. These include the physical exam and laboratory and other tests. First let's look at liver disease. We found that in this group, liver enzymes were abnormal in some. The one which seemed to be most commonly abnormal was the SGPT in eight people. One of the things we found in other groups that we have studied, is that this inflammation of the liver is something that develops relatively early and in a lot of people sort of burns out. This doesn't mean that the liver disease is gone—only that it's become low grade and chronic.

Liver biopsies done in some suggest that it doesn't go away. Groups that we studied many years after exposure did not show a lot of enzyme abnormalities, nor did they show a lot of abnormalities of bilirubin, which is a chemical produced in the liver. Some showed an abnormality of an enzyme called alkaline phosphatase which is something we see when there is increased bone activity in the body, but also something we can see where there is chronic liver disease and it may, in fact, represent chronic liver disease.

We also found abnormal levels of fatty substances (lipids) whose production is generally controlled by the liver. And we know that dioxin causes disturbances in fat metabolism. And, in fact, half of the people that we examined had abnormally high triglycerides. Many of them had abnormally high cholesterol. And even more had depressed high density lipoproteins (HDL), a type of fatty substances the body wants. People with high HDL have less coronary disease generally. The more you have of it the better off you are. In this group, 28 had a depression of HDL. They also had abnormalities of lipoprotein electroporesis, which is another way of looking at these fatty substances.

This disturbance of fat metabolism in the body is very important because the brain and the peripheral nerves of the body use lipids in their function. Also high tryglycerides and cholesterol and low HDL are associated with heart disease, stroke and high blood pressure.

Another critical body activity is porphyrin metabolism. There is a rare genetic disease with disturbed production and excretion of porphyrins called porphyria. More recently it has been shown that toxic chemicals including some of the benzenes, dioxin, and PCB's, can cause abnormalities of porphyrin metabolism. Porphyrins are essential in the production of red blood cells in the body. They also are very important in the formation of special proteins, called hemeproteins, which are critical to the formation of those enzymes that I talked about before. And when the body starts overproducing enzymes as happens after absorbing dioxin, it requires large amounts of these proteins. This and other factors cause a very severe disruption of normal porphyrin metabolism with some porphyrins abnormally increased and others abnormally decreased.

We also found in these people abnormality of a critical muscle enzyme called CPK. Twenty-two of our forty-seven patients had abnormally low CPK.

We also found abnormalities in prothrombin which is involved in bleeding and clotting. The abnormalities were not enough to cause hemorrhaging in people, but they were present. And we have an explanation for it which we think is a reasonable one which will be published shortly. And there were abnormalities of another bleeding and clotting component called PTT.

These abnormalities generally relate to liver function. The liver is a very complex organ. It has multiple functions which begin or take place in the liver. We also found abnormalities of proteins, particularly of globulins. And this too is something which is affected by that endoplasmic reticulum and processed in the liver. What we are seeing now is a pattern, a complex of findings which you just don't find in other diseases.

In regard to the kidneys, we found a significant number of abnormalities in kidney functions with abnormal levels of BUN, creatinine, and uric acid.

We know also that in animal experimentation, dioxin certainly can affect the kidneys. And in other groups of humans that have been studied, it also has affected the kidneys.

In regard to the central nervous system, what we did was to develop a very extensive neurobehavioral battery of tests. Our psychologists who administer this test feel and we feel that you can differentiate psychological from organic brain damage by these tests.

We found extensive abnormalities in concentration, retention and memory, which we feel represents diffuse cerebral dysfunction; that is, damage to the cerebral hemispheres of the brain. And on the neurologic physical examinations, we found in significant numbers, changes which we felt indicated some damage to the central nervous system.

In regard to the peripheral nervous system, we found that seven of these people had abnormal EMG's. Six of them had abnormal nerve conduction, a slowing of nerve conduction.

The second time we examined them, there seemed to be a decrease in peripheral neurologic conduction abnormalities. But the EMG abnormalities, which generally reflect irreversible damage remained abnormal at seven. And on the neurological physical examination, which incudes sensory abnormalities, touch and pinprick, there were large numbers that were abnormal.

Now, let me again say that all of these things were looked at in relation to the symptoms. But the physicians who took the history on these patients were not the same people who did physical examinations. The people who did the physical examinations were other physicians who performed them on the same day and had no knowledge about what was found in the history. So these were indepentent activities which were then looked at in an integrated fashion. And then at the end, we would look at the symptoms, the physical findings, the laboratory findings for each organ system and integrate them.

Since each component was done by another physician or group, there was a great deal of objectivity in looking at these findings. The physicians who did the physical examinations did not take a history and were not influenced by the patient's history.

In regard to examination of the lungs, as I pointed out before, we did not find a great deal. Now, in regard to the skin, some of them had—what looked like a burn. And that may have been from the phenol, which went in and went out of the body fairly rapidly. It doesn't stay around like dioxin does.

Others had changes we call sclerodermatitis—like changes. It's a thinning out of the skin which becomes thin and fragile. It bleeds easily. It breaks easily. And it doesn't heal well. We found this in a fair number.

In regard to chloracne, 14 of our patients, 25%, had chloracne. In other groups, we found less. And in one group of people who worked directly with the production of Agent Orange and even cleaned out reactors, we found extraordinary numbers with chloracne. Some of them were people who were in an explosion in 1949, and developed chloracne after three or four days, which they called weed bumps. And they have been squeezing—that chloracne material out of those bumps for 30 years, 40 years some of them.

Many of them still have severe chloracne. But those were people who had massive exposure. And those were the people who were seen by the skin doctors who then said "well, if you don't have chloracne, you don't have dioxin intoxication."

But, you know, when we first began to see tuberculosis, people would see us because of hemorrhaging from the lungs. Nobody today would say that if you don't have hemorrhaging you don't have tuberculosis. What hemorrhaging is to tuberculosis, that is a late manifestation of the disease, chloracne is to dioxin.

And if you just look for chloracne, you are going to miss 80 or 90% of your cases. Certainly this is true in Seveso. It's true in our group. You tend to find it in younger people. And you tend to find it in people who have a history of acne vulgaris. Those are people who seem to be more prone to the development of chloracne.

In regard to precancerous lesions, what we call keratoses, which look like basal cell cancers and which may or may not be early cancers, we found nine. And we found four people with skin cancers which developed after exposure. One man had six cancers. One of them had recurred three times. And then he had three others removed. So that skin cancer was a serious problem.

The reproductive system was also seriously affected in some cases. I pointed out to you that every animal that has been studied has shown an abnormality of testicular function. And we found that 18 of our patients had abnormal, depressed testosterone level. And 17 of them had abnormal sperm counts. One repeat examination, after 1½ years of the number decreased. There was one man with a very low sperm count. The next time we saw him about a year later, his count improved considerably. And, in fact, his wife had become pregnant. So in some cases individuals seem to have gotten better. We also looked at sperm motility and sperm activity. And we found very large numbers who had a decreased level of activity. Normally at the end of four hours, 60% of sperm should be active. And we found people with 40%, 20%, 10%, and some where the sperm were all dead when we examined them. The other thing that we found which is very interesting, is a deformity of the penis.

I mentioned the CPK was also abnormal. We also found that 11 people had abnormal blood sugars. There was an increase in diabetes.

Dioxin can affect the pancreas.

We did extensive testing of the immune system along with everything else. I understand that Dr. Prince will discuss in more detail, later today these tests on our patients. Many were found to be abnormal which causes reduced resistance to infection and to development of cancer.

We did not find a lot of abnormalities in pulmonary function. In regard to cardiac function, a fair number of murmurs were found, but not large numbers of abnormal EKG's.

We also found some abnormalities of the blood, including some people with anemias. We found a lower than normal number of leukocytes. Normally, 50% or more of the white blood cells are leukocytes. We also found in the same people an increase in lymphocytes—another kind of white blood cell. These were elevated. This pattern is seen when the immune system is depressed.

Various urinary tract abnormalities were found. Significant numbers had bacteria or pus cells in the urine, four had blood on microscopic exam and two had elevated glucose (sugar) suggesting diabetes.

To reiterate—this was a group of people—healthy, rural, hard-working people who were suddenly exposed to a chemical and who then proceed to develop a series of problems which fit a common pattern. Not only did they develop similar things among themselves; so it wasn't an individual thing, but it was very much like what we expected to find based on what we knew about animal findings and findings in other groups of humans who had been exposed.

When you have that kind of pattern, and that kind of a picture, you can with scientific cer-

tainty, which again is a high level of probability, say that this is a disease entity.

To find an individual in this society who has not been exposed to this chemical with immune dysfunction, with abnormal testosterone, with abnormal porphyrins, with all of the things that we found would be extraordinary and way beyond probability.

But again, if it walks like a duck and it talks like a duck, you know, it can be a chicken, but it isn't a chicken. And I think that there is no mystery.

There is still a tendency to make a mystery of all of this. Does dioxin really do this, or what does it do? We don't know enough. I have twenty volumes of reprints on scientific articles, hundreds and hundreds and hundreds of scientific articles which represent an enormous body of knowledge.

And it's virtually uniform in what it says and what it finds. And I think that what this means to you for those of you who are interested and concerned about making a determination about whether the veterans who are alleging damages or are, in fact, damaged. And if they are damaged, are they damaged from dioxin?

What is necessary is to develop such a protocol, carry it out dispassionately and see what you come up with. And I think if you do that, then you will lay to rest a lot of the concerns, frustrations, fears, and angers that have been exhibited in some places by so many people.

And I think it's something that will have to be done. And I think that we certainly have the scientific expertise to do it.

Thank you very much.

(Applause.)

MR. O'CONNELL: Thank you, Dr. Carnow. This morning we will go through our morning speakers, and prior to the lunch, we will have a question and answer session. There is a microphone at the back of the room. If you wish to address a question, identify yourself for the record since it's being transcribed. As to the transcription of today's seminar, order forms are available in the hall to request the transcript of this morning's symposium.

So if you wish to order, please fill out that form. There is a five dollar copy charge for the transcript.

Our next speaker has come to us from the State University of New York in Stonybrook.

Dr. Elof Carlson is a distinguished teaching professor in the department of biochemistry at the State University of New York at Stonybrook. He is a geneticist whose interests are experimental mutagenesis in fruit flies, and in spontaneous mutation in humans. He is the author of *The Gene, A Critical History*, written in 1966. And *Genes, Radiation, and Society, the Life and Work of H.J. Muller*, written in 1981.

He has worked on mutagenesis testing and ionizing radiation alkylating agents, LSD, and herbicide components. Dr. Carlson will speak to us on the genetic development and biological effects of herbicides, and will also give his appraisal of Vietnamese data presented at a symposium in Ho Chi Minh City, formerly Saigon, last January. Dr. Carlson.

DR. CARLSON: I will discuss the genetic and biological effects of Agent Orange and their components. First, as a background, in Vietnam, three major herbicides were used in the spraying program. 61 percent of the herbicides we sprayed were Agent Orange, which is a one to one mixture of herbicides 24D and 245T. A second agent used was Agent White, which consists of 24D and a compound similar to 245T in its effects, called picloram; 28 percent of the spraying involved Agent White. Both Agent Orange and Agent White were mainly used for forests and jungle growth. Agent Blue,

which constituted 11 percent of what we sprayed, was intended mainly for crop land. Agent Blue consists of cacodylic acid, an arsenic compound. It is not a herbicide of the same category as 24D, 245T or Picloram. TCDD or dioxin is present in the synthesis of 245T.

Early spraying involved commercial production with high dioxin content. After 1968, a decreased temperature was used in the synthesis of 245T, diminishing the amount of dioxin present. Visually, 24D does not produce dioxin as a consequence of synthesis.

There is some debate about how much herbicide was sprayed. American estimates claim about 75 million liters sprayed on about 14 percent of the land mass of South Vietnam. The Vietnamese claim a much higher amount sprayed on their land and claim 44 percent of their land mass was sprayed. That's the background.

There is one other item of background interest I want you to bear in mind. I will talk about mutagenesis and other biological studies in which doses are expressed in parts per million or parts per trillion. Other than astronomers and a few other scientists who play with the very small or the very large numbers, most of us don't appreciate what a part per billion or a part per trillion means. But if you were to run a string from this room to the moon, and you were to move one sixteenth of an inch, you will have moved one part per trillion. It's a very small dose.

If it is a very small dose, and if we are talking about dioxin in parts per trillion for its toxic effect, and we are talking about experimental studies with 24D and 245T in parts per million, then recall that for each gallon sprayed, there was approximately 24 pounds of 24D and four pounds of 245T. This is not parts per million, but parts per ten.

At its release on the jungle canopy, the spray had a very severe effect on the life, both plant and animal, that was present in the sprayed areas. There would, of course, have been a dilution from the aerosol mist, from drift, from the percolating down motion, most of which would have been absorbed through the leaves. Troops or Vietnamese civilians who were underneath the jungle growth would have received lesser amounts. But it is very difficult to estimate what the ground level exposure was, either for those veterans who were exposed directly or for those who were following proper procedures and entered into sprayed areas 30 days or so after exposure.

Estimates will vary from parts per trillion of actual veteran exposure to parts per ten for many who were hit by prop wash and other accidents that may have occurred as a consequence of the way in which the spraying took place.

Early studies on mutagenesis (attempts to induce mutations in a number of experimental systems) were inconclusive. Bacteria are studied by spot tests. A drop of a known concentration of mutagen is put on a petri dish which has an agar growth. This was spread over with bacteria, before the drop of the agent is placed on it. A clear zone arises where the bacteria are killed off. You can look for certain survivors that would have been induced as a result of mutations in these tests and you can count the number of colonies.

Those spot tests were mostly negative for herbicides in bacteria tested. But some bacterial strains were positive, particularly bacterial strains in which the herbicide had a reduced PH. The interpretation of the conflicting evidence between positive and negative results seems to be whether or not the cell takes in 24D or 245T.

A bacterial cell has a thick wall around it, underneath which is a membrane. It may be that either the wall itself or the membrane serves as an impenetrable barrier for the movement of 24D or 245T into the cell. A test of plant and animal cells grown in tissue cultures has also been inconclusive.

but the main findings seem to be this: in plant cells, the herbicide 24D or 245T acts as a plant hormone stimulating cell division. The rate of cell division increases.

In animal cells, the herbicide acts as an inhibitor of cell division. The interference in cell division involves two things, one of which is specific for the animals, which is an interference in DNA synthesis. One of the four components that go into DNA is not produced in its normal quantity, and it slows down cell division.

The other consequence to animal cells is an interference not at the level of the gene or the chromosome, but of fibers that move chromosomes during cell division; they are called spindle fibers. The fibers are made up of chemical units called tubulin. They are improperly put together as a consequence of exposure to 24D or 245T. As a result, in both plants and animals, when spindle fibers are not normally formed, chromosomes lag. Chromosome breaks form. Chromosomes get duplicated or doubled in number.

The technical names for this defect, polyploidy or endoreduplication, will appear in the literature. These have been observed in both plant and animal tissue culture. Most of these would be self-eliminating. For example, veterans exposed and who may have in their tests polyploid sperm reproductive cells, would not be able to produce normal children from such sperm. In fact, the chance of an implantation of the fertilized egg at an early stage of pregnancy would be very slim for such polyploid or endoreduplicated cells. There is no evidence of such sperm forming either spontaneously or induced by herbicides.

In animals, there are a number of other tissue culture abnormalities. Studies done on hamster cells, on mouse and rat cells, and human tissue culture are fairly consistent. They show the slow mitosis. Also, when standard procedures are used to stain the chromosomes; cut these out after photographing and make what is called a karyotype, a size plate arrangement of the chromosomes. The chromosomes show chromosome breakage. Usually the breakage involves one, not both, of the strands that are usually present in the chromosome at the time when the chromosome is prepared for the karyotype. These are called single-break or chromatid events and they are characteristically seen in standard cytological techniques. A second abnormality is called a multibreak event. These multibreak events produce unusual chromosome figures that look like a maltese cross under the microscope. They are also recognized in mouse, rat, hamster, and human tissue culture studies depending on the dose and depending on the investigator's techniques. It is a mixed result. Not all studies have consistently shown these abnormal figures.

My own field for experimental mutagenesis uses fruit flies. Fruit flies were first used in 1926 to demonstrate that X-rays induce mutation. They were first used in the 1940s to show that alkylating agents such as, mustard gas and nitrogen mustard induce mutation. Fruit flies were the first organisms used to show that chromosome breakage is induced by ionizing radiation and by chemicals. The number of techniques available to test the particular category of genetic damage is well worked out in the 50-year history in which fruit flies have been used for such studies.

In addition to studying radiation induced mutagenesis and its characteristic effects, I have also studied a number of chemicals, including ethyl methane sulfonate, a very potent alkylating agent, a compound that not only alters genes but also breaks chromosomes, although not as effectively as X-rays do for chromosome breakage. In general, chemical mutagens are far more efficient than X-rays in altering individual genes.

In the 1960s, I studied LSD because a particular compound I was working with at the time,

quinacrine mustard, was very similar in structure to LSD.

I remember discussing with several students in my laboratory whether or not LSD, because of the similarity of its structure, might be mutagenic or not. At that time, a number of papers came out claiming that LSD was a very potent mutagen. Most of these were based on karyotypes, on chromosome analysis, looking for single breaks, or for multiple breaks with these curious cross-like configurations.

When we ran our experiments on LSD, we injected it into fruit flies, through the abdomen — you have to have steady hands for this because the fly is an eighth of an inch in length. We injected them until they bloated up like a balloon. I calculated that the dose I administered to the male fruit flies was 75,000 times a human trip dose. This was a massive concentration. Approximately 500 parts per million was the actual concentration of LSD being used. It produced no mutation, no chromosome breakage, no loss of chromosomes, and no evidence of any genetic abnormalities whatsoever.

One of the things one learns in the field of mutagenesis is that the same organism, for the same testing procedure, can be used very satisfactorily for ionizing radiation or very potent alkylating agents, giving unambiguous results; yet it becomes extremely difficult to use that same system, when you are looking for agents whose genetic effects, if any, are rather modest.

Now, I am going to show slides in which I will very quickly show the data on my own work. And then I'm going to discuss the Vietnamese work. This first slide shows a standard technique, the one that Herman Muller first developed in 1927 to show how X-rays are induced. The technical description is complicated, but essentially what it looks for is the absence of an expected category of ...es, which just don't appear. All the other progeny that should be there are there, but the one category that should be present is missing. And in the case of different treatments of 24D up to a concentration of 500 parts per million there is no difference from the control.

At a concentration of 125 parts 245T per million we found no lethals induced. An Agent Orange mixture which I made artificially by using a one to one mixture of 24D and 245T, 75 parts of each, giving AO 150 showed one percent lethals. But the control rates vary up to one percent. This shows there was no significant difference in that experiment.

A repeat of the 24D 500 showed no difference from the control. So the X linked lethal data is not supportive of, but doesn't necessarily rule out, a weak mutagenic effect at those doses. These doses of 500 parts per million are comparable to the doses of ethyl methane sulfonate that would produce about 30 percent X linked lethals. If 24D or 245T induced mutations they could not be inducing more than two or three times the control rate for the sample size we observed, but even here we did not find evidence of that.

A second series involved a particular gene mutation called dumpy, a reasonably mutable gene that I studied with X-rays, quinacrine mustard, and ethyl methane sulfonate. It mutates at a spontaneous frequency at about one in seven thousand flies showing a new dumpy mutation. With X-rays at about ten times a human mean lethal dose, mainly at about 4500 roentgens, you would get about a one percent or a little less than a one percent mutation rate.

With ethyl methane sulfonate at about 500 parts per million or quinacrine mustard at 500 parts per million, I would get a one to two percent dumpy mutation rate. As you see in the slide for the 24D work there were two out of three thousand. The control had one out of three thousand. This was not significant. So there was no evidence at the individual gene level that either 24D in this particular

case was mutagenic.

A third experiment involved a phenomenon called nondisjunction. If spindle fibers are not properly attached and the chromosomes don't separate normally, you pick up abnormal offspring. The expected abnormal offspring, which are represented in the lower, bottom, horizontal line did not appear, indicating the absence out of some 1100 progeny of any nondisjunctional events. This again suggests that if there is an effect on abnormal cell division in which chromosomes should lag as a result of spindle fibers being improperly put together, these should show up; but they didn't.

The final test of this mutagenesis was for a normal type of chromosome breakage found in our sex cells. Whenever we manufacture our own sperm or eggs the chromosomes we obtained from our mother and the chromosomes from our father come together and exchange pieces. This is called crossing over. I looked for a category of crossing over in which the middle of the three genes switched places between the original chromosome that came from the sperm and the chromosome that came from the egg of that individual female fly. The results showed no difference in 24D at a concentration of 500 parts per million for double crossover flies.

In contrast to those negative results for chromosome breakage, chromosome mutation, and loss or gain of chromosomes in their total number, my students and I found developmental effects which were strikingly significant. You can see in this slide that control flies begin hatching out approximately ten days after the eggs are laid. They reach a very dramatic peak two days later and then this peak crashes and plateaus very rapidly. Within about 16 days or so, most of the flies have emerged. Also, females tend to emerge earlier than males. The ratio of males and females will eventually show about a one to one ratio.

On the other hand, when 24D or 245T is placed in the food and the flies lay eggs in that food, a phenomenon arises that I call developmental delay. The life cycle is dragged out. On the 12th day when most control flies are hatching out, the 24D or 245T flies are still in a maggot stage, and most have not undergone metamorphosis. The herbicides slow down the metabolism and life cycle of these flies. Also, males tend to hatch out much earlier than females and in greater numbers.

It's very difficult to extrapolate what this developmental delay means in human terms because the way the fruit flies produce offspring are clearly different from the way humans produce offspring. Also, among the thousands of flies that were produced as a consequence of developmental delay, I looked for any evidence of teratogenic effects that produce abnormalities of the wings, legs, eyes, malformities of the genitalia, or other components of the fly; and I found none that I could identify as teratogenic consequences.

That doesn't mean in a mammal or a human these delaying effects, might happen, particularly those in those tissues that are lipid rich, and cause abnormalities.

If we gave the flies an option of what food to choose, using four dishes — one of control, one of 24D 500, one of 245T, and one with the Agent Orange mixture — they usually laid eggs on the control dish. We allowed them to lay eggs in a population cage in which there were four dishes. We set this up three times with the dishes to eliminate temperature grades and other possible factors in the background. Consistently, the flies laid more eggs on the control food. The fruit flies recognize the food as being toxic and it inhibits egg laying. This we tested repeatedly, and consistently found that an aversion to laying eggs on either 24D, 245T, or Agent Orange food.

I'm going to shift now to the conference in Vietnam, and discuss some of the work done there.

fingers. People who developed this developed a neuropathy; would have aching in their legs and in their arms, which they would decribe as a deep ache. They couldn't put their finger on it. And it's the kind of thing that keeps you awake at night or wakes you up at night. That is classic neuropathy.

And it may or may not be associated with weakness. When you have extensive neuropathy, you get foot drop and wrist drop. But with a lot of these people, there seemed to be a sequence. The first thing seemed to be numbness and tingling. If they rested their arm on the car window ledge, it would fall asleep. If they crossed their legs, the legs would fall asleep fairly rapidly. All of us have had that experience after a long period of time, but it happens to them very rapidly. And a lot of those people don't have peripheral nerve conduction abnormalities. So that, in some people, we would find the symptoms, they would have the symptoms, but we would find the abnormality.

In some people, we found peripheral neuropathy or a slowing of conduction. And some of them didn't have numbness and tingling. But there is generally a pattern, a pattern with the central nervous system function, in which we found large numbers of people related to attentional deficits, some memory deficits.

So, if you want to do a quick and dirty you would do a digit span. You read forward numbers and backward numbers. They can read forward numbers, but they can only read a few numbers backwards. There are other deficits in concentration—in memory that we found. That seemed to be a common pattern, the kind of pattern that you see in the diffuse cerebral dysfunction from toxic agents.

Not all of them had general urinary symptoms. Not all of them had liver enzyme abnormalities, but a large number of them did. One of the things that I did not discuss was gastrointestinal dysfunction. A lot of them had symptoms that sounded like ulcers. And a lot of them had x-rays taken. In many, no ulcers were found. What was found, were diffuse inflammatory changes. We are not sure what the mechanism of that is. Of course, each one of these symptoms and every one of these findings can be caused by another disease because the body can only react in a certain number of ways. The difference is that you get a group of these things. It's almost like picture games we played as children where you would expose one eye, then the nose and try to identify a person. Eventually, you say, Oh!, that is Frank Sinatra or John Wayne, when you had enough information.

DR. ANDERSON: That's what I was trying to get at. Is there some—that's—obviously, people have it and people react in different ways. But in your 47 people, which you characterized very carefully, were there some groups that were much more common and occurred together than the others? Was the nerve conduction—was it sensory or motor—or both?

DR. CARNOW: It was more motor than sensory, but we saw a fair amount of sensory. It was median nerve neropathy, diagnosed by orthopedic physicians as, carpal tunnel syndrome, because it affects the nerve as it goes through a tissue tunnel. But you see, the carpal tunnel is where the median nerve is compressed and therefore susceptible to damage. It is our experience that when you have toxic damage to a nerve, it is going to occur at the point where the nerve is under the greatest trauma, because damage where a nerve is moving the most is where it tends to be traumatized when it is deficient. That is why painters who were exposed to lead, would get wrist drop of their working arm, because that was the nerve that worked the hardest, and the one that needed the most nutrition. And so we found the earlier signs tended to be of the median nerve in the carpal tunnel.

MR. DIESNER: Senator Diesner from Minnesota. Dr. Carnow, you listed a whole group of laboratory tests here as being abnormal. And I was wondering about the degree of abnormality. Are

these things borderline abnormalities or mild abnormalities?

DR. CARNOW: Well, when we say abnormal, what we are talking about are two standard deviations from the mean.

So, when we are talking about something being abnormal, we are not talking about one standard deviation. We are talking about something that is more than two. That makes it abnormal. So when you say mildly abnormal, you are talking about something that is already beyond two standard deviations.

We did not find that a lot of these people had gross abnormalities—some did. For example, triglycerides are abnormal above 170. We found some people with 900, 1,200, 1,400—I had never seen anything like that before. So we saw some people with prophyria. Any uroporphyrin that is over 60 is very, very high. Now, we say that normal is from 15 to 60. But, the number of people that I saw with 60 or 58 is extremely low. So, it is very hard to give you an answer to how sever is severe.

MR. DIESNER: May I use your terminology?

DR. CARNOW: Sure, go ahead.

MR. DIESNER: How many of those were beyond three or four standard deviations?

DR. CARNOW: I don't know. I can't tell you that.

MR. DIESNER: A few or a lot of them?

DR. CARNOW: It depends on what tests you are talking about.

MR. DIESNER: Well, pick any.

DR. CARNOW: I don't know. We did not look at it that way.

MR. DIESNER: Thank you.

MR. McCARTHY: Frank McCarthy, President of the Vietnam Veteran Agent Orange Victims, and representing the Connecticut State Commission.

Doctor, what we are trying to find out at this point that is most crucial to us is treatment for the various symptoms and effects. Now, the Vietnam veterans were all medically scrutinized prior to going to Vietnam. They were considered medically fit, physically fit and combat ready. We have literally put some of our veterans in a blender. And we realize that there are quite extensive variables which are involved which are exposed to Agent Orange, Pink, Purple, White, DDT altheine, and various other chemicals aside from the illnesses from Vietnam.

But those of us with chloracne—now, the Veterans' Administration is telling us that it's of a teenage-type. And we realize that that is not true. But with your trackworkers who were definitely diagnosed as having chloracne, is there any treatment being administered to these people or do you know of any treatment?

DR. CARNOW: Well, a lot of people who have very severe chloracne would have them evacuated. That's all they could do. If they didn't evacuate the material, they would develop this material which has a terrible, terrible odor. In severe chloracne they would evacuate them. And dermatologists tried all sorts of treatments; none of them really worked. In some people, they go away after a year or two. And I said there were others who have had it now for 40 years. And their wives still squeeze out these bumps when they get bad enough.

But I don't know that any treatment has helped. Some of these people had radiation for the skin early on in the 50's. That would be extremely hazardous in my view.

MR. McCARTHY: Doctor, last question. We have been told that the fat biopsy is a way of detecting dioxin within the fatty tissue. In your opinion, is it not true that dioxin could have entered

the system, done the damage, and then left the system without leaving any residue?

DR. CARNOW: Well, I think that we all agree that that may be the case. I think that there may still be some residue, but it's diffused. You are talking about a very small quantity to begin with. You then diffuse it because it's found in the pancreas, the liver, the adrenals, the brain, the kidney, and other organs, and the fat.

In some cases, biopsies were done and the highest concentrations were found in the pancreas, some in the liver, and some in the fat. So it's very, very difficult to measure. You would probably need a huge amount of fat because you are talking about a very small concentration, a very small concentration of material.

Such surgery would be somewhat mutilating and—probably not a useful procedure. What we are doing is we are getting access to this autopsy material and all the workers who were exposed years ago and who are dying. And we will be doing measurements in their tissues to see what levels we find. Some of these people have not been exposed for 10 or 15 years. And that may be very useful information. But until we have better information, I think that if somebody is exposed, if they have this kind of a symptom complex or at least some of the things that we find here, it seems to me that it would be reasonable and prudent to make a judgment that they were exposed and affected. But again, it depends on what you are looking at. You are looking at medical prudence.

MR. O'CONNELL: I'd like to return at 11:15 so we can get on with our latter part of the morning. At this time I'd like to thank Dr. Carnow and Dr. Carlson on a very interesting presentation.

(Applause.)

(Whereupon, a short recess was had.)

MR. O'CONNELL: Could we start the program?

Since we began this morning we have had the arrival of several other states. Connecticut has arrived with Frank McCarthy. Ruth Leverett from New York arrived. Hank Hahn from California has arrived. Dr. Anderson, of course, came in from Wisconsin. So we have a pretty good representation. We welcome our next speaker back to his hometown of Chicago. Dr. Mark Thoman is a graduate of the University of Missouri School of Medicine. He is currently the president of the American Academy of Clinical Toxicology. He is a Fellow of the American Acadeemy of Pediatrics, and a clinical faculty member at Drake University in toxicology and pharmacology. This is to name but a few of his many qualifications.

Dr. Thoman will discuss dioxin past, present, and future with an emphasis on fetal abnormalities and on the effects of dioxin on future generations. Dr. Thoman.

DR. THOMAN: Thank you. Well, it's good to be back in the hometown.

I would like to bring us up to date and touch on some of the things that have already been discussed very adequately by Dr. Carlson and Dr. Carnow, and not go over old ground. I think for brevity and to give us some time for questions at the end of the session this morning, I would like to talk about a very basic thing. I would simply and initially talk about the complexities of those of us in clinical practice in clinical toxicology. The Academy of Clinical Toxicology has been around since 1968. So it's a relatively new specialty. I graduated from medical school in 1962. And toxicology and ecology were words that we heard, but we just didn't think were ever going to be much in the way of specialties. But then in the 1930's and 40's...for those of us that were around in the early 30's and 40's, we grew up with the phrase "Better Living Through Chemistry." I think that we are seeing one thing,

and that is we eventually "pay the piper." I have given quite a number of presentations in reference to specifically, the chlorinated hydrocarbons. I'm going back to the PCB information that came out some years ago as it related to the so called cola-colored babies that occurred in Yusho, Japan and this is a chemical cousin to the dioxin we are talking about. But they have their own characteristic chemical effects.

Now, let's talk about how one gets poisoned. Let's talk about basic toxicology. Ed Press in Evanston, Illinois, started the first poison center as a pilot study associated with the Northwestern University. This was primarily for other doctors who would call in saying, "I've got a child that's taken grandpa's medicine." And the physician would say what to do about it, and the signs and symptoms that you look for.

Pediatricians took care of the children that would accidentally ingest toxins. They are big enough to get into things, but not big enough to know any better. The toddler is the one who is a main candidate for poisoning. This has now expanded.

Over the years, we don't just have the accidental ingestion of poisoning by the toddler, but we also have the intentional ingestion by some people that want to get a high with certain chemicals. So the first way you get poisoned, or most common way most of us think of is the ingestion.

Second is inhalation. And when we talk about dioxin, we talk about not necessarily ingestion, but inhalation. Inhalation is breathing in the material.

When it's breathed in, it is swallowed with the mucous. It is often coughed up, then swallowed, hence, an indirect ingestion.

This is a cycle that often incorporates other methods of toxicity. We talk about simple contact or simple inhalation. We are often talking about a more complex situation than that. But inhalation can be accidental as it is in most cases in situations where there is an incident of a workman working around dioxin, the railroad worker we talked about in the previous study. We talked about lead poisoning and so on. And this can cause the industrial toxic exposure.

Contact is a real problem in the agricultural states, such as Illinois, Missouri, Iowa. And the contact with the organophosphates—contact with this particular group of toxins certainly has to be considered. There are situations where someone can absorb enough by contact that it would cause overt signs and symptoms where it would hamper function...therefore have a toxic effect. I'm talking about malathion-parathion insecticides and herbicides. Contact is also a problem with dioxin.

Injection does not necessarily apply here, but injection is the next way one gets poisoned. Now, this could be accidental or intentional. Accidental would be someone inadvertently—giving an injection—the wrong material is given to a patient. The deliberate injection is where someone is giving themselves something to give them some kind of an effect; such is the case in heroin addicts or cocaine users. I was director of the heroin clinic for eight years in my city.

Finally, radiation. And Dr. Carlson had mentioned this earlier regarding the effects of radiation. In fact, when we talk about the teratology or the effect on the developing fetus, we really thought that the fetus was fairly safe, encapsulated in a room all its own, that isn't affected by outside world influences.

But in the 1940's we found out that rubella (or 3-day measles virus) could cause certain predictable effects in the fetus. We thought it was a fairly unique capsule until then.

However, now with radiation and with three-day measles we know now that cataracts, congenital heart disease, and certain abnormalities are predictable. And that's why the pattern that Dr.

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The conference was held in January of 1983. It was an international symposium with representatives from 20 nations; about a third of them from European and Western Hemisphere nations. There were some 13 American delegates. The delegates were selected through a meeting that initially began when the Vietnamese Ambassador in the United Nations contacted Cyrus Vance who used to be one of the negotiators for the treaty settlement in the Vietnam war. Vance was asked by the Vietnamese delegate to see if he could get an American delegation to go over. Arthur Westing in the United States was then contacted by Vance, and he asked him to identify a number of people who were working with Agent Orange. They included physicians studying clinical effects, epidemiologists, toxicologists, geneticists, and ecologists.

The purpose of the conference was to study the ecological and health effects of Agent Orange. The conference lasted 12 days and consisted of some plenary sessions at the beginning and at the end. There were seven workshops, four dealing with ecological effects and three dealing with health effects. Delegates could only work in one workshop. So I can only report on direct-hand experience on the workshop effects dealing with toxicology and genetic effects.

We took two field trips. One was to an area about 75 miles northeast of Saigon (now called Ho Chi Minh City) surrounded by two rivers, the Ma Da River, and the Dong Nai River. Between the Ma Da and the Dong Nai River is the Ma Da Forest. The Ma Da Forest was sprayed in the early 1960s to cut a road across the two rivers because it was very difficult to transport men and material along the rivers. To cut time, the road went right through the forest. The forest was not a human inhabited forest; it was primarily a wildlife preserve. The spraying continued from roughly 1963 through 1968 everal times a year the road would be sprayed. The road produced by spraying still there today. What you see in the foreground of this picture of the road is grass. The grass is called imperata grass.

The imperata grass is a replacement for the trees that you see in the background. For a distance of approximately a quarter of a mile in each direction, left and right of the road, there are no trees except for a few straggler trees that have survived the spraying. Also what you see in the background, is the jungle as it looks today. If you could see the jungle as it existed before the spraying, the trees would not only be taller, but there would be a canopy on top of them. The canopy was wiped out for a considerable distance from the effects of 24D and 245T in the spraying.

The imperata grass tends to get very dry during the dry season, and may burn either from lightning or natural events; it may also be artificially burned by those who want to establish slash and burn agricultural techniques. When the fires occur, they move all the way to the tree line, sometimes taking away more trees. Instead of the jungle coming back, the jungle has been moving back on either side of the road. This is approximately ten years after the spraying has stopped. Note in this next slide the straggler trees. Here is a burned one that shows the effects of the burn and the imperata grass has grown back in the foreground.

The second field trip was to a war museum. This was a propaganda museum that had anti-personnel equipment of various sorts, such as captured American tanks. There were cannisters with a drogu parachute that were dropped with explosive jelly, blasting out an instant landing pad for helicopters. Note in this slide the stripe on the drums that indicate the different herbicides: Agent Orange, Agent White, Agent Blue. This drum was Agent White because the stripe was painted white. f this had been Agent Orange, there would have been an orange stripe on those drums.

Inside the war museum were some photographs of abnormalities and preserved specimens of various birth defects. These cannot be taken as good science data, however, because there are no

charts, showing frequencies of abnormalities and control rates.

But three things are represented called hydatidiform molar pregnancies. These are quite common. The specimen in the middle shows conjoined twins, what are called Siamese twins, which occur very rarely in all parts of the world. The Vietnamese have reported such twins occurring with unusual frequency in sprayed areas.

The third specimen is a monstrosity from which you see a rump and leg sticking up in the lower right of the battery jar, but you don't see a torso. This is an acardiac monster which is usually associated with twins and may or may not be significant.

And now, I will go into the Vietnamese data. The evidence for Agent Orange health effects that the Vietnamese presented came in several parts. First, they claim that there were teratogenic effects in the sprayed areas as well as among South Vietnamese veterans who went back to the North Vietnamese and married North Vietnamese who were not exposed. Among the abnormalities that were associated with this, both in the males that went back to North Vietnam and those who married in South Vietnam and are still there, were the conjoined or Siamese twins and what are called clefting anomalies. These are very gross mutilations of the fetus which sometimes causes amputations of fingers or limbs, and sometimes causes horrendous disfigurement of the face. It caused by an adhesion of the fetal tissue to the membranes that surround it. As the embryo or fetus grows, there is a tearing apart with strands of tissue cutting into the developing tissue.

A third defect that they also showed at the war museum as photographs were abnormalities similar to the thalidomide abnormalities found in Europe during the 1960s, which were called phrocomelic or ectromelic deformities where the arms or legs are absent, look like a sea lion's flippers, or look disfigured with slim bones with missing digits.

These defects are relatively rare throughout the world. In fact, when the thalidomide case first broke in Germany and people were looking for photographs of infants that were born with phocomelia, the best that German medical schools would come up with were steel-cut engravings from the 1850s, because they were so rare they didn't have any recent cases.

The frequency of miscarriage rates in the heavily sprayed areas are very high. They report up to 50 percent miscarriage rate in the pregnancies in the most heavily sprayed areas.

None of these claims by themselves were convincing because their control rates were so low. Unlike the very beautiful work we heard about this morning from Dr. Carnow, there were no double-blind nor triple-blind experiments. There is, instead, an ascertainment bias. The persons who report damage consciously or unconsciously may be looking for something to blame, and may identify themselves as having been in a sprayed area when they may not have. There is no way to check for independent veracity, to see if the reported claims are what they are. Perhaps the reason that the control rates are so low in Vietnam is that many of the people who should have been in the control group are in the positive group. They may have claimed that their infant is abnormal because they were in a sprayed area. This shift of self-reported birth defects would produce an abnormal amount of low control rates. When I raised this question in the workshop their response was that they were a Third World Nation. They were not heavily industrialized, they were not exposed to chemicals and other pollutants that the West has. In fact, then claimed that the control rate in the West is abnormally high.

There is a way to check this. I hope someday someone will do so because one could check in the rural areas of Malaysia and other areas of Asia that are nearby and comparable to the development present in Vietnam.

I felt the most convincing piece of evidence that they presented was on the hydatidiform moles. Let me describe these pregnancies. A molar pregnancy in the West is relatively rare; about one in fifteen hundred or so pregnancies have this. They are fairly common in tropical areas, with a frequency about one percent in South American and other parts of Asia.

In Vietnam, the pregnancies in the sprayed area have a molar pregnancy rate of 10 percent. This is a very high percentage. It is also a high risk pregnancy because molar pregnancies have a tendency to become cancerous. The thing that I did not know at the time of the meeting but which I found out in articles that appeared in *Nature* after I got back was the origin of molar pregnancies. Molar pregnancies are produced by the fertilization of an egg by a perfectly normal sperm. The egg has no nucleus in it. Normally, when an egg is produced in a woman's ovary, she throws out one of the two nuclei that are formed in cell division into a little bud called a polar body. The other nucleus, which is the egg nucleus, is held in reserve for the fertilization. In a molar pregnancy, both of the nuclei are tossed out so that you have an empty egg. The empty egg is fertilized by a normal sperm. The normal sperm represses the cell division and it leads to a chromosome number of 46. So the 23 chromosomes from the male's sperm now become 46 male chromosomes.

The hydatidiform mole results in an abnormal mass of cells that acts as an implanting unit with the outer rind of a blastocyst but lacking the inner cell mass that should become the embryo. It cannot form an embryo but it can implant and form the placental membranes that are characteristic of a pregnancy.

I believe we can respect the data because unlike the claims they made for ectromelic limbs and he abnormal clefting defects or other birth defects occuring in the sprayed areas or among the spouses in North Vietnam of veterans returning to North Vietnam whose wives were not sprayed, they claim the molar pregnancies did not increase in the North. This is consistent with the idea that pregnancies would have nothing to do with whether a veteran was exposed to Agent Orange components or not. I think that's something that's also worth looking into because Dr. Carnow mentioned the importance of lipid metabolism and the importance of that agent getting into lipid-rich tissues.

This is true in my own data on the developmental delay where the females are differentially killed at a higher rate than the males and females are more seriously affected than males.

On the other hand, the work done on chromosome breakage among the Vietnamese in either the sprayed areas or in the returning Vietnamese veterans who moved back to the north in both cases I felt were seriously flawed. They lacked double-blind experimentation. They lacked more reliable techniques available in the West. Vietnam, of course, is an impoverished nation and they lack both funds and equipment. Their preparations of karyotypes were not better than the state of the art in the U.S. in the 1960s. If you look at the karyotype techniques and preparations done in the West and the United States today, you would see how much more detail you can get from the modern studies. The flaws associated with the LSD studies on chromosomes in the 1960s were present in these Vietnamese studies. Small sample sizes of six people sprayed versus eight people who are controls were used in one study. Those are not good numbers to use. You need to use hundreds of individuals in order to get statistically significant differences.

You have to use double blind precautions to make sure that the person who is doing the analysis doesn't know whether the tissue culture came from a person in an unsprayed or sprayed area.

The Vietnamese data I felt was suggestive enough of many things that need to be done. First, we have to remember that unlike all except a few people exposed to acute exposures from accidents,

the Vietnamese received massive quantities of 24D and 245T in concentrations that are greater than is normally used in forestry or agricultural practices in the rest of the world. The evidence, epidimiologically and developmentally, is very suggestive that something is going on. There should be more animal tests. I was appalled in looking through the literature at how few careful experiments have been done for tests of chromosome breakage, chromosome mutation, loss of chromosomes and the like. Why this is so in the literature I don't know. It just may be that people aren't interested in working on weak mutagens and feel it's just too much work and effort for too little results.

But certainly, I would try to encourage more of those studies because I think the evidence has suggested enough that there are biological effects of Agent Orange and its components even if the direct evidence for mutagenesis is very weak.

(Applause.)

MR. O'CONNELL: Now I would like to get into a question and answer period for Dr. Carnow and for Dr. Carlson. Following the question and answer period, we will then break for coffee, which will be available right outside. So when you offer the question, please state your name for the record.

MR. WOJOWOTA: My name is Jack Wojowota. I'm with VietNow. I have a question for Dr. Carnow. Will these problems that you studied—is it passed down to the children?

DR. CARNOW: Well, I think that's better addressed by the person who spoke after me. We found, and others have also found, some teratogenic effects from dioxin including finding a retarded development. We found a number of children who were exposed not in utero, but were children when exposed. Their bone growth was about a year or year and a half behind their chronological age. And we are not sure what this means. We will know more as they go through puberty.

MR. WOJOWOTA: I have one for Dr. Carlson. What is the life span of the dioxin? Is it still taking effect on the forests?

DR. CARLSON: Yes, the dioxins in the soil have a life of ten years. In human tissue it's probably less than a year. Most evidence for 24D risk is after one year. It's not detectable.

I would like to ask Dr. Carnow about the synergistic effects on cancers. If lipids pick up herbicides, and herbicides are very poorly soluble in water and preferencially get into tissue and other lipid rich areas, would this suggest that one reason for the chloracne showing up as a first symptom would be the amount of fat that's deposited in the skin? Because the Vietnamese have very little chloracne and they don't have as much meat and fat in their diet.

DR. CARNOW: That's possible. The question of whether the chloracne is related—to lipid metabolism has not been determined. What is known is that those with a history of teenage acne tend to be more prone to develop chloracne.

Chloracne is the most obvious finding because it is cosmetically disfiguring—but it is not the most common finding. You can't depend on the presence of chloracne to make a judgement about whether or not somebody may have been significantly exposed.

DR. CARLSON: When do melanomas normally show up? And have there been any reported incidents of increases in melanomas to veterans who live in the Sun Belt compared to veterans who live in the South?

DR. CARNOW: Well, we have a concern about that. One of the things we do is advise all of our patients, all people we have examined who we felt have been significantly exposed, to stay out of the sun. Or if they go into the sun, to use a sun block. That's hard to tell to a Missouri

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backwoodsman. But we tell it to them anyhow for two reasons; one, because they have porphyrin abnormalities. And people who have porphyria, which is too much porphyrins in the blood, may be very sun sensitive and get blistering and a very bad sunburn with little exposure.

The other thing about it is that the sun can cause skin cancers particularly in people who are very light skinned—sailors, farmers, develop skin blemishes called actinic keratoses, which can become cancerous. Dioxin seems to accelerate those remarkably. And some people that we have seen have had 20 or 30 cancers removed from their skin. So we strongly recommend that.

We also strongly recommend that they stop smoking because while we have not established a synergism between cigarette smoking and dioxin, dioxin is an extraordinary cancer promoter. Cigarettes are an initiator. Dioxin is also an initiator, but not as strong as a promoter, which means that there is another carcinogen around, dioxin may accelerate its activity up to a million times.

A major problem we have is that we can't get the dioxin out of the body. We know of no way to alter changes which have taken place in the tissues, the changes in endoplasmic reticulum I mentioned at the beginning. So what we have developed is kind of a secondary prevention program for our patients which tries to protect them by having them avoid other exposures which might add to the risk imposed by the dioxin.

DR. WOLFSON: Paul Wolfson of Quad Cities Vets, a Vietnam Veterans' group.

Dr. Carnow, I have a couple questions for you. Number one, are these endoplasmic reticulum—are you—are they the granular, smooth or both?

DR. CARNOW: Well, I was, talking about both. Rough endoplasmic reticulum is probably affected more because when we talk about rough endoplasmic reticulum, we are talking about ribosomes. I don't want to get into a whole thing about this. But it would appear that both are affected.

Now, there is some evidence that suggests that what, in fact, may occur is a transition from smooth to rough endoplasmic reticulum. And there is also some evidence that suggests some changes in the endoplasmic reticulum, at least in animals, which appear to be irreversible. They become rough and striated. You can only see this under an ultramicroscope. But they seem to be changed. The problem we have is first in knowing whether or not dioxin is removed from the body. And the second is if it is removed from the body, what changes in the endoplasimc reticulum are permanent and what are reversible. We don't know all of the answers to that.

The problem, of course, relates to the half life in the body of the dioxin. Once it gets into the fat or once it gets into the pancreas, brain, liver or whatever, it causes changes and is also very slowly removed if at all. The problem we have with 2, 3, 7, 8, TCDD is that one of the ways of removing chemicals from the body is by a process called hydroxylation. That makes chemicals more water soluble enabling them to be removed from the body. This happens normally at the 2, 3, 7, or 8 position. And the 2, 3, 7, 8 positions of dioxin are blocked by the chlorine.

And so it's one of the reasons we think dioxin may stay in the body for a long time. The two big sets of changes, probably irreversible, are the changes in the endoplasmic reticulum and in the mitochondria. We now have some biopsy material which show a crystalization of the mitochondria. They are destroyed and crystalized. And the mitochondria are the starting point for the cycle which gives muscles their energy. That cycle is blocked. That is one of the reasons people feel weak.

We are trying to develop a kind of secondary prevention approach because we really don't have any way of removing the dioxin. So what we are trying to do is protect those organ systems which

have already been affected to keep them from being affected even more.

DR. WOLFSON: Is the Golgi complex affected also?

DR. CARNOW: Yes, that is part of the mitochondrial system.

DR. WOLFSON: And just one more quick question on the astrocyte central nervous system and the oligodendroglia—are they affected? Have you done anything in that area?

DR. CARNOW: No, we haven't. We have not seen a lot of autopsy material. Part of the problem—is that the brain is a heavy oxygen demand system, and the ability of the body to use oxygen is impaired.

So I can't tell whether those cells are damaged. We do know that cells of the peripheral nervous sytem demyelinate and are damaged. Early myelin tends to rejuvenate itself, but with recurrent damage, irreversible damage to the nerves occurs.

DR. CARLSON: When would you look for or expect to find cancers of the central nervous system? Most solid cancers take 20 to 40 years to show up.

DR. CARNOW: That is correct. Now, the sarcomas apparently have been showing up a little sooner and there is unquestionably a relationship. Some studies that were done showed a marked increase in bladder cancers. The problem with that is that some of the people who showed up with bladder cancers, were also exposed to Para-amino biphenyl (PAB). I believe that the combination of PAB and the dioxin caused the bladder cancers. Certainly, soft tissue sarcomas are in excess and skin cancers are in excess.

And again, it may be that there has not been a long enough time for the cancers to appear. One group of people that we have studied were exposed a long time ago. And the problem with that is that their exposure was so massive, a lot of them died before they could develop cancer. It's very hard, given the latency period of cancer, to give you any more answers.

There are some reports, I think from Times Beach, but I haven't seen them published. They are heresay. There was a statement made, at a congressional hearing that I appeared at some weeks ago, in which there appeared to be some neuroblastomas that developed in children, two children in one family.

A VOICE: Dr. Carnow, in your work, have you noted any increased incidents of lipomas in the veterans and civilians that you have examined, and if so, do you have any hypothesis as to the mechanism and the cause of these lipomas and how you are treating these?

DR. CARNOW: The way you treat a lipoma is you remove it if it is big enough and bothersome enough. In one group, we saw a lot of them. In another group, we did not see very many of them. And I'm not sure why the difference. Part of the problem that we have is we think that people who have less exposure may not necessarily have less disease. It's just that clinical disease may come on later. We find that the latency period is greater in those less exposed. We found that some of them didn't develop anything until three years after exposure. So there was a latency. And they tended to be the ones who were exposed less. But some of them had diseases which were quite severe. One of the big problems we have with dioxin, of course, is that some people are more sensitive to its effects than others.

Dioxin affects a system called the aryl-hydroxylase (AH) system. Now, people have a genetic predisposition to having an AH system which is more or less active. The more active our AH system is, the more prone we are to develop compounds in our bodies which may cause cancers.

People who have a more active AH system tend to get more cancers. Those people would

tend to be much more sensitive to dioxin. One of our problems is we don't have a good test to make a determination of who has more AH inducibility than other people.

DR. O'GRADY: My name is Dr. Michael O'Grady. I'm an environmental physician. I have a couple questions for Dr. Carnow, if you don't mind again.

Are you aware of any deaths that have occurred as a result of dioxin exposure in the literature anywhere? Are there deaths that are directly attributable to dioxin?

DR. CARNOW: Now, you say directly attributable to dioxin. I'm not sure what you mean by that. I had one man who had multiple fat embolisms in his blood vessels. He had a triglyceride of 1400. Before his exposure, his triglyceride was normal. I consider that directly attributable.

DR. O'GRADY: But, sir, what I mean is, has the cause of death been given as the dioxin exposure?

DR. CARNOW: Well, I don't know that there are a lot of physicians who have diagnosed people as having dioxin disease. And so, I think the cause of death may not have been given as dioxin exposure. The tendency would be to diagnose the disease as liver, kidney, brain, etc., depending on which organ failed.

DR. O'GRADY: And the subjects you are examining for the railroad, the 47 people, would agree that these people had a knowledge of why they were being examined.

DR. CARNOW: Yes. But they were examined long before we examined them and long before anybody knew anything about dioxin. And they had the same symptoms and the same findings when examined by their local physicians in Missouri which is why they saw those physicians. If you are suggesting that this group of people, many of whose fathers worked for the railroads for 40 years, and who come from rural Missouri, people who have never taken a nickle from anybody in the whole world, suddenly have become malingerers—I suggest you are wrong.

To suggest that a man who has worked for the railroad for 35 years, who worked a 400-acre farm for 40 years, is a fake who is trying to get a couple of bucks out of somebody, you know, it's just unreal.

So I reject that. I think that possibly there may have been people who were examined and who attempted to exaggerate their story. Our biggest problem with these people is that they tended to minimize their symptoms because they were afraid to admit to themselves that they were sick. And they were ashamed of the fact that they couldn't work because these were men who worked hard all of their lives and felt, somehow, that they were not adequately discharging their responsibilities to their families because they couldn't work.

So they would minimize their problems with the people that we would say to them, "You are healthy—you can work." And, in fact, a lot of them continued to work. Many that we examined are still working, but they are having great difficulty in working. The fact that these people knew what they were being examined, unless they were students of medicine—and a lot of students of medicine didn't know about the symptoms of dioxin—it would be remarkable to get this kind of symptoms complex.

Also, unless they talked to the people in Czechoslovakia, who also had the same symptoms or the people in the Soviet Union, or the people in Vietnam, or the people in BASF in Germany, or the people in Newark, unless they discussed it with all of these people, you would have to say this is an enormous international conspiracy to develop symptoms of dioxin poisoning. I find that even more difficult.

These people had not been told that there was anything there. They did not know there was dioxin, only phenol. There was a lot of objective damage, objective disease. Peripheral neuropathy in 20 or 30 people, central nervous system damage, you can't malinger immune suppression, porphyria, or any of the other things that these people had.

There is a pattern there. Now, I'm suggesting to you that these are not people who want a handout somewhere along the road. But, I'm not sure that people have been adequately examined to make such a determination. I think a determination was made in advance. And I think that what is needed, instead of the kind of discussion which I am having now, which I think is a bad one—I'm sorry, I lost my cool. But the thing that I am suggesting now is that a protocol be generated and developed; that people do get an adequate workup, and then a judgment can be made about what the score is.

And I think that there would be so much less conflict and so much less difficulty if that were done. I am not suggesting that everybody who comes forward is sick—on the other hand, dioxin is extraordinarily toxic. And we found a disease which we say fits a pattern of dioxin intoxication because it looks like what happens in animals, and it's like what happened to a lot of people around the world who were exposed to dioxin in industrial explosions or other activities.

And those people don't know what dioxin is—they just know that they were sick and they couldn't work.

DR. O'GRADY: I'm afraid you misunderstood the question. I'm not in any way suggesting that the 47—and certainly not the veterans—

DR. CARNOW: Well, I apologize. But the question of whether or not they knew whether they were being examined for dioxin, I don't think is relevant.

DR. O'GRADY: The purpose of the question was to point out the fact that there were people who were aware of what was going on, rather than a control group. Also, there is no introduction of the word malingerer into the question.

I would like to ask a question of Dr. Carlson—just one question. Is there any mechanism that you know where a male exposing can transmit a genetic deficiency in the case of dioxin or for that matter, any other type of exposure?

DR. CARLSON: Oh, yes, radiation. High doses of radiation can lead to damage; either a reduced fertility or spontaneous abortion. Hiroshima-Nagasaki data showed a lot of the abnormalities in pregnancy in the first few months after exposure. But you are quite right in the implication that most mutagens even in massive doses do not show a lot of genetic effect.

That doesn't mean the genetic effect wasn't induced. Less than one percent of all gene mutations are dominant mutations. 99 percent of induced mutations in all organisms studied, mice, fruit flies, corn, many other systems, show that they are recessive. So even in Hiroshima and Nagasaki, geneticists predicted long before the Atomic Bomb Casualty Commission began its study that they would not find offspring showing gross abnormalities. There are two reasons for this. Not only will an induced recessive be protected by the normal gene corresponding to it from the other parent, but also even among the dominant mutations, very few of what are called dominant mutations produce monstrosities.

Most monstrosities are not a consequence of gene mutation, but a consequence of chromosome abnormalities. Most chromosome abnormalities that are induced are gross enough to abort. Very few come to term. So it's only the tip of the iceberg to look for deformed infants as a

measure of radiation damage to a population.

When the Atomic Bomb Casualty Commission begins to look at children who are the product of first cousins, some 70 or 80 years down the line from the initial exposure of an individual at Hiroshima or Nagasaki, they may be able to uncover some of the recessive abnormalities. Part of the difficulty of epidemiological studies, is that they stress monstrosities. It is easier to pick up monstrosities of a nongenetic sort than it is to induce monstrosities by genetic means.

MR. CHAIRSKO: Dr. Carlson? My name is Mike Chairsko of Mid American Radio News. You had mentioned when discussing the application of TCDD or—I'm sorry, Agent Orange over Vietnam that TCDD applications for concentration vary from a few parts per trillion to a few parts in ten. Could you elaborate on that?

DR. CARLSON: Yes, the actual mixture in the spraying on any one run involved a thousand gallon tank with an aerosol spraying for a four-minute run in Operation Ranch Hand, which was the name of the project for spraying the forests or fields. The mixture is approximately four pounds each of 24D and 245T. That's parts per ten. A difficulty arises in estimating how much herbicide did a veteran get. Sometimes a ground crew that was loading a plane may have gotten prop wash and spray where they were getting parts per ten each. If they washed off immediately afterwards (and not all may have had the luxury under battle conditions to do that type of washing) that would still give quite a bit compared to the parts that we usually talk about.

When we are talking about experimental studies of mutagenic or toxic doses, these are measured in part per million.

MR. CHAIRSKO: But were these veterans exposed to parts of ten of TCDD?

DR. CARLSON: No. Not of TCDD itself; only of Agent Orange in some cases.

DR. CARNOW: Let me just add in some of the federal data—Air Force data. It was suggested that eleven and a half million gallons of Agent Orange was sprayed. And analysis shows levels of up to 40 parts per million. Now, it was highly variable. But there was also Agent Purple and Agent Green. Those were some of the other combinations. Earlier batches had much higher levels of dioxin. Those batches were dirtier in terms of dioxin than were the others.

DR. ANDERSON: Dr. Anderson, with the Wisconsin Division of Health. Your data is very interesting. But, I was wondering when you were saying you are seeing a pattern of disease, if you could perhaps elaborate on that. It's very obvious that our group has a pattern, but I was wondering whether you could give a little more specific data on whether we can recognize a pattern in an individual. What were the hallmarks of the abnormalities you saw?

DR. CARNOW: There are a series of problems. One is the dose, generally, the duration and he intensity of exposure. Secondly, is the individual susceptibility or sensitivity based on AHH inducibility. So you are going to get some variation in the onset of the symptoms. Generally, as I pointed out, the symptoms that we saw—and this is in a large group of people now, that we have examined, almost 400, I believe, involved headaches, frontal, bitemporal, top of the head headache, fairly severe. Depression was very common, generalized fatigue, very common; weakness, less common; loss of libido in a lot of people. These are symptoms, if you are looking for symptoms.

DR ANDERSON: But, do you get clustering of the symptoms in the same individual? If you get one, are you likely to get the other?

DR. CARNOW: No, generalized clustering—again, you don't find every symptom in every individual, obviously. And you find more in some than in others. Numbness and tingling of the

fingers. People who developed this developed a neuropathy; would have aching in their legs and in their arms, which they would decribe as a deep ache. They couldn't put their finger on it. And it's the kind of thing that keeps you awake at night or wakes you up at night. That is classic neuropathy.

And it may or may not be associated with weakness. When you have extensive neuropathy, you get foot drop and wrist drop. But with a lot of these people, there seemed to be a sequence. The first thing seemed to be numbness and tingling. If they rested their arm on the car window ledge, it would fall asleep. If they crossed their legs, the legs would fall asleep fairly rapidly. All of us have had that experience after a long period of time, but it happens to them very rapidly. And a lot of those people don't have peripheral nerve conduction abnormalities. So that, in some people, we would find the symptoms, they would have the symptoms, but we would find the abnormality.

In some people, we found peripheral neuropathy or a slowing of conduction. And some of them didn't have numbness and tingling. But there is generally a pattern, a pattern with the central nervous system function, in which we found large numbers of people related to attentional deficits, some memory deficits.

So, if you want to do a quick and dirty you would do a digit span. You read forward numbers and backward numbers. They can read forward numbers, but they can only read a few numbers backwards. There are other deficits in concentration—in memory that we found. That seemed to be a common pattern, the kind of pattern that you see in the diffuse cerebral dysfunction from toxic agents.

Not all of them had general urinary symptoms. Not all of them had liver enzyme abnormalities, but a large number of them did. One of the things that I did not discuss was gastrointestinal dysfunction. A lot of them had symptoms that sounded like ulcers. And a lot of them had x-rays taken. In many, no ulcers were found. What was found, were diffuse inflammatory changes. We are not sure what the mechanism of that is. Of course, each one of these symptoms and every one of these findings can be caused by another disease because the body can only react in a certain number of ways. The difference is that you get a group of these things. It's almost like picture games we played as children where you would expose one eye, then the nose and try to identify a person. Eventually, you say, Oh!, that is Frank Sinatra or John Wayne, when you had enough information.

DR. ANDERSON: That's what I was trying to get at. Is there some—that's—obviously, people have it and people react in different ways. But in your 47 people, which you characterized very carefully, were there some groups that were much more common and occurred together than the others? Was the nerve conduction—was it sensory or motor—or both?

DR. CARNOW: It was more motor than sensory, but we saw a fair amount of sensory. It was median nerve neropathy, diagnosed by orthopedic physicians as, carpal tunnel syndrome, because it affects the nerve as it goes through a tissue tunnel. But you see, the carpal tunnel is where the median nerve is compressed and therefore susceptible to damage. It is our experience that when you have toxic damage to a nerve, it is going to occur at the point where the nerve is under the greatest trauma, because damage where a nerve is moving the most is where it tends to be traumatized when it is deficient. That is why painters who were exposed to lead, would get wrist drop of their working arm, because that was the nerve that worked the hardest, and the one that needed the most nutrition. And so we found the earlier signs tended to be of the median nerve in the carpal tunnel.

MR. DIESNER: Senator Diesner from Minnesota. Dr. Carnow, you listed a whole group of laboratory tests here as being abnormal. And I was wondering about the degree of abnormality. Are

these things borderline abnormalities or mild abnormalities?

DR. CARNOW: Well, when we say abnormal, what we are talking about are two standard deviations from the mean.

So, when we are talking about something being abnormal, we are not talking about one standard deviation. We are talking about something that is more than two. That makes it abnormal. So when you say mildly abnormal, you are talking about something that is already beyond two standard deviations.

We did not find that a lot of these people had gross abnormalities—some did. For example, triglycerides are abnormal above 170. We found some people with 900, 1,200, 1,400—I had never seen anything like that before. So we saw some people with prophyria. Any uroporphyrin that is over 60 is very, very high. Now, we say that normal is from 15 to 60. But, the number of people that I saw with 60 or 58 is extremely low. So, it is very hard to give you an answer to how sever is severe.

MR. DIESNER: May I use your terminology?

DR. CARNOW: Sure, go ahead.

MR. DIESNER: How many of those were beyond three or four standard deviations?

DR. CARNOW: I don't know. I can't tell you that.

MR. DIESNER: A few or a lot of them?

DR. CARNOW: It depends on what tests you are talking about.

MR. DIESNER: Well, pick any.

DR. CARNOW: I don't know. We did not look at it that way.

MR. DIESNER: Thank you.

MR. McCARTHY: Frank McCarthy, President of the Vietnam Veteran Agent Orange Victims, and representing the Connecticut State Commission.

Doctor, what we are trying to find out at this point that is most crucial to us is treatment for the various symptoms and effects. Now, the Vietnam veterans were all medically scrutinized prior to going to Vietnam. They were considered medically fit, physically fit and combat ready. We have literally put some of our veterans in a blender. And we realize that there are quite extensive variables which are involved which are exposed to Agent Orange, Pink, Purple, White, DDT altheine, and various other chemicals aside from the illnesses from Vietnam.

But those of us with chloracne—now, the Veterans' Administration is telling us that it's of a teenage-type. And we realize that that is not true. But with your trackworkers who were definitely diagnosed as having chloracne, is there any treatment being administered to these people or do you know of any treatment?

DR. CARNOW: Well, a lot of people who have very severe chloracne would have them evacuated. That's all they could do. If they didn't evacuate the material, they would develop this material which has a terrible, terrible odor. In severe chloracne they would evacuate them. And dermatologists tried all sorts of treatments; none of them really worked. In some people, they go away after a year or two. And I said there were others who have had it now for 40 years. And their wives still squeeze out these bumps when they get bad enough.

But I don't know that any treatment has helped. Some of these people had radiation for the skin early on in the 50's. That would be extremely hazardous in my view.

MR. McCARTHY: Doctor, last question. We have been told that the fat biopsy is a way of detecting dioxin within the fatty tissue. In your opinion, is it not true that dioxin could have entered

the system, done the damage, and then left the system without leaving any residue?

DR. CARNOW: Well, I think that we all agree that that may be the case. I think that there may still be some residue, but it's diffused. You are talking about a very small quantity to begin with. You then diffuse it because it's found in the pancreas, the liver, the adrenals, the brain, the kidney, and other organs, and the fat.

In some cases, biopsies were done and the highest concentrations were found in the pancreas, some in the liver, and some in the fat. So it's very, very difficult to measure. You would probably need a huge amount of fat because you are talking about a very small concentration, a very small concentration of material.

Such surgery would be somewhat mutilating and—probably not a useful procedure. What we are doing is we are getting access to this autopsy material and all the workers who were exposed years ago and who are dying. And we will be doing measurements in their tissues to see what levels we find. Some of these people have not been exposed for 10 or 15 years. And that may be very useful information. But until we have better information, I think that if somebody is exposed, if they have this kind of a symptom complex or at least some of the things that we find here, it seems to me that it would be reasonable and prudent to make a judgment that they were exposed and affected. But again, it depends on what you are looking at. You are looking at medical prudence.

MR. O'CONNELL: I'd like to return at 11:15 so we can get on with our latter part of the morning. At this time I'd like to thank Dr. Carnow and Dr. Carlson on a very interesting presentation.

(Applause.)

(Whereupon, a short recess was had.)

MR. O'CONNELL: Could we start the program?

Since we began this morning we have had the arrival of several other states. Connecticut has arrived with Frank McCarthy. Ruth Leverett from New York arrived. Hank Hahn from California has arrived. Dr. Anderson, of course, came in from Wisconsin. So we have a pretty good representation. We welcome our next speaker back to his hometown of Chicago. Dr. Mark Thoman is a graduate of the University of Missouri School of Medicine. He is currently the president of the American Academy of Clinical Toxicology. He is a Fellow of the American Acadeemy of Pediatrics, and a clinical faculty member at Drake University in toxicology and pharmacology. This is to name but a few of his many qualifications.

Dr. Thoman will discuss dioxin past, present, and future with an emphasis on fetal abnormalities and on the effects of dioxin on future generations. Dr. Thoman.

DR. THOMAN: Thank you. Well, it's good to be back in the hometown.

I would like to bring us up to date and touch on some of the things that have already been discussed very adequately by Dr. Carlson and Dr. Carnow, and not go over old ground. I think for—brevity and to give us some time for questions at the end of the session this morning, I would like to talk about a very basic thing. I would simply and initially talk about the complexities of those of us in clinical practice in clinical toxicology. The Academy of Clinical Toxicology has been around since 1968. So it's a relatively new specialty. I graduated from medical school in 1962. And toxicology and ecology were words that we heard, but we just didn't think were ever going to be much in the way of specialties. But then in the 1930's and 40's...for those of us that were around in the early 30's and 40's, we grew up with the phrase "Better Living Through Chemistry." I think that we are seeing one thing,

and that is we eventually "pay the piper." I have given quite a number of presentations in reference to specifically, the chlorinated hydrocarbons. I'm going back to the PCB information that came out some years ago as it related to the so called cola-colored babies that occurred in Yusho, Japan and this is a chemical cousin to the dioxin we are talking about. But they have their own characteristic chemical effects.

Now, let's talk about how one gets poisoned. Let's talk about basic toxicology. Ed Press in Evanston, Illinois, started the first poison center as a pilot study associated with the Northwestern University. This was primarily for other doctors who would call in saying, "I've got a child that's taken grandpa's medicine." And the physician would say what to do about it, and the signs and symptoms that you look for.

Pediatricians took care of the children that would accidentally ingest toxins. They are big enough to get into things, but not big enough to know any better. The toddler is the one who is a main candidate for poisoning. This has now expanded.

Over the years, we don't just have the accidental ingestion of poisoning by the toddler, but we also have the intentional ingestion by some people that want to get a high with certain chemicals. So the first way you get poisoned, or most common way most of us think of is the ingestion.

Second is inhalation. And when we talk about dioxin, we talk about not necessarily ingestion, but inhalation. Inhalation is breathing in the material.

When it's breathed in, it is swallowed with the mucous. It is often coughed up, then swallowed, hence, an indirect ingestion.

This is a cycle that often incorporates other methods of toxicity. We talk about simple contact or simple inhalation. We are often talking about a more complex situation than that. But inhalation can be accidental as it is in most cases in situations where there is an incident of a workman working around dioxin, the railroad worker we talked about in the previous study. We talked about lead poisoning and so on. And this can cause the industrial toxic exposure.

Contact is a real problem in the agricultural states, such as Illinois, Missouri, Iowa. And the contact with the organophosphates—contact with this particular group of toxins certainly has to be considered. There are situations where someone can absorb enough by contact that it would cause overt signs and symptoms where it would hamper function...therefore have a toxic effect. I'm talking about malathion-parathion insecticides and herbicides. Contact is also a problem with dioxin.

Injection does not necessarily apply here, but injection is the next way one gets poisoned. Now, this could be accidental or intentional. Accidental would be someone inadvertently—giving an injection—the wrong material is given to a patient. The deliberate injection is where someone is giving themselves something to give them some kind of an effect; such is the case in heroin addicts or cocaine users. I was director of the heroin clinic for eight years in my city.

Finally, radiation. And Dr. Carlson had mentioned this earlier regarding the effects of radiation. In fact, when we talk about the teratology or the effect on the developing fetus, we really thought that the fetus was fairly safe, encapsulated in a room all its own, that isn't affected by outside world influences.

But in the 1940's we found out that rubella (or 3-day measles virus) could cause certain predictable effects in the fetus. We thought it was a fairly unique capsule until then.

However, now with radiation and with three-day measles we know now that cataracts, congenital heart disease, and certain abnormalities are predictable. And that's why the pattern that Dr.

Carnow had mentioned regarding the profile of those that had been exposed to dioxin reminded me of a paper I had given in Tokyo in 1965 dealing with the first uses of computers in poison centers. This went along with what we call the toxic profile.

What I did in this particular presentation, was to take the signs and symptoms that are fairly well-known to the profile of a particular toxin.

You would ask for, let's say in this case dioxin to give you the signs and symptoms and related incidents in a particular individual or group of individuals; next what tests can be done, the SGOT or SGPT. Some tests would be abnormal, and give standard deviations and references and so forth.

The other function would be to put the signs and symptoms of the individual who has been poisoned against an unknown toxin and see what relative matching that did with the profile of the toxin in question.

And I think people are going to have to accept that this is a real thing. The problem that we have in the clinical process, is that the diagnosis and the confirmation of the onboard load of dioxin is very difficult. Working with the VA Hospital, the surgeons and the people in my area, we can get a laboratory in our state that will give us figures up to one part per billion which is not very close. We need to get a lot closer than one part per billion because we know that one part per trillion would be better if we could do it, going back to our PCB experiences. And in St. Louis, Monsanto has been unable to get lab tests for us regarding the PCB's, and I not only refer to the teratology effects of PCB and high doses for the incident in the Yusho incident, but also the mothers who were exposed from the omnipresent PCB because it not only goes to the fetus when the mother is exposed to this chemical but it also affects her system as well. It's fat bound as we discussed earlier, as is dioxin. And then it can go out through the breast milk if she breastfeeds her baby.

And I think that you are probably seeing a trend. In fact, very close to this airport is Franklin Park, which is the headquarters of La Leche League International, which is a group of mothers that the Academy of Pediatrics in Evanston worked with and encourage nursing. It has helped to triple the population in the nursing mother population now as opposed to 20 years ago when most of them would use formulas.

So we have a whole new area here, and that is that a mother who is exposed to a toxin between the 15th & 60th day following conception, and as has been pointed out by Dr. Carlson, is that if something is toxic enough in the early pregnancy of the human or animal in this case, it will not be conducive for implantation. It would cause a toxic reaction. And I am paraphrasing and adding comments to Dr. Carlson's comments. Implantation may not take hold, and hence there is no conception. It is in fact, lost because the mother is so unable to be in a position for normal implantation to take place. I think that once about 90 days is passed, and this is what we call in medicine the first trimester.

This is the time when we are worried about chemicals coming in contact with the mother either through the various ways I mentioned or radiation, which is the fifth toxin. Then one has to be very cautious. It's difficult to say this is related to this. I think that you have been aware of the bendectine problems because there are 1,311 cases of bendectine where phocomelia or other abnormalities, including limb defects have been reported. Bendectine was recently pulled off the market with the idea that it was very expensive to carry on the litigation.

But now, the CDC has just come out this week stating that there has been a causal relationship by an epidemiological study in a particular problem. And I have just the initial report, that there

have been a higher incidence in those that have been in double blind studies where bendectine has in fact, caused considerably more problems with certain types of limb defects than in the controls.

These are early studies, and one that litigation people are certainly interested in on the Plaintiff's side. The Defendants don't want to hear about that. But up to now, we haven't been able to go back—and if it wasn't for the fact that pediatricians sat down in the early 60's and found out that in Germany there were a lot of phocomelia cases, and they were trying to figure out what the common denominators were, they may not have picked up the fact that thalydomide affected that early fetal development.

So I think if we don't look, we are not going to find out. And we don't know. I think that at this point I would just like to say as the executive officer of the Academy of Clinical Toxicology, I want to thank the people who put the program on and Mr. O'Connell for getting some of us together who have been feeling like we are the Lone Rangers out on the prairies of Iowa and New York.

But this gives me an opportunity to—and I have discussed this—to take this type of interchange and information and publish this in the journal.

It's called Aaction, A-a-c-t-i-o-n. It's the American Academy of Clinical Toxicology Newsletter. And I have a number of people who have written me letters who are members of the board of trustees who say that this is nothing but a lot of hype, a lot of press hype, which reminds me of some article that I cut from the paper. I'm sorry I don't have it prepared as a slide, but let me describe it. It shows Noah's Ark in the background in a cartoon. And on the front of the paper, there is a little word box. And one said if the flood's over, why can't we leave the ark. And the answer was dioxin.

So it is with a number of things we have seen in the press, and we have to balance this out. The studies that have been done so far have been very helpful to me. I have a large bibliography and a file on this chemical. I don't have the several thousand pages that my colleague Dr. Carnow has. But I do have a number of articles. And I think that with this interchange of information we can all benefit.

It's not a problem we can run away from. And I think we can come up to one thing, and that is that dioxin certainly is not going to be considered a vitamin.

At any rate, speaking of running away and wanting to be brief so there is enough time for my colleagues and their presentations and questions, is that I recall a couple fellows that were sitting next to the fire at the end of the woods next to the lake and this gigantic bear shows up. And he is about 20 feet from them. And he comes to a point near them. And this one fellow looks at the other, and he looked back at the bear. And this guy started taking his knapsack and he started taking his running shoes out and started putting them on. So the guy asked him, you are putting on your running shoes? You can't outrun that bear. And the fellow said to the first, I don't have to outrun the bear. I just have to outrun you.

DR. THOMAN: Thank you very much.

MR. O'CONNELL: Thank you, Dr. Thoman. You are absolutely right about the significance of this seminar in that the transcript will be available for other researchers throughout the country.

Next, we have another gentleman who is making his second appearance at an Illinois Agent Orange Commission Medical Symposium. Dr. Robert Ginsberg is the research director for Citizens for a Better Environment based here in Chicago. Dr. Ginsberg received his Ph.D. in inorganic chemistry from the University of Wisconsin in 1978. Since that time, he has served as the research associate in the Division of Occupational-Environmental Medicine at the University of Illinois School

of Public Health.

He has been a technical consultant to OSHA. He has been a member of the Medical Committee of the Chicago Area on Occupational Safety and Health.

Dr. Ginsberg will help us today in drawing certain parallels between the use of Agent Orange in Vietnam and the domestic use of dioxin.

Dr. Ginsberg.

DR. GINSBERG: Thank you. It's a pleasure to be here again. Unfortunately, I won't have the jokes that the previous speaker had, nor the wealth of clinical data that you heard earlier this morning. I'm going to present a slightly different perspective on the problem and discuss the widespread use of pesticides in this country.

You might think it's somewhat unusual for a public interest/environmental group to be here several times now, three times in the last year and a half, speaking before the Agent Orange Commission and discussing Agent Orange.

But there is a very simple explanation. Pesticide use in this country is unbelievably widespread, and the pesticides used are very similar to those that were used in Vietnam. Because a few of the pesticide uses are so ubiquitous (almost omnipresent) the problem is ignored. It's almost invisible. You rarely hear anybody talking about the public health consequences. Perhaps as Dr. Thoman said, we are going to pay the piper for better living through chemistry. And the piper will be paid in the next few years.

If you actually look at people from public health departments or agriculture departments at both state and federal levels, you find in most cases a certain cavalier attitude towards the question of pesticides. Their comments range from it is perfectly safe to there is no problem. The most recent example that comes into mind, is from Minnesota where they had an outbreak of encephalitis. And very properly, they were taking some actions, in particular area spraying with malathion. But they weren't telling the public that they should be concerned about the malathion as well; "Malathion is perfectly safe." That's not entirely what I would consider a prudent attitude. I agree that one should control for encephalitis, but not to ignore or down play the other problems. Perhaps a bit more extreme example concerns an unnamed official in Illinois who once stated at a public meeting on spraying for gypsy moth that when helicopters would spray carbaryl, he considered it to be so safe that he would stick his tongue out and catch the drops on his tongue. Oh, yes, he is alive and still operating. Hopefully it will have an effect on him one of these days.

He is still working which is one of the reasons he remains nameless. But that attitude permeates most official agencies and responses. Many professionals will go to meetings, on insect control or plant control, and attack me because I'm quote-unquote an environmentalist. Apparently I have caused all the ills in the country that they perceive. They will bemoan the loss of pesticides like DDT, toxaphene, 245T. And they will go on in great length about how we have destroyed the country, and how we are going to be overrun by insects. I think this is another misnomer. Unless I truly am the agent which will cause a biblical plague. They haven't unfortunately quite lost those pesticides. 245T, is still approved for use in range land, rice fields, airport runways, industrial sites along fencelines. There are a lot of uses. Silvex, related to 245T, is still approved for apples and pears, sugar cane, rice fields, and range lands.

DDT is still produced in this country for export. Toxaphene still has a number of uses—it still can be used in the U.S. in an emergency. It's used in Puerto Rico and the Virgin Islands. It's used on

cattle and sheep, too. So we still have a lots of toxaphene around.

And I can go on with a list of chemicals that were supposedly banned which we are still running into problems with. But this disregard for the hazards of pesticides is also reflected in the whole problem with Agent Orange and the attitude of the Veteran's Administration and by the chemical companies. Actually, it's quite reasonable from the chemical company's point of view. If it's proved that in, for example, environmental situations these pesticides and herbicides will pose a problem in human health, it would be very hard to deny it to the veterans. It's quite logical that they have a problem if the converse is true, i.e. if we have problems with veterans, it's also going to be a public health problem. In that case, all pesticides use in this country would have to be reexamined.

We have to examine very carefully what we are doing, and actually start looking for health effects and developing the protocols such as Dr. Carnow talked about earlier. To say that cancer is the only end point of concern is very midleading and restrictive. The potential public health impacts of all types are staggering. From the chemical companies point of view, the finanical impacts will be equally staggering. Nevertheless, we must be very concerned about the whole problem of Agent Orange exposure—and it's more than just Agent Orange, as discussed earlier it's also agent white, agent blue, and agent purple. There is a whole rainbow of colors that were described at a previous hearing and to actually say what are the effects from these pesticides or herbicides.

Unfortunately chronic health effect data in this country is nearly nonexistent in part, because there is not that much research into the problem.

It's further complicated by the fact that any long-term occupational studies and environmental studies are hampered by the unavilability of groups of people uniquely exposed. For example, try and find this country a group of people uniquely exposed to DDT. It would be a very difficult task because of our universal exposure to that pesticide. So there is a virtual absence of any data on the use of pesticides, particularly in nonagricultural settings.

I am based in Chicago and we are concerned about the amount of pesticides used in northeastern Illinois-northwestern Indiana. About a year ago, Citizens for Better Environment began a long-term research project to actually collect data on the extent of pesticide usage in nonagricultural settings, particularly residential areas. In such circumstances millions of people are exposed to some level of pesticides. And we have no idea of the extent. We do not contend that these people are exposed to as much as the 60 or 70 million pounds of pesticide active ingredients applied annually to corn and soybean crops in Illinois. But substantial quantities and rates of application are occurring. To our knowledge, there has been no such data previously collected in the midwest, or in Illinois, on pesticides usage. It is our assumption that once you know pesticide usage, you can make some estimates of pesticide exposure. Therefore I will present some of our preliminary data and then discuss how that problem is related to veterans—as Dr. Carlson did earlier with 24D.

Before proceeding, I am obliged to present several caveats for all this. There are no official records available in the state of Illinois regarding pesticide usage outside of the agricultural setting. All of our data had to be collected from what I would call primary sources, stores that sell pesticides, surveys of homeowners, surveys of nurseries, golf courses, cemetaries. As you can imagine, this is a somewhat time-consuming, labor-intensive operation.

We divided usage into three categories—first, home professionals, i.e., structural pest control, cockroaches and termites, and, a new phenomenon, the lawn care professional who goes around spraying to make your lawn green. The second category is public area, i.e., golf courses, which also

have to be green, cemetaries, parks, mosquito abatement programs and forestry work. And finally, the third and largest category is personal purchases. This last category is by far the largest and probably most uncontrolled source of pesticides exposure in this country. One can go to the supermarket and see the rows and rows of insect spray and weed killers. There is a tremendous amount of advertising that goes on for pesticides—I won't use product names. If you actually start reading the labels the vast majority contain 24D. Rarely will you find anything containing 245T. But, in some of the smaller stores, you will still find old batches of material containing 245T.

Very simply what we have found is that rates of application in residential areas are on the order of five (5) to eight (8) pounds per acre per year. That includes averaging over an entire town's area. That means streets get averaged in, sidewalks, your roof, which does not normally receive much pesticide. So that actually if you start looking at individual homes or golf courses or a park, the totals tend to be three to four times the amount. For comparison, I take the 1976 data on agricultural application rates for corn and soybeans. The rates are four pounds per acre per year and two pounds respectively. So on an average, we are putting more pesticide per acre in our urban areas than we do on our agricultural areas or our food crops. We have been ignoring a potentially disastrous public health problem.

Now, I just want to take a bit of time to go through and describe what actually is used and break it down by source. We find in-home professionals, the people who come to the house or someplace else and spray these materials accounts for about 15 to 20 percent of the actual pesticide use. There are variations, and I'm not going to go into the data here, based on economic status. Generally, the wealthier the community, the greater the use of such professionals. Though oddly enough, the use of lawn care companies is almost independent of the economic status of a community. Even in lower income areas, apparently, they want to have green lawns. In terms of poundage, 24D is the most widely used chemical by home professionals. It's either used alone or in combination with other herbicides, like dicamba and MCPP.

Application rates vary from one or two pounds per acre for most companies to one company which puts on 16 pounds of 24D per acre. Applications vary from one to four times per season. We are talking about phenominal rates of application and exposure. If the U.S. government had put on Agent Orange at that rate in Vietnam, I'm not sure a tree would still be standing today. Furthermore you have other herbicides that go on at rates of three to twelve pounds per acre generally once a season, but sometimes more. Clearly actual public exposure to these herbicides, these chemicals, is much higher than it has been thought previously. And we have no idea what the public health consequences are going to be.

Pesticide use in public areas, has a similar breakdown as residential lawn care. Three quarters of all the golf courses, sod farms, cemetaries in Illinois apply herbicides to keep the weeds down. Of those, almost 90% entirely use 24D and dicamba. Perhaps it's the ultimate revenge on the chemical company executives when they go play golf; they are exposed to the pesticides that they sold in the first place.

Finally, personal purchases account for three quarters of all the pesticides used in residential areas. Given the prevailing attitude towards pesticides in this country, there is little reason to believe that most people apply the pesticides with proper precautions as the label requires. It is also unlikely that most people are aware of the potential health effects. Most people will have the worst exposure through inhalation, through ingestion, and skin absorbtion. Perhaps the group at greatest risk is

young children.

There are very few states—and Illinois is not one of them—that have any recording of pesticide poisoning. Illinois—there are no records that I can find after 1973. California is the only state—one of the few states—that actually keeps detailed records. And even that situation has many problems and faults with the data.

All one can reasonably conclude, is that we have a vast array of herbicides and pesticides used at what I would consider unacceptable levels. We don't know the real exposures. We don't know what the public health effects are going to be. The only data on what might happen in the U.S. is what has happened to Vietnam and Vietnam veterans. It is the only data we have to make a public health decision that's going to affect millions of people in this country.

There is almost a continuum that we've described—The workers, i.e., the railroad workers, and the people in Vietnam, both the veterans and nonveterans who were exposed. We must now take that data and carry it through to see what we are actually doing to the rest of the public. Thank you.

(Applause.)

MR. O'CONNELL: We will have some time for some questions of Dr. Thoman and Dr. Ginsberg.

(No response).

MR. O'CONNELL: Well then, I would like to ask a question of Dr. Thoman.

You had reviewed the data done by Dr. Carlson or as relayed by Dr. Carlson of the Vietnamese study of child effects. Is there anything approaching that type of testing that's been done in this country?

DR. THOMAN: There is—in clinical medicine, a registry of fetal abnormalities that is beginning. But nobody has really correlated—and perhaps somebody here might have more information on it. The—there are two problems on it, and I didn't get into it. And I would like to say that generally, when you think about the teratogenic effect of a chemical or drug, you think about that period of time in the first trimester I talked about. But there is another effect which I'm sure is well known by many here, and that is the effect on the male, as it was pointed out in an earlier presentation. And this is the case in Times Beach that I had reviewed last week. And this was an individual who had the various signs and symptoms that were classically the more common symptoms described by Dr. Carnow. But in addition, there was a 40 percent abnormal sperm count. And the sperm itself had these smaller sperm head, the tail was too short, the enzymes were weak because of the pathology of the sperm itself would not be adequate enough at conception. And if so, then the damage of the fetus could be much higher. And I am simplifying it because there are a lot of things that go on with it, and because there are things that we see that go along with the altered morphology of the sperm, the sperm count and so fourth.

So these are other measurable objective things. As far as what we are doing to see if there is a correlation, I think it's a matter of going back. And unfortunately, we used to use our retrospectoscope rather often when it talks about tertology. We don't do double-control studies. We are not taking this group and giving them a certain amount of chemical exposure, and say okay, let's see what happens in the next 30 years.

So retrospective studies are the ones we have to rely on in most cases.

MR. O'CONNELL: Maybe Dr. Carlson can join in this answer. The exposure in Vietnam was to the women themselves and men in most cases. In the States however, it was the men that were

exposed, not the women. But we draw a distinction.

DR. CARLSON: I think that is an important distinction because if males are primarily exposed, and women are not, the only entry for contribution to the child is through the sperm. When a sperm fertilizes an egg, it is the sperm nucleus that enters. The tail of the sperm does not enter. That means any damage of cytoplasmic organelles, such as mitochondria, endoplasmic reticulum and the like would have to be contributed from the female's egg, not from the male's contribution.

This essentially limits male damage to chromosomal or gene damage. The forms of chromosomal or gene damage are limited. I mentioned that for gene damage, you won't see most of that. For chromosomal damage, most would abort because any abnomal excess or deficit of chromosome would be incompatible with fetal development or embryo development. Very few get through. That limits other types of chromosomal damage that might get through to multi-break events. Multiple-break events are detectable by studying a karyotype of the chromosomes.

My own feeling is that the birth defects that veterans associate with their own children are unlikely to be associated with herbicides. The possible errors that I have just described are also found among spontaneous abnormal births for people who have never been exposed to any herbicide or pesticide. Five percent of all births have some sort of birth defect requiring major medical attention. Also, to show the difficulty of this problem, in an epidemiological survey that is done on the veterans, one has to recognize that ten percent of all married couples (whether veterans or not) are sterile. That's a high rate of sterility. When you look at the cause of sterility, about half are due to male sterility. When you look at the causes of male sterility, you find the double-headed sperm, the tail wrapped around the head, the short tail, and other types of abnormalities.

Now, that's among your normal or unexposed sterile males. Also compounding the difficulty is that one out of every five women in her reproductive lifetime will experience a spontaneous abortion or miscarriage. Somewhere between 40 and 60 percent of all fertilizations have an abnormal chromosome number to begin with. And most of these very early embryos eliminate themselves because they are incompatible with life.

Now, that's your control rate. If you are dealing with agents that are weak mutagens, and they are increasing, the control rate of abnormalities from 20 to 22 percent, it's very, very hard to measure this in a population.

You would need huge samples and very careful studies. You would need double-blind procedures. There are so many confounding variables that it's a frustrating point from an epidemiological perspective.

This is one reason why animal models, tissue culture models, microgial models are so important to do carefully because when you find an experimental system that you can control, and abnormalities are induced, you can suspect that these are actually induced. Then you can zoom in on a specific type of abnormality. But it is a very difficult problem.

MR. O'CONNELL: Are there studies that can isolate the control group? And are there studies being done?

DR. CARLSON: I think there are many that can be done. Some are long range and some are immediate. I think that the studies that Dr. Carnow described where he is attempting to look for a specific syndrome of toxic effect is an extremely valuable one, particularly because many agents do not have unique abnormalities the way thalomide does.

Thalomide also produced heart defects and other typical types of abnormalities. If it weren't

for the peculiar limbs, it may never have been picked up as teratogenic in a screening of the population. So that is a problem. You could find the syndrome that should be looked for—and I think this is likely. It will be useful for a down-the-line study of who gets cancer. I think that problem is very important. There are some epidemiological approaches that should control this.

I think that any design of a veterans' questionnaire on a national scale should have a lot of input into its composition. Abnormalities that are seen will have to be matched against unexposed veterans. This requires a lot of thinking and experience to do.

MR. McCARTHY: Are the Vietnamese doing a study of the NVA who traveled down, left their wives like we did, traveled down the Ho Chi Minh Trail, came into Vietnam, were exposed, went back and then saw their children with birth defects?

DR. CARLSON: Yes. They claim they have these birth defects and they are higher than among the veterans who did not go to the south, who fought in the north. But they also claim that these defects are not as frequent as in those who stayed in the south and married South Vietnamese women.

They do claim this, but I find it very difficult to know what the causes would be. It would very difficult for me to think of a genetic or a chromosomal mechanism that would increase the frequency of conjoined twins. And I wouldn't rule out that maybe conjoined twins may be associated with some abnormality in the membrane of the sperm. These monstrosities would be a one-time thing, they would not be passed on from generation to generation.

MR. McCARTHY: Please excuse my academic ignorance on this question.

Now, I may be way out of line because I have to answer it—I have to ask it because it was brought to me. If the DNA molecule is affected by dioxin, if, in fact, the enzymes that create the double helix are affected so that the splitting of the double helix occurs, yet those enzymes will not create the double helix again, in the same way—in other words, intercept the message to the fetus, is that possible?

DR. CARLSON: What you are describing, I presume, is some route for creating an abnormal sequence of nucleotides, copying errors, or the like which will lead to mutations?

MR. McCARTHY: Yes.

DR. CARLSON: As I said, the chances that you would pick up an abnormality of that sort are very slim. For every hundred changes in DNA that you would induce, you would only be able to pick up one as a dominant mutation.

Now, certain dominant mutations in a population are relatively rare. The chances of an achondroplastic dwarf being born are one out of every one hundred thousand births. I would suggest that the United Nations, or other groups who have an opportunity, look at the dominant mutation data in Vietnam because that should involve a million or more children. That would be sufficient to look for disorders like retinoblastoma, achondroplastic and other dominant mutations that usually arise from a brand new mutation.

If they are being induced, they should be occurring with a higher frequency than the background frequency for these disorders, which is well known from many studies. I would suggest for a veterans' survey that a list of the severe, dominant mutations be included in such a study, and then those results can be compared to those who are not exposed—such as veterans who did not go to Vietnam.

MR. McCARTHY: And the last question. Isn't it true that the chemical composition of dio-

xin fits into the DNA molecule, the double helix?

DR. CARLSON: That's much more difficult to tell. You are referring to an intercalating agent. There are compounds—double-ringed-compounds, that do work through this mechanism.

These produce frame shift mutations. Most of these will turn out to be recessive, and will not be picked up for the same reason that applies to most recessive mutations. The induced mutation encounters the normal corresponding gene and it won't manifest any damage to the offspring. The only way the veteran's offspring will show damage is if that gene mutation produced by intercalation or any other means is dominant.

It has to be through a dominant expression to show something systematic in the field.

MR. McCARTHY: And one for Dr. Ginsberg.

Is it not true that Northwest Coalition for the Use of Pesticides—I forget the name of it exactly—that they found dioxin, TCDD in 24D?

DR. GINSBERG: I don't know of any studies which have found TCDD in 24D. There have been several other isomers of TCDD found in 24D samples.

MS. WEST: I have a question for Dr. Carlson. I'm Hillary West from the Illinois Legislative Council. I believe after Hiroshima and Nagasaki, didn't they look at changes of sex ratio in the offspring, and wouldn't that be done and more immediately tell the effects of mutagens?

DR. CARLSON: The thinking behind changes in sex ratio is based on earlier work that was done in fruit flies, where if you would radiate a population of flies and you induce mutation on the "X" chromosome, the males that pick up an "X" chromosome with some induced lethal recessive would manifest it. Whereas, those mutations that are not an "X" chromosome would be protected.

If enough "X" bearing eggs are damaged this will reduce the numbers of males in the population. The female, however, has two "Xs." If the male has a sperm with a defective "X," the normal "X" coming from the female egg will protect the damaged "X" from the male. That's the thinking behind the sex ratio change.

It's easy to pick up this "X" chromosome in fruit flies where the "X" chromosome is 20 percent of the total genetic constitution of the fly. Unlike flies, we don't have a chromosome number of 8. We have a chromosome number of 46. The "X" chromosome is less than five percent of the total genetic material. So the amount of genetic damage you are producing in the "X" chromosome in the human is relatively minor compared to the amount of damage you would be picking up in all the genetic material.

It becomes much more difficult, unless you have massively high doses, to produce enough mutations on human "X" chromosomes to show a dent in the sex ratio. The larger the amount of genetic material you have for your sex chromosome, the easier it is to see—using the sex ratio method. So that's the difficulty with humans.

MS. WEST: And no one has really bothered to look at that?

DR. CARLSON: I doubt that you would find anything with studies of Agent Orange exposure and sex ratio. Even with Hiroshima and Nagasaki victims who were receiving doses of 100 to 300 roentgens, which is close to a mean lethal dose, there was no detectable change in the sex ratio. But many geneticists would have predicted that we wouldn't have found it.

DR. CODARIO: I'd like to make a point in clarification for the laymen in the audience, particularly the veterans. And Dr. Carlson, you can comment on this. In the course of the discussions, we have heard a lot about teratogenesis and mutagenesis. And in seeing patients—the veterans that I see,

question is very often asked of me: "Doctor, I have a child. And I was in Vietnam and exposed to Agent Orange." And for the benefit of the laymen, we have to differentiate—and I want you to all understand what it means when we say that something is teratogenic and something is mutagenic.

When something is mutagenic, that means it causes chromosome damage. An example of that is as Dr. Carlson pointed out, we are born with 46 chromosomes. An agent that is mutagenic is an agent that is going to have us have 47 chromosomes or 45 and a half chromosomes.

An agent, on the other hand, that is teratogenic, will cause an individual to be born—as we talked about—with very small arms, or the absence of an arm. That may not be associated with an obvious chromosome damage.

Now, here comes the hundred-dollar answer. Here is something that you have to understand. It is very important to understand in all the studies that we do, we look at birth defects. But we are just beginning to scratch the surface in terms of finding out how that cell gets from one small organism, one cell, to the complex chemical factory, if you will, that the human body is.

We don't even understand how that develops. We don't know why. For example, if you look around this room, you will see 37 or 40 different personalities. How did that happen. That happens, obviously, on a chemical level. There are many chemical reactions that occur in the body. We don't know how the body goes about regulating those things.

Why do two children in a family—one child is six four, the other is five nine? Where does that come from? Obviously, it's controlled somewhere in that genetic code. But we don't know where that control is. And just because we don't know where that control is, we are just in our infancy in looking into how agents like TCDD can cause problems of that type.

Many veterans come up to me and say my child has multiple infections. Is that due to Agent Orange? The answer is we just don't know. We really don't know. We are just beginning to scratch the surface as to how the human body develops.

I think in that respect, Dr. Carlson, dioxin is a lot smarter than we are. Dioxin knows how to do it, but we don't know how to do it yet.

DR. CARLSON: I share the importance of making that distinction between teratogenic and mutagenic effects. It's very difficult for me to conceive of the teratogenic effects coming out of the sperm other than some initial defect that sets up abnormal twins; something that happens almost immediately at fertilization. Once fertilization is on its way, it's hard to see how the sperm plays any role other than a mutagenic effect, rather than a teratogenic effect.

On the other hand, in the eggs I can easily see how the Vietnamese exposed women can have these high frequencies of moler pregnancies because the egg is a fat factory. It's about a hundred to a thousand times bigger than a sperm. it's loaded with yolk material, which is lipid rich. So you differentially stack the egg with herbicides which are fat soluble.

I can understand how that can toxify the development in the egg, and toss out the nuclei in the polar bodies. That makes sense. But it's very hard for me to think of any mechanism by which the sperm could do the same thing.

MR. O'CONNELL: On behalf of the Illinois Agent Orange Commission, we would like to invite everybody to lunch. We will be in the room next to us. And I would also like to thank Dr. Thoman and Dr. Ginsberg. And again, Dr. Carnow and Dr. Carlson for their excellent presentations.

(Whereupon, a luncheon recess was had.)

MR. O'CONNELL: Could we all take our seats, please? We are filibustering right now until

we get a new lightbulb in the camera. Several of my colleagues on the Illinois Agent Orange Commission have arrived since our introduction this morning. State Representative Larry DiPrima, who is the dean of the Illinois House of Representatives, and has been a stalwart representative of the veterans in Illinois is with us this morning. He is a member of the Illinois Agent Orange Commission. And we also have Bob Mitchler, who is not on the Commission, but works very earnestly for the Illinois Veterans' Association.

Jim King from AMVETS is also a member of the Illinois Agent Orange Commission and is with us, and has been an outstanding member of our state commission since its inception. Joan Maiman who has been with us is also a commissioner.

The format for tomorrow will be to delay the breakfast. Instead of starting at 7:30, we will have a breakfast buffet at 8:15. I think with the size of the group, we can accomplish what we want to by starting the breakfast at 8:15.

I think it will serve as a good forum to exchange ideas and possibly get some direction for our respective state commissions, and to get some ideas. I know we in Illinois—our next project after this is to complete our questionnaire, which we have been working on for some time, and would like to finalize pretty soon.

So we welcome our other states' input on that issue. Well, our afternoon session will begin with a presentation on the advances made in diagnosing Agent Orange medical conditions. Dr. Ronald Codario of Philadelphia, was also with us a year ago, and we appreciate his coming back to Chicago for a return visit. Dr. Codario is a graduate of Hahnemann Medical College, and is presently on the teaching staff of three Philadelphia hospitals. And he is the administrative aide of the Division of Internal Medicine at St. Agnes Hospital. Dr. Codario is also the distinguished recipient of the 1981 Freedom Foundation Award at Valley Forge for his work with Vietnam veterans.

I'd like to have you join us in welcoming Dr. Ronald Codario.

(Applause.)

Dr. CODARIO: I would like to thank the Illinois Agent Orange Commission for being gracious enough to ask me to come back again this year. It's always a pleasure to come to Chicago and to attend the Illinois Agent Orange Commission meeting. And I think that the commission has demonstrated that they are one of the finest in the country. So I am certainly happy to be here.

What I would like to do today is to just give you an overview as to some of the changes (I'd like to say advances—I hope they are advances) in diagnosing this perplexing problem, and some of the newer tests that we have come up with that I hope will shed some light and maybe give some people some thoughts in this room about how we can go about looking into this very perplexing problem of diagnosing and proving that a lot of the symptoms and signs that the veterans have are related to herbicides and their effect.

This is the chemical structure of our friend tetrachlorodibenzoparadioxin. As you can see the chloride molecules in the 2,3,7,8 positions. As already alluded to, there are 75 different isomers of this chemical compound. It's a very flat symmetrical molecule that conveniently drifts into the cell membrane. And then it begins to wreak havoc with the body chemistry. And that's where the fun begins.

We have to begin determining several years thereafter what chemical effects have taken place, and what signs and symptoms are related to this biochemical disarray. In the last year or so, I've devoted most of my attention to looking into two particular problems. One is chloracne and the other is the syndrome of neuroesthenia. Now, if you review the medical literature and you spend some time

looking at all the published reports on humans that have ingested these herbicides as suicide attempts and humans that have been exposed as a result of industrial accidents, one thing is certainly clear—what the veterans are complaining about is not something that has recently been described. These symptoms and syndrome complexes have been reported in civilians who have been exposed to 245T with its contaminant dioxin and 24D as well.

So that these whole hosts of symptoms are not new in exposures. But as we mentioned last year, they are certainly characteristics of human exposure that you can pick out and say are reliably found in people that are exposed to TCDD or what we commonly refer to as dioxin.

And as we say, chloracne is the most consistently reported health effect. And as Dr. Carnow mentioned, you do not have to have chloracne to have later demonstrated side effects of TCDD.

One of the problems with chloracne is that it can run the gamut from innocuous-looking blackheads on the fact to rather disfiguring eruptions, as we see here. Now, this is an individual that had a skin biopsy that had a characteristic finding of chloracne. And we are going to talk about that in a minute. I wanted to just contrast this veteran's skin with this individual who is an individual who has been exposed to polychlorinated biphenyls and nitrofurans. He was in Taiwan, and exposed as a result of an industrial accident there.

One of the big problems with diagnosing chloracne, and one of the common misconceptions is that you can diagnose it simply by looking at it. And that simply isn't true. If you look at all the published reports by the experts in the field, particularly James Taylor of Cleveland Clinic, Dr. Kenneth Crone of London, England. One of the key points that is made is that a skin biopsy is certainly critical in making the diagnosis. Let's talks about some skin biopsy findings.

Now, this is a section, in essence, of normal skin. And for the laymen in the audience, the skin is divided into two general areas, the epidermis and the dermis. The dermis is this darkened, pink area. And this is the dermal area here. And the changes that we see in chloracne involved not only the epidermis, but the dermis. We see acanthosis or a thickening of the epidermis. We see an absence of bacteria and leukocytes in the dermis. Contrasted to acne vulgaris, or the adolescent's acne, where we see a lot of round cells in the dermis and a lot of bacteria in the dermis, and in the hair follicles. And this is a hair follicle here, a normal hair follicle. We see disruption of the normal cells in the hair follicle so-called squamous metaplasia and deposition of keratin chloracne. And this is demonstrated here in this slide taken from a rabbit ear. There is a large amount of keratin deposited in the hair follicles, with the surrounding squamous metaplasia that has taken place.

Now, Dr. Crone of London, England, feels that if we are able to see this type of eruption in two particular areas, the eyelids as listed here, and the groin and the scrotal areas listed here, that we may be able to forego skin biopsy and make the presumptive diagnosis of chloracne. The reason for that is that usual garden variety of acne vulgaris just doesn't usually or normally occur in these areas. So if you have an individual that has eyelid involvement, you certainly have scrotal involvement or anal involvement, as we see here. You may suspect that the individual may have chloracne and forego the skin biopsy.

Now, these are slides that were provided to us with the courtesy of Dr. Renata Kimbrow at the Centers for Disease Control in Atlanta. And these again are Taiwanese people who were exposed to dibenzofurans. And you can the disfiguring type of eruptions that have taken place in this particular individual. But remember, chloracne does not have to be a disfiguring eruption.

Now, James Taylor of the Cleveland Clinic is treating his patients with vitamin A derivatives,

and has had some success in treating his patients with those substances I'll have to admit in my clinical practice, I have not been able to share that enthusiasm. The patients I have given vitamin A to, I haven't been impressed with that agent as being remarkably helpful in relieving the symptoms of chloracne.

One of the newer agents, accutane, which is a vitamin A derivative, may prove to be of some benefit in treating these patients that have chloracne. But that certainly remains to be seen. One of the problems with accutane is that you certainly have to monitor and watch liver function very, very carefully. And as was illustrated prior to this, many of these patients do have liver involvement, if not from Agent Orange or dioxin per se, perhaps on drugs or other types of chemical substances that they may have been exposed to.

So I think as of this time, I can't really say that there is any real accepted treatment for chloracne. Vitamin A has been tried both topically and systemically. Usually the patients do not respond to tetracycline for some lay effects. Dr. Crowe uses derm abrasion which is literally scrubbing the surface of the skin, with some effectiveness, but certainly a lot more research needs to be done in this particular area.

One of the more fascinating areas of endeavor and an area that is really my interest has been the post-Vietnam stress syndrome, the delayed syndrome. And the psychologists and psychiatrists have certainly worked out an excellent clinical diagnostic entity. The key question and one that I think should peak out interest is what is the cause of this post-traumatic stress entity. It is really just that it was unpopular war, and the veterans weren't accepted properly when they came home. They might have a predisposition to developing psychological problems. Is is just a simple as that? Or maybe is there another factor? And that factor might be that the chemical themselves, either the herbicides or dioxin or a combination of the herbicides and dioxin may be playing the role and causing delayed mental illness. It's a very frightening and rather poignant question. If you review the literature, we certainly have loads of evidence that toxic agents can affect the mind. The classic example is the Mad Hatter syndrome, those individuals that work in mercury factories and have been exposed to mercury and develop the madness of the hatters when they used to use the mercury to line the hats in the factory. These individuals when exposed to that substance eventually become mentally ill and insane. They all developed the same type of mental syndrome.

Could we be seeing—could this post-Vietnam stress disorder be nothing more than a manifestation of herbicide poisoning? And with that in mind, with the aid of Dr. Herbert Kaye of Stonybrook, we have been able to do certain specialized testing in Vietnam veterans which involves the use of a computerized electroencephalogram.

Now, this picture is kind of a graphic illustration of what I was talking about. And I think a picture is worth a thousand words here. This was an article written in Seattle, Wasington, by Eric Scigliano. And with the aid of some work given to him by Dr. Malcom Barr of Australia, he was able to write some interesting articles on this particular theory. Now, if you look in the literature, certainly as we said, this type of neuroesthenia syndrome has been described previously. What the veterans are complaining about is not something that does not have any precedent in the literature. It is in the literature. It is found there. These are not new complaints.

And getting back to what Dr. Carnow was saying, I really believe that too. I have now looked at 550 individuals. I am not impressed when I stand there and talk to an individual about—this is an individual that is coming in and that's been coached, that spent one year giving his life in Vietnam and

is now coming to a doctor to try and goldbrick and try to make up symptoms, complaints that individuals have been reported to have with Agent Orange poisoning.

And I think that's an oversimplication. And I think that if you look at the literature and you talk to the men, you find that the symptoms are peculiarly similar: weakness, fatigability, headaches. And I think one misconception we all have as physicians and scientists, if we can't prove something scientifically, it simply must not exist or it must not be significant. And that's a gross oversimplification. I think it's a fault in our scientific method. And the burden is on us to find out why these gentlemen are having fatigue.

And Dr. Carnow may have shed some light on an interesting issue about the muscular involvement in the abnormalities of the mitochondria. And that certainly has to be looked into. But clearly, when a veteran says he is complaining of fatigue, despite the fact that we can't prove it through a blood test, fatigue has been reported in the past, as well as the weakness, the vegetative dysfunction, mental depression, lack of drive, lack of sexual drive, by Basherov in the Soviet Union in workers that were exposed to TCDD and herbicides.

Now, this is basically some electroencephalographic data. And I want to give it to you as an overview to give you some background as to what we are finding in these computerized electroencephalograms. Basically when you do an EEG, a standard electroencephalogram, for the laymen in the audience, it's kind of like the EKG of the brain, if you will.

We are hooking up electrodes to the brain, and we are measuring brain-wave patterns in different areas of the brain. And there are certain brain wave patterns that are normal in particular areas of the brain, and for particular types of activity that an individual is engaged in. And there are four types of waves that we see in the standard EEG; alpha, beta, theta, and delta. And they are all designated by the number of blips or count per second that you see when an individual is hooked up to such a machine.

Now, this is what the standard EEG looks like. And these are the areas of the brain that correspond to these abnormalities. Now, what do we look at? What are we looking for when we look at what appears to be a lot of chicken scratch up there?

Well, first of all, the left side of the brain and right side of the brain have similar patterns; that is, the amplitude of the left side and the right side of the brain should be the same. These deflections upward and downward should be the same size in both sides of the brain. In addition, we should see the deflections occurring symmetrically. When the left cortex deflects, the right cortex deflects. So that's one area that we can look at.

And this phenomenon where we look at the symmetry, if you will, of the waves on both sides of the brain is referred to exactly as that, symmetry. Convergence is referred to as the ability of the left side of the brain to correlate well with activities in the right side of the brain. And the blips per second that we see here are the number of areas or the areas of the brain where we are seeing this various type of activity.

Now, it turns out that delta wave activity which is very slow waves, three to eight cycles per second, is found in a very limited number of clinical settings. We see it in some children, and we see it in some individuals that are sleeping. And we see it in individuals that have brain damage. Now, the neurometrical uses many more of the standard electrodes and uses a computer to interpret the results. This computer and this technique has been used for over 50 years to look at the cause of learning disabilities in children. And with this technique, we have now studied over 50 veterans. And we have

been able to find some interesting patterns, patterns that as this time don't in and of themselves prove something. But they certainly indicate to us that there is something more that has to be investigated.

We are finding a large number of delta wave activity. 84 percent of the veterans that we have looked at have abnormal amounts of delta waves in their frontal lobe and in their temporal parietal lobes indicating that there is some type of brain injury. Now, is there any type of precedent for this in the literature?

Yes, there is. If you review the literature, on animals that have been exposed to this substance and you do an EEG on animals, you actually find that they have EEG abnormalities, that they do have delta wave abnormalities. When you sacrifice those animals and you look at the brain under the microscope, you actually find that certain areas of the brain, particularly what we call the pyramidal tract, that has lost some of the fat lining of the nerve itself. And this process is known as demyelination.

And it's a very intriguing process because peripheral nerve tissue is lined with fat. Central nerve tissue is lined with fat. If you go back and you review the literature, this phenomenon has also been described in nerve tissue. Peripheral neuropathy (damage to the peripheral nerve) has been reported in humans that have been exposed to herbicides, in humans that have been exposed to TCDD and in animals that have been exposed to TCDD and exposed to herbicides.

And the precedent has certainly been set. What about peripheral nerophathy? Is it something that's rare? It is not rare. There are many types of toxins that can cause peripheral nerve damage. For the laymen in the audience, peripheral neuropathy is characterized by numbness in the hands, numbness in the feet. It may be characterized in the later stages by weakness in the muscle. But the classic symptom that the patient has is numbness. Many times when we get a standard electromyogram, it's measure to design the nerve conduction in the nerves. It may be normal. Physical examination may be normal. If careful attention is not taken to all types of sensory stimulation, particularly vibratory stimulation. So peripheral neuropothy is quite often a missed diagnosis. It's not often a serious problem. It's not a problem that may cause death to the individual. And as a diagnostician and as a physician, I can tell you that the peripheral nerves are something that are quite often missed and glanced over when a physical exam is noted.

Nonetheless, when you look at the types of peripheral neuropathies, there are two general types. There are types that cause damage to the long sheath of the nerve in a segmental fashion. And there are types of nerve damage that causes damage to the end of the sheath and the sheath then begins to deteriorate in a backward fashion. Nerve tissue consists of two types of components. There is the nerve cell body, which actually looks like a star, the dendrite. Emanating from the star that is a long cord, the axon. And the toxins damage the nerve by damaging that axon. And there are all different ways that an axon can be damaged. All these different types of chemicals cause different types of damage and phenomena. And they cause it in all different ways, like interfering with the biochemistry of that nerve, various enzymes, various vitamins are interfered with. Arsenic, for example, (one of the key ingredients of agent blue) causes a peripheral neuropathy, a dying back neuropathy that usually responds to thiamin, a multivitamin.

Some of the medications that are available on the market, like INH, (which is used for tuberculosis) can cause peripheral neuropathy.

And strangely enough, our old friend porphyria can cause peripheral neuropathy. And we have heard about porphyrin damage in Vietnam veterans. And last year, I talked about the porphyrin

problems that we are seeing in many of the veterans. Other types of damage that are caused directly by some of the agents that we may have heard about today, many of the pesticides, the organophosphorous compounds fit into this category. Dapsone, which was used in Vietnam as a prophylactic ingredient to fight malaria, can also cause peripheral neuropathy. And strangely enough, we suspect that TCDD or dioxin may fit into this group three category. I will tell you some information about that as we go on.

Now, the key question becomes a clinician when a patient complains of numbness in the peripheral nerves, how can we make that diagnosis of peripheral neuropathy? We said that many times, the standard EMG and nerve conduction study may be normal. Well, if the patient has peripheral neuropathy, why is that normal? It may well be that the EMG is not as sensitive as it should be or can be. A very interesting paper was put out in the Archives of Neurology last summer by Schaumberg & Abrusi in New York. And they did fairly extensive work on diagnosing peripheral neuropathies. And what they basically did was, they exposed a monkey to an agent called acrylomide. And acrylomide causes this dying-back type of neuropathy that we are taking about. They then went about doing two things. They wanted to find out how they can prove that this monkey had a peripheral neuropathy, and that was the best test, the best way to go about doing that. And then, they sacrificed the monkey and looked at the peripheral nerves, looked at the spinal cord, looked at the brain, and found out what was happening on a micromolecular basis to explain their clinical findings. A very interesting model, to look at peripheral neuropathy. And here is what they found. And this is very important to the clinician. They looked at two types of nerves, the perineal nerve and the median nerve. Again, for the laymen in the audience, the median nerve is one of the main nerves in the upper extremities. The perineal nerve is the nerve in the leg. And they wanted to find out if there is any difference between the arm and the leg. And it turns out that there is a very significant difference. The perineal nerve seemed to show many more abnormalities in terms of the degree of dampening of the response, the stimulus, and the time period that it took for that response to be dampened. Well, big deal. What does that mean? What it means is that when we look at peripheral neuropathy, maybe we are making an oversimplification to just say this fellow has a peripheral neuropathy. Let's just do the upper extremities. Or this fellow has a peripheral neuropathy, let's just do the lower extremities. Because it turns out that when you look at the perineal nerve, and you take the somatosensory evoked potential, which for the laymen in the audience means the nerve conduction as we go all the way up to the brain—remember, when you get a stimulus in your fingertip, you are able to sense that in you brain. And the reason you are able to sense it is because that stimulus goes up your arm—or if it's the perineal nerve, it goes up your leg through the spinal column and into your brain. And it turns out that if you look at the perineal nerve, which is the nerve of the foot, and you check the conduction of that nerve as it passes through the cervical spine area, that the abnormalities are much more significantly pronounced.

This means that when you do—when you are attempting to diagnose peripheral neuropathy on a toxic or a toxin basis, which should or may well be very, very important to look at not only the upper extremity, but also the lower extremity, particularly the perineal nerve. But more importantly, not only the perineal nerve as it goes from the foot to the spinal cord, but up the spinal cord and into the brain. Because the cervical spine area seems to be the area that's much more sensitive to electrical pickup. We are able to pick up the abnormalities much more sensibly in the cervical spine area.

Now what they did in this study, which is very interesting, they exposed the monkey from day

one to this substance which causes peripheral neuropathy. They then measured the electrical conduction and the tranmission of this electrical stimulus in this nerve 12 days after acrylomide administration and 20 days after acrylomide administration. And as you can see, they saw two interesting phenomenon. They saw first of all that the response was dampened. So that the nerve wasn't able to conduct the stimulus as well. And they also found that there was a one millisecond delay as time went on in conducting that impulse, an abnormality; a way of proving that this individual has a peripheral neuropathy.

They then did something that was even more fascinating. They looked at the peripheral nerves. And they looked at the spinal cord. And they found that the particular area of the spinal cord where the nerve from the leg terminates had much more significant neurological damage; demyelination, loss of fat. Then the area where the median nerve terminates. Now, the perineal nerve terminates in an area called the gracilis nucleus, which is indicated right here. The median nerve terminates in the cuneate nucleus, which is indicated here. And what they found was a large amount of loss of fat, demyelination in the gracilis nucleus. Now, why is that? Well, that's something that is open to discussion. But it appears as though the structure of the gracilius nucleus is much more different than the other nucleus. What does that have to do with the Vietnam veterans?

Well, if indeed this is true in humans, and once again, not only do we have a specialized test for proving peripheral neuropathy, but it has to be done in a specialized way, and it has to be looked at in a particular area. With that in mind, with the aid of Chestnut Hill Hospital in Philadelphia, we have now been looking at somatosensory evoked potentials in veterans. And I hope to have some very interesting findings about this in the future about whether this technique will be effective in looking at humans. One interesting patient that we have had in practice that hopefully will be reported soon, is a gentleman that served in the III Corps area in Saigon for two years as a medic.

This gentleman, shortly after his service in Vietnam, contracted what was listed as Guillain-Barre syndrome. He recovered from that, and eight years thereafter, began developing numbness in his hands and in his feet. And has now progressed to the point where not only does he have sensory abnormalities, but he has muscular abnormalities as well, and he has a severe peripheral neuropathy.

This gentleman also has elevations of coproporphyrin, uroporphyrin, and intermediate porphyrin. And fortunately and thankfully, there is no history of drug abuse, there is no history of neurological disease in the family, there is no history of alcohol abuse. So the question is what is causing this mixed neurological disturbance.

Is it multiple sclerosis that many of the veterans are diagnosed as having? Well, we did a spinal tap. And the spinal tap did show an oligochlonal band that we sometimes see with multiple sclerosis. But his nerve biopsy did not show what we see in multiple sclerosis. And I want to present the findings of the nerve biopsy because they were very, very interesting. First of all, when you take a nerve biopsy, you don't just lop out any segment of nerve and send it down to the pathologist and say here, tell me what's wrong with this nerve. You have to take a certain length of the neuron of the nerve tissue that you want. And it's usually suggested that you take the sural nerve, which is the nerve in the lower extremity, the leg.

Interestingly enough, it seems to be the nerve of choice because if you look at toxic ex-

posure, particularly with Schaumberg's data, you may think and you may suspect that the lower extremities are affected before the upper extremities. So certainly if a lower extremity nerve seems to be the nerve that you want to look at, it's very important to preserve that nerve in paraffin to get a good long longitudinal section, as well as a cross-section. The longitudinal section should be stained properly so that you actually demonstrate the areas of nerve damage and determine the type of damage that this individual has. Most importantly of all, in addition to doing this standard test, one must also examine nerve tissue with the electron miscroscope. And that was alluded to by Dr. Carnow when he talks about looking at liver tissue in Vietnam veterans. And he talked about the thickening of the endoplasmic reticulum. Because it seems as though to make this diagnosis, the toxin induced neuropathy, the electron microscope has to be used to actually demonstrate it. This is the standard section of the nerve tissue. And obviously, to most individuals, maybe all individuals, even myself, it looks like a cross-section maybe of a salami. But these are actually bundles of nerve tissues. And there is actually a set ratio of the myeline fibers to the unmyelinated fibers. And that ratio of myelin to unmyelin should be one to three. So there is a set ratio in nature that we see. Now when we looked at this individual, we found that this individual has a dramatic increase in the unmyelinated fibers, that the myelin sheath around the nerve had been eaten up and destroyed. Now, what we see in the electron microscope, is a nerve which looks like some fettuccini or thin strip of spaghetti. But if you look at that strip of spaghetti under the microscope, you actually see that there are a lot of nerve bundles in there. And we see some very interesting and unexplained phenomenon in that nerve. First of all, we see that there are a lot of fibers that have lost their myelin. And strangely and peculiarly enough, we see a lot of dark granules in the center area, the medulla of the nerve.

We are not sure what these granules are. If you read the literature on peripheral neuropathy, they describe dark granules in this area, and they talk about deposition and deteriorating myelin, deteriorating fat tissue. We just did not know what this particular abnormality constituted. But it certainly is a peculiar one indeed. And it's one that I think merits further investigation. But nonetheless, if an individual has a peripheral neuropathy, and you want to determine the cause of the peripheral neuropathy, a special somatosensory evoked potential study is critical in making that diagnosis.

And if there is certainly any question as to the cause of the peripheral neuropathy, nerve biopsy certainly would give you an important indicator as to the cause. We talked about dapsone. We said that dapsone can cause peripheral neuropathy. I want to clarify that. I had an opportunity to review the literature on dapsone because I got a letter from the Dow Chemical Company suggesting that dapsone was the cause of peripheral neuropathy. And I had an opportunity to call the company and the individual who produced dapsone. And they graciously sent me all the literature on the substance. It's been used on eleven million lepers throughout the world to treat leprosy. It's used in doses eight times more potent than the Vietnam veterans received. And it's used quite often intravenously to treat leprosy.

Of the eleven million lepers, there have been eight reported cases of peripheral nerve damage secondary to dapsone. So I think it might be a little bit presumptuous to assume that anyone who has peripheral neuropathy has it on the basis of dapsone. But certainly, it's an agent that was used. It was stopped in 1968 when there were eight reported deaths due to agranulcytosis, which was a wipeout of the white blood cells of the veterans that were given dapsone, chloraquine,

and quinine as a prophylactic for malaria. They no longer use that combination. And they weren't really certain as to what agent caused that. Maybe all three acting together might have caused it. But it doesn't seem as though by the literature that we can explain or blame dapsone for these particular phenomenon that we are seeing. There is much—a lot has been written recently of melioidosis, the time bomb of melioidosis that is a condition caused by pseudomona pseudomalic, a bacteria that was present in Vietnam.

And once again, there have been very few reported cases of melioidosis since the war has ended. The last count—there were 16 reported cases at the center for disease control. There are two large studies of returning Vietnam veterans in '67 and '68 done by the Air Force where they looked at 1750 returning veterans, and did blood tests for exposure to this bacteria. And they found that 25 percent of those returning veterans had elevated blood tests. But just because you have an elevated blood test that says you are exposed to this, that doesn't mean you have the disease, and it doesn't mean that you are going to develop the disease. It just means that you were exposed. So it doesn't seem as though the veterans are suffering from melioidosis. And it's an important point to keep in mind, however, because the disease can remain dormant for several years, and can reactivate itself. And when it reactivates, it presents as abscesses in the lungs, abscesses in the prostate glands, and abscesses under the skin. Now, it's very important to understand that when you have melioidosis, it is a very severe disease. You don't walk around with a cough every summer and see your family doctor and he gives you an antibiotic and it goes away. You are very severely ill. And if not diagnoses properly, you go on to die in a reactivation of this disease. So don't think that if you have a cough every winter that you have melioidosis and it's been going on undiagnosed for years. This is a very severe debilitating illness associated with very high fevers. And the individuals are extremely sick. And fortunately, we have powerful antibiotics now that can cure this condition.

But if any of you are physicians in the audience or patients, to have Vietnam veterans present themselves at the hospital and have abscesses certainly it would be very important to get melioidosis titers. And it is very easily done by sending them down to the Center for Disease Control in Atlanta.

This is the data that we presented last year. We have now gone over 550 Vietnam veterans. And again, the data is presented not to suggest that these symptoms prove that these fellows all have Agent Orange exposure, and all the symptoms are related to the herbicides, but rather to give you an idea of what the fellows are complaining about. They all seem to be complaining about the same things. Personality changes in 86 percent of 300, fatigue in 78 percent. Loss of concentration in 74 percent. Numbness in 68 percent. Photophobia, which is an interesting and perplexing phenomenon. We've had an opportunity to look at several veterans. Our survey is now up to 30 that have this photophobia. And we have been unable to demonstrate why they have it.

We have been doing visual evoked response tests. We have been doing tests for the retina. And right now, it still remains an enigma as to why the veterans have to wear sunglasses when they go out in the light. That doesn't mean that it's not occurring. It just means that our level of scientific sophistication just hasn't explained it. Dr. Malcolm Barr in Australia claims that the visual evoked responses in his veterans are abnormal, and that indicates that there is retinal damage. But we haven't been able to produce that in the United States.

The birth rate defect is 18 percent, but it's a skewed population and can't be used right now to

prove anything one way or the other.

The interesting abnormalities are the clinical abnormalities; 70 percent of evidence of peripheral neuropathy. And I can't emphasize too strongly for the physicians in the audience that when a gentleman comes to you complaining of effects that he may feel are herbicide related, it's very important in addition to obviously taking a very careful history, that a very careful physical exam must be done, particularly with reference to the peripheral nerves. Test the individual for pinpricking, for cold and temperature sensation, and most importantly, test that individual for vibratory sensation.

In most of the individuals that we have seen, they have an impairment to vibration. This doesn't mean that they cannot feel any virbratory stimulus. It means that their vibration sense is impaired. Vibratory sensation is tested with a 125E tuning fork. The individual is given the tuning fork. Duration of vibatory sensation is measured. A 20-year-old individual feels that tuning fork for five seconds and you as a 34-year-old can feel it for 25 seconds, there is some explanation for that abnormality. And that may be one of the only clues that the individual has to peripheral neuropathy. Porphyrin abnormalities in 60 percent. And again, it is a statistic that is interesting in that it has been reported before, but one that needs more analysis.

Porphyrins are very interesting because as you know, they are building blocks for hemoglobin that carries oxygen in the red blood cell.

And the fun thing about collecting porphyrins is that they are passed out in the urine. So all you have to do is get your patient to collect his urine for 24 hours. And if you get the lab to analyze that, you are in business. If you make a mistake, if the test is invalid, you can always go back and get some more urine at no cost to the patient. One of the big problems in getting porphyrins analyzed the United States is that the world authority for porphyrin analysis is in Minnesota. And they have published an extensive battery of papers with world renowned acclaim on porphyrin analysis. And fortunately, I was able to get my porphyrins at the Northwestern Hospital.

And there are some people here from Minnesota. To get these tests done would be very much appreciated because if you review the literature, and Dr. Johan Strik's analysis of porphyrin is very important in associating this exposure to TCDD or dioxin.

If you look at all the chemicals that were sprayed in Vietnam, there is only one chemical that causes these symptoms, and that was dioxin. Arsenic caused porphyrin problems, but those subsequently go away. Only dioxin causes permanent porphyrin damage. So if you have an individual that has porphyrin abnormalities, you then must find out what other substances that individual may have been exposed to in the United States thay may have caused porphyrin problems. This is very, very important.

Finally, the Pennsylvania Medical Society in conjunction with the Pennsylvania Agent Orange Commission is now putting out a text and I have been priviledged to do a lot of the writing. It's going to go out to all physicians in the state of Pennsylvania. And what this text will include (when it finally comes out) is a review of the literature as well as suggested texts for diagnosis. I may suggest that in looking into this particular problem, it's certainly very important to look at all aspects of liver functions. You also get the GTTP. All of this is very important. In fact, the GTTP is possibly the most sensitive indicator of derangement, next to the urine porphyrin. And it's very important to understand the importance of this.

When you collect our porphyrin, it has to be in a container that's protected from the light. If it's not, then the porphyrins are going to be ruined. The porphyrins are also very sensitive to temperature. They must be collected on ice and transported to the laboratory on ice. So that's very, very important. And recently—now, in addition to the other battery of tests that include C.T. scans of the head, chest X-ray (if the individual has problems in that area) we are now doing the tests to demonstrate peripheral neuropathy. The purpose of the EEG is to get more insight into explaining why these individuals are having their problems.

This slide is among one of the most sobering slides and probably one of the toxicologists that had given the talk prior had mentioned this particular phenomenon. Unfortunately, the Agent Orange story did not begin and end in Vietnam because according to the U.S. Department of Agriculture figures that we have listed here, 50 percent of all 245T that was produced between 1961 and 1969 was sprayed right here in the United States. Only 33 percent was sprayed in Vietnam. So that means that more 245T was dumped here than was in Vietnam.

So it was a problem that was not only peculiar to the Vietnam veterans, but unfortunately, it's a problem that we are going to have to come to grips with as time passes. It's very, very important not only to help the veterans that stood up and fought for the country, but it's going to be very important for future generations that we do all we can to lick this problem and try to keep an open mind as we possibly can, and at the same time trying to maintain our objective.

Thank you very much for your attention.

(Applause.)

MR. O'CONNELL: Just as Philadelphia has Dr. Codario, Chicago has Dr. Orris. Our next guest is no stranger to the Illinois Agent Orange Commission. He appeared at our hearing at O'Hare last year also. Dr. Peter Orris is currently a member of the staff of Cook County Hospital, Division of Occupational Medicine, as well as being associated in a private medicial practice.

Dr. Orris holds a masters in public health from Yale University, and a medical degree from the Chicago Medical School. At Cook County Hospital, Dr. Orris is a supervisor of house staff in the internal and occupational medicine departments. He is a clinical assistant professor at Northwestern University School of Medicine and is also involved in occupational and epidemiological research.

I'd like to present Dr. Peter Orris.

(Applause.)

DR. ORRIS: Thank you very much. I'm going to speak for a few minutes today to point out a number of developments in the literature. Since your previous hearings that I think bear some emphasis. I will then specifically discuss how a clinician might evaluate a patient who is concerned about dioxin intoxication, either domestically or in Vietnam. This approach will attempt to balance the need for indepth evaluation of patient problems with a concept of avoiding subjecting a patient to a variety of invasive testing that may show little result.

Now, by way of an update, there are two articles that I think are quite significant within the last year and a half. The first article comes from Prague. It appears in the Archives of Environmental Health, published in the United States, in the January/February '81 issue (Vol. 36, No. 1, P-5-11). It is entitled The Development and Prognosis of Chronic Intoxication by Tetrachlorodibenzoparadioxin in Men, and recounts an exposure of workers in a factory between 965 and 1968 of which 55 were reexamined after 10 years.

The significance of the study is that it gives us some feeling of the natural history of this intoxication. They looked at people initially in the first month, two months, three months after exposure. And then again ten years later. And what is fascinating within this, is that the neuropsychiatric and peripheral neuropathic disorders most of which showed up in the first three months after exposure, were in fact, more prevalent ten years later. The other signs of intoxication the chloracne, the liver dysfunction, were becoming less frequent ten years later. That's a very interesting development I think.

The other article appeared recently, 1982, in the American Journal of Industrial Medicine. (Vol. 3, No. 2, P. 179-189). It recounts an accidental exposure at the Air Force base in Germany on November 17th, 1953, and a mortality analysis 20 years later.

When the proportioned mortality rates were compared with the Federal Republic of Germany as a whole, as well as with those of the immediate area around the base, they discovered that those people with exposure had a more deaths due to gastric cancer than expected. This is only one report, yet it is significant in that it may indicates an association with cancer of other organ systems other than the soft tissue sarcomas and lymphomas that have been previously reported. I would commend both of those papers to you as significant new developments in the literature. Clinicians may see patients exposed to dioxin in Vietnam or in the United States. In the United States a growing source of exposure is due to fires in electrical transformers. These transformers often have oils composed of polycholorinated biphenyls and chlorinated benzens. When these burn above 600° F dioxins and furans are produced. The furans are much less understood. Yet they would appear to behave very similarly to dioxins. We are currently investigating incidents in Minnesota and Chicago. There were large fires there recently, as well as in San Francisco and New York. What does a clinician do? I will give you my approach. But I stress that there are many different approaches.

The most important thing in these evaluations is to assume that there is reality to the victim's complaints. And unfortunately, the symptoms are so diffuse and so confusing, and often very hard to document that it overwhelms physicians, and their response is often that this is psychiatric in origin. You have all heard that.

The second important emphasis—and I think equally important—is that these symptoms may come from something other than a dioxin exposure. There must be the aggressive search for other causes. Diabetes, chronic liver disease, et cetera.

After excluding other causes, it is important to attempt as much as possible to document the subjective symptoms. In depth work I think is clearly indicated when a patient has specific symptomology, but I would not put a patient through a battery of tests without the symptomology. And that is when people come in complaining of numbness, tingling, difficulty holding pencils, clumsiness of the hands, a full indepth and peripheral neuropathic studies are certainly indicated. If those are not the presenting symptoms, it is not worthwhile as far as I am concerned to send everbody through these tests.

Further, I believe it is not worthwhile to send people through a variety of tests that have not been proven or well suggested by the literature as being associated with dioxin intoxication, unless you are participating in a study. Such things as C.T. scanning I do not feel is indicated in patients with neuropsychiatric complaints or peripheral neuropathic complaints.

Now, as far as the history is concerned, a clinician must get a clear impression of the ex-

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posure. the frequency of exposure. the source of exposure. For exposures in Vietnam this is hard to get, but it must be emphasized and documented as much as possible.

A good internal medicine physical evaluation is needed and laboratory testing including urine, and blood, tests to assess liver, kidney, cardiac, gastrointestinal, neurologic, and pulmonary systems. More indepth testing, once again is indicated only when history and physical examination make it likely to be helpful. Sperm analysis and chromosomal studies: To this time, that has not been documented in the literature that male exposure will cause reproductive problems. To justify this testing for males a history of spontaneous abortions in female partners and or congenital abnormalities in children should exist. Exposure of female is clearly associated with reproductive problems though the mechanism for this effect is not clearly defined and therefore investigators in this area are primarily to define if any other abnormality exists.

Urinary porphyrins: Due to presistant reports of liver abnormalities in the literature, I believe quantitative uro and corprophyrins should be part of a basic work up. Fat and blood samples for TCDD levels: These are quite expensive, between $530 and $1,000 a sample. I think blood TCDD level are well worthwhile in any acute intoxication and that's anybody that's been exposed to TCDD in the last several months. TCDD may be stored in the fat. But there is some controversy about this. Therefore fat levels may be helpful as well. It should be added that there are not firmly established normal background TCDD levels in the body. Therefore results of these tests may be hard to interpret. The laboratory must be able to identify the 2, 3, 7, 8, tetrachlorodibenzoparadioxin because there are many other less toxic dioxins.

Now, what about the Vietnam veteran with exposure 11-15 years ago. I would think that ese studies are advantageous if one highly suspects the diagnosis of TCDD intoxication. But it nust be pointed out that the results are hard to interpret.

But I most certainly recommend getting that on somebody that is highly suspected to be intoxicated, because if it comes back as 200 parts per trillion or 300 parts per trillion in the fat, that vill support your overall clinical impression. We are currently working on a conceptual approach to the diagnosis of TCDD intoxication at the Division of Occupational Medicine at Cook County Hospital. We are trying to define exactly what constellation of symptoms and signs indicates TCDD intoxication. And as with any other occupational or environmental exposures, the diagnosis is based on the three leg stool of a history of exposure, a physical examination that is consistent with that history, and laboratory tests supportive of it. Due to difficulty in defining exposures and lack of an established syndrome of TCDD intoxication it is harder in this situation to make that stool stand up.

We are using a point approach, that puts together points to give relative weights to arious signs, symptoms, history, and laboratory tests as based upon our analysis of the literature nd clinical experience. Above 15 points, we consider definite intoxication. Ten to fifteen, probable intoxication and six to ten possible. Below six we are unable to assess the relationship.

With respect to the history, the most important part of the history, if you can get a definite history of exposure by a known quantity of TCDD. Fewer points are given to a history of exposure to a substance with a definite presence, but unknown amount to TCDD. And then we me down to the bottom, a history of possible exposure to a substance with TCDD present. As u know, this last category is where we at for most of the veterans. If this is put together with ultiple signs and symptoms, we feel that you can make a probable or possible diagnosis of

TCDD intoxication, even ten years later.

In the area of physical findings: Acne beginning within three months of exposure and no prior history of acne is very important. Acne beginning within six months of exposure and no prior history also has some significant weight. Acne beginning within six months of exposure with a prior history of acne within the last ten years without a prior history has less weight. This is the approach that we take to try to differentiate acne from chloracne.

Hepatitis occurring within three months after exposure we think is very important. Porphyria cutanea tarda occuring within three months of exposure is also very important.

Chronic heptatic porphyria, that is a derangement of porphyrin metabolism within three months of exposure we think is also important. But from the literature, less well associated.

Peripheral neuropathy, once again is important, especially within three months of exposure. The acute neuropsychiatric disorder once again right after a significant exposure and possibly even developing chronically is given weight as well.

Soft tissue sarcoma, as rare as it is, and as definitive as the association is becoming today, we think is also quite important.

I would call to your attention that in the literature, the development of the soft tissue sarcoma takes place usually between 14 and 28 years after exposure. So be very cautious on interpreting negative studies about the lack of that cancer when there is only a ten-year followup on the patients. We see a lot of negative studies in the literature today. Most of them are either based on too few people or too short a time of observation. The lymphomas and the gastric carcinomas are given less weight.

We believe that a carcinogen in one organ system will probably be a carcinogen of another organ system if it is delivered to that organ system at sufficient quanitity at the right time. Therefore, we believe the development of cancer in other organ systems may also be found due to exposure of TCDD. And certainly, that's been found in animals.

Now, with respect to the teratogenic effects, spontaneous abortions in females exposed have been clearly defined in animals. The question of whether congential defects in offspring of exposed male or female without other probable etiology is due to TCDD is a point of considerable controversy.

Going to the laboratory tests, once again we place a lot of value on high levels of TCDD in fat or blood. The nerve conduction velocities are important as well. If liver enzymes, are elevated within three or four months this is given a lot of weight. Elevated cholesterol and triglycerides are perhaps the most sensitive abnormality. .

Elevated uroporphyrins in the urine, is also given some weight.

And finally, the increased frequency of breaks and gaps in chromosomal analysis, which was noted in one study after the Seveso accident; we think should be in the hopper here, as well.

Therefore, I bring to you more confusion, today, I'm afraid, because I believe that this issue is not well defined as yet. I bring to you a feeling that we are continuing to struggle with this problem. But I don't have the magic key, and I don't think it exists yet. Thank you.

(Applause.)

MR. O'CONNELL: Thank you, Dr. Orris. Our final guest speaker for this afternoon is Dr. George Anderson, who is the director of the Texas Veterans' Agent Orange Assistance Program. Dr. Anderson is a graduate of Harvard University with a master's degree in public health.

He is also a graudate of Yale's School of Medicine. After serving for 24 years as a physician in the United States Air Force, Dr. Anderson began a distinguished career with the Texas Department of Health, where he has served in several capacities, and is currently the department consultant for occupational medicine and toxicology.

Please welcome from the state of Texas Dr. George Anderson.

(Applause.)

DR. ANDERSON: I'm going to change the protocol a little bit here. I brought a hundred and twenty five of these handouts. But each of you should have one of each because I'm going to speak from them and then explain them to you as we go along. I want to give you a bit of a run-down on our program as it involves the legislature in the state of Texas, back in the spring of 1981. Our veterans became quite concerned beginning in the late 70's as the situation became known. So our legislature in '81 passed into a law a program which they gave to the Texas Department of Health as the administrative agency to develop a coordinated program with the University of Texas systems, which contained five medical centers, to look at the problem and to see what should be done.

The law has been amended. The last legislature in the spring added an advisory committee to the program and expanded the types of studies which the University of Texas Health Science Centers are attempting to carry out. Our legislature meets only once every two years for a short period, and then they give us our money for a biennium. So we live in a political-free environment for periods of almost two years at a time, which makes it nice getting the job done.

They gave us a half a million dollars for the first biennium, which we spent most of. And they gave us $588,000 for the second biennium to carry out the program for another two years. So we are now in our third year of the program. The first year of the program was a windup, to get started, locate the veterans, the outreach, develop the protocols by the university system, and get the administrative backup set up, which brings me to a statement. Everybody needs something to carry home with them. Know your strengths and weaknesses, both in your program and in your resources. Study and develop your program and keep the tenets of epidemiology in mind. I am basically an occupational physician. However, I function more as an epidemiologist than anything else because when you deal with this type of thing, you are dealing with people and problems.

The tenets that we developed were first—the nature and the extent of the exposure must be documented. We went to the literature and we know that Agent Orange was used in Vietnam. You have to just get that basic in your thinking in the beginning. Secondly, the exposed population must be precisely defined. Third, the disease and dysfunction in the exposed population must be diagnosed as well as possible. And the relationship between exposure and disease must be evaluated with rigorous statistical methodology in which a patient gives a response relationship, and that's a tough one. I don't know if we will ever get there. But what you have been listening to today is the type of background that we have looked at, or we are looking for. It's what those of us face who are in the middle of the problem dealing with the veteran on a daily basis with his problems in the evaluation process.

All that you have heard today fits. We don't want to lose any of this. The research practicality of the physical examination, we can argue back and forth for the good, the bad, the so forth. But we have to remember our goal is all the same. We are after the facts. We are after the truth.

Now, I would direct your attention to the pilot studies. These were developed about two and a half years ago at the University of Texas and were approved by their independent research councils. They were not developed by the Texas Department of Health. They were developed by the scientific staffs of the University. At that time they had reviewed the literature and decided that they would come up with six protocols. I will tell you as we go along what has happened to each of these protocols.

First, of course, is the mortality study. In the Department of Health, we have the vital statistic tapes for the state. The death certificates are filed. We had a marker on our death certificates. We ran the tapes through the computer and we can identify Vietnam veterans only up through 1979, because at that point in time, the death certificate identifiers were changed. And since that time, the front of our certificate only says whether they were or were not a veteran. It must be turned over and then it's up to the coroner or the physician to fill out as to a veteran of what; World War II, Korea, whatever it is. And in many cases, it's not filled in at all. So we find a combination of lack of data and in some cases misinformation.

For instance, many of the veterans when they died; we noticed that they were 60 years old. We say, well, he is probably World War II. Then again, he could have been Korea. He's probably not Vietnam, but he could be.

We had many who had been in all three or in two. And—say back in 1975, they would only list World War II. But then when we go through, we actually find out that he was in Vietnam; he was a career man. So the statistics fell through. We finally realized that we could not get a good identifier. Then those that we did identify, we broke out the cause of death. And what did we find? We found that they were dying from exactly the same things that their age group at that point in time was dying from. The first thing that the Vietnam veteran did when he got back from Vietnam was go out and get himself a high-powered sports car, fill it up with gasoline, get out on Interstate 10, and he would be killed just like anybody else in his age group.

So we looked at our homicides and our suicides and we found that we could not find a significant difference in looking at the normal cause of death in that age group. So we dropped our morality study hoping that the Feds in their mortality study would be able to pick up where we left off and do a much better job with it.

The second study evaluated birth defects in offspring. This is a study that is at Southwest Medical School in Dallas. Dr. Friedman is heading that one. We had an ongoing birth defect program in the State of Texas in which all children with birth defects in the State of Texas are registered. So it's a retrospective study in which Dr. Friedman can go back and check with the father and check out whether or not he is a Vietnam veteran. This one has been moving along rather slowly. I believe to date we have only found six in which we have a positive relationship. Psychogenetic testing, of course, is looking for chromosome breaks. There is a lot of conjecture whether or not this is going to show much. But our people felt that since they had excellent capability at the M.D. Anderson Hospital in Houston that they would go into this. And to date I believe 44 of our veterans have had their lymphocytes characterized.

The fourth study was the effect on sperm. This is being done at the Medical Branch in Galveston under Dr. Legator. The sperm samples are sent there by federal express. He cannot do a motility study because of the distance they have to travel and the time involved. However, they are doing a morphology study. And they are looking for bodies. We have not yet taken any of the

reports of these studies and broken them out by breaking the code. With every veteran that goes into the study, we do have a match control. And I want to cover that a little bit later.

The immune evaluation of veterans is a rather comprehensive immune profile. I believe we are doing some 15 different procedures in our profile. The fat tissue analysis we have virtually droppped out of our program. We found early that no surgeon would go into a belly and take out any fat, particularly since our people wanted 60 grams, without a very good reason to go in.

And we were told that if we have a veteran in which he has chromosome breaks, a compromised immune system, and a history of the proper symptoms, and he has a very definite exposure, then they might think about going in and getting fat. Of course, the other question is how would you ever find a control.

Now, we do have a double-blind study. The individuals at the University of Texas where the samples are sent do not know who the veterans are from the controls. We had a distance and time problem in Texas. They wanted the samples within 24 hours. And I can tell you to get from up in the Panhandle down to Galveston in 24 hours even with federal express it's tough. But we did put out a contract with them and we have to date 44 veterans who have been tested. The laboratory results are back on my desk. I have not yet broken the code to separate them out. We are not planning on doing that for some time yet because we don't think we have enough. We don't want to compromise the studies at all until we are at a certain point in time.

We draw five vials of blood on each veteran and get a sperm sample. And this, of course, is sent by federal express to the three separate laboratories; two in Houston and one in Galveston. We do three sperm studies; that means three samples six weeks apart. And this is running into a lot of money. It's $23 every time we ship a sample. It's $15 to get the sample drawn. We usually bet this done through either a local health department or clinic or physician, anybody who has the capability of drawing blood.

Now, you can see, I think, in the short descriptions of each of the protocols that are attached. I didn't bring the total protocols because each one is about 25 to 30 pages thick. I bring your attention to how the veterans come into our program. He must be referred in with a medical diagnosis. The law was changed in the last legislature. A veteran may refer himself directly into the program now, and then we will follow it up with a medical diagnosis. We like to have both the veteran's symptoms as he sees it, his presenting symptoms, and then what a doctor says. We also like to have and get the Veterans' Administration Agent Orange physical. To date, in Texas 4,500 have. We have 470 in our program so far. All but I think five or six have had the physical. I'd like to get the Agent Orange physical for a very good reason. It does give me additional information when I review medical records. Now, if you will look at the listing of how they come into our program. As soon as the veteran's referred in—we send him a questionnaire which is a five-page questionnaire, which he fills out and sends back to us. We review it, and then we send to him authorization forms for release of medical records. And we go back and get medical records from the—both military Veterans Administration records as well as all civilian medical records that he has had over the last ten, fifteen, twenty years.

We then review these records as they come in. And that's where I spend most of my time is going over them. Last week when we got medical records in on one of our veterans, I put a ruler alongside of them, and they were nine inches thick, just the medical records that had accum-

mulated on him.

Now, once we have this, we also get his military personnel records along with his military records. I review his personnel records to verify where he was at in time, the unit he belonged to. And with this information I've gathered, I can usually spot where his unit was at any point in time in Vietnam. So that if he says he was with the 9th Infantry, 4th Battalion Company D, I know he was with the 25th Division up near Tay Nihn in 1967, which was very helpful.

Also, I have an advantage that many don't have as I can pick up the phone and ask any of these veterans a question concerning his unit. And if he says that he was sprayed on or that if he was in a certain area at a certain time, and this and that happened, I sit down and talk it over with him. I want to get a vivid description of what the airplane looked like, how the spraying went, the speed it was going, the direction it was going that day, because I have the tapes which I am working with at the same time along with this to determine whether or not he was within the spray pattern or close to it. And in some cases, I even came so close that Mr. Christian, of course, who heads the Army's Task Force on Agent Orange—couldn't believe, but one of my veterans took a picture of a C-123—actually two of them in the picture, flying down the road spraying trucks and vehicles on that road with Americans in them. I was able to give the mission number, the date, the direction of flight of that aircraft, and the unit, the engineering company he belonged to and took that back to the Army and said, "How do you like that?"

(Laughter)

DR. ANDERSON: So things can be done. We can get pretty close. We can get down to where we may be able some day to get an estimate of what the dose was on some of these fellows. Now, on that guy we may be able because I think we can work out the batch number of the Agent Orange that was sprayed that day. We are getting a little bit closer.

So after I had gone that far, we keep on getting all the records we can. And then I work out an exposure index in which I haven't put into numbers. It's only high, medium, or probable, or probably possible, and maybe, or something like that. I take all this to the University of Texas, and I sit with the selection committee of the researchers who are doing the work. And I mean they are the ones that are really doing the work. They are going to produce the information.

We select out veterans. Now, we don't select in, we select out. If a veteran says he came back from Vietnam and has been exposed, we select him out. He cannot be a candidate in our program for studying if he has been working in agriculture and he has been exposed to pesticides, he is selected out. We finally narrow it down to those that we have determined have a high probability of exposure with their unit and time when they were over there. And he has not since that time had any exposure or anything that would compromise the test that we want to give him. Then we look at his signs and symptoms. If he has a history of acne or in some cases maybe even chloracne, in that case, it might make him a better candidate. If he has peripheral neuropathy, it makes him a good candidate. We look at all of signs and symptoms. And then we review the Agent Orange physical. Particularly, we are interested in laboratory findings in some of his hospital admissions. Some of them we go back 15 or 20 years to see if somebody did just happen to do a cholesterol on him at that time. In a few cases, we can find some of the old career types in which they did have some pertinent laboratory work done during that very time period, which may give us a little bit of a base line to compare him currently with that period of time.

Once he has gone through this system and his blood has been drawn, and his sperm has

been analyzed and so forth, what happens next? In the meantime, George, that's me. He is sitting back at the health department. He is collecting data.

I'd like you to take a look at the other handout. Every month I update this, and it shows 405 males in programs I think the other day case number 411 came across my desk. This was as of August 31st. If you take a look at the left-hand column, on page 2 you will see the age distributions. I don't think anyone in this room would disagree with the fact that this is what you would expect to be the age distribution of Vietnam veterans; ranging from 29 to 62. And it has the proper distribution. So I think we are in line. So what I am saying is our base line statistics, data that we are accummulating as we go along, is fitting the proper patters, which is a very important item in an epidemiological type of study.

By sex—and I hate to have to say this—but the girls just aren't coming into our program. We only have two. They are both nurses, and neither of them has been selected for our study for other reasons, based primarily on their medical problems themselves. They just didn't fit the pattern.

By race, we have the proper distribution, white, black, and hispanic. This falls within what we would expect in the state of Texas. By service, it again falls in line.

Now, some people may argue that the Army and the Marines perhaps had a heavier exposure as ground troops. But we must remember to take into consideration the Air Force Ranch Handers, and those Air Force personnel that worked with the C-123 and handled the drums of Agent Orange. So the distribution from a service point of view can be looked at several ways. It depends pretty much what service you were in as to how you look at it. We have in our study three of the Ranch Handers who were in the Air Force study. I can assure you that at least two of them have heavy exposure. The second page as you can see is by county. That is in there because the legislators in our state wanted to know how many from my county, where I am from, are in the program.

So we put that in. We have ten veterans in our program who are deceased. About half of these—and don't quote me exactly on that number—have died since they came into the program during the last year. Most of them, of course, have died from cancer. One was a heart attack, but cancer is the leading cause.

We had six reported into the program who are not eligible: these are out-of-staters. The way the law is written, you must have entered the service from the state of Texas or been a resident in the state of Texas on the 31st of March, 1981. So a few are not eligible. We have five who are residing in other states and that gives us a problem if we would like to bring them into our studies because of logistics.

The next on page 3 is the duty performed by the individual. I didn't break this out by service. We just took what the veteran himself said, "This is what I did when I was over there," on the questionnaire. You can see that it has fallen into several groups. Air Crew 23, which includes helicopter crews as well as Air Force crews; also several Marine pilots and others, thirteen were artillery men. Communications specialists, twelve. I'm just reading the larger numbers. Infantry, 133. Mechanics, ten. Anywhere you wen in Vietnam there were vehicles, so you would expect to have a large number of mechanics in every unit. You notice we just had two nurses. It's hard to decide sometimes when he says I was a finance specialist where he really was. He could have been closer to the jungle than somebody else.

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Turn to page four. What is he doing today? And it's interesting. If you move on down to disabled, medically unemployed, 37. And then we have another over here on the next page, which is I believe unemployed, 30. Now, these are separate. We separate them out. 37 are not working because they cannot work for medical reasons. And most of them are veterans who are already on some form of a pension. We have 33—and I think by now we probably have 34 veterans who are over in Huntsville (state prison) serving time. When they come into the program, we contact the authorities and we get their medical history and their physical from the institution and that's a fairly current one in some cases. Some have been there a number of years, and they give them periodic physicals. So you can get a good idea of what their current physical condition is. They are a group where we always know where they are. You don't have any trouble finding these fellows. Now, we have had two released in the last two or three months. We do have a problem with them in getting controls. For some reason or other, it's difficult to find a control for an inmate. And we don't want to use other inmates. I can't think of any good reason why not. But the researchers in the university do not want to use other inmates.

You notice there are six lawmen, most of these are policemen. They were military police when they were in the service.

Now, of the total of 407, 89 had reported that their wives or girlfriends had had miscarriage or stillbirths sometime since Vietnam, after their return. And those reporting children with birth defects or medical problems present since birth, 90. We have not gotten a good handle on this one yet as to what these birth defects really are because the study in Dallas has not moved ahead as rapidly as the other three studies. But we will be looking into that one. Symptoms or initial complaint as reported by the veterans as they came into the program on page 6. You go down through here and you will find essentially what you have been seeing on the screen all day. And you will see them pretty much in the same proportions as you have been seeing them on the screen. You will see the high percentage of depressions. You will see the problems coming out, 21 with cancer, and 19 with birth defects. We will look later at a listing with the physician's diagnosis. These are what they reported as the primary reason for coming in the program. This was their problem. Some hair loss, I didn't pay much attention to that; your secondary was more important. Headaches, 23 as the presenting symptom. Nerve problems, 19. Numbness, 31.

We did separate those out and put them together. We realize that these were probably many of them, the same thing. Rash, 89, which means about a third of those in the program—more like about a fifth or a quarter have rashes. They have that rash as their presenting symptoms today. Tingling in the extremities which goes back to the neuropathies again, nine.

In the next page, of course, we get to the diagnoses as reported by the physicians who referred them into the program. And we began to find things that aren't showing up as a presenting symptom. The veteran will say that he has one thing, and the physician will diagnose something else. Many times they are the same sometimes not. And that's a much longer list because the physicians have an ability, just due to vocabulary, to make a much longer list. So the numbers don't become quite as pronounced. But you will notice as you go through, there are a number of cancers. And this is one we are really going to have to look at. And then as you look at the types of cancers, adenocarcinomas of the colon, basal cells, diffuse bilateral adenocarcinomas metastasis, giant-celled tumors of the bone, Hodgkin's disease which is an interesting one to be in here. In the larynx, melanomas, two of them.

We anticipate a high instance of melanomas in certain ethnic groups, of course, in Texas. We have a large population of northern Europeans. We also expect a high amount of skin cancer due to

being a Sun Belt state. We always have to take this into consideration as a confounding factor. Convulsive disorders. Three cases of physicians who actually said this man had chloracne, which seems to me as a bit of a surprise because those of us who were physicians back in those Vietnam days didn't really have chloracne in our vocabulary. We knew what acne was, but that was about it. Depression with anxiety, ten, confirmed by physicians. Depressive neurosis. For instance, we didn't even put diabetes, and diabetes mellitus together because we used the actual diagnosis of the doctor. Diabetes mellitus, seven. Now, this can be when it is confounded with other symptoms. Hypertension, 13. I think we can expect that in number of veterans because of the age group we are dealing with. I probably want to take a little time later and go down through and match these up with some of your experiences, particularly those up here to see if the patterns that we are looking for of signs and symptoms are starting to evolve. Notice numbness in the extremities, 14. Just in that alone. Numbness, ulner aspect, upper extremity, one.

I have not attempted as of yet to break these out and put them into proper categories so that we can say these are various symptoms or these are all skin conditions of these are all cancers. It's raw data. And no attempt at this point has been made to analyze it. We will be doing that shortly. I have to let you know that my new computer is just arriving, and they are setting it up, and we'll be ready to start putting this into our computer. Then we will bring the laboratory data from the University of Texas, and we will start the matching program, breaking the code, and see what it begins to tell us.

Ten paranoid schizophrenics. And two more effective types of schizoid-type disorders. These fellows, most of them have had periods of time in the state hospital. They are true schizophrenics. There is no doubt about it. And one of them came in the other day and I saw him. He had some queer ideas, but I enjoyed talking to him. He remembered everything that happened. The only thing was, he just couldn't put things in a proper time. And they were still after him. There was no doubt about that. And he was all right. I had one call the other day, he said I am in jail. What can you do for me? I just killed a guy down in the bar. It looks like I'm going to get a little time. This is the way of life when you are dealing at the grass roots level with the veterans and their problems on a daily basis. They come into the program, and we become another part of their medical care system. They look to us for help. And the law as written in the state of Texas says that we will assist the veterans by referring them to agencies for assistance; medically, financially, in any way that we can to assist them. Which means that if necessary, I will end up in court testifying in his behalf if necessary, based on the medical records that we have developed in support of what his problem is. To date, I don't think we have anything which we can carry into a courtroom and say that we can relate this to his exposure to Agent Orange. But we are building up to the point that we hope the day will come when we can start to bring the medical evidence in and the data in and put it together and start to make some sense out of this whole problem.

On page 11 you might find it of interest, we were asked by the University of Texas to break out the types of cancer in the veterans. And they wanted those who were over age 36 and those under. Here we have case numbers. We have their age at the time they were diagnosed. And you will notice with the asterisk that a number of these individuals were treated in Veteran's Administration hospitals.

I have not yet been able to identify those cases that would be called a soft tissue sarcoma or a lymphoma. We are only dealing with a small number, four hundred and some. We are dealing with sarcomas which is something that is very rare, and it may not have shown up. Perhaps if our program

goes to where we are up into the thousands, we may well find one. But a number have already died. I hate to have to say that. It happens. You can't save them all.

On page 12 children with leg deformities. This is something that our cancer center in the Anderson Hospital asked us to have these listed hoping that we might be able to find some connections or at least have an incidence of how many among veterans there are. 62 of our veterans have current rashes today. Last Wednesday, one of the veterans was in my office, and he was covered with a rash over his shoulders and his back and down his arms, which would be very suspicious. I am not a dermatologist, and I would not attempt to really diagnose chloracne, but he does have an extensive rash.

And the number of cases with tingling and numbness in the extremities—it's interesting to take a look at the year that they state that this started. The diagnoses of these cases, most of them are rather recent. Some do go back to the time of Vietnam or the time they first came back. However, these are only those that have been diagnosed and confirmed by physicians. 101 veterans have the complaint. So we are always left in that bit of a dilemma between the veterans' and the physician's diagnosis. And it takes us time to get it confirmed.

On page 13 miscarriage and stillbirth. We have to take into consideration here what happened to the veteran as he came back from Vietnam. The first thought in his mind was I want to get married and have a bunch of kids. And you will note that there were a number that had the problem, or their wives had the problem. But it is pretty much throughout that whole time period of the '70's up into the early '80's. I wish I could give you a further insight into what this means. But it's going to require some analysis before that can possibly be done.

On page 14 we get into the schizophrenics. Now, these are substantiated by medical records and competent diagnoses by physicians, psychiatrists. Look at the list of them. Now, does this mean that we have a problem of mental illness related to the veteran who served in Vietnam? Or does this mean that this is the kind of program that the schizophrenic likes? And he is going to come into it. Or is it that he has such a problem, and the physicians know about it; they have heard about this program and referred him in. We haven't been able to determine this yet. But we are going to have to answer these questions because in a program such as this in which it is self-selected individuals, we are always criticized by our peers when they review the data. First thing they say, "is it a self-selected study?" Okay, it's not going to hold too much water. Your controls. Well, there is a problem there. You've got incomplete data here. There is a problem there. Anybody that goes in a study like this is going to have to have a thick skin and know how to ride through it because it's not a clean, straightforward-type of study. It's a very complex study with incomplete information on which you base judgments. So it become a judgment evaluation in many cases as to the direction you are going as you move along. And I'm sure that the gentlemen at the table up here can agree with me that this is exactly the way it is. This is the real world.

On page 15 then we took medical conditions that they listed which were not their primary presenting symptoms, and you can see that although some of them listed one, a lot of other things began to show up as a secondary. Some of them in large numbers. Gastrointestinal disorders, which didn't show up as a primary symptom, but as a secondary symptom. 140 said they had gastrointestinal problems. 127 have emotional problems. 137 have headaches as a secondary, which means we are getting up in the high percentage of the totals, which began to fit the pattern on what you saw on the screen today.

140 nerve problems, with 68 separate out from that as just numbness. I want to give this to you to give you some insight as to the type of data which is collected as the program evolves, and the information begins to pile up.

We really came into existence in September of 1981. It took us about six months to get wound up to get everything going. The average time that it take us to get the medical records together, or I guess the case file you have to call it, because it contains more than medical records; ranges from three months if you are lucky to at least a year. In fact, we are still working and getting records together on cases which are well over a year old, but we don't give up. We keep right on going trying to get them.

I thank you very much for listening to me so attentively. I didn't prepare it in a logical manner. I just gave it to you as I see it. Thank you very much.

(Applause.)

MR. O'CONNELL: Thank you, Dr. Anderson. At this time why don't we entertain some questions of the panel.

DR. CARLSON: You mentioned that it's very difficult to get a control for a fat analysis. But many people carry an organ donor card. For instance, when a person has an organ donor card it could be modified to say for organ donation or for pathological examination, because then you would have autopsy material available from accidents for analysis to control tissues.

DR. ANDERSON: There is no reason. Now, just out of interest, we do have one fat biopsy, autopsy specimen, which was collected on a Navy man that died from cancer. Unfortunately, we collected it they put it in the deep freeze in Galveston. I went through and did an exposure index on him, and I cannot validate his exposure. There is no way I can do it. He was in the wrong place at the wrong time or the right place at the wrong time, whatever which you want to put it. But I cannot say that this man had exposure, even probable exposure.

DR. CARLSON: One other question I wanted to ask on the cytogenetic analysis. There has been a recent technique. It's about a year old or so, in which sperm can be used to fertilize hamsters. And the sperm fertilizes the hamster egg, but it eventually aborts. But the male chromosomes can the be studied. This technique yields beautiful male chromosomes obtained directly from the sperm. Since there seem to be so many testicular problems that have been identified with the herbicide exposure syndrome, this may be a very usable system to use.

DR. ANDERSON: I will mention that when I get back.

MR. O'CONNELL: A question back there.

A VOICE: I have a question for Dr. Codario of Philadephia concerning the central nervous system. The ventromedial nucleus of the hypothalamus. When you have a tumor, it's been known as occasions to come along there, not quite so rare, but every so often. I don't know the exact numbers. But this causes very aggressive behavior if I am not mistaken, and also, I believe, if I remember correctly, an insatiable desire for eating or drinking that you just can't seem to stop it.

The question is: Does the TCDD—could that possibly have an effect on the Vietnam vets, and could that explain something as far as their aggressive behaviors?

DR. CODARIO: What you are talking about is what we call satiety center. If you review the literature on all the animals, there are not any case reports of central nervous system tumors occurring in animals exposed to TCDD. All the literature deals with the association of pyramidal tract disease, demyelinization in the area of the pyramidal tract in animals. There is one reported cause of neural tube defects in animals that hasn't been substantiated scientifically to occur in humans. But we do not

have any model to draw from in any of the animals in central nervous system tumors. Based on what we know about TCDD, just giving you an opinion, it would be difficult to say that a Vietnam veteran that had an abnormality in the satiety center that might be related to TCDD. It would be almost impossible to say because looking in the literature, the only thing that's reported in animals is demyelination in the central nervous system and in the peripheral areas. And so if an individual developed central nervous system disorders—and this is a clustering in Vietnam veterans. We can't make that assumption scientifically.

A VOICE: I have a question for Dr. Orris. I'm very concerned about the diagnosis for chloracne. In the various class action lawsuits, they have defined the various types of health effects that they feel are a result of their exposure to the dioxin. And they have listed 11 various effects of chloracne.

Can anyone give me any understanding of that?

DR. ORRIS: Well, I'm also not a dermatologist. And that's the critical expertise that you need with respect to chloracne. But it's our understanding from consulting the dermatologists that chloracne is diagnosed on the basis of the distribution—the history of exposure and the characteristic physical skin findings. If you just take one of those—and that is skin findings, even if you go to biopsy, it cannot to our understanding realiably be differentiated from vulgaris. There are several experts in the country with respect to occupational determatitis that could be solicited with respect to that. Dr. Adams in California, Dr. Birmingham in Michigan, Dr. Suskin in Cincinnatti.

A VOICE: I have the Skin Diseases in Vietnam from '65 through '72, Volume of Military Medicine. And they state that the most common illness in veterans in Vietnam was, in fact, skin lesions. And they did an epidemiological study on one of the units. And one of the findings—one of the men is in El Paso, Texas. And they list all the various types of skin disorders that Vietnam veterans manifested. And chloracne was the highest. I'm just trying to get this straight in my mind. If a veteran had no predisposition of any acne throughout his lifetime, and he leaves Vietnam with chloracne, I'm trying to find out how we can discern if it was tropical acne or various other types of acne.

DR. ORRIS: The history of exposure was there. If he developed it following that exposure, and if it is in a distribution that is characteristic of chloracne, and typical for chloracne vulgaris. We would be quite happy with the diagnosis of chloracne in that situation. And we have seen people who have chloracne who we believe got it from Vietnam when they were exposed.

A VOICE: I have several veterans in our organization that have been diagnosed by seven different dermatologists that it was chloracne. But the VA denies his claim.

DR. CODARIO: Just as a point in elaborating the term chloracne, it was coined in 1898. It was felt—it was a condition that resulted from chlorine gas. It was only later in the late '50's that we began realizing that there were a number of chemicals that caused this type of eruption. At the last international symposium on dioxin and related chemicals in Arlington, Virginia, in 1981; Dr. Kenneth Crowe from London, England, Dr. Renata Kimbrow from the Center for Disease Control in Atlanta, Georgia, presented two separate symposiums on chloracne in which they went into detail about discussing the pathological findings that we see in acne vulgaris and we see in chloracne.

And both of them specifically made the points, and this is of record in the International Symposium in Arlington, that there is a difference between acne vulgaris pathologically and chloracne. As true as Dr. Orris says, there are distributions that we sometimes see. These distributions are in the eyelid and in the groin. Those are the areas at which chloracne tends to occur, as opposed to acne

vulgaris. The point is, that if you lined up ten individuals and looked at their skin you would have almost an impossible task differentiating chloracne from acne vulgaris.

A skin biopsy may also have a hard time differentiating. And that may be because the individual has chloracne and acne vulgaris. And in the biopsy, you see bacteria and the same information you see in the dermis. But strictly speaking, there are criteria that are used for pathological differentiation of chloracne by skin biopsy. And these are quite accurate in the criteria that I mentioned. Many of the Vietnam veterans might be very difficult to diagnose after all these years. But certainly, if there is any debate, the skin biopsy may be rather valuable in that determination.

A VOICE: As far as for disabled veterans, what resources have we or do we have or what we could do to get our children checked, because at this time the Veterans' Adminstration will not handle it.

DR. CODARIO: Well, I think the saddest part of the entire Agent Orange story are the children of the Vietnam veterans, because we just have very little information other than just guesswork as to what's going on with the children. We are just going to look at the veterans themselves and as I alluded to in my earlier discussion, we are just beginning to unravel the mystery of the genetic code.

And right now, if you take your children to any geneticist anywhere, he is going to be hard-pressed to give you an opinion as to whether or not the findings that you are seeking in your kids, be they frequent infections, learning disabilities, loss of an arm, heart murmur, heart defect, there is nobody on this planet that's going to be able to tell you yes, John Smith, your child has that learning disability because you were exposed to dioxin in Vietnam.

And part of the reason for that is the scientific inadequacies of the past, and in a large part, in the scientific inadequacies that we have right now in unraveling the mystery of genetics.

A VOICE: I see in my own child what they call cerebral dysfunction disorder, which has a neurological basis. Could that be transmitted let's say as far as—let's say my wife and I made love and as a result of that our daughter was born. Could the Agent Orange that I was exposed to have an effect on the embryo?

DR. CODARIO: That's a problem and very unfortunate one.

MR. O'CONNELL: I might add that we have also with us Dr. Michael O'Grady from the VA in Milwaukee, Wisconsin. I think you indicated that you would be willing to answer any questions of anyone. As to setting up the program format, we felt that it would be productive to have those from the private sector and also our colleagues of the Texas Commission. But VA has been involved in their willingness to answer any questions that we may have of them at this time.

A VOICE: Is your commission planning to do any outreach for the veterans?

DR. ANDERSON: Well, the law—I know why you ask the question—did not include an outreach program in the beginning. In other words, the veterans had to come to us. Now, the legislature due to certain pressures this last time did put into the law an outreach portion by stating that the veterans can now apply directly to the program, which does not preclude our going out and contacting them. And we are now in the process of sending out the VA Agent Orange Registry listing. We got the names and addresses from Washington just about a week ago, and we are in the process now of mailing out 4400 brochures. Now, these are fellows that have already had the VA physical, the Agent Orange physical. Now, beyond that we have already ordered 50,000 brochures which we were going to be putting into the mail. We are working in developing our mailing list, which when you have

153,000 veterans to start with, it's a bunch. But we are working primarily through the veteran's organizations and through the Veterans Affairs Commision hoping that we can reach the rest. And we have two or three very serious problems in Texas in just getting to people. What you send out in English also has to be translated into Spanish. So you have to pick and choose the areas. We also have a lot of sparsely populated areas. We have one county which is just about the size of Rhode Island in which only 67 people live. That leaves you a problem of locating a veteran among those 67. Now, we also have had the additional problem of being one of the Sun Belt states, of having a large immigration of Yankees. Is that what they called them? I was originally a Yankee. I came in and became a Texan. They are ineligible for our program. The law said, 31 March 1981, our population by 1980 will equal that of either Florida or New York. And shortly after that, Texas will be the second most populated state in the country. We are growing that rapidly. Austin, Texas, when I moved there nine years ago has doubled its population just in nine years. Houston is becoming huge. Everybody wants to go south and enjoy the nice weather.

A VOICE: Doctor, are you using any of the data from the VA Registry in Washington for Texans?

DR. ANDERSON: Only the names and addresses to contact the Texans. That's all.

A VOICE: They won't give you any of that data?

DR. ANDERSON: Oh, we have it all, yes.

A VOICE: The name that the VA provided you from the Agent Orange Registry, did you ask for it?

DR. ANDERSON: I asked for it last June, and it arrived a few weeks ago. Now, I can explain that a little better. They have this prepared for any state that would like to go out to get it. It's just a matter of asking for it. And they were in the process of, at that time, getting it through their computers.

A VOICE: Are you trying to get a list of just your names from the State of Texas?

DR. ANDERSON: We have no such registry in the State of Texas because when a veteran comes home from the wars in Texas, his 214 is sent to the Veteran's Affairs Commission. And they immediately send it right on down to the county service officer, who then puts it into a file somewhere. So we have no central Texas file. So if we want to find our veterans, we have to go to each individual service officer by county. And you know how these veterans keep moving around. We are already 15 to 18 years behind the power curve.

A VOICE: Dr. Anderson, now let me say for 100 percent disabled veterans would the VA in the future initiate the program for our children, because of different governmental payments, most doctors will not handle it.

DR. ANDERSON: I am not VA.

A VOICE: Maybe you have some input on that.

DR. ANDERSON: Perhaps the good doctor here could better explain that. But I will answer the last half. The law as it was amended last spring added the children of veterans who allege that they have children born to veterans with birth defects who alleged their problems related to exposure to Agent Orange. Now, it becomes part of our program and they will be referred for evaluation. They were already eligible for assistance in another way. But nobody is going to write them out a blank check.

A VOICE: Doctor, I'd like to add something but in terms of exposure to veterans, we all in

this nation have come to believe that the majority of spraying was done by Operation Ranch Hand. And this has become more or less the bible to us. All I have been privy to see is some of the discovery on the Agent Orange class action lawsuit where the government has turned over 340,000 papers that they have on it. And, in fact, the spraying by this was much more intensive than the Ranch Hand. And perhaps I can tell you that I have discussed this with Mr. Christian, who heads the task force. We were looking at this about a year or so ago as a possibility because several of the veterans had said to me look, I don't know about those Air Force airplanes up there. But those choppers up there were doing a pretty good job of it. Then we have some of the fellows using backpacks and playing games out of spraying each other. But at any rate, there was a lot used in that manner.

And Mr. Christian has assured me that they are now developing some data which will be useful in the determination. And I, of course, have been asking to get this as soon as it's been developed to start to apply it to some of the fellows in our program in which we have been unable to substantiate a good Ranch Hand spray.

But he does give a history of it. This is particularly true with the 9th Infantry Division. They did a lot of their own spraying.

MR. O'CONNELL: I'm going to remind the state commission officials that tomorrow we will be discussing the registry, and hopefully get into the key areas where we can exchange some information on that. I know that we in Illinois are most anxious in getting our questionnaire out.

If there are no more questions, I'd like to announce that there will be approximately a one-hour long movie for anyone who wishes to stay. It is entitled The Secret Agent. It's a historical look at the use of Agent Orange. And anyone who wishes to stay is welcome to do so.

Before these gentlemen leave, I would like to thank both Dr. Orris and Dr. Carlson, and of course Dr. Anderson for the presentations this afternoon. I would like to commend our executive director of the Illinois Agent Orange Commission, Dave Weisbaum, who has put together a very interesting and a very productive session here today. He has been assisted by our secretary, Pat Lamsargis. And the public relations work for this project has been done by Joan Maiman of this commission. I think that we will all agree that the ultimate answer to the question of whether there is a causal relationship between exposure to Agent Orange and the problems that have been surfacing over the past decade, and will likely continue to surface, will be answered by medical research, by the medical expertise that we have at our disposal. We think that today's symposium with the valuable and intelligent discussions that we have had transcribed will go a long way toward that end.

And those of us who represent in the political and governmental spectrum the residents of our respective states can ask no more of us than to do our part to elicit the facts, elicit the evidence that will hopefully quickly arrive at a very definitive answer to the question that we have been asking for a long time.

Do we have something to worry about because we have served in Vietnam? And do our children have something to worry about because we served in Vietnam?

So I want to commend all of you for spending your Saturday—some of you coming long distances to share your day and your contributions with us, and to the overall effort in finding an answer. Those of you who are with the various states and do intend to stay tomorrow, please advise me or Dave Weisbaum so we will have a good idea as to how many to expect tomorrow morn

ing. We will spend approximately three hours exchanging information. I understand there will be a press conference at 1:00 o'clock tomorrow afternoon.

If there are no further questions, I will then thank you all and adjourn the meeting.

(Applause.)

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AMERICAN HEALTH - DIOXIN SYNDROME (JAN. FEB. 1984)

Environmental Toxin

The Dioxin Syndrome

Researchers find contamination effects are overlooked

Dioxin is one of the most potent toxins known, but so far the search for toxic effects has yielded surprisingly little. The reason, says a team of Illinois doctors, is that physicians have looked at the wrong thing.

For 20 years, doctors have considered a sudden eruption of blackheads and acne known as chloracne a hallmark of dioxin contamination. But Drs. Bertram Carnow and Shirley Conibear, of the University of Illinois, say that the eruption occurs only [illegible] of the time. More typically, they find, there's a long list of variable signs and symptoms that add up to the "dioxin syndrome."

They include: general fatigue and weakness, difficulty in holding hands steady, headache, severe headaches starting over the eyes, depression, irritability, memory loss, lack of concentration, stomachlike symptoms and ulcers. And they don't show up until two or more years after exposure to the poison.

The dioxin syndrome has been there all along, say Carnow and Conibear. But because the neurologic symptoms are vague and doctors often write them up to psychological problems. In fact, they [illegible] other organs.

Further, scratch the surface and there may be deeper signs: abnormal levels of porphyrins, a component of red blood cells, enzyme systems, hormones and muscle metabolism; depression of the immune system; and malfunction of fat metabolism leading to extremely high levels of triglycerides and elevated blood cholesterol.

Absence of chloracne does not mean someone escaped the toxic effects of dioxin, Carnow and Conibear say. It just means the victim doesn't have the skin-eruption feature of the syndrome. No more than 15% of those exposed to high concentrations of dioxin develop chloracne.

Carnow, professor and director of the Great Lakes Center for Occupational Safety and Health, and Conibear, an assistant professor of preventive and occupational medicine, have studied some 400 dioxin-exposed patients, 100 of them women and children. The syndrome is not easy to pin down. It takes 14 hours of tests, and costs a whopping $7,000.

Many of these patients, after complaining to no avail for years, have developed psychological problems. But, Carnow says, neurological testing, along with a history of contamination, can get underneath the psychological overlay down to the dioxin-caused physiological dysfunction.

Once the poison is in the system, there's no way known to counteract it. Carnow and Conibear concentrate on trying to protect systems most likely to be affected: the heart, arteries, liver, skin. They prescribe special diets and lifestyle changes. —*G. V.*

CARNOW + CONIBEAR

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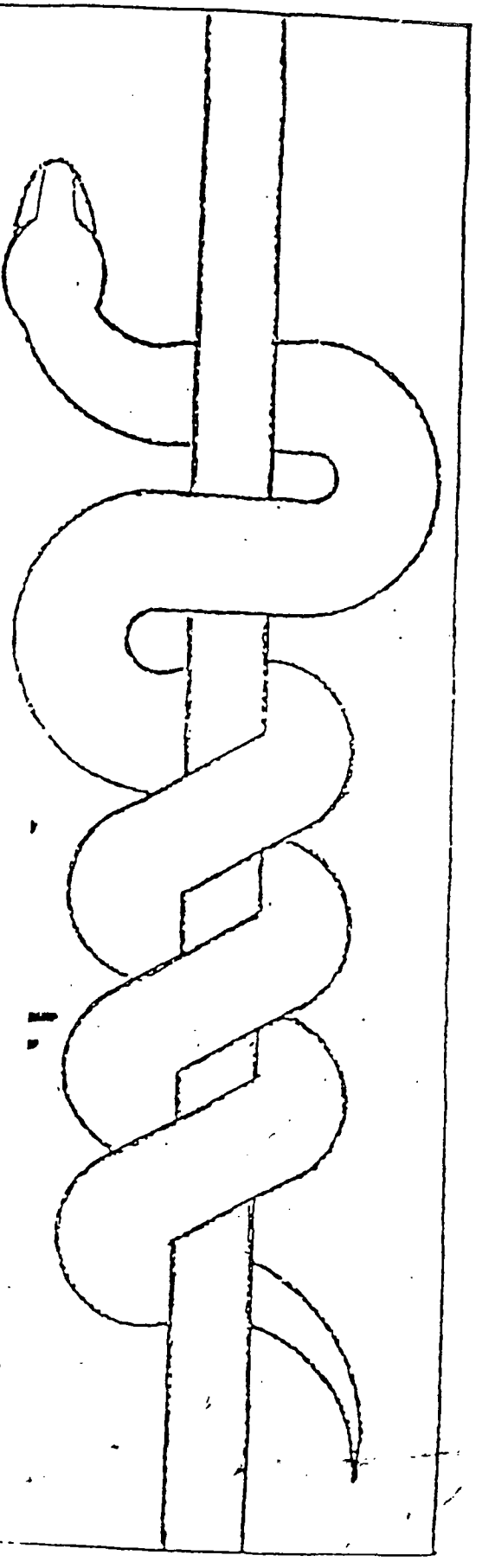

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Environmental Health

Dioxin, an undesirable by-product in the manufacture of herbicides, disinfectants, and other chemicals, is the most toxic of all man-made substances. Compared with the most powerful naturally occurring poisons, it ranks fourth, just below the bacterial toxins responsible for botulism, tetanus, and diphtheria. A portion of Seveso, an Italian town near Milan, has been cordoned off since 1976, when a chemical-plant explosion contaminated the area with dioxin. Recently more than a hundred sites in Missouri have been found or are suspected to have dioxin-contaminated soil. The most publicized of these locations, the small town of Times Beach, has been purchased by the U.S. government, and its citizens offered the option of relocation. Dioxin has also been detected in fish and in river water from Michigan, in other U.S. communities, and in Vietnam. The extraordinary toxicity of this chemical, its high stability, its insolubility in water, and its widespread presence make the problem of protecting people especially serious and difficult.

What is dioxin?

Although the term dioxin has become a popular synonym for one specific dioxin, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, technically it refers to any of a group of chemical compounds called dibenzo-*p*-dioxins. Structurally the dioxins consist of two benzene rings connected by a pair of oxygen atoms. Each of the eight carbon atoms on the rings that are not bonded to oxygen can bind with hydrogen atoms or atoms of other elements. By convention these positions are assigned the numbers 1 through 4 and 6 through 9. The dioxins of greatest concern carry chlorine (Cl) atoms at these positions. Theoretically, 75 possible combinations, called isomers, can be formed by adding one or more chlorine atoms. There are 22 possible arrangements for dibenzo-*p*-dioxins that contain four chlorine atoms; these 22 isomers constitute the family of tetrachlorodibenzo-*p*-dioxins (TCDD's). The most toxic dioxin is a member of this group, with chlorine atoms at the 2, 3, 7, and 8 positions. This isomer, 2,3,7,8-TCDD, is extremely stable chemically even at temperatures as high as 700° C (1,290° F), possibly because of its symmetrical structure. Moreover, this isomer is virtually insoluble in water and in most organic compounds but is soluble in oils. It is this combination of properties that allows dioxin in soil to resist dilution with rainwater and causes it to avidly seek and enter fatty tissue in the body if it is absorbed.

Dioxin serves no useful purpose but is formed as an undesirable by-product during the synthesis of 2,4,5-trichlorophenol and some other useful compounds. For example, if the mixture of reactants used to synthesize 2,4,5-trichlorophenol exceeds 180° C (360° F), an exothermic (heat-generating) reaction occurs, and some dioxin is formed. In fact, many accidental releases of dioxin have resulted from such overheating, producing a runaway explosive reaction. 2,4,5-trichlorophenol serves as a raw material for making the herbicides Silvex and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid). The latter compound is a major active ingredient of Agent Orange, a defoliant formerly used in Vietnam by the U.S. military and in the U.S. on railroad, highway, and power-line rights-of-way and in forested areas to kill unwanted vegetation. 2,4,5-trichlorophenol is also used in the production of hexachlorophene, an antibacterial agent formerly used in deodorants and soaps but banned since 1972. If 2,4,5-trichlorophenol is contaminated with dioxin during manufacture, then dioxin appears in these end products.

When Environmental Protection Agency workers tested the soil in Times Beach, Mo., they found dioxin levels so high that the U.S. government offered to buy the town's 800 homes and relocate its 2,000 frightened residents.

The toxicity of dioxin renders it capable of killing some species of newborn mammals and fish at levels of five parts per trillion (or one ounce in six million tons). Less than two millionths of an ounce will kill a mouse. Its toxic properties are enhanced by the fact that it can pass into the body through all major routes of entry, including the skin (by direct contact), the lungs (by inhaling dust, fumes, or vapors), or through the mouth. Entry through any of these routes contributes to the total body burden. Dioxin may affect the skin upon contact, then enter the blood and move into the fat and fatty tissues of many organs. An autopsy of a resident

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of Seveso who died some months after exposure showed the highest concentrations in fat tissue, with decreasing levels in the pancreas, liver, lungs, kidneys, and brain. In animals dioxin also appears to enter the thymus and the adrenal gland, and it has been found in human breast milk.

What makes dioxin so toxic?

A great deal of scientific information on the mechanisms of dioxin's toxicity has been gathered from numerous studies of laboratory animals and human exposure victims. One productive approach in these studies has been to look at the way in which dioxin enters a cell and what it does once it gets in. Contained in cell membranes are protein molecules, called receptors, that normally function to move substances into the cell. Dioxin avidly binds to these receptors and, as a result, is rapidly transported into the cytoplasm and nucleus of the cell, where it causes changes in cellular processes. Experiments in animals suggest that after entering the cell, dioxin affects tiny protein strands called smooth and rough endoplasmic reticula. These structures participate in the synthesis of a large number of enzymes that, in minute quantities, regulate important chemical reactions in the body, including the production, conversion, and storage of proteins, carbohydrates, and fats. Called mixed-function oxidases, these enzymes are also responsible for the breakdown of some sex hormones, drugs, and other substances, thus enabling their removal from the body.

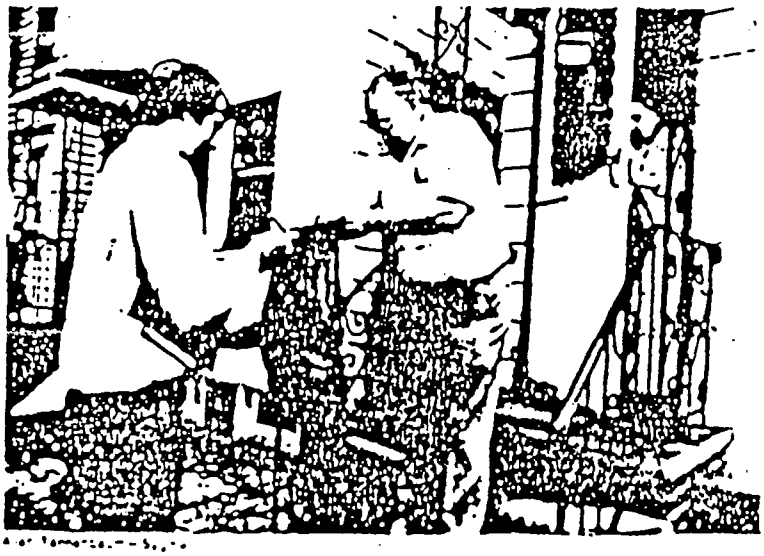
Mixed-function oxidases are produced in many organs of the body, including the liver, skin, kidneys, lungs, and those white blood cells called lymphocytes. They appear only when they are needed and are "turned on" by the presence of various other chemicals called inducers. Dioxin is the most potent enzyme inducer known. It has long been recognized that increased production of some of these enzymes greatly increases the cancer rate in animals exposed to carcinogens. Another potent enzyme inducer, 3-methylcholanthrene (3-MC), has been used for years in cancer research because of its potency as an inducer. Dioxin is 30,000 times more potent an inducer than 3-MC, and its effect is many times longer lasting—further reasons for its extraordinary toxicity. In addition, the presence of chlorine atoms at key locations in dioxin's structure apparently protects it from some of the major biochemical breakdown processes by which the body disposes of toxins.

The flood of enzymes stimulated by dioxin leads to the malfunction of many organs and to the excessive destruction and excretion from the body of certain essential chemicals such as estrogens. On the other hand, chemical building blocks pile up in the body because some basic processes cannot go forward to completion. For example, iron and compounds called porphyrins, both of which are components of hemoglobin, may accumulate in the blood and tissues.

Significance of animal studies

Because information about the direct effects of dioxin on people has been limited primarily to studies of victims of inadvertent exposure, investigators have relied heavily on monkeys, guinea pigs, rats, mice, and other laboratory animals to gain a better idea of what dioxin does to the human body. While results from animals vary somewhat among various species because of differences in enzyme systems or in the degree of enzyme induction, many common effects have been found. These consistencies increase the likelihood that other species, including human beings, may be similarly affected.

In most species, except in cases in which very large doses were administered, the effects of dioxin appeared only after considerable delay, possibly because of the time needed for enzyme induction to occur. In



In the summer of 1983, high levels of dioxin were discoverd in a Newark, N.J., neighborhood near a chemical plant that once produced the deadly herbicide Agent Orange. A local swimming pool was closed because of dioxin contamination, and agents from the EPA went door-to-door collecting household refuse to be analyzed for the possible presence of dioxin.

In 1976 an explosion covered the town of Seveso, Italy, with a toxic dioxin cloud. Today former Seveso residents continue to suffer from a variety of skin disorders.

every species studied, dioxin destroyed testicular tissue and tissue of the thymus gland. In some animals the skin, liver, and kidneys and the endocrine, gastrointestinal, cardiac, and central and peripheral nervous systems were affected. In some animals the immune defense system was suppressed. Birth defects, particularly cleft palate and neural tube abnormalities; embryotoxic effects, including abortion, miscarriage, and resorption of the fetus; and mutagenic effects appeared in a number of species. Many species experienced a striking increase in cancer incidence, particularly when dioxin was administered with chemicals known to be cancer initiators.

That dioxin increases the chances of cancer, birth defects, and genetic mutations in any species is of particular concern. It is often difficult, if not impossible, to determine the least amount of a substance sufficient to cause genetic abnormalities because of the long latent period between exposure and the appearance of disease. Consequently, the question shifts from finding a level of exposure where no one is affected to finding a socially acceptable level. The Centers for Disease Control (CDC) in Atlanta, Ga., has recommended that exposure to dioxin be limited to less than one part per billion, based on an estimate that a group of one million people exposed to this concentration in their lifetimes would experience one excess cancer death.

Human experience with dioxin

Most people known to have been heavily exposed to dioxin have been the victims of industrial mishaps involving the explosion of a reactor vessel or a blown safety valve. Workers in the vicinity at the time of the incident or who came in afterward to clean up were usually exposed for a short time to high concentrations. In the past 30 years more than 200 such episodes have occurred worldwide. The first happened at a Monsanto plant in Nitro, W.Va., in 1949, when 228 workers were reported to have been exposed following an explosion of a reactor vessel.

Other accidents include those in the BASF plant in Ludwigshafen, West Germany, in 1953; the Rhone Poulenc plant in Grenoble, France, in 1956 and again in 1966; and Coalite & Chemical Products Ltd. in Derbyshire, England, in 1968. Another such incident occurred at the Philips-Duphar plant in Amsterdam in 1963. Decontamination was apparently impossible at the BASF and Philips-Duphar plants, which were dismantled, put into ships, taken out into the Atlantic Ocean, and sunk. In another instance a plant was dismantled and buried after more than two years of attempts to remove the dioxin. Later a large stainless steel vat salvaged from that plant was installed at a new site over a three-day period by two workers who had never entered the old plant. Both of the workers developed disease due to dioxin, and the son of one worker acquired a severe skin disorder called chloracne, one of the manifestations of dioxin-caused disease, from wearing his father's scarf.

Other workers exposed to lower levels of dioxin over longer periods of time—ranging from months to many years—have been examined and also were found to have disease. They include groups from the Diamond Alkali plant in Newark, N.J., a plant in Spolana, Czech., the Dow Chemical plant in Midland, Mich., and the Monsanto plant in Nitro, W.Va.

A report of dioxin-induced disease in three laboratory workers in England was published in 1975. Their exposure was only to dioxin, and they knew of its toxicity. In spite of the fact that they took extreme precautions, which included the use of ventilation hoods and protective clothing, all three developed various symptoms and findings associated with dioxin exposure, including abdominal pain, excessive fatigue, decreased ability to concentrate, irritability, blurred vision, decreased muscle coordination, and excessive oiliness or severe acne of the skin. In addition, all experienced elevated serum cholesterol levels that persisted for at least three years. One showed no symptoms until three years after exposure, a delay also noted in some of the Czech workers.

In January 1979, 47 railroad workers sent to clean up a chemical spill in Sturgeon, Mo., came in contact with chemicals that included phenol, orthochlorophenol, and dioxin. The dioxin was present in concentrations

ranging from 22 to 36 parts per billion, and exposure ranged between 8 hours and 90 days. Several extensive examinations over a three-year period uncovered disorders of all major organ systems. Laboratory abnormalities were similar to those found in other exposed groups, and again in some individuals disease did not appear until more than two years after exposure.

Perhaps the most publicized industrial accident involving dioxin occurred in 1976 near Seveso, Italy. The source was a chemical factory belonging to Hoffman-La Roche that produced trichlorophenol. An accidental rise in temperature in a reactor vessel caused a safety valve to open, sending a cloud of dioxin-contaminated trichlorophenol into the air. Within three weeks 700 residents had to be evacuated after thousands of small animals, birds, and insects were found dead. More than two-thirds of these people showed signs of dioxin poisoning. Contaminated crops within a region extending five miles south of the plant were burned. The area around the plant was divided into three zones based on the levels of contamination thought to be present. As of 1983 the most heavily contaminated zone remained fenced in and uninhabited.

Of more imminent concern than the occupational exposures is the growing realization that land sites and entire communities have been contaminated by the improper disposal of chemical waste containing dioxin. In 1971 waste oil was sprayed in several horse arenas in eastern Missouri to keep down dust. Within weeks hundreds of rodents, insects, dogs, cats, and birds were found dead in and around the arenas. More than 80 horses that had stood or were ridden in the arenas became ill, and within 16 months most developed multiorgan disease, became paralyzed, suffered extraordinary wasting, and died. Children and adults also appeared to be affected.

The oil was eventually recognized as the source of the problem, and several inches of topsoil were removed from the arenas. By the time dioxin was identified as the toxic agent (one arena showed a concentration of 33,000 parts per billion), some of the excavated soil had been used as landfill for homes in other areas of Missouri. In addition, the same dioxin-contaminated oil was sprayed on dusty roads in Times Beach and apparently hundreds of other areas in Missouri. It was later found that the waste oil had been mixed with thick, oily, dioxin-contaminated sludge from a plant that had manufactured herbicide and hexachlorophene. In 1983 Times Beach residents were told that the U.S. government would purchase their 800 homes from a "superfund" established in 1980 to finance toxic-waste cleanups.

Dioxin has also been found in soil and streams surrounding a waste-disposal plant in Arkansas and has been detected in fish taken in parts of New York and in fish and water from the Tittabawassee and Saginaw rivers in Michigan. High dioxin levels continue to plague the Love Canal area of Niagara Falls, N.Y., a residential community built on land used as a chemical-waste dump in the 1940s and 1950s. In 1979 the U.S. Environmental Protection Agency identified 31 cities whose chemical industries were likely to be a source of dioxin-contaminated waste.

Dioxin and Vietnam

About 20 million gal of phenoxy herbicides were among those used to defoliate vast areas of tropical forest in Vietnam between January 1962 and September 1971 in an operation called Ranch Hand. Various combinations of the phenoxy herbicides 2,4-D (2,4-dichlorophenoxyacetic acid) and 2,4,5-T, the latter contaminated with varying amounts of dioxin, received names according to the color coding on the barrels in which they were shipped. Approximately 276,000 gal of Agents Green, Purple, and Pink were spread over 2.5 million ac of forest between 1962 and 1964. The measured levels of dioxin were as high as 45,000 parts per billion in some samples.

From 1964 until 1971 the major defoliant used was Agent Orange and a modification called Orange Two. During this time 11,250,000 gal of Orange were spread over five million acres of land. The stated military objectives of forest defoliation were both offensive and defensive: to increase visibility for air strikes and monitoring of enemy troop movements and to clear land along highways, loading zones, and military bases used by U.S. and South Vietnamese forces. A third objective was to destroy crops in order to reduce food sources in areas controlled by Viet Cong.

About 2.6 million U.S. military personnel served in Vietnam between Jan. 1, 1965, and March 31, 1973, the time of heaviest use of Agent Orange. Those likeliest to have been exposed include crew members of helicopters used for spraying and those who loaded, unloaded, and serviced the crafts. In addition, soldiers spraying from backpacks, boats, and trucks had potentially heavy exposure. Because of the persistence of

Variation among species of lethal dioxin dose

animal	LD_{50} (μg per kg body weight)*
guinea pig	1
rat (male)	22
rat (female)	45
monkey	less than 70
rabbit	115
mouse	114
dog	more than 300
bullfrog	more than 500
hamster	5,000

*LD_{50} median lethal dose

Kimmel and Poulson, Annual Review of Pharmacology & Toxicology, 1982

dioxin, personnel in camps where perimeters were sprayed and others on foot and in vehicles in forested areas that had been sprayed were also exposed.

The effect of exposure to dioxin on the health of Vietnam veterans has yet to be adequately assessed. Various governmental agencies have been given responsibility for carrying out a study. Most recently this responsibility has shifted from the Veterans Administration (VA) to the CDC. Meanwhile, more than 16,000 veterans have filed with the VA for disability benefits for health problems claimed to be related to exposure to Agent Orange. Studies to examine the effect of Agent Orange on the Vietnamese people are also being carried out.

How dioxin affects human health

The first human health problem from dioxin to be noted was chloracne, a particularly unsightly form of acne with large whiteheads and blackheads, pustules, and sometimes abscesses. Although chloracne was initially thought to be an essential manifestation of dioxin poisoning, more recent studies in Seveso and of the Sturgeon railroad workers revealed that only about 15% of those affected developed chloracne, usually younger people and especially those with a history of teenage acne. This condition can be very persistent; some victims of the 1949 Nitro accident who developed chloracne still had it 34 years after exposure.

Other skin effects include increased pigmentation and increased facial hair. Skin cancer has also been reported. In the railroad workers, for example, 15% developed one or more skin cancers within three years after exposure.

The liver is a major organ for the synthesis and processing of proteins, fats, and carbohydrates. It also plays a major role in detoxifying and removing unwanted substances from the body. For these reasons it is particularly affected by dioxin. Many studies have revealed abnormal enzyme elevations resembling those seen in hepatitis; in some cases these abnormalities persisted for years. A disturbing finding in studies of both humans and other animals was the profound derangement of lipid metabolism with raised levels of triglycerides and cholesterol, both of which can be harmful. Also noted were decreases in high-density lipoproteins, which are beneficial to the body. Individuals with this lipid pattern are much more prone to atherosclerosis, or hardening of the arteries, stroke, and heart disease.

Dioxin also seriously affects human reproductive organs and their function. Although few studies exist of dioxin's effects on male reproduction, some men, including Vietnam veterans, have reported impotence and loss of libido. More than 40% of the Sturgeon railroad workers were found to have abnormally low sperm counts and high percentages of inactive sperm. Eighteen of the 47 workers had abnormally low levels of testosterone, the male hormone responsible for libido and secondary sex characteristics.

Studies of the offspring of people exposed to dioxin-containing herbicides in Vietnam and Australia revealed increased abnormalities of extremities, particularly fingers and toes; neural tube defects; and other birth abnormalities. Abnormal births have been reported among the families of exposed U.S. Vietnam veterans. One study of women exposed to herbicides in a town in Oregon revealed abnormally high miscarriage rates: 130 per 1,000 births, compared with 46 per 1,000 births for a similar town not exposed and used as a control. These rates peaked dramatically each June for six years, about two to three months after the spring spraying of 2,4,5-T in the area.

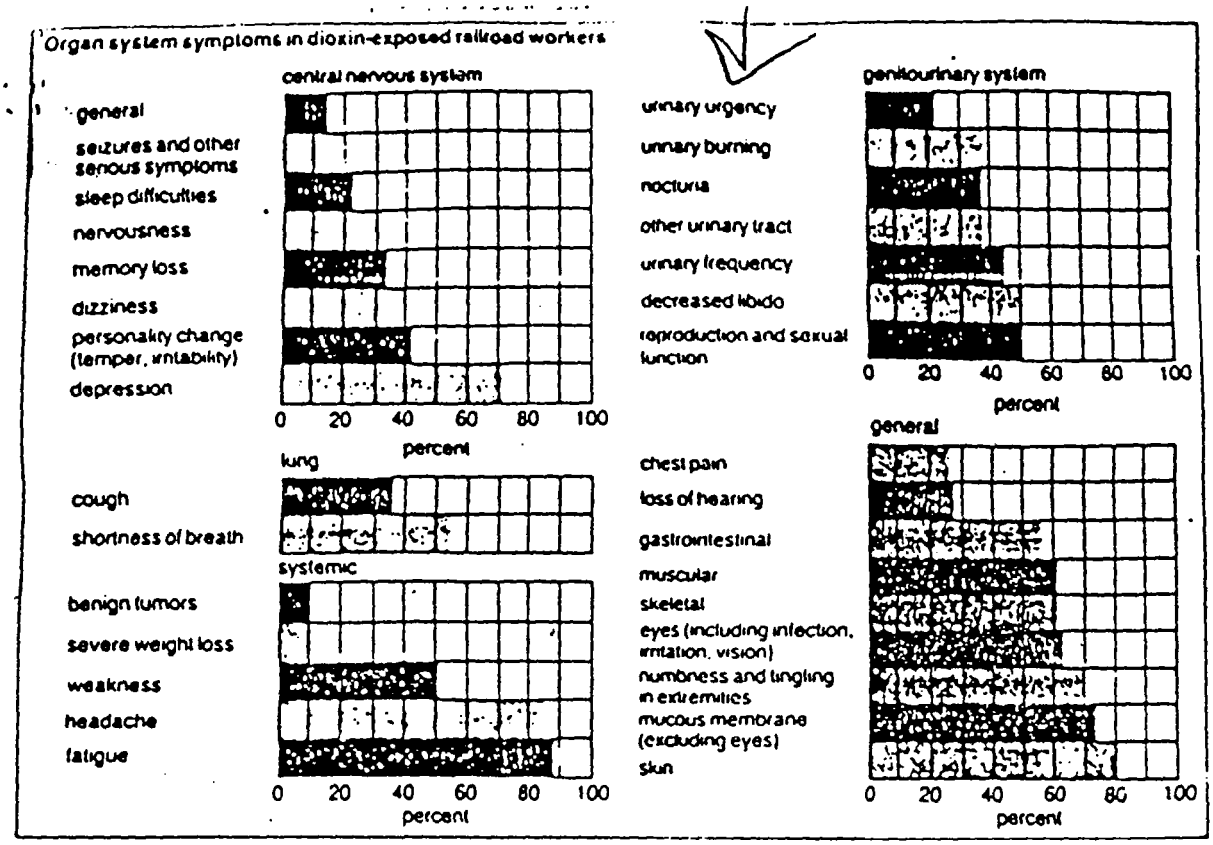
In studies of the Sturgeon workers, the genitourinary system also appeared to be affected. Some of these abnormalities might have been related to the toxic effects of phenol and orthochlorophenol present with the dioxin. Difficulties included inflammation, obstructed urine flow from the bladder, and, in some persons, loss of sensation of the need to urinate.

Studies carried out in Seveso and among the Sturgeon railroad workers revealed suppression of the immune system in both groups. In a large percentage of Sturgeon workers, activity of white blood cells called T-lymphocytes was particularly suppressed. T-lymphocytes play a major part in the development of immunity against disease and in preventing cancer by destroying newly formed cancer cells.

The central and peripheral nervous systems are also major targets of dioxin. Many of the reports of exposures document symptoms of increased and long-lasting irritability, severe headaches, profound fatigue, sleep disturbances, and in some cases seizures. A major symptom in these groups was depression, which appeared to be chemically mediated and not of psychological origin. Memory loss was also a significant finding in some of the studies. An extensive battery of neurobehavioral tests given to the railroad workers revealed many with central nervous system dysfunction.

Effects on the peripheral nervous system manifested themselves as numbness and tingling in the fingers and toes. Nerve damage, evidenced by slowed and impaired transmission of electrical impulses in the nerves, was found in some people along with abnormal reflexes and weakness of the extremities.

Joint stiffness and weakness of the muscles also were common in many dioxin victims. Loss of muscular strength, particularly in the extremities, after brief work suggested impaired energy transfer mechanisms, which are essential to muscle function. One component of the cell affected by dioxin is the mitochondrion, a structure that has responsibility for processing chemicals to provide ready energy to muscles. In experimental animals mitochondria were shown to be swollen and damaged after exposure to dioxin, a finding that may



help explain the reason for muscular weakness.

Other organs and tissues affected by dioxin include the blood, heart, lungs, kidneys, and mucous membranes of the eyes and nose. In some exposed groups pancreatic function appeared to be impaired, resulting in an increased incidence of diabetes.

Dioxin also appears to be linked to an increased incidence of cancer in exposed humans. One study carried out in Vietnam showed an increase in primary liver cancer. A significant increase in soft-tissue sarcoma, a form of cancer, was found in Swedish workers exposed to 2,4,5-T. An increase in cancer rates among BASF workers was also noted years after the accident there. Because cancer frequently has a long latency period between the time of exposure and the appearance of disease, long-term observation of exposed populations is necessary, particularly in view of animal studies showing dioxin's potency as a cancer promoter and its ability to suppress the immune system.

The work ahead

Dioxin's stability, toxicity, and potential for wide dissemination in the environment make decontamination a difficult problem. Two proved methods, irradiation and incineration, are workable only under certain circumstances. Stores of Agent Orange and Orange Two that remained after the Vietnam conflict were eventually taken to Johnstown Island in the Pacific, put on an incinerator ship, taken out to sea, and burned. This method was costly and was possible only because the chemical was in a reasonably concentrated, liquid form. Incineration is not practical for treating contaminated water, buildings, or tons of soil. Chemical degradation methods are being explored but are still in the laboratory stage. There is currently no good, acceptable method for disposing of or neutralizing dioxin in most situations.

Much more information needs to be gathered regarding nearly every facet of the dioxin problem. Efforts are being made to identify other communities that may have been exposed to dioxin so that measures can be taken to protect individuals living in them. In the U.S., administrators and legislators at various governmental levels are under pressure to toughen inspection and enforcement programs aimed at the producers and transporters of hazardous waste and to improve methods for identifying sites where dioxin is likely to be created.

A better elaboration of toxic pathways may ultimately enable medical researchers to block or neutralize dioxin or remove it from the body. For example, it has been found that animals placed on low-iron diets appear to be somewhat less affected than those with normal iron stores. Current treatment is supportive and consists mostly of attempts to protect those organs that have been affected or may be affected in the future. Dioxin victims have been advised to stop smoking and to avoid excessive exposure to sunlight in order to lower their cancer risk. Doctors have also recommended diets low in cholesterol and triglycerides to reduce the levels of these lipids in the blood. Such preventive medicine is seen as a stopgap until such time as measures to block or remove dioxin can be developed.

—Bertram W. Carnow, M.D.

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CARNOW, CONIBEAR & ASSOCIATES, LTD
Occupational and Environmental Health Consultants
111 West Wacker Drive, Chicago, IL 60606, 312/782-4486

December 12, 1985

Mr. Phillip McMath
McMath Law Firm
711 W. Third Street
P.O. Box 1470
Little Rock, AR 72203

Dear Mr. McMath:

I am writing this letter to report to you the results and findings of our examinations on your twelve clients that took place in Chicago, Illinois in September and October, 1985.

Based on the medical and environmental histories, physical examinations and laboratory and other medical testing, it is my medical opinion that these twelve individuals were exposed to and absorbed dioxins, including 2,3,7,8-tetrachlorodibenzo(p)dioxin, and other related compounds into their bodies through one or more portals of entry including through the skin, inhalation, and ingestion. As a consequence, they are suffering from chronic chemical poisoning involving multiple organs and organ systems with damage to them of a permanent and irreversible nature.

The organs manifesting dysfunction and damage from these systemic poisons and the frequency of abnormalities found include:

Eyes

In excess of 80% of persons examined had one or more complaints of visual difficulties or pain of various types. Five individuals had complaints of irritated, burning eyes, three had complaints of blurring of vision and four complained of watering of the eyes either now or when they resided in Jacksonville.

On physical examination, two individuals exhibited evidence of chronic inflammation of the membranes covering the eyes, the conjunctiva.

Ears

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Two-thirds of the group had one or more symptoms of difficulty with their ears, including drainage, itching, and congestion. Of great

concern were the findings in one third of the group of tinnitus (ringing in the ears), frequently a sign of eighth cranial nerve damage and, in more than 40% of the group (5 of 12), complaints of a decrease in hearing acuity. Four of the patients revealed some evidence of ear drum or other abnormalities on physical examination. Of great significance were the findings on hearing testing. Audiograms performed on the group revealed eight individuals with abnormal findings. In six of them the abnormalities revealed hearing loss, most of them in the higher frequencies. This pattern of hearing loss suggests damage to the eighth cranial nerve. Adding to this concern is the fact that in all six individuals, the hearing loss was bilateral.

Respiratory Tract

There were a wide variety of complaints relating to the nose and throat and, to a somewhat lesser degree, to the lungs. Twenty-five percent of the group (3 of 12) complained of shortness of breath with the same number complaining of nasal discharge, nosebleeds, and sore, irritated, or dry throat. The most frequent symptom, nasal congestion, was found in almost half of the people examined. On physical examination of the nose, 3 of 12 showed evidence of inflammatory changes and mucous membrane damage bilaterally.

Cardiovascular

Symptoms relating to the heart included abnormal rhythms in 2 individuals and palpitations which also probably represent abnormal rhythms in 4 of the 12. Two also complained of chest pain. On physical examination, 2 patients showed abnormal heart rhythm and one of those also had an abnormal pulse rate. Electrocardiograms taken on these individuals revealed that 5 of them had electrocardiographic tracings which were not completely normal.

Gastrointestinal System

Ten of the twelve had one or more complaints relating to the gastrointestinal system. Those appearing most frequently included epigastric (upper abdominal) pain or distress, nausea and generalized abdominal pain. These symptoms may represent inflammation of the upper intestine or stomach or be a result of the prophyria which can cause severe abdominal pain. The most common symptom was diarrhea, a condition complained of by 5 of the 12 persons examined (42%).

Liver

The liver generally does not cause "symptoms." One individual, however, did have complaints of jaundice of the eyes and skin and his laboratory tests revealed an elevated bilirubin. Laboratory tests of the liver, a major target organ of dioxin and related compounds, revealed that all 12 had two or more abnormalities of this organ with 4 having five abnormal lab tests and one each having six and seven abnormal tests. These generally reflected abnormal liver metabolism. Of great concern were the findings of abnormal porphyrin metabolism including porphyria, a normally very rare genetic disease. In this group, 8 had porphyria of one type or another. 7 of the 12 (58%), an extraordinary number, had coproporphyrinuria. Two of these also had porphobilinogenuria, and one had three porphyrins abnormal. While in a normal population this is a rare disease and these findings rare findings, they have been shown to be caused by exposure to dioxin and related compounds, which are known as porphyrinogenic agents. These abnormalities of porphyrins are a reflection of profound disturbance of major enzyme systems regulating body function. In addition, 11 of the 12 showed high density lipoproteins (HDL cholesterol) below the laboratory's normal range which reflects abnormal lipid metabolism, damage also associated with exposure to dioxins. Seven of eleven individuals had abnormally elevated prothrombin time which may represent abnormal bleeding and clotting damage, also shown to be associated with exposure to dioxin. Because of the large number with prothrombin time abnormalities this will need to be repeated since, occasionally, delay in testing of blood samples might cause this test to be somewhat abnormal.

Genitourinary System

Two-thirds of these individuals had difficulties relating to the genitourinary or reproductive system.

Those symptoms found most frequently included frequency or increased urination; nocturia, that is, frequent waking during the night to urinate; and decreased libido, that is, decreased sexual desire in three of the twelve.

Central Nervous System

The central nervous system is one of the major target organs affected by systemic poisoning from dioxin and related compounds. A wide range of symptoms referable to the system was present in this group. Those complained of by two or more individuals included episodes of anger, aphasia, difficulty in concentrating, dizziness, and sleep difficulty

including frequent waking, difficulty in falling asleep and nightmares. Twenty-five percent of those examined complained of anxiety, decreased recent memory, depression and abnormal drowsiness or sleepiness. The two symptoms most commonly complained of were increased irritability in a third of the people questioned and headaches in more than 80% (10 of 12).

In addition, a number of those examined showed one or more physical findings referable to the central nervous system including 3 with abnormal reflexes. Laboratory testing included a large battery of tests of neurobehavioral function. Forty-two percent of those tested (5 of 12) revealed some evidence of brain dysfunction and damage. Fifty percent also showed abnormalities of the Zung scale which is a measure of anxiety, and 3 of 10 individuals tested showed depression according to the Beck Depression Inventory.

Peripheral Nervous System

Eight of those examined had one or more symptoms suggesting abnormality of the peripheral nervous system. One of the most common complaints referable to this system was of tingling and numbness or pins and needles in the extremities. Six of the 12 individuals had this complaint. On physical examination, 7 of the 12 had one or more abnormal physical findings including abnormal response to touch and pinprick, the latter mostly in the upper extremities. Three showed abnormal reflexes of the type seen in peripheral neuropathy. The laboratory examination found 5 (42%) with abnormal nerve conduction. Two of the five had two abnormalities and one each had three, four and five abnormalities of conduction reflecting severe peripheral polyneuropathy. Two of those examined had EMG abnormalities of the upper and lower extremities reflecting axonal degeneration of nerves, evidence of far advanced neurologic damage.

Musculoskeletal System

There were many complaints of muscle and joint difficulty. A number complained of spasms and cramps in the muscles with almost half (5 of 12) complaining of pain. Even more had complaints relating to the joints, including swelling, and stiffness in the joints in 50% and, in two-thirds of those examined, joint aching or pain. Three of twelve had evidence of abnormal muscle metabolism with two having an elevated CPK and one an abnormally depressed CPK. CPK is an enzyme, which when abnormal, reflects muscle dysfunction.

Immune System

All of the 12 individuals examined had 3 or more abnormalities of the test battery done to evaluate immune function. Four had seven abnormal test results and one each had eight, nine and ten abnormal results. Those with the greatest frequency included total lymphocytes and the percentage of total lymphocytes, a depression of "B" lymphocytes, abnormal numbers of OKT-8 cells (suppressors), cells percent of OKT-10 percent, and abnormal mitogen response with abnormal unstimulated CPM in 8 of the 12 examined.

Male Reproductive

Four male patients had fertility analysis carried out. A variety of abnormalities were found in three including depressed sperm counts in two and an increase in the total number of abnormal cells found.

Hematopoietic System

Six of those tested have some abnormality of the red cell indices. Two of those had three and four abnormalities respectively. In three, the hematocrit was decreased, suggesting a smaller than normal number of red blood cells.

As you can see from this summary, these people have suffered damage to many organ systems as a result of chronic poisoning by dioxins and related chemicals. These include particularly, 8th nerve damage reflected in a hearing loss, multiple abnormalities of liver metabolism including an extraordinary number of individuals with abnormal porphyrins, normally an extremely rare disease in populations not exposed to porphyrinogenic agents, the central and peripheral nervous systems, the immune system and reproductive system. This is not only reflected in the symptoms presented by this group, but in confirmatory physical findings and, particularly, laboratory findings of abnormal function and disease.

We have examined hundreds of individuals who have been exposed to dioxins under similar or related circumstances, and find that the organ systems which have been damaged and the type of damage which has been done to these organ systems in your clients are those that we have seen in others similarly exposed. This is particularly true of those chronically exposed; that is exposed over a period of time. People acutely exposed, for example, workers exposed in explosions following a runaway exothermic reaction, often will also develop

chloracne and other acute symptoms and findings, and, during the acute phase of the disease may show some differences from this group until chronic effects set in.

I trust this will be helpful to you. Time constraints did not permit me to completely check all of my additions. I believe the figures to be correct; if there are any changes, I will let you know. We, of course, will continue to assist in every way that we can in providing medical advice and treatment for your clients.

Sincerely,

CARNOW, CONIBEAR & ASSOCIATES, LTD.

Bertram W. Carnow, M.D.
President, Senior Scientist

BWC:dp
8009-03

MEMORANDUM

TO: VERTAC CHEMICAL PLANT SITE

FROM: ALISON PETTIETTE

RE: LIABILITY ISSUES CONCERNING THE VERTAC CHEMICAL PLANT IN JACKSONVILLE, ARKANSAS

DATE: July 29, 1986

I. Liability Against Dow Chemical Company, U.S.A., Midland, Michigan

We have obtained a suitcase full of documents from the Area Supervisor for Vertac Chemical Company, who began working as an operator in 1971. Jerry L. Keister was the Area Production Supervisor at Vertac Chemical Company and retired in March of 1986. He produced the documents which substantiate the following testimony. In 1971 the plant site in Jacksonville, Arkansas, was purchased from Hercules Chemical Company by Transvaal, Inc. Transvaal, in about 1976 or 1977 changed its company name to Vertac Chemical Co. It is my understanding that Hercules Chemical Co. has its home office in Wilmington, Delaware, that Transvaal, Inc., and now Vertac Chemical Co. have their home office in Memphis, Tennessee. Hercules Chemical Co. was the author of a chemical process in approximately 1966 or 1967 to reduce the amount of dioxin contamination of their 2,4,5-T to less than 1 ppm. Hercules Chemical Co. attended a meeting in March of 1965, in Midland, Michigan, held by Dow Chemical Co., U.S.A., as a major manufacturer of phenoxy herbicides. These herbicides were used by the United States government as chemical warfare and as a way of clearing out the Vietnamese jungle. The major chemical companies met in Midland, Michigan in 1965 to discuss the problem posed by their manufacturing of a substance known as 2,4,5-T. The government's names for these herbicides were Agent Orange, Agent Purple and Agent Pink. Agent White was 2,4-D alone and Agent Blue had arsenic in the 2,4-D. The other colors had 2,4,5-T as a major component part. In 1969 and 1970, the United States government banned the use of phenoxy herbicides in Viet Nam. By 1971, all the major manufacturers had lost their contracts with the United States government to produce the chemical herbicides used in Viet Nam. It was at this point in time that Dow Chemical Co., according to Keister, began

providing shipments from Midland, Michigan, of crude benzene and trichlorophenol (TCP) and 2,4,5-tetrachlorobenzene, which are used in the manufacturing process of 2,4,5-T. The documents provided to us by Keister substantiate each tank car and shipment from Dow Chemical Co. in Midland and other manufacturers of the raw materials used in the Transvaal/Vertac Chemical processes. From 1971 through and including 1979, Dow Chemical Co., U.S.A., purchased the end product, 2,4,5-T with its contaminant, dioxin, from production in the United States totally. It was at this point that the manufacturing of 2,4,5-T was totally shut down at the Vertac Chemical Co. plant site in Jacksonville, Arkansas. One hundred percent (100%) of the crude benzene and 100% of the trichlorophenol was shipped in in tank cars from Dow Chemical Co., Midland, Michigan, and are verified by the production records produced by Keister. The 2,4,5-T end product was sold back to Dow Chemical Co. pursuant to a contract which we do not have access to at this point in time. However, the production records indicate purchases during the years 1971 to 1979 of pounds of Transvaal/Vertac 2,4,5-T by Dow Chemical Co., U.S.A. Christine Hilbert, a client and ex-employee of transaal, saw in her capacity as lab technician that Transvaal/Vertac's 2,4,5-T was labelled with Dow's label before shipping in Jacksonville.

The supplier of inherently dangerous raw materials, who had knowledge of 1) what these chemicals are being used for, 2) the effective process being used by Transvaal/Vertac Chemical Co. and 3) the inherent risk of populations posed by these particular chemicals has an independent duty to provide such information to the employees of that corporation. Dow Chemical Co. provided no such information to anyone at Vertac or Transvaal. Secondly, the process that Hercules devised in 1966 or 1967 to reduce their dioxin levels in their final end product 2,4,5-T was well documented and known to Dow Chemical in the early 60's. Hercules provides a process without Dow Chemical Co.'s help to reduce the dioxin contamination of their 2,4,5-T to less than 1 ppm if they kept manufacturing processes within certain limits. The process that Hercules used was to use a toluene wash on the 2,4,5-T end product in the Recovery Unit and remove all the solvent and waste contamination, including dioxin from their end product, 2,4,5-T. The waste product removed from the process left the waste in Jacksonville, Arkansas, on the Vertac Chemical Co. plant site. Hercules dumped open barrels into open pits in the 60's while it was producing Agent Orange, as well as other phenoxy herbicides for the government. Hercules left dioxin contamination when it left Arkansas in 1971.

II. Liability Against Hercules Chemical Company

There are two theories of liability against Hercules Chemical Co. One, they sold a defective process to Transvaal/Vertac Chemical Co. in 1971. Hercules knew that its process left the majority of its waste contamination on the plant site and off the plant site where it had dumped its own waste during the last decade. Secondly, Hercules knew that dioxin could not be biodegraded by 1971, that it was a poison that would bioaccumulate in the human body. 2,3,7,8-TCDD is the worst poison ever made by man according to the United States EPA. It will be necessary to obtain the contracts where Hercules sold the plant site in Jacksonville, Arkansas to Transvaal, Inc., which later changed its name to Vertac Chemical Co. Vertac, at this point in time, wishes to close its own plant in Jacksonville, since it has had so much pressure from the governmental agencies and various lawsuits which have been filed against it by the citizens of Jacksonville.

During the relevant years of Keister's employment, which include 1971 through and including March of 1986, various chemicals were purchased from other manufacturers. However, in and of themselves, those chemicals are not inherently dangerous except when given in acute and/or lethal doses. Vertac purchased many products from Diamond Shamrock, including chlorine and caustic. However, Diamond Shamrock, according to Keister, did not buy back the 2,4,5,-T end product. Therefore, the case against Diamond Shamrock is much weaker than that against Dow Chemical Co. Diamond Shamrock is one of the Agent Orange defendants; however, since Diamond Shamrock did not buy back Transvaal/Vertac's end product, it would be harder to prove that they had actual knowledge of what this company was doing in Jacksonville, Arkansas, with their chemicals. Transvaal/Vertac bagged their acid (2,4,5-T) and shipped it to Dow Chemical Co. in Midland, Michigan. We have the production records from this era, 1971 through and including 1979. These are 55 lb. bags of acid.

III. Operations Manuals and Lack of Warnings

In addition, Keister has provided with the Operating Manuals for all the units on the Vertac Chemical Co. plant site, which includes 1) Chlorinator; 2) the Dechlorinator or Sputnik where they made Trichlorophenol (TCP); 3) the Acid Unit where they put molten Trichlorophenol and Proprionic Acid and made Silvex (2,4,5-T) or they would load 6,000 lbs. of Trichlorophenol with Monochloric Acetic Acid and 50% Caustic, reacted that and made the 2,4,5-T. They bought crude benzene from Dow Chemical Co. and 1,2,3,4-Tetrachlorobenzene and chlorinated it to make 2,4,5-Tetrachlorobenzene. At one time, they were using so much benzene that they had to buy benzene from Dow Chemical Co. in order to keep up production, and to make their own tetrachlorobenzene; 4) in the early 70's they had a Benzene

Unit to make their own benzene from the crude benzene that they purchased from Dow Chemical Co. They had a Benzene Grinding Room because benzene freezes in the winter months if it's not kept above a certain temperature and they would have to grind solid benzene in an interior room near the lunch room in order to put it in the reactor. They purchased Caustic from Hooker Chemical Co. Until 1971, they purchased all benzene from Hooker. Transvaal bought Trichlorophenol from Dow Chemical Co. and Caustic from Diamond Shamrock. Transvaal bought their Chlorine from Diamond Shamrock as well. They also bought from Tennessee Eastman and Celanese Corp. monochloric acetic acid.

A. Chlorination Unit

In the Chlorination Unit, Transvaal/Vertac (hereinafter referred to as the "Vertac process") used acetic anhydride and acetic acid in a 2,000 gallon tank filled with gas and introduced liquid chlorine vapors through sparger gas spickets at the bottom and heated this reaction to make either Monochloric Acetic Acid or Proprionic Acid. There were three heat exchangers cooling the water and reflux towers in the Chlorination Unit to make Monochloric Acetic Acid in the Chlorination Unit. Vertac made approximately 7.2 million pounds of Monochloric Acetic Acid from 1971 to 1976, which was used to make the 2,4,5-T in the Acid Unit. In the Chlorination Unit they also had the capacity to make Proprionic Acid by using a red phosphorous catalyst and a heated reaction to 90 degrees centigrade, which was combined with 2,4,5-T and Proprionic Acid to make Silvex (2,4,5-TP). Vertac made a half million pounds a year of Silvex from 1971 to 1976. The Chlorination Unit added chlorine to the reaction to make Monochloric Acetic Acid or Proprionic Acid. Between 1971 and 1981, production at the Vertac Chemical plant site was a dirty, nasty place and all operators were working 16 to 18 hours every day. Production was up. Cleanup was introduced in 1979 when OSHA and/or the EPA came down to begin monitoring this plant site. It was at this time that Vertac Chemical Company began being fined for the wrongful disposal of hazardous waste off plant site and on plant site, which up until that time had been dumped by tank trucks which were filled up at the various units with waste products and just dumped into the fields and open pits dug by the workers and lined with dirt only. Vertac started using visqueen and other clay liners in these pits after 1980.

B. Dechlorination Unit (Sputnik)

In reactor tanks, Transvaal/Vertac put 1,2,3,4-Tetrachlorobenzene and loaded reactors from the top in 22 inch manways which were bolted down. Vertac put Tetrachlorobenzene into Methanol, methyl alcohol in a 750 gallon tank. The temperature was 150 degrees farenheit

under 300 pounds of pressure and 100% Caustic to make Trichlorophenol (TCP). The Acid Unit took the Monochloric Acetic Acid and the 2,4,5-Trichlorophenol and blended it together to make 2,4,5-T or it could make Trichlorophenol and Proprionic Acid in the Acid Unit and make 2,4,5-TP (known as Silvex, trade name). The Acid Unit could make 2,4-D as well, which is the other component of Agent Orange and causes such things as neuropathy, and can also be a cause of chloracne. There are three Recovery Units that were used during various stages of this process. Hercules had two Recovery Units. These were cooling ponds or a settling pond where they took the waste in a cooling pond and recovered the water and sent it through the system again. The recovery pond is now built up into Vertac Mountain which is a clay liner to contain the waste on the plant site. However, the clay is leaking because it is nonimpervious to dioxin contamination. In fact, dioxin will not photodecompose in sunlight, although, at one time Vertac had tried to dry out the dioxin in the sun light to photodecompose it. The Recovery Unit that Hercules devised and that was used by Transvaal/Vertac was devised by Hercules in 1965 to 1967, which used toluene washes in an agitator, which on the plot plan is symbolized by "A" to settle out the solvents and the other undesirables into a 2,000 gallon vessel; this waste was barrelled and dumped in open fields between 1971 and 1973 on the plant site itself; and later the company got a dump truck with a large tank on it which was filled up with waste everyday and on the night shift was dumped into the open field or pit by the workers themselves.

C. Recovery Unit

In the Recovery Unit, all the 2,4,5-T went through a system which had nine washes, three dirty washes and six clean washes of toluene in an agitator to drop out the solvents and the solids and distill them into a tank at the bottom of this reaction to take everything that was not supposed to be in their end product 2,4,5-T and dump it in the Jacksonville plant site area. Vertac buried these barrels in the fields in pits and then, without protective clothing, Vertac set the barrels in the fields on top of the ground at first and then later Vertac buried them after the EPA got out there in 1980. Vertac hauled 2,000 gallon vessels every day filled with dioxin contaminated waste and dumped them into large pits that the workers built in the field. Every twenty-four hours Vertac made dioxin waste. Vertac stored some of the barrels in storage sheds until the drums started leaking and in 1985 Vertac capped the cooling pond, which at one time was a Recovery Unit to provide cooling water to all the plant sites. Vertac had no rain suits. Vertac had cotton coveralls, a hard had and goggles and that was the only protective equipment that workers received for these

operations. Workers had no respirators at all and they were not even required to wear respirators until the last year, 1985. Vertac had one chlorine gas mask available. The cotton coveralls provided were not chemically treated until after Pelton died in 1983. Workers did not know until James Cox died that Dichlorophenol was lethal when you got it all over you. James Cox poured himself a sample of Dichlorophenol and died. Cox was burned to death by the acid. This was in the Chlorinator Unit. Before that, two guys had been killed at the Dechlorinator Unit when there was a fire in the reactor. Marco Brolo has died. Mrs. Brolo, who Keister believes is a good friend of Mackey Pierce. The Dechlorinator Unit had an operator and the Chlorinator Unit operator was to help him. He was called the #2 Acid Man and he was to help the Dechlorinator Unit operator load the reactors in the Sputnik to make Trichlorohenol. Sputnik reactors had 22" manways. The Sputnik Unit had a floor and had three dechlorinator tanks with wooden staircases up to the platform of the tank and 22" or 24" manways at the top which could be unbolted. With a runaway reaction for the Dechlorinator Unit there would be these pipes with safety valves. When the reaction ran away there would be spewing black tarry stuff from the Sputnik reactors out of these pipes. When you opened the manways there was fire inside the reaction. The reaction was called "runaway" because at high temperatures the temperature was off the instruments and so was the reaction. There was no way to know how hot it was burning or at what pressure. In the middle 70's for one year Transvaal/Vertac had a joint venture with BASF to make a product called Dalapon for a short while and then it was banned.

D. Benzene Unit

The Benzene Unit had big dryers in it and Vertac brought their crude benzene in on conveyors; ground it; and put it into hoppers in order to use in the remaining process. If benzene gets cold it freezes. Keister believes that the people that own Vertac are the DeNore brothers from Italy via a holding company in New York called Didecon Investments. Keister believes that Transvaal/Vertac had a plant in West Helena, and in Mississippi. He also heard that Formenta was a Swedish company has bought Vertac. This is unsubstantiated at this time. With the documentation by Keister and the testimony by the ex-employees and current employees, even in 1979 and 1980 when Mt. Sinai was paid by Vertac to come in and give employees physicals, the company's position was the dioxin can't hurt you and you can eat it for breakfast. Doc Sidwell, who was instrumental in devising the "Hercules process" with the toluene wash in 1965, did sample it with his nose and mouth in front of workers in order to show them that he could drink it for breakfast and still live.

Doc Sidwell is currently hired as a consultant by Transvall/Vertac Chemical Company and can go on the plant at will. There were five basic units at one time or another at the Vertac Chemical Company plant site.

IV. Plot Plan

We have obtained an accurate plot plan of this plant site in Jacksonville, Arkansas, which includes references to the old Hercules P & I.D. drawings, which were used by Vertac in its 1985 revision. It clearly shows where the Dalepon Unit, the Benzene Unit, the Chlorinator, the Dechlorinator, the Acid Unit, as well as the Recovery Unit, were located, which I have been referring to on the map. It also can be referred to to show where the barrels of redrummed contaminated waste are being stored presently on the plant site itself. As I have said, the entire place is contaminated, more so on the plant site than off the plant site.

V. Statute of Limitations

It is very important that we have " solvent" defendants who can be held negligent or strictly liable on the basis of Restatement of Torts, products liability and/or some other theory of law. It is equally important to find out what is the best forum to bring these lawsuits and whether that state has borrowing statutes which would make the choice of law an interpretation of Arkansas law. Arkansas compensation statute for death and/or occupational disease is strictly interpreted by the state courts of Arkansas. Basically, in order to avoid the Arkansas compensation statute on a negligence basis of any sort, you have to show specific intent to kill each individual. This cannot be shown under the facts and circumstances of this particular case on behalf of the employees themselves. However, Arkansas has a product's liability statute as of 1973 (adopted Restatement of Torts 402 A & B and it would seem to me that we can avoid the workers' compensation statute by suing the manufacturers of raw materials who bought the end product, such as Dow Chemical Company, and equally sue Hercules Chemical Company for (1) using a defective process; (2) inventing and selling a defective process to a successor corporation; and (3) leaving there their dioxin waste in open pits and burying them all over the plant site itself.

VI. Exposure

In addition to the direct exposure for the workers, the wives and children had direct exposure to the chemicals and the waste on Vertac plant site because they were allowed at will to visit their husbands. The wives brought family members on the plant site itself and strangers were

permitted on the plant site at any time during the past fifteen years that Vertac has operated this plant. All the wives had direct exposures, so did the children. There may be property damage cases for the people that currently own homes in Jacksonville, Arkansas, or in a location which is south or southeast of the Jacksonville, Arkansas plant site. The EPA has published, as of July 15, 1986, that Off-Site Feasibility and Remedial Investigations concerning the off-site contamination of Jacksonville, Arkansas. Commercial fishing has been closed from Jacksonville south and southeast all the way to the mouth of the White River which flows into the Mississippi River. South of the Jacksonville plant site, the EPA and the FDA has closed commercial fishing from Rocky Branch Creek in and around Lake Dupree to Bayou Meto and to the mouth of the Arkansas River, which crosses Little Rock, Arkansas. The Arkansas River flows into the Mississippi River as well. We have obtained evidence from other plant workers of documents obtained from the plant site itself showing that in 1983 Vertac and Hercules entered into a consent decree with the Environmental Protection Agency. We must obtain the on-site samples taken by the United States EPA and the FDA from Region VI in Dallas, Texas and in Washington. All the sampling and the routes of exposure have been done by the EPA and published by the EPA, which was just finished July 15, 1986. Representatives from Washington, Atlanta and Dallas appeared in Jacksonville on July 15, 1986, and held a public hearing before the citizens of Jacksonville to tell the public that they were contaminated if they lived in the town of Jacksonville. After seven years of studying this plant site and doing numerous water and soil samples in the ponds and flood plains in and around Jacksonville, the EPA said that they should not eat any livestock, poultry, fish, etc., drink any water or use their toilets in Jacksonville, Arkansas if they lived anywhere from Vertac south or southeast all the way through Lonoake towards the Mississippi River. The EPA did not test upstream, even though the prevailing winds were from the south or southwest, which would cause the wind to blow contamination towards Cabot, Arkansas, where some clients live. Also, fish swim upstream and no fish samples were done upstream of Jacksonville. As far as residential contamination, I do not think we have any problem with anyone that has lived in Jacksonville, Arkansas while working for Vertac.

VII. Medical Causation

It became apparent from individual client interviews and review of available medical records that most of our clients have reported their symptoms to doctors in and around Jacksonville and Little Rock. Many of them have had surgery and had been diagnosed with chloracne, at least by Mt. Sinai. Many of them have nervous disorders, such as

peripheral neuropathy and other forms of neuropathy, which can be chemically induced. All of the chemicals which Vertac made, including 2,4-D and 2,4,5-T, can cause nervous disorders and have been known to cause chloracne. The combination, along with the dioxin waste, as noted by the EPA last week, is the most poisonous of all the chemicals and the most long lasting. The EPA said it would take 10,000 man years for the amount of dioxin to biodegrade as found in the EPA Off- Site Investigations. The EPA did not mention their on-site investigation pursuant to the consent decree to keep all of this quiet. The On-Site Investigation I'm sure reveals dioxin contamination was found on the lunch table in the break room (locker room), in the shower stalls, it was tracked on shoes all over the place, it was seeping out of the ground, oozing a black tarry substance. It is running into the creeks and bayous and contained in the soil samples. Dioxin does not mix with water, but adheres and leaches to the soil through the waterways and is moved by the water. It can be blown by the wind. We need a Memorandum of Law concerning the laws in Michigan, Delaware and other states where Hercules and Dow Chemical Company do business, including Texas, and the choice of laws that would be applied by the various courts in any given state. We also need to look at the Arkansas products liability law to see whether the discovery rule applies.

Jules R. VITERBO, et ux, (Patricia Viterbo), Plaintiffs-Appellants,

v.

The DOW CHEMICAL CO., Defendant-Appellee.

No. 86-2806.

United States Court of Appeals, Fifth Circuit.

Sept. 11, 1987.

Individual exposed to chemical herbicide and his wife brought action against chemical company to recover damages for alleged toxic effects of herbicide. The United States District Court for the Eastern District of Texas, Howell Cobb, J., 646 F.Supp. 1420, granted chemical company's motion for summary judgment, and individual and wife appealed. The Court of Appeals, E. Grady Jolly, Circuit Judge, held that information available to physician lacked foundation and reliability necessary to support expert testimony.

Affirmed.

1. Federal Civil Procedure ⇐2545

District court may inquire into reliability and foundation of any expert opinion to determine admissibility, in determining whether to grant summary judgment despite party's producing expert to support its position. Fed.Rules Evid.Rules 403, 703, 28 U.S.C.A.

2. Evidence ⇐555.2

Generally, questions relating to bases and sources of expert's opinion affect weight to be assigned that opinion rather than its admissibility and should be left for jury's consideration; however, in some cases source upon which expert's opinion relies is of such little weight that jury should not be permitted to receive that opinion, such as when opinion is fundamentally unsupported. Fed.Rules Evid.Rules 403, 703, 28 U.S.C.A.

3. Evidence ⇐555.10

Sources upon which physician based opinion that individual's exposure to herbicide caused individual's physical and emotional problems lacked foundation and reliability necessary to support expert testimony and, therefore, opinion could be excluded; sources of opinion were individual's incomplete oral medical history, tests conducted by physician indicating that individual suffered from some sort of toxic reaction, but not implicating herbicide, and study concerning exposure of rats to chemical in herbicide. Fed.Rules Evid.Rules 403, 703, 28 U.S.C.A.

Appeal from the United States District Court for the Eastern District of Texas.

Before WRIGHT,* GEE and JOLLY, Circuit Judges.

E. GRADY JOLLY, Circuit Judge:

In this case today we consider the question whether it is so if an expert says it is so. Although the plaintiff's expert here said it was so, the district court excluded the expert's opinion and granted summary judgment in favor of the defendant, 646

* Circuit Judge of the Ninth Circuit, sitting by designation.

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F.Supp. 1420 (E.D.Tex.1986). We uphold the district court because the plaintiff's expert brought to court little more than his credentials and a subjective opinion.

I

From April to September 1981, Jules Viterbo used Tordon 10K, a pesticide manufactured by Dow Chemical Company (Dow), to eliminate tallow trees on a 700 acre tract of land in Jefferson County, Texas. On weekends he would pour the Tordon 10K pellets into a bucket and walk through the fields throwing the pellets on the ground. On Christmas Eve 1981, Viterbo experienced his first alleged symptoms of exposure to Tordon 10K. On that day, he cried, was nervous, and had itching on his arms and legs. The symptoms continued until April 1983, at which time he "felt [he] was more or less out of the woods." At the time of his deposition in July 1984, he stated that he still suffered from a rash and felt "about 80 percent mentally aware [as he] was before [he] got sick." Beginning in 1982, Viterbo saw a number of doctors, including psychiatrists. These doctors diagnosed a variety of ailments, including endogenous depression, depressive neurosis, essential hypertension, and allergies.

In April 1984, Viterbo was admitted to Northeast Community Hospital where he underwent a battery of tests conducted by Dr. Alfred Raymond Johnson to determine the source of his ailment. At that time, he was exposed to a diluted form of Tordon 10K and showed no reaction. Blood tests revealed a high level of certain chemicals, including dieldrin, a herbicide. A fat biopsy was also performed but misplaced by the lab before it could be analyzed. Additionally, tests were performed indicating renal failure and hypertension, for which Viterbo was already taking medication. Finally, an electrocardiogram, CAT scan and immune system studies all produced normal results although allergy tests revealed sensitivity to a variety of molds.

The Viterbos initiated this action to recover damages for the alleged toxic effects on Jules Viterbo of Tordon 10K. After discovery had ended, Dow moved for summary judgment on the ground that the Viterbos were unable to prove the necessary causation and alternatively that the Viterbos' expert testimony was not admissible under Federal Rules of Evidence 703 and 403.[1] The district court agreed with Dow and granted summary judgment.

II

In granting Dow's motion for summary judgment, the district court concluded that the expert testimony of Dr. Johnson was inadmissible under Federal Rule of Evidence 703. The district court examined the underlying data on which the experts' opinion was based, and found them to be lacking in reliability and probative value. Specifically, the district court held that Dr. Johnson lacked objectivity in that he diagnosed Viterbo's condition as resulting from exposure to Tordon 10K based only on the patient's oral history and without the benefit of medical tests. Additionally, Dr. Johnson had no scientific literature to support his position and the tests which Dr. Johnson performed did not establish a causal link between Viterbo's symptoms and Tor-

1. The district court also excluded the testimony of another expert, Dr. Raymond Singer, offered by the Viterbos. At argument, however, counsel for Viterbo withdrew him as an expert and conceded the district court properly excluded his testimony. We therefore do not consider the district court's ruling on the admissiblity of his testimony.

don 10K. The district judge further noted that Dr. Johnson had no experience with Tordon 10K and that none of the four of Viterbo's treating physicians would diagnose Tordon 10K as the cause of Viterbo's condition.

III

[1] Whether summary judgment was appropriate in this case is solely dependent upon whether the district court erred in excluding the testimony of Dr. Johnson. In rulings on the admissibility of expert opinion evidence the trial court has broad discretion and its rulings must be sustained unless manifestly erroneous. *Crawford v. Worth*, 447 F.2d 738, 740–41 (5th Cir.1971); *Rodrigues v. Olin Corporation*, 780 F.2d 491, 494 (5th Cir.1986). There is no dispute here that Dr. Johnson was properly qualified as an expert. The dispute centers on the source and basis of the expert opinion that he tendered. We first look therefore to Federal Rule of Evidence 703, which reads:

> The facts or data in the particular case upon which an expert bases an opinion or inference may be those perceived by or made known to him at or before the hearing. If of a type reasonably relied upon by experts in the particular field in forming opinions or inferences upon the subject, the facts or data need not be admissible in evidence.

Although Rule 703 expanded the acceptable bases of expert opinion at common law, *see Soden v. Freightliner Corp.*, 714 F.2d 498, 502 (5th Cir.1983), this expansion does not extend to "make summary judgment impossible whenever a party has produced an expert to support its position." *Merit Motors, Inc. v. Chrysler Corp.*, 569 F.2d 666, 673 (D.C.Cir.1977). The court may still inquire into the reliability and foundation of any expert opinion to determine admissibility. *Soden*, 714 F.2d at 502–03; *In re Agent Orange Product Liability Litigation*, 611 F.Supp. 1223, 1239 (E.D.N.Y.1985).

[2] The district court should, initially, approach its inquiry with the proper deference to the jury's role as the arbiter of disputes between conflicting opinions. As a general rule, questions relating to the bases and sources of an expert's opinion affect the weight to be assigned that opinion rather than its admissibility and should be left for the jury's consideration. *See Dixon v. International Harvester Co.*, 754 F.2d 573, 580 (5th Cir.1985). In some cases, however, the source upon which an expert's opinion relies is of such little weight that the jury should not be permitted to receive that opinion. Expert opinion testimony falls into this category when that testimony would not actually assist the jury in arriving at an intelligent and sound verdict. *See* J. Weinstein & M. Berger, *Weinstein's Evidence* § 702[1] (1985) (assistance of trier of fact is central concern of Federal Rules of Evidence regarding opinion witnesses). If an opinion is fundamentally unsupported, then it offers no expert assistance to the jury. Furthermore, its lack of reliable support may render it more prejudicial than probative, making it inadmissible under Fed.R.Evid. 403. *See Barrel of Fun, Inc. v. State Farm Fire & Casualty Co.*, 739 F.2d 1028, 1035 (5th Cir.1984) (evidence admissible under Rule 703 must satisfy Rule 403 which excludes evidence "if its probative value is substantially outweighed by the danger of unfair prejudice, confusion of the issues, or misleading the jury").

Against this brief background, we now turn to decide the case before us. As we

are reminded by *Soden:* "Though courts have afforded experts a wide latitude in picking and choosing the sources on which to base opinions, Rule 703 nonetheless requires courts to examine the reliability of those sources." *Soden*, 714 F.2d at 505. "Those sources" here are Viterbo's oral medical history, tests conducted by Dr. Johnson, and a study of the effect of picloram on rats. We examine each source in turn.

IV

A.

First Dr. Johnson relies on Viterbo's oral history given during his examination of Viterbo. Although a patient's oral history is generally considered reliable, *see* J. Weinstein and M. Berger, *Weinstein's Evidence* § 703[2] (1985), the history Dr. Johnson used lacked reliability because it was incomplete in a critical area.[2] In forming his opinion, Dr. Johnson was not aware that Viterbo had a family history of depression and hypertension, and that several of his relatives had been hospitalized and treated for these symptoms. This omission is particularly damaging to the reliability of Viterbo's oral history because Viterbo was experiencing symptoms characteristic of depression and hypertension, and Dr. Johnson admitted that hereditary traits could cause symptoms similar to Viterbo's. Thus Dr. Johnson's failure to take into account this family history seriously weakens this source as a foundation for Dr. Johnson's expert opinion.

B.

Next Dr. Johnson relied on the tests he conducted. The tests, at best, support a conclusion that Viterbo suffers from some sort of toxic reaction. The only supportive test results on which Dr. Johnson relies are those showing hypertension and renal failure, both being characteristic of toxic exposure. Neither these test results nor any test result implicates Tordon 10K as the basis for Viterbo's symptoms.[3] Viterbo was, however, exposed to a small amount of Tordon 10K to which he showed no reaction. Dr. Johnson explained that the hospital board would not allow a patient to be exposed to a large amount of a chemical to which they appeared to be sensitive, even though there was no evidence, except Viterbo's subjective belief, that he was sensitive to Tordon 10K. Dr. Johnson further explained that Viterbo adamantly refused closer contact with Tordon 10K, even though, as noted by defense counsel, Viterbo brought Tordon 10K pellets to Dr. Johnson's office. In attempting to explain Viterbo's failure to react, Dr. Johnson stated that the amount was so small that he did not expect a reaction; the fact remains, however, that Viterbo did not react in the slightest degree. However, blood tests did reveal a high level of another chemical, dieldrin, which can cause depression; Dr. Johnson recognized that the level was high

2. The district court rejected Dr. Johnson's reliance on Viterbo's oral history on the ground that Dr. Johnson formed his opinion before conducting any test. We agree that an expert who forms an opinion before he begins his research is biased and lacking in objectivity: *See Perry v. United States*, 755 F.2d 888 (11th Cir.1985). Because we reject Dr. Johnson's opinion on other grounds, it is not necessary to resolve this question. We would note, however, that this could be an additional ground indicating lack of reliability of his opinion.

3. Dr. Johnson himself admitted this at his deposition: "I have not had any scientific proof on a challenge that [Viterbo] is sensitive to Tordon 10-K."

but ignored this chemical as a cause of Viterbo's symptoms, based again on Viterbo's oral history that he had not been in contact with that chemical. According to Dr. Johnson, the dieldrin test was merely an indication of Viterbo's chemical hypersensitivity, but there was no explanation as to how the substance was in Viterbo's blood.

The significance of the lack of objective evidence linking Tordon 10K to Viterbo's ailments is heightened by Dr. Johnson's admission that the symptoms could have a number of causes. When asked to name other potential causes of these symptoms, Dr. Johnson stated, "You know, you read the textbook of medicine, and any page you turn to, you will find those symptoms can be caused by any disease process." It is clear to us, as it was to the district court, that Dr. Johnson's reliance on these test results as a source of his opinion that Tordon 10K caused Viterbo's illness is unfounded.

C.

Finally, Dr. Johnson relied on a study of the effect of picloram on rats that showed that when exposed to large amounts of the chemical, the rats developed cancerous tumors and died. He admitted that the effects of chemicals differ between humans and rats. Here, of course, there was no evidence Viterbo had been exposed to comparable amounts, nor that his symptoms were similar in any respect. We then are left to conclude that the study, at most, is only evidence that picloram may produce some unidentified effect on humans. Such evidence is clearly not sufficient to provide a source of support for an opinion that Tordon 10K caused Viterbo's depression, nervousness, hypertension, renal failure and other ailments.

V

[3] In summary, then, Dr. Johnson's opinion rests on Viterbo's statements that he experienced certain symptoms and that Tordon 10K was the only possible cause. This opinion simply lacks the foundation and reliability necessary to support expert testimony. As an unsupported opinion, it does not serve the purposes for which it is offered, that is, objectively to assist the jury in arriving at its verdict. We do not hold, of course, that admissibility of an expert opinion depends upon the expert disproving or discrediting every possible cause other than the one espoused by him. Here, however, Dr. Johnson has admitted that Viterbo's symptoms could have numerous causes and, without support save Viterbo's oral history, simply picks the cause that is most advantageous to Viterbo's claim. Indeed, Dr. Johnson's testimony is no more than Viterbo's testimony dressed up and sanctified as the opinion of an expert. Without more than credentials and a subjective opinion, an expert's testimony that "it is so" is not admissible. The district court properly excluded and granted summary judgment for Dow.

The judgment of the district court is therefore

AFFIRMED.

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CURRICULUM VITAE

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PRESENT POSITION AND ADDRESS:

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BIOGRAPHICAL:

Date of Birth:	June 27, 1926
lace of Birth:	Chicago, Illinois
Marital Status:	Married
Children:	Three
Home Address:	70 Colony Park Galveston, Texas 77551
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EDUCATION:

1948	Microbiology-Biochemistry	B.A.	University of Illinois Urbana, Illinois
1948	Biochemistry	M.S.	University of Illinois Urbana, Illinois
1951	Microbial Genetics-Biochemistry	Ph.D.	University of Illinois Urbana, Illinois

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PROFESSIONAL AND TEACHING EXPERIENCE:

1976-present	Professor and Director	Division of Environmental Toxicology Department of Preventive Medicine and Community Health University of Texas Medical Branch Galveston, Texas
1972-1976	Professor of Genetics	Brown University Providence, Rhode Island
1968-1972	Professor (part-time) General and Medical Genetics	George Washington University Washington, D.C.
1962 - 1972	Chief, Branch Genetic Toxicity Branch	Food and Drug Administration Washington, D.C.
1952-1962	Head, Animal Health Program	Shell Development Company Modesto, California
1951-1952	Senior Microbiologist	Julius Hyman Company Denver, Colorado
1948-1950	Instructor	University of Illinois Urbana, Illinois

COMMITTEE RESPONSIBILITIES:

UTMB Committees:

University Cancer Center Committee (through 1982)

University Appointment, Promotion and Tenure Committee (through 1980)

University Fellows Grants Committee

Department of Preventive Medicine and Community Health Executive Committee

Department of Preventive Medicine and Community Health Steering Committee

Department of Preventive Medicine and Community Health, Appointment Promotion and Tenure Committee

Outside Committees:

1987 Member, Water Quality Advisory Committee, Texas Water Commission

1985 Member, Scientific Review Panel for the National Library of Medicine

1984 Board Member, Committee for Responsible Genetics

1983 Member, Food and Nutrition Board's Committee on Food Chemicals Codex (expires October 31, 1987).

1983 Member, Board on Toxicology and Environmental Health Hazards' Committee on Epidemiologic Investigation of Air Pollutants (expires March 31, 1985).

1983 Member, Agent Orange Advisory Committee to the Texas Department of Health (expires January 1, 1988).

1983 Environmental Protection Agency Science Review Panel for Health Research

1983 Subject Selection Committee of the Texas Veterans Agent Orange Assistance Program

1980 March of Dimes Committee on Reproductive Hazards (Chairman)

1980 Environmental Protection Agency Research Grant Review Panel

1980 Environmental Protection Agency Criteria Document Panel

1980 Environmental Protection Agency Committee Chairman, Gene-Tox Program (HMA)

1980 Science Committee of Food Safety Council

1975 Oversight Committee for Proctor and Gamble to determine adequacies of toxicological procedures

1975 Committee 17, Analysis of Methodology of Mutagenicity Testing

1973 National Academy of Science Committee on Biological Hazards of Low Levels of Radiation

1972 Member of Swedish Government Sponsored Committee on Mutagenicity Testing

1971 Japanese and United States Government Committee on Toxicology

1971 Member of World Health Organization Committee on Use of Hycanthone

1971 Chairman of Government Hearing on Safety of Immunological Preparations

1970 Member Steering Committee on Industry-Academic, Committee on Toxicology

1970 National Institute of Mental Health - Committee on Genetics Effects of Drug Abuse

MEMBERSHIP IN SCIENTIFIC SOCIETIES:

American College of Toxicology
Co-Founder and Member, Environmental Mutagen Society
New York Academy of Sciences
Society of Occupational and Environmental Health

HONORS:

Honorary Health Advocate Award - "... awarded in recognition of outstanding contributions in health advocacy and promotion of the public's health to Marvin S. Legator." Health Policy Advisory Center, New York, New York, November 15, 1983.

Food Safety Council 1976-1982 - "With deep appreciation for the tireless effort that Marvin Legator devoted to help the Food Safety Council achieve its goals. This experiment in concensus building has shown that representatives from industry and non-industry with different viewpoints can work together toward a better way for making food safety decisions."

U.S. Environmental Protection Agency Certificate of Award - Presented to Marvin S. Legator in recognition of noteworthy contribution and special achievement for the U.S. Environmental Protection Agency, Cincinnati, Ohio

Visiting Scholar Award at Western Michigan University 1980

Nominated for 1980 Distinguished Faculty Research Award

F.D.A. Award of Merit - Presented to the Genetic Toxicology Branch (M. Legator, Chief), 1971

Key Lecture Award by the American Genetics Association for Outstanding Contributions on the Implementation of Genetics for Human Welfare and Improvement, 1970

U.S. Government Award - Technique Advance in Cell Culture, 1965

ADDITIONAL INFORMATION:

Areas of Teaching and Research Competency:

Mutagenicity
Cytogenetics
Reproductive Studies

Biochemistry
Molecular Biology
Tissue Culture (Post Doctorate Course, University of Wisconsin, Madison, Wisconsin)

Consulting Activities:

Panel Member, Toxicology Panel on Psychochemicals, Commission on Life Sciences, National Research Council, National Academy of Sciences, 1983
Expert Witness, Texas Senate Subcommittee on Consumer Affairs, 1982
Expert Witness, U.S. House Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce, 1982
Consultant, Hooker Chemical Company, 1980
Consultant, JRB Associates, 1980
Consultant, Toxi-Genics (Fabrizio), 1980
Consultant for Environmental Protection Agency, 1976-1980
Consultant for Lady Clairol, 1976-1978
Expert Witness, Committee on Science and Technology, 1975
Dow Chemical Company, 1974-1979
National Institute of Drug Abuse, 1973-1980
Consultant, Senate Committee on Public Works, 1970

Other Activities:

Elected Member, Collegium Ramazzini, 1983
Member of the Board of Directors, Committee for Responsible Genetics, 1983.
Member, Critical Issues Committee on Accreditation, Certification and Standardization, Environmental Mutagen Society, 1983-84.
Co-chairperson, Workshops and Training Committee, Environmental Mutagen Society, 1983-84.
Member of the Board, Texas Center for Rural Studies, Inc. The corporation is organized to provide research and educational services regarding the quality of life in Texas, including, but not limited to, the health, economic and environmental effects of pesticides and other chemicals; public policies effecting the rural economy; and the enhancement of the role of family farmers, farm laborers and rural residents in Texas agriculture, 1983, Austin, Texas.
Co-Director of Workshop, Environmental Influences on Fertility, Pregnancy, and Development: Directions for Future Research, May 24-25, 1982, Cincinnati, Ohio
Director of CME Workshop for Practicing Physicians, Recognizing, Diagnosing, and Treating Chronic Toxic Chemical Effects, July 16-18, 1981, Galveston, Texas
Director of Annual Genetic Toxicology Course, Galveston
Director of Annual Genetic Toxicology Course, Hunt Valley
Co-Director of Annual Toxicology and Law Course, Houston
Director of Annual Workshop on Carcinogenicity, Mutagenicity and Teratogenesis
sponsored by the March of Dimes Birth Defects Foundation
Faculty member of short course on Toxicology at Wayne State University,

1976-1979
Coordinator of Workshop on Occupational Monitoring for Genetic Hazards, March 27-29, 1975
Visiting lecturer to Heidleburg University, Germany, 1971

Editorial Responsibilities:

Editor, Journal of Teratogenesis, Carcinogenesis, and Mutagenesis
Editorial Board, Journal of Environmental Mutagenesis (through 1981)
Editorial Board, Toxicology and Industrial Health
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Reagan's moment of truth

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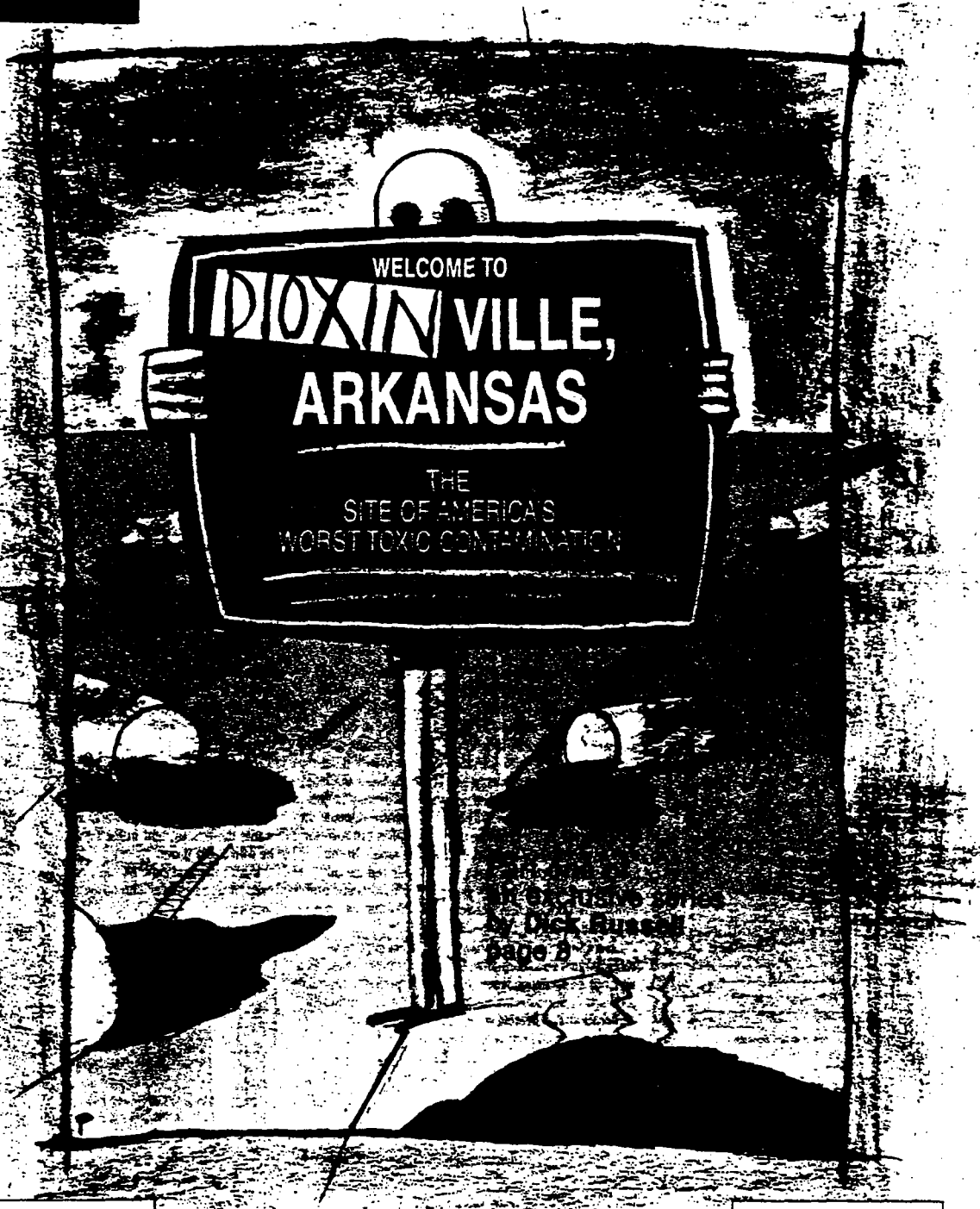

1988 Peter Hannan

A Walk in the Woods
Nukes on Broadway

Heinemann's Vietnam
A veteran author's tale

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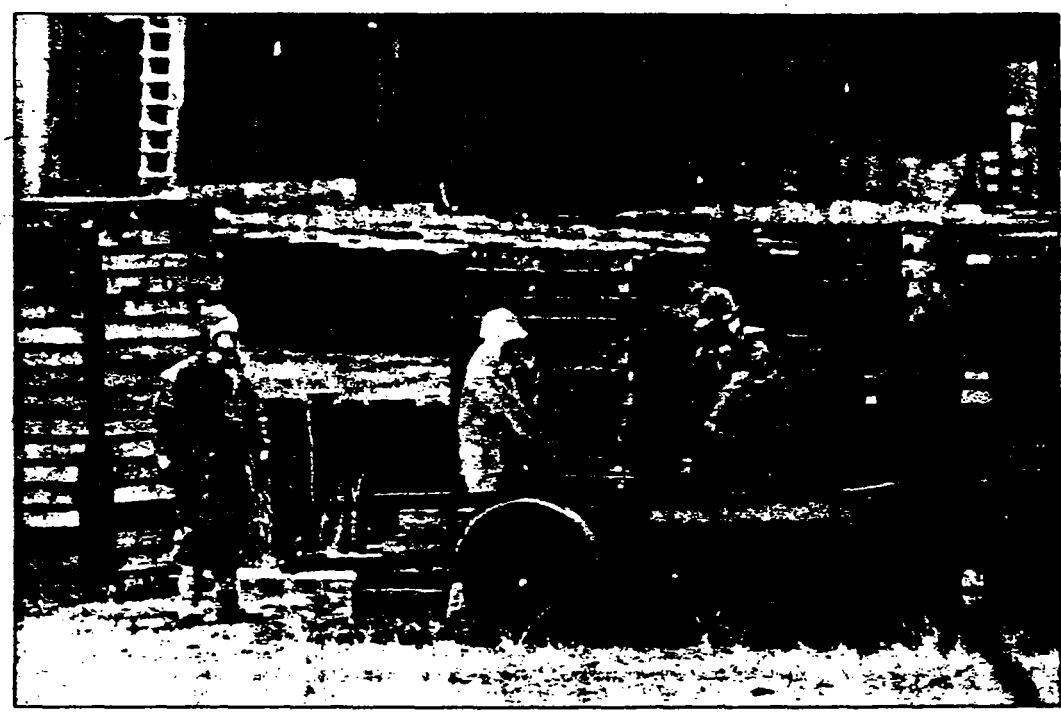
WELCOME TO DIOXINVILLE, ARKANSAS



This is the first part of a three-part series of articles on the chemical contamination of a small Arkansas community. It is the worst hazardous waste situation yet known in the U.S., more serious than those that forced evacuation of residents from Love Canal, N.Y. and Times Beach, Mo.

Babies are dying and adults succumbing to sudden disease in three neighborhoods that border EPA Superfund cleanup sites in Jacksonville, Ark. But the ramifications reach far beyond these sites.

Jacksonville holds a mirror to larger national questions surrounding toxic wastes, incineration and the continued production of deadly chemicals. It also reflects neglect and mismanagement by federal and state governments. And the picture encompasses not only the Pentagon and its Agent Orange and rocket fuel contracts, but the hidden involvement of multinational corporations and foreign entanglements.

The Arkansas saga is a microcosm of a much bigger problem in an increasingly toxic America, for what has happened in Jacksonville is far from an isolated phenomenon. Particularly in the rural South, many similar communities fighting for their economic survival have become dumping grounds. While state and local officials as well as business leaders protect their interests, the impoverished suffer—and take on the struggle against greed and indifference. In dozens of areas, people like Arkansas' Patty Frase are running the gauntlet to fight the pollution affecting their homes. This is their story, too.

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By Dick Russell

JACKSONVILLE, ARK.

IT IS A QUIET SUNDAY AFTERNOON IN THIS CITY OF nearly 30,000 residents 12 miles northeast of the state capital of Little Rock. Patty Frase turns her station wagon off the freeway and onto Route 67 leading into town, then says, "Just don't touch the food, drink the water or even wash your hands in Jacksonville."

Some local citizens don't call their hometown Jacksonville. They refer to it as "Dioxinville," and to the Arkansas Department of Pollution Control and Ecology as the "Department of Political Corruption and Endangerment." And with good reason: this Arkansas community is the site of the worst dioxin contamination in the U.S., with levels of the poison found in local soil testing well above the range that led to the Environmental Protection Agency's (EPA) 1983 evacuation of Times Beach, Mo.

"The people of Jacksonville should have long ago been given the right to evacuate and received compensation for their homes," says Lois Gibbs, director of the national Citizen's Clearinghouse for Hazardous Wastes based in Arlington, Va. "The dimension of the problem is just outrageous—babies dying, whole neighborhoods with unbelievable cancer rates. When I was there three years ago, they were talking about dioxin being in the drinking water supply while the federal Centers for Disease Control (CDC) was saying there was no cause for alarm. The truth really has never been exposed."

Frase has been working around the clock since 1981 to get the truth out. She says she finds herself up against many formidable opponents seeking to keep the lid on an expensive situation: the [illegible] the EPA, Dow Chemical, Arkansas Gov. Bill Clinton, his state bureaucracies and a local Chamber of Commerce-sponsored group called Jacksonville People With Pride.

"Witch's brew": Ever since World War II, three different chemical companies had manufactured a growing range of toxic chemicals here. The first plant, locally owned Reasor-Hill Chemical, was originally located on Little Rock Air Force Base property. After moving in 1948 to the current plant site, the company continued to manufacture the since-banned DDT, aldrin and dieldrin pesticides and insecticides. Hercules, Inc., which took over the site in 1961, produced at the plant nearly 20 percent of the Agent Orange shipped overseas for defoliating the jungles during the Vietnam War. After Hercules sold the Jacksonville operation, Vertac Chemical Corporation continued to manufacture for domestic use both of the herbicides used in Agent Orange. They were 2,4,5,-T, banned as a cancer-causing agent by the EPA in 1983, and 2,4-D, also a suspected human carcinogen.

The result, as described in one federal court proceeding, has been a "witch's brew" of contamination of air and water, not only in Jacksonville but also stretching for miles along the Bayou Meto flood plain. About 20 chemicals have been measured in Jacksonville's air, including 12 that were also found in tests at contaminated Love Canal, N.Y.

Then there is dioxin, a contaminant byproduct of Agent Orange, 2,4,5-T and possibly 2,4-D herbicides. According to a publication of the EPA's Office of Research and Development titled *Dioxins*, "It is reasonable to presume that the slightest trace of 2,3,7-8-TCDD [the most lethal form of dioxin] in the environment may have adverse effects on both human and animal populations."

Dr. Samuel Epstein, one of the nation's foremost experts on the health effects of toxic chemicals, says TCDD is the most potent cancer-causing and birth-malforming substance known, producing effects in experimental animals at [illegible] as 10 to 100 parts per trillion. (See story on page 38 for more on dioxin.)

The EPA considers liquids dangerous to human health when they contain one part per billion. Anything above that "action level" is supposed to compel the EPA to begin cleanup. Just one part per million is therefore 1,000 times more toxic. In Jacksonville dioxin was measured in about 2,800 barrels of 2,4,5-T herbicide waste stored at the chemical site at concentrations as high as 111 parts per million. The average was 40 parts per million. Some of the barrels of 2,4-D waste were discovered to be leaking when the EPA moved onto the site in 1987 and initiated re-drumming and other cleanup. Altogether, at least 30,000 barrels of hazardous materials still await disposal.

Levels of dioxin higher than one part per billion have also been found in two soil samples taken from residents' yards near Vertac, as well as in the air, in the city sewer system and lagoons, in the sediments of the nearby flood plain, and in fish and wood ducks.

The Jacksonville chemical plant currently ranks 18th on the EPA's Superfund list of nearly 1,000 priority toxic waste cleanups. As an EPA official testified at a 1984 hearing, even if dioxin were not present, "the highly toxic nature of the other chemicals would cause it to be included."

And the people of Jacksonville face another, even grimmer, possibility. At a court proceeding against Vertac in Little Rock last summer, U.S. District Judge Henry Woods reiterated concerns he had expressed since 1980 that the wastes are stored in "tornado alley." Added Judge Woods, "Certainly we won't want a Chernobyl-type disaster with this spewed all over Arkansas. Some plan needs to be developed to get rid of that material. I'm sick of it."

Prior to failing to meet standards for the discharge of pollutants into the city sewer system, Vertac closed its doors in January 1986. The plant was sold [illegible] and now stands idle in the Jacksonville industrial district.

"The plant was shutting" for years, Patty Frase says, symptomatic of the local economy—the chemical plants and the Little Rock Air Force Base. Since the mid-'70s, Frase's father had served off and on as acting base commander.

"In 1974 my father had just retired from the military at 51 and was in good shape," Frase says as she turns onto Macarthur Road toward Vertac. "Then he woke up one morning, went into a coma and was dead by noon. There was a major fire at the plant right before this, a blowout when the reactor vessel caught fire one night. It destroyed everything around that area. All the oaks, every hardwood practically disintegrated overnight. There were dead dogs, dead squirrels. All the fish died in the discharge area into Rocky Branch Creek.

"For years we'd lived a few blocks away, and I have no doubt that my father died of chemical poisoning," she continues. "They did an autopsy, but couldn't find anything, so they decided that his colon burst.

"My mother started checking around the area, and said, 'Everyone here is dying of cancer. We're moving.' Right after that she went into the hospital with liver cancer. She had just turned 50, and nobody had ever had cancer on either side of our family. The day before she died she told me, 'Go get 'em, Patty, and watch out for your health.'"

So she did. Despite her own mounting health problems, Frase organized the Arkansas Chemical Clean-Up Alliance and eventually was named to the Governor's Task Force on Hazardous Waste. Moving with her husband Tommy to the town of Benton, 30 miles on the other side of Little Rock, she had six miscarriages before finally conceiving a daughter, now age two. Their son, who is deaf in one ear from peripheral nerve damage, and suffers periodic bouts of severe [illegible] (skin lesions resulting from contact with TCDD) as well as [illegible] ance that finds her gaining and then losing large amounts of weight, one of 45 Jacksonville residents who opted out of court with Vertac in a potential injury and wrongful death class-action lawsuit the day before Vertac shut down its operations.

"When I was in high school and a lot of us kids had our lymph nodes start to get huge, the doctors at the base told us we were allergic to deodorant," Frase continues. When, after her mother's death, she first approached Vertac officials to ask about the chemical odor in the air, "I was told that it wasn't coming from Jacksonville, that I was smelling the paper mills in Pine Bluff. I went to the state regulatory agencies, but nobody there would give me any straight answers either."

Frase slows down as her car approaches the 140-acre Vertac compound, its interior shielded by a tall chain-link fence and a series of pine trees contracted by the city as part of a "beautification program." Pointing out the window, she says, "Jacksonville wants to make it look good, so they hired a company to put pines where all the hardwoods used to be. The hardwoods' roots are so long that they'd get into the contamination and die."

EPA's delayed reaction: Today a chemical odor continues to linger in the air for blocks around the Vertac site. Behind the wall of trees stands a waste mountain containing the highest levels of dioxin ever measured in the U.S. Nobody knows how many more barrels were long ago buried here and elsewhere, or their contents simply dumped into the Rocky Branch Creek that curls away from the site to empty into the flood plain and eventually the Arkansas River. Despite

Continued on following page

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health complaints and reports of massive fish kills as far back as the '50s, the dioxin threat was not brought to public attention until 1979. At the time, following criticisms of the EPA's handling of the Love Canal waste crisis—a situation the agency admitted was far less severe than Jacksonville's—an EPA spokesperson told the *Washington Post* that the agency would move faster on cleaning up Vertac than on any previous site.

But while the EPA did conduct testing for contamination, eight years passed before the agency sent a team of workers in "moon suits" to begin the cleanup. Not until Vertac said it could no longer afford to continue to re-drum corrosive wastes there did the EPA take responsibility on Feb. 1, 1987.

The team sent to Jacksonville found "drum alley," a large storage area with thousands of the heavy corroding barrels stacked three-high, in violation of federal regulations. And they found "Vertac mountain," where 20,000 cubic yards of dioxin-contaminated sludge dredged from old lagoons on the site had been piled about 20 feet high. Altogether, more than 100,000 cubic yards of contaminated materials, enough to cover 20 football fields three-feet deep, were discovered within the plant's perimeter. Besides the leaking drums, soil was eroding, allowing contamination to wash off the site.

Many of the buildings contained "wall-to-wall, ceiling-to-ceiling drums," the EPA's on-scene coordinator, David Woods Gray, told the *Arkansas Democrat*, one of Little Rock's two daily newspapers. Some of the drums were packed tight in concrete bunkers, a carry-over from the site's original use as a World War II ordnance plant. The *Democrat* reported that aisle space proved inadequate to perform inspections or maneuver equipment to remove the leaking drums. Not only were the buildings structurally unsound, the EPA found, but also heavily contaminated. One tank had been leaking dioxin for so long that stalactites and stalagmites made of the gummy chemical had formed under it. A similar substance ran regularly into the floor drains leading to the site's central drainage ditch. One of the four ditches drains directly into the Rocky Branch Creek.

During the EPA's first six months on the site last year, workers built two huge barns to house some of the drums and erected 10,000 feet of four-foot-high fencing around the perimeter. The agency also re-drummed an average of 500 to 600 leaking barrels a week. The EPA, still on the site today, has authorized $4.6 million for maintenance at Vertac. But after only nine months, it had already spent about $3 million.

"This is one of the most serious public health disasters in the U.S.," says Adrienne Anderson. "The number of mysterious SIDS (Sudden Infant Death Syndrome) deaths is horrifying."

The contamination at the site, however, is only the beginning of the toxic chain.

Bottom of the barrel: An EPA study to determine where dioxin and other chemicals had migrated, conducted between the fall of 1983 and spring of 1985, found the worst contamination below the Jacksonville sewage treatment plant's outflow into the Bayou Meto flood plain. The city's entire sewer system was deteriorating, filled with broken lines. For years after heavy rains, sewage overflows occurred regularly in the residential area south of the plant. And during dry periods, the EPA noted, chemicals likely filtered into the shallow groundwater adjacent to the sewer lines. The average dioxin concentration in the sewage collection system was 21.5 parts per billion (ppb), and dioxin was detected as high as 200 ppb—200 times the EPA's action level for cleanup.

Then there was the flood plain itself, mostly irrigated farm land, laced with dioxin contamination after heavy rains. Out of 324 soil and sediment samples taken by the EPA in a study of off-site pollution, more than one-third contained TCDD-dioxin. In tests of fish taken from the stream running along the Bayou Meto flood plain, TCDD-dioxin was detected at 35 times the Food and Drug Administration's action level, with dioxin showing up in fish as far as 80 miles downstream from the Vertac plant. So did a host of other persistent chlorinated hydrocarbon chemicals, some of which, like the banned DDT, hadn't been manufactured for years.

Since the early '80s officials of the state Game and Fish Commission have periodically discovered contaminated fish in Arkansas markets. And in 1985 officials in Memphis, Tenn., complained to Arkansas officials that fish from the flood plain area reeked of chemical phenolic odors.

During the '60s, the late Dr. Rex Hancock, a dentist in Stuttgart, Ark., first began sounding the alarm about fish kills and the biological destruction of the Bayou Meto. He and some friends went to the chemical plant, then owned by Hercules, and took photographs documenting the deliberate discharge of chemicals into Rocky Branch Creek. At the time thousands of hunters and fisherman signed petitions that were presented to the governor, but the state took no action against the companies. In subsequent tests Hancock conducted with Frase in the streams around Jacksonville, minnows put in the Meto water survived no longer than two seconds. Later, Hancock, desperate for action, poured catfish juices onto the lap of an EPA hearing officer, telling him, "Oh don't worry, it doesn't cause fertility problems."

Ralph Wiggins, a former plant engineer at Hercules who underwent triple-bypass heart surgery at age 38, recently informed the EPA about the time he became alarmed at dumping into the creek and was told by company bosses to remove all containers marked Hercules because "we don't want a big fish kill and be responsible for it." But the fish kill happened anyway.

Fish haven't been the only casualties. In 1985 plant worker James Cox died shortly after toxic chemicals accidentally splashed on him. Paul Koros, a fire department paramedic, tried to revive him and also suffered chemical poisoning. Koros, now 24, suffers recurring seizures and shows signs of leukemia. While his $800,000 negligence suit against Vertac is still pending, the Arkansas Fire and Police Pension Review Board denied Koros' requested disability benefits in December, when its physician stipulated that dioxin poisoning could not be proven.

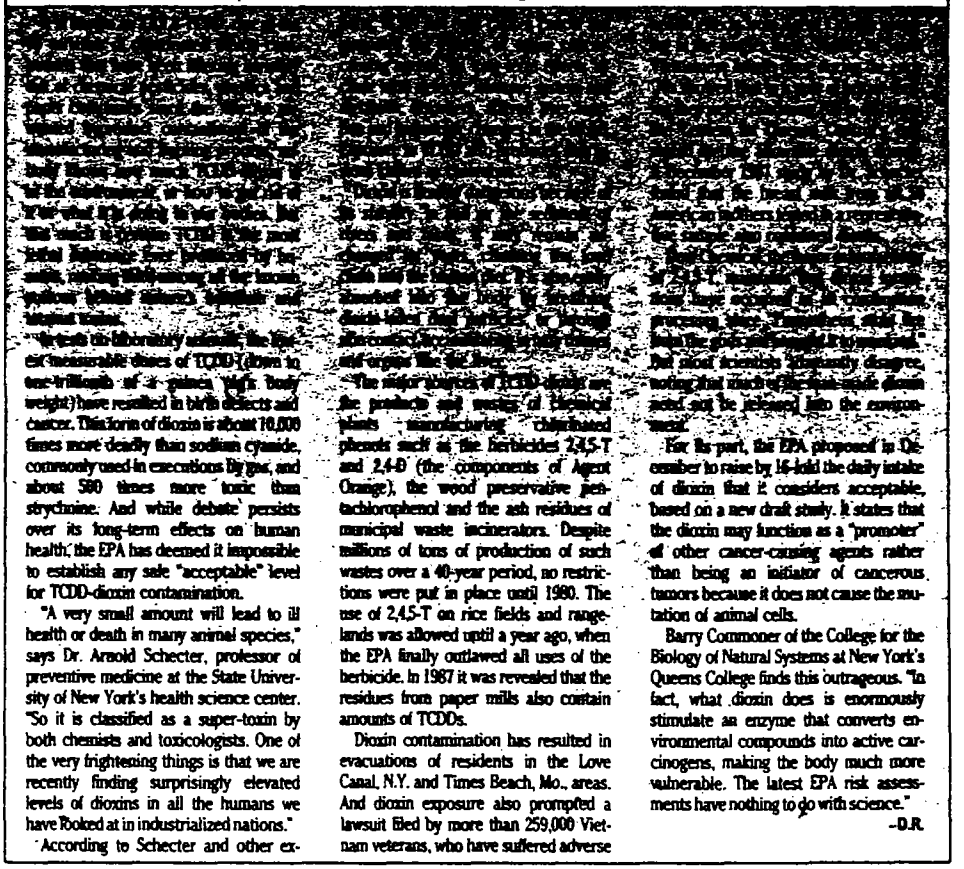
Welcome to cancer alley: In the neighborhood bordering the Vertac facility, just around the corner from a nursing home and a hospital, not a soul seems to be stirring. The air is still, but eyes are burning. "Your ears will ring after a little while," says Jack Park, a 23-year resident now in his early 60s. Park, who worked at the plant when it was owned by Reasor-Hill and who headed the laboratory under Hercules, maintains that some chemicals used to make Agent Orange were brought to Jacksonville in bulk. He says some came from Hooker Chemical in New York, the company responsible for Love Canal.

"We brought tetrachlorobenzene from Hooker by the train carload," he says. The toxic chemical was later found in fish along the local flood plain.

A few years ago Park suffered a stroke. "This is cancer alley," he says matter-of-factly. "My next-door neighbor is dying of liver cancer right now. When some of us got tested by Dr. Aubrey Worrell in Pine Bluff, I had the honor of having the highest levels of chemicals in my blood. I got a petition drawn up by a lawyer friend asking for a health evaluation door-to-door. That was 10 years ago. It's never happened."

Hobbling outside with his cane, Park points out the spots where hydrochloric acid

Dioxin: the most lethal substance ever produced by humans



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Clay Carson/Arkansas Democrat

Patty Frase (pictured here addressing members of environmental groups): "Just don't touch the food, drink the water or even wash your hands in Jacksonville."

has eaten away the cement in his driveway. "For every pound of herbicide, the plant used a pound of hydrochloric acid. It came in by the carload." He picks up a grape plant, gnarled and twisted with mutation, and shakes his head.

Mozelle Bergschneider, 71, has lived two blocks from the plant since 1946. She has conducted her own survey within a four-block radius of her home. On her list of 50 deaths in recent years, she says most of these were cancer victims. Another 17 people, she says, are undergoing chemotherapy or other cancer treatment programs. Since no state or federal study of the area's cancer rate has ever been conducted, residents are the only monitors.

Bergschneider tells of running her tongue around her mouth certain mornings and finding a sweet taste. "That's dioxin," she says. "The problem is we have smelled it for so long that our olfactory nerves are about gone. This is a dead town, not fit for human habitation, or animal. But I have no place else to go. That's true for 99 percent of the people here."

A few miles from the Vertac facility, sandwiched in among a rural neighborhood of homes, are the Graham Road and Rogers Road dump-sites. Although both Hercules and Vertac officials have denied under oath that any of their products ended up at the two landfills, some of the same wastes buried at the plant site were found by the EPA at both, including open drums. The EPA estimates that more than 1,000 barrels were discarded at the landfills over the years. Dioxin, herbicides, PCBs and numerous other chemicals have been detected in the soil.

The EPA also reported finding one form of dioxin in a family's tap water, and two different forms in a municipal well near the dumps. But the agency later said these results were mistakes, because the samples had been accidentally contaminated during laboratory analysis. According to some local residents, dioxin mixed with waste oil was sprayed on the rural roads to control dust, the same situation that forced the evacuation of Times Beach. *In These Times* was unable to confirm the spraying.

Alsie Glover, 53, lives right between the two dump-sites and raised four children there. Two of her sons bought homes nearby, before anyone knew about a contamination problem. Last August she joined about 100 other residents in suing Vertac, Hercules and the city of Jacksonville, seeking unspecified damages for property and health effects. The city was dropped from the case, Vertac settled out of court with the citizens, and on March 1 Hercules was acquitted by a jury in a Little Rock federal court.

The city owned and operated the Graham Road landfill, allowing the dumping of hazardous chemicals until 1973, when the state ordered it closed because of the high water table and poor drainage.

Nowhere to go: Now the EPA, which finally added both dump-sites to the Superfund cleanup list last summer, is paying a visit. Three women from the agency's Dallas regional office sit around Glover's kitchen table, seeking to determine the extent of the damage.

A few years back, Glover recalls being told by another EPA official, "If I were you, I'd get my family out of here." But she told him she couldn't afford to move. Before the city dug ditches last year, water from the creek below the Rogers Road landfill would stand in her yard for a week or two at a time.

"It would flood over the barrels," Glover says. "We didn't know for years they had anything bad in them. I'd pay the city man who ran the site $2 apiece for them to burn trash in. So did a lot of people.

"Several times I got just deathly sick," she continues. "One time you'd turn your faucet on and it'd stink so bad you couldn't stay in the kitchen. Wasn't no such thing as opening up your house in summertime, because of the odors. The cinders from burning the trash down there would be all over the car. When they finally closed the dump, they had the pigpen right there."

The EPA officials do not follow up Glover's last statement. Yet in June of 1985 another EPA crew had discovered some pigpens sitting where the waste was once burned. The pigs had been contracted out to a local farmer to raise by the Tyson Chicken company, one of the largest poultry producers in the world, based in Springdale, Ark. The pigs, which wallowed regularly amid the toxic barrels, were eventually sold to slaughterhouses for market, "going into," as Frase puts it, "your TV dinners or bacon."

She adds, "The state was talking about giving the farmers compensation for their contaminated pigs long before they told people not to eat from their gardens or let their children play outside there."

Despite a letter Glover received from the state Health Department warning that her well water was unfit to drink, the Jacksonville City Council balked for months at pumping a public water supply to the area. Now that residents have finally received city water, their water bills run as high as $90 a month, far beyond what most Jacksonville families can afford.

When Glover asks the EPA representatives if they'd like to take a drive through the neighborhood, they reluctantly agree.

What they witness is a house-to-house chronicle of disease—from allergies and respiratory problems, to cancer and heart disease, both of which have affected numerous people before they reach 50. Glover does not wish to talk about her own health problems, only the allergy shots that her daughter-in-law and little granddaughter must take weekly.

In a 1985 report about the dump-sites, the EPA noted that "seven dead dogs were found in the two drainage ditches" and "it appeared that children had played there quite extensively."

It is, beyond a doubt, the children of Jacksonville who have suffered the most. An informal survey taken in 1985 by the *Arkansas Democrat* of children living in close proximity to the dump-sites (most of whom attended an elementary school in the same area) found 10 of 18 with serious health problems, including spina bifida (fluid on the brain), seizures, an infant with a hole between the chambers of the heart and a baby born with part of her brain outside the skull. While no direct link to dioxin could be established, some state health officials told the *Democrat* that the unusual situation merited further study.

Some of Jacksonville's children never survive at all. "This is one of the most serious public health disasters in the United States," says Adrienne Anderson, western director of the National Campaign Against Toxic Hazards. "The number of mysterious SIDS (Sudden Infant Death Syndrome) deaths is horrifying."

Residents refer to a section of a local cemetery as "babyland," where babies under six months old whose parents can't afford

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to bury them in family plots can be interred at no cost. Of nine babies known to be buried here, seven died in 1985. One of them was three-month-old Joseph Shelton, whose mother had grown up near the dump-sites and whose family was then living a few blocks away. The story of events following this infant's death paint a still-larger picture of governmental indifference, even cover-up.

Ignoring the evidence: On Sept. 6, 1985, after the then-healthy Shelton baby received a 2 a.m. bottle feeding, the young parents awoke to find him dead in his crib. A week later another child, 17-month-old Jeff Shelton, began having seizures and was rushed to the hospital. The director of pediatric neurology at Arkansas' Children's Hospital, Dr. Robert Woody, suspected something unusual after an intern ruled out spinal meningitis.

Hospital tests on Jeff seemed to reveal the existence of a high-level chlorophenol chemical in his blood. The physicians then closely examined tissues from an autopsy that had already been performed on Joseph, a standard Arkansas practice for SIDS deaths. Dr. Marge Brewster, who heads the hospital's Metabolic Laboratory and is in charge of Arkansas' Reproductive Health Monitoring System, then contacted the Enviro-Health Systems laboratory of Richardson, Texas, one of the few private labs in the U.S. that is equipped to do further testing. As a favor, it agreed to do an unusual assay (analysis) of the deceased child's liver and kidneys, looking for specific toxic chemicals.

"Part of what we asked for," says Dr. Brewster, "was an assay for chlorophenols, thinking that those being released at the time through the Jacksonville sewer system could potentially be volatilized and available for exposure."

In December the hospital received the test results. Levels ranging as high as 508 parts per billion of six chlorophenols—the class of chemicals used in the manufacturing of 2,4,5-T, 2,4-D, 2,4-DB and Silvex herbicides—were found in the Shelton baby. At least three of them were known to cause cancer in lab animals, and one was a mutagen that alters cells' genetic material. Dr. Woody told the *Arkansas Democrat* that the amounts were "above usual levels for urban adults," adding that there are no "normal" levels of such chemicals in the blood. Other chemicals, phenoxy herbicides, were also found in two urine samples taken from the mother, 19-year-old Brenda.

"We then requested that the Centers for Disease Control in Atlanta utilize the other half of [Joseph's] tissue we had stored to repeat the assay," Brewster says. "At the time we had stored approximately 100 other babies' tissues from SIDS deaths that could have been assayed simultaneously."

When the story broke in the *Arkansas Democrat*, citizens began to demand some answers from state officials. At one gathering state epidemiologist Dr. Tom McChesney, a retired Air Force veterinarian, commented that the autopsy findings had been "prematurely released" and that it was "most difficult to assess what they mean," noting they were being sent on to the CDC. He then suggested the chemicals may have come from herbicides sprayed around the Shelton home.

At another meeting of the city's sewer commissioners, Frase remembers, "Somebody had the audacity to say, 'I wonder if she was bathing that baby in Lysol,' and they all had a big chuckle about it. This woman might be poor and uneducated, but she's not gonna bathe her baby in Lysol."

All the Sheltons' could figure was that the chemicals might have gotten into Joseph's body from the water that was mixed with his formula. Or, as Dr. Brewster suspected, they could easily have been passed on during pregnancy.

A Vertac spokesperson, however, says the baby's death was more likely caused by burning treated wood in the family's woodstove or by pesticide traces state inspectors detected around the kitchen sink.

"After quite some time," says Dr. Brewster, "the final answer we got from the CDC was that no, they would not re-assay the tissues or anybody else's either. The reason they gave me was that they had sent an investigator and were not pleased with the quality control at the Texas lab." Besides, said the CDC, their scientists had researched medical literature and had found no record of chlorophenols ever showing up in human liver and kidney tissues.

Asked why the CDC wouldn't pursue it anyway, Brewster replies, "I was very disappointed at their approach. CDC has billed itself as being the nation's public health laboratory, and with a question of this type, it's really the only resource we have to go to for an answer. I thought we had all the material they needed to get some very definitive answers, and their excuse doesn't make any sense to me."

The ultimate decision, Brewster says, came from Dr. Vernon Houk, director of the CDC's Center for Environmental Health. Explaining that decision Dr. Houk says, "The [Texas] lab is lousy. Their quality control is not sufficient for them to do the things they say they can. Any lab testing parts per billion in autopsy materials that have been preserved in formalin is not worthy of being called a lab."

Dr. John Lasiter, director of the Texas laboratory, would not comment on the controversy, saying only that his lab is CDC certified and that it is a "political situation." Lasiter has served on the EPA's Science Advisory Board longer than any current member.

Asked why the CDC didn't do its own testing on the Shelton baby, Houk replies: "Well, what are you going to test? You cannot test the tissues because once they have been in formalin, no one knows what the impurities in the formalin are when you're talking about low parts per billion. Like in the early days of Legionnaire's Disease, before we knew what it was, there was a lot of speculation because there were trace amounts of nickel in the autopsy tissues. Well, the source was really nickel plating of the autopsy instruments."

As for dioxin contamination, Dr. Houk adds, "Our concern about the human health effects of chronic low-dose exposure are much less than they were in 1980. We have gotten a lot of information that appears that humans are not as sensitive to dioxin as the most sensitive laboratory animal. Everybody in this country has TCDD in their body, up to 18 parts per trillion measured in fat. It is no cause for alarm."

Dr. Brewster, asked whether she believed the CDC simply didn't want to create a stir over the Shelton baby incident, comments: "I think in general the CDC's attitude with regard to these toxics questions is one of skepticism. They tend to wait until there's ample evidence of a problem before bringing any big guns to bear upon it. That places people in the situation of gathering their own evidence, before the best set of expertise gets into the picture at all."

Back in 1983 Arkansas' health department director, Dr. Ben Saltzman, had requested federal help after citizens complained about ill health. The CDC had agreed to analyze data on Jacksonville chemicals. Up to that point, the only other tests had been conducted on 55 former workers at the chemical plant by the Mount Sinai Medical Center, which found "effects of unknown significance" on nerve conduction in 46 percent of them. Blood, fat tissue and urine samples were sent back to New York, but test results never came back. Arkansas itself doesn't even have a statistical cancer registry, which can help a state identify unusual cancer clusters in specific areas.

A CDC cover-up? Even prior to the Shelton baby incident, the CDC had hedged. Despite a state recommendation that all toxics be considered in the CDC's investigation, the CDC examined only the EPA's measured environmental dioxin levels in Jacksonville. Then in July of 1985 the CDC decided not to undertake a fatty-tissue study of residents. Their reasoning, which was contradicted by EPA studies, was that Jacksonville's dioxin problem was not as bad as Times Beach's.

After the CDC turned down further testing of the Shelton baby, Dr. Brewster personally contacted four EPA/CDC labs. Each of them also turned her down. Finally, a California lab said it would examine 10 unlabeled baby assays, including the Shelton's, for a $10,000 fee.

In the interim, according to Brewster, the other 100 tissue samples of SIDS victims being preserved by Children's Hospital were thrown out, apparently by accident, by a morgue attendant. "I feel now that I should have gathered them in a safe," she says.

Jacksonville's dioxin disaster: a chronology

1946–The World War II Arkansas Ordnance Works is sold by the federal government to Reasor-Hill Chemical Corporation, which begins to formulate the insecticides DDT, aldrin, dieldrin, toxaphene and others. Drums of wastes are stacked in an open field near the operations area.

1957–Reasor-Hill starts production of the subsequently banned herbicide 2,4,5-T, in addition to its other chemicals including the herbicides 2,4-D and Silvex. More drums are added to the field and untreated waste water is discharged from the plant, where it runs downhill into Rocky Branch Creek.

1961–The plant is acquired by the Hercules chemical company. The old waste drums are buried in the same area. Hercules adds chlordane to its chemical repertoire and discharges processed waste water into the creek.

1967-68–Hercules manufactures the defoliant Agent Orange for shipment to Vietnam.

1972–Hercules leases the plant to Transvaal, Inc. Herbicide production, halted briefly in 1971, resumes. Burial of drums of concentrated waste continues until 1974.

1976–Transvaal and four other companies merge into Vertac.

1978–Vertac companies are under protection of the federal court during bankruptcy procedures. The company is brought out of bankruptcy by new owners, through a Panamanian holding company.

1979–It becomes publicly known that the plant is contaminated by dioxin. The Environmental Protection Agency (EPA) reports finding leaking wastes containing up to 40 parts per million of dioxin. Rocky Branch Creek, Jacksonville's Lake Dupree and the Bayou Meto are quarantined. Vertac ceases 2,4,5,-T production voluntarily.

1980–The EPA and Arkansas Department of Pollution Control and Ecology sue Vertac and Hercules, and a federal court orders cleanup of both the plant and off-site contamination.

1982–The chemical plant site is placed 18th on the EPA's national "Superfund" cleanup list. Negotiations continue among state, federal government and chemical companies on the cleanup plan.

1983–The Arkansas health director asks for EPA help after citizens complain about ill health. The Centers for Disease Control agree to analyze existing data on chemical pollution in Jacksonville. A multi-million-dollar consolidated lawsuit is filed by citizens against Hercules and Vertac. A former Hercules worker identifies the old Jacksonville city dump as an area where wastes from the plant were buried.

1984–The EPA releases a report stating hazardous waste contamination poses a continuing health danger to the area. Vertac, Hercules and the state fight the EPA, seeking to reduce a $20 million cleanup plan to $2 million. A federal court judge rules in favor of the low cost plan.

1985–A Vertac worker is killed when less than a gallon of a chemical mixture spills on him. A three-month-old baby dies of apparent chemical contamination. Vertac and the state announce plans for an Arkansas company, Ensco, to incinerate the leaking waste barrels on-site. Citizen protests ensue. Another ex-plant worker identifies a landfill as an area where plant wastes were buried.

1986–The EPA announces a cleanup plan for off-site contaminated areas, including waterways, flood plains and the city sewer systems, with cost estimates ranging as high as $380 million. Dioxin contamination is found in Arkansas wood ducks. The citizens' lawsuit against Vertac is settled out of court. Vertac ceases production of 2,4-D and shuts down the plant.

1987–Vertac transfers its assets to a new corporation, pays off a debt to Dow Chemical, and leaves Arkansas and cleanup responsibilities behind. The federal government and the state take Vertac to court for fraud, naming Dow in the suit. More than 100 residents near two dump-sites added to the EPA's Superfund list file suit against Jacksonville and the chemical companies in federal court, seeking damages and city water supplies. International Technologies, Inc., of California is selected to incinerate the Vertac wastes on-site.

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Finally, under prodding from Arkansas doctors and health officials, the CDC did agree to do a study to gauge children's exposure level to chemicals, using "control groups" of 100 children from Jacksonville and Conway, a town 30 miles away. The study did not show substantially higher levels of chlorophenols in the Jacksonville children, although some doctors questioned the wisdom of comparing samples from communities in such close proximity.

Brewster then asked state health officials if they could obtain the CDC's samples from the urine of the Jacksonville children, but her request was denied. "The reason given by the CDC was that the remaining volumes of urine were too small to test," Brewster says. Frase's group contacted the CDC and asked officials to comply. But the CDC and the state Health Department refused a second time, because, according to Frase, "they didn't want Children's Hospital doing quality control on its own."

"I worry a lot about exposure to chemicals in the environment, because I think it's quite large," concludes Dr. Brewster. "The dioxin issue is the unknown, and is extremely difficult to test for. We need more studies of exposure that might affect the immune system, better epidemiological studies of health effects and more work on analyzing low-dose exposure to environmental chemicals. But it could all be resolved if the money, and the politics, were there to resolve it."

Dr. Paul Connett, a biochemist at New York's St. Lawrence University and founder of the organization Work on Waste, is convinced after a visit to Jacksonville that "politics" explains why the CDC called off further investigation into the sudden, inexplicable death of the Shelton baby.

"I'm sure someone told them it's a bombshell," says Connett. "Because one of the claims that the industry always makes is that no one has ever died from dioxin or related chemicals. And once that can be shown, it's a whole different ball game—for the Vietnam veterans exposed to Agent Orange and many other people."

"I ain't gonna let up": Jeff Shelton, the father of Joseph and Jeff, sits at a kitchen table inside his small trailer. Jeff Jr., now three, is on medication to control his seizures. A five-month-old daughter is on a heart monitor, just in case.

Rubbing a hand over his eyes, the father says, "There was a baby died a few houses down from where ours did, a couple months after we moved. Started having breathing problems, and by the time they got him to Children's, he was dead. But they haven't wanted to get into all this.

"I protested, went to the governor's office and did some things I regret," he continues. "There was a time I took a coffin up there, to make a statement. I had been trying to get ahold of Governor Clinton a long time, and was getting ducked. I'd call and they'd say he was busy with his campaign. So this was the only way I could figure to get their attention. It really tore me up inside. My intention was to follow him around his campaign trail. Some of my family agreed with it, some didn't, so I never did. The governor's staff told reporters they hadn't forgotten, and would let us know as soon as they investigated more. That was two years ago."

Shelton plans to return soon to his hometown in Indiana, where an uncle says he'll hook him up with some attorneys. "I ain't gonna let up," he says. "One of these days maybe I'll be able to lay my head down and think I did something to help somebody else. Twenty years ago if they had dealt with this problem, fact is my son might be with us today and maybe I'd have some healthy children."

He pauses a moment, this man who paints satellite dishes for a living and never had much formal education, and says: "Our government, back in the '60s, these companies made the Agent Orange for 'em. I figure that's probably got a lot to do with us having a hard time. That's the Pentagon. That's where the power's at."

Pentagon keeps its distance: For 20 years, the Little Rock Air Force Base was the military's primary location for Titan II missiles, which were recently dismantled there. Outside of the state government, the base is the largest employer in Arkansas, which "competes" with Mississippi for the dubious distinction of having the highest illiteracy rate and lowest income level in the U.S. And

The EPA sent a team of workers in "moon suits" to clean up the Vertac site.

Jacksonville News

the base is a plum that neither Arkansas officials nor the Pentagon wants to see jeopardized.

Some of the base property was originally donated by Reasor-Hill Chemical, the predecessor of Hercules and Vertac. Mystery continues to shroud the relationship between the base and Hercules' contract with the government to manufacture Agent Orange. The military used C-130 cargo planes to transport the defoliant overseas. The base is still the country's main training center for C-130 pilots, but the military maintains that none of the planes based in Arkansas were used to ship Agent Orange. One reporter was told that the cargo planes didn't even arrive on the base until 1971.

But Frase, who was living there when her father served as acting base commander in 1969, insists she saw C-130s at the time and wonders "why they're denying those planes were here for those couple of years." She says base engineers told her that they tested bay and cargo areas of some of the planes and found them highly contaminated.

The Pentagon appears intent on keeping its distance from Arkansas' dioxin controversy. Late in 1985 Arkansas Rep. Tommy Robinson, a member of the House Armed Services Committee, asked the military to take charge of Vertac's contaminated barrels and dispose of them at Arkansas' Pine Bluff Arsenal. Robinson insisted that since much of the problem resulted from the military's Agent Orange contract with Hercules, they bore equal responsibility.

In a letter to Robinson dated December 13, 1985, then-Defense Secretary Caspar Weinberger personally responded: "For DoD [Department of Defense] to take on the disposal responsibility for private sector wastes would simply impose on DoD someone else's responsibility to satisfy permitting requirements and conditions for protection of the environment." Besides, Weinberger added, Pine Bluff wasn't technically equipped to handle highly toxic dioxin.

Robinson followed up by saying he would seek an amendment to a Defense appropriations bill to rescind a federal regulation that banned the military from assuming any responsibility for civilian-produced waste. Adding that he intended to raise questions at hearings of the Veteran's Affairs Committee, Robinson said, "This will allow me to open a Pandora's box about Agent Orange."

But Robinson never pursued the matter further. The congressman is now pushing for mobile-based MX missiles on railroad cars to be stationed at the base.

Kept in the dark: Questions remain, however, especially about possible large-scale chemical contamination on the base.

Max Pierce, now 55 and burdened with health problems, was employed during the early '50s by Reasor-Hill Chemical. "At one time there were two plants," says Pierce, "and one was located about where the PX, the commissary and the NCO club are now. We used to get cars full of barrels of toxaphene. It was nothing just to lay 'em on the ground and chop 'em up. Wherever you found a spot you just dumped. Those barrels were taken around different places where the base is—2,4-D, cotton dust, dieldrin, all different types of chemicals. Who thought back then that this stuff could get into the groundwater and be a problem for people?"

Pierce says he believes much of the waste ran off into the nearby creek and probably into a lake on the base. "I'm sure if the EPA or the state did some tests, they'd find foreign substances still in the soil. If I was on that air base and shopping in the commissary or the PX, it'd kinda make me wonder what lies under that ground."

The DoD has tested for some chemicals on the base, but Frase and others say they never looked in the right places. A pilot still on duty there, who requested anonymity, says he's heard rumors of more toxics being buried under the base golf course.

For years military personnel were kept in the dark about the situation. Recently, however, due to escalating local pressure, the base's public affairs office assigned someone to assemble a one-page briefing sheet. He was told to contact the EPA, the state pollution agency and the Chamber-sponsored Jacksonville People With Pride.

"I think the fact sheet is being put together because the criticism could easily be made that the Air Force has done absolutely nothing to inform its people of the problem there," says the pilot. "A lot of men have come and gone, and never knew they were exposed to anything. Now the base is gonna say that the bad news is that you don't want to get a house real close to certain areas, but the good news is that the EPA is gonna come in and fix everything. Their shield is this huge government agency we can supposedly rely on called the EPA. The commanders won't say anything where they could get criticized from the boys downtown, the local Chamber or the real estate people or the mayor. Now when a reporter calls, they can say a highly qualified officer looked into the problem and put together this briefing for everybody on the base. In fact, it's a half-truth. But that's the way the military is."

A healthy 25-year-old first lieutenant in his squadron died in the early '80s, according to the pilot. "They sent him off to the VA Regional Center, and nobody knew. They never did tell us exactly what happened to him, other than he apparently got cancer of the liver, like a lot of people in this town."

Frase says, "I know that a lot of military men [at the base] who've taken ill have been sent to Pennsylvania to be treated. They die there, but the death certificate never reads Little Rock Air Force Base."

A physician at Little Rock's Veterans Administration Medical Center responds, "If anything like that is going on, I've seen no evidence of it. The base does air-evacuate a certain proportion of people who need surgery, which we don't have here, to major 'teaching hospital' military centers in Texas." The physician says he has not noticed any unusual rate of cancers that might be associated with toxic chemicals, but adds that the base has a relatively young population.

Yet when a woman whose husband was on active duty in Jacksonville began raising questions about contamination at the base, a transfer came through to a base in Minot, N.D. "They were continually harassed by the military," says Anderson of the National Campaign Against Toxic Hazards. "We have documentation of other families who have since left the base, been harassed, and who have not been given proper medical support despite their clearly documented contamination."

Frase says that "no people should be allowed to come to the base and expose their families at the rate the government is bringing them in. There are dump-sites on the base that need remedial action immediately."

According to a source on the base and other residents, the Air Force has quietly taken a few other steps. No longer will the local Veterans Administration (VA) approve loans on homes in particular areas near the plant. But few personnel ask too many questions when they are able to purchase a $100,000 home for $35,000. A VA spokesperson denies both allegations.

When in 1984 Frase discussed the base situation with an aide to Sen. Edward Kennedy in Washington, the staffer finally threw up his hands. "If they announced there were problems," he said, "the military would have to pay those men hazard pay for just being there. No way. The government will do anything to protect it, and so will the state of Arkansas."

"Played for fools": As the sun sets over Jacksonville, Frase maneuvers her car onto the highway heading home. Shaking her head, she says softly, "Most people in this community, with all their money tied up in their homes and children, don't want to believe that everything they've worked for might be useless. We are played for fools here, but these people have no outlet. In all these years, the EPA has agreed to hold only one public hearing. But after all, who are you going to believe? A bunch of yelling housewives, or the EPA, the CDC and the Department of Defense?" □

Dick Russell is a freelance writer whose environmental reporting regularly appears in national publications.

(Next week: The cover-up in Jacksonville, and Arkansas Gov. Bill Clinton's pellmell rush to "burn the evidence.")

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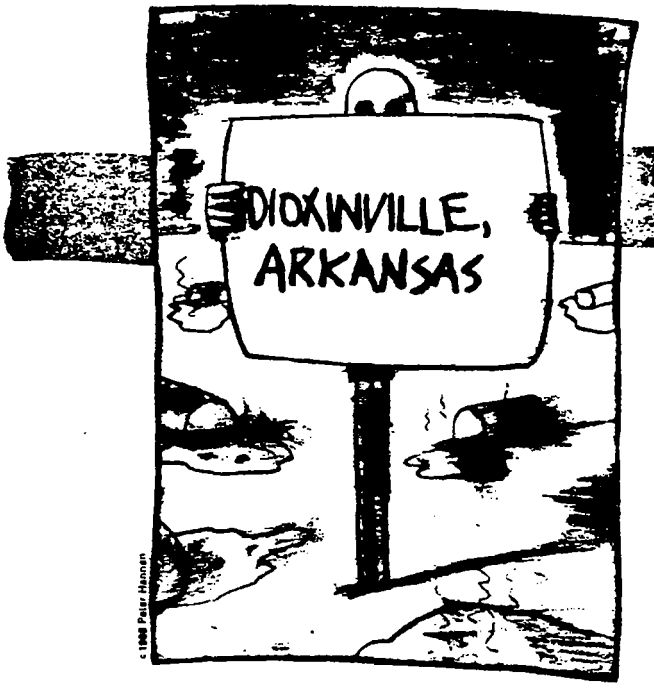

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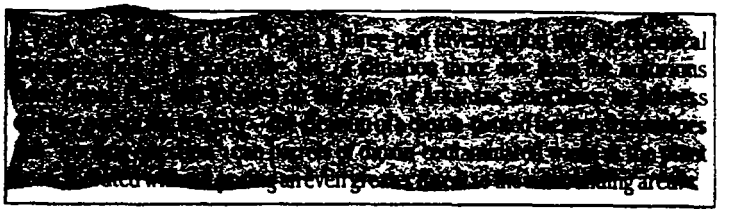


Arkansas Democrat Alex Brandon

By Dick Russell

JACKSONVILLE, ARK.

IN THE HEART OF THIS CITY OF 30,000 PEOPLE, THE chemical plant that the Environmental Protection Agency (EPA) has called "one of the most serious uncontrolled hazardous waste sites in the U.S." is now abandoned and secluded behind locked iron gates. Inside the plant, some 30,000 barrels of poison, including many containing dioxin-laden waste from the cancer-causing herbicides, await disposal. Many of the barrels continue to leak into local groundwater.

The city sewer system, a creek adjacent to the plant, a flood plain, parts of the nearby Little Rock Air Force Base and two city dump-sites have already been severely contaminated.

TCDD dioxin has been detected here at the highest levels ever found in U.S. soil. An unwanted contaminant byproduct of the herbicide 2,4,5-T, it is the deadliest man-made chemical known—about 500 times more toxic than strychnine. Many residents who live near the chemical plant or the two dump-sites suffer severe health problems ranging from birth defects to cancer. The EPA has put all three contamination spots on its Superfund list of toxic site priority cleanups.

Jacksonville used to be a quiet community, a semi-suburban enclave of tree-lined streets only 12 miles from Arkansas' state capital of Little Rock. The air base and chemical plant were considered among the hallmarks of the local economy. Shortly after World War II, Reasor-Hill Chemical began production of a wide range of pesticides, three of which have since been outlawed due to their toxicity. In the '60s Hercules, Inc. took over the site and went on to make 25 percent of the Agent Orange defoliant that the Pentagon shipped to Vietnam. Vertac Chemical Corporation was the most recent plant owner, manufacturing Agent Orange's component 2,4,5-T and 2,4-D herbicides for use in domestic agriculture. 2,4,5-T has since been banned by the EPA, and 2,4-D is now facing similar scrutiny for its damaging effects to human health.

The powers that flee: In January 1987 Vertac declared itself unable to fulfill its financial responsibilities for maintaining the corroding waste drums and left Arkansas be-

hind, transferring its assets to a new Memphis-based corporation. In federal court, the EPA, the Justice Department and the state of Arkansas are now attempting to force Vertac to follow through on its cleanup obligations. The EPA and the state don't want to be saddled with a cleanup tab that the agency has estimated could reach nearly $400 million.

Simultaneously, the EPA and the state pollution agency are preparing to have the hazardous wastes incinerated on-site by a private company with a dubious reputation and are planning to overturn a Jacksonville City Council ordinance and a peoples' referendum against incineration. The townspeople, along with many experts, are concerned that the relatively untested incineration process will send more dioxin into the environment, even as it destroys most of the wastes. Yet the EPA and the state are ignoring alternative technologies, adamant that incineration is the only viable solution.

It is a tangled web indeed, with companies and government officials alike looking to juggle financial liabilities and come up with a quick fix. But it may only exacerbate the problem. The saga of this environmental disaster shows that powerful corporate and military financial interests have long been appeased and protected by public regulators. Although local people began finding evidence of contamination in the '50s, not until 1979 did the full extent of the disaster become public knowledge. Ever since, Arkansas officials have sought to downplay the damage. While state officials repeatedly delayed efforts to address the problem, they allowed chemical production to continue until Vertac itself halted operations in 1986.

But Jacksonville's dilemma has no easy answers. Arkansas ranks near the bottom of the nation's economic ladder. If state officials had squarely faced the problem, impoverished Arkansas would have risked losing not only its chemical industry and air base, but also its herbicide-dependent agricultural rice economy. Millions of dollars worth of property and other businesses might have been rendered worthless. Given these possible consequences, government and industry officials have given short shrift to local residents' well-being. Officials have used "cost-benefit analysis"—which pits business "costs" against human "costs"—to justify their stance. At best, they are guilty of benign neglect, at worst, callous greed.

Only the people with nothing left to lose, like the low-income citizens whose homes surround the contaminated dump-sites, are tackling the situation head-on. To them, it is a simple matter of being able to survive, for they have nowhere else to go.

A family affair: "Charity," for the chemical companies and other business interests, begins at home—with Jacksonville's "first family," the Wilsons. Pat Wilson, owner of the First Jacksonville Bank, was born here in 1919. In the mid-'50s, Wilson and a group of about 15 others donated part of the land to entice the Little Rock Air Force Base (today the state's second largest employer, with about 10,000 military personnel) to locate in Jacksonville.

One of Pat Wilson's sons, Mike, briefly attended the Air Force Academy, became a local lawyer and entered Arkansas politics. Today, at 43, he is serving his eighth term as the area's state representative.

One member of the firm with which the younger Wilson's law practice was affiliated represents Vertac in Arkansas. Wilson says that arrangements with the law office specify that he shall never personally receive any money from Vertac, and that his relationship with Vertac's lawyers is his own business. Wilson also admits to owning "a half-interest in 160 acres down the road from or cattycorner to the old city dump [one of the EPA Superfund sites]. We hope to develop it eventually, but have no firm plans." If the extent of the contamination were fully acknowledged, of course, the land would be virtually valueless.

In 1986, Wilson and Joan Zumwalt, the wife of retired air base commander Mac Zumwalt, founded an organization called Jacksonville People With Pride. According to its brochure, the group's goal is "to foster a positive image for Jacksonville with regard to environmental issues." Titled "The Facts About Jacksonville and Dioxin," the 16-page booklet downplays the chemical dangers, insisting that Jacksonville is no more contaminated than any other industrial area.

With backing from the air base and the Chamber of Commerce, and with the assistance of a public-relations person, Jacksonville People With Pride has blitzed the city with the brochure and brought in an array of speakers to lend it credibility. According to Wilson, the organization has about 1,000 members. In letters to the EPA and federal Centers for Disease Control (CDC), Wilson has urged the federal government to ease up on its standards for taking action on dioxin contamination.

In the spring of 1986, shortly after Vertac ceased operation, city tests revealed that the company had subsequently dumped some of its remaining herbicide inventory into the city's sewers at more than 100 times the allowable level. For more than 40 illegal discharges of chlorophenols and other chemicals into the sewer system, Vertac was fined $10,000. The city has since built a new facility to treat its waste water.

At a news conference on the city's water situation, the bank owner, Pat Wilson—who also serves as head of the Jacksonville Water Commission—commented: "Our water tests have shown no impurities. We're proud of our water and we drink it every day." Simultaneously, Pat Wilson urged the Jacksonville City Council not to approve pumping city water to residents living alongside the outlying city dump-sites—even after the EPA had found contaminated water in some wells. The EPA had also found contamination at the dumps and in 1987 added both sites to its Superfund list for emergency federal cleanup.

Sensing that the local government was not going to act on their behalf, some Jacksonville residents went to the governor, who sent them to the pollution control agency, which referred them to the Soil and Water Conservation Commission. Eventually, their demand for city water was met—but the water bills of these low-income families have since ranged as high as $90 a month, an expense few can afford.

The sound of silence: Pitted against the Wilsons is Patsy Frase, a longtime area resident who founded the Arkansas Chemical Clean-Up Alliance four years before the Pride group started up.

As Jacksonville People With Pride set out to counter the so-called "radicals" in Frase's Alliance organization, local publicity about the chemical problems began to dry up.

"A lot of people who were making noises suddenly stopped helping us," says Frase. Pride officials also worked hard to undermine the work of a crusading environmental reporter, Bobbi Ridlehoover, who writes for the *Arkansas Democrat*, one of Little Rock's two newspapers.

Sitting in his law office recently, State Rep. Mike Wilson shrugged away "the distortions, half-truths and outright falsities" disseminated about Jacksonville's contamination.

In Wilson's eyes, all this pollution talk is bad for business in Jacksonville. "Sure," he added, "we could avoid a lot of environmental problems by giving everybody 40 acres and a mule again. We can live on a level with nature alright. But we as consumers demand plastics, and newsprint with colors in the ink, and nylon stockings. We demand all sorts of things from industry and we'll pay a price for 'em."

An avid hunter, Wilson was named the Arkansas Legislature's Conservationist of the Year in 1985 for successfully protecting 6,000 acres of bottomland for hunting and public use. Mounted on the office wall behind him is a duck that he bagged on the flood plain. A state Game and Fish Commission study found wood ducks in that area with contamination levels of TCDD-dioxin five times higher than the limit established by the Food and Drug Administration for safe consumption as food. That didn't seem to bother Wilson. "Yeah," he said, "that's my dioxin duck," and laughed.

Wilson is a Democrat. So is Gov. Bill Clinton, one of the youngest governors in the country, a man with a populist reputation who considered a run for president in 1988.

Toxic trouble: The governor has tried to keep a safe distance from the Jacksonville situation. The links among the chemical companies, the military and the state's rice growers were a political hot potato long before his election in 1978.

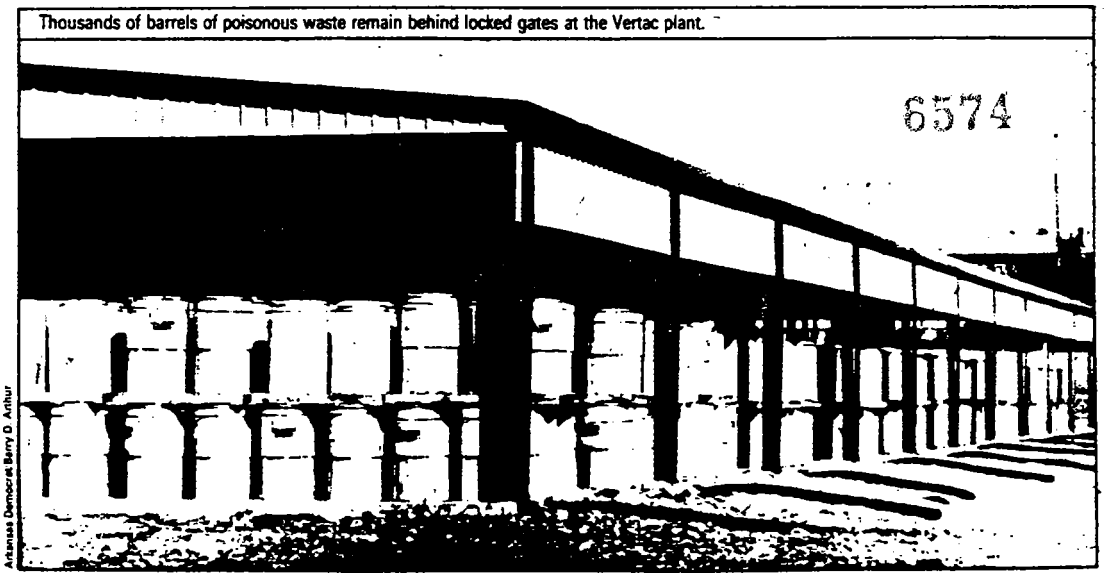
One-fourth of Agent Orange—the controversial Vietnam defoliant—was made in Jacksonville until health-effects studies forced the military to suspend the compound's use in 1970. But until a complete EPA ban 15 years later, 2,4,5-T herbicide—one of two components in Agent Orange—was allowed to be used on American rice fields.

Rice is Arkansas' number-two agricultural commodity, so the high levels of 2,4,5-T in the soil continues to be cause for alarm. In 1984 an *Environmental Forum* article reported that 52 percent of Arkansas and Louisiana soil samples taken after the herbicide was sprayed in 1979 showed dioxin in concentrations ranging from 1.13 to 13.01 parts per billion. Sixty-seven percent of rice samples from the same study contained 2,4,5-T—which would indicate the presence of dioxin—in concentrations ranging from 3 to 227 parts per billion.

"Some federal health agencies consider 1 part per billion of dioxin to be the maximum acceptable level for human exposure, although many people argue that there is no acceptable level," wrote the article's author, EPA environmental counsel Richard Mays.

Continued on following page

Thousands of barrels of poisonous waste remain behind locked gates at the Vertac plant.



Arkansas Democrat/Barry D. Arthur

[redacted] Jacksonville and

[redacted] any 2,4,5-T and dioxin on the rice is passed on to the public and consumed with the rice."

In his more than seven years as governor, Clinton has done little to solve the state's looming toxic problems. Among southern states Arkansas still ranks a close second behind Texas in the amount of other pesticides applied annually; more than 20 million pounds worth were used in 1987. Yet Arkansas is one of only five states with no program to monitor groundwater for pesticide contamination.

In 1986 the EPA undertook 100 enforcement actions against Arkansas violators of federal surface water pollution standards, with only Texas receiving more (172 violations). The 1988 "State of the States" ranking on environmental protection by the Renew America project finds Clinton's Arkansas tied for 48th place with Mississippi, the same two states that regularly "compete" for having the nation's highest illiteracy and percentage of population below the poverty line.

When it comes to keeping up with polluters, the New York-based Council on Economic Priorities in 1986 gave Arkansas a "D" for its laxity in punishing companies that violate hazardous waste laws.

"We have an extremely bad situation with our state legislature being maintained by special interests," says Bob Bland, organizer of a recently formed environmental group called the Arkansas Alliance. "And they have recently allowed hazardous waste operators to just roll over them."

As for the governor, Bland says, "Clinton was a shining light during his first term [1979-80]." But Bland says that since his 1982 re-election, the governor has "done nothing but accommodate industry."

Disappointing appointments: Evidence to substantiate this charge came with Clinton's appointment of Dr. Ray Harbison to the Task Force on Hazardous Waste, a state body formed in 1985 to deal mainly with the mounting Jacksonville outcry. Harbison, a toxicologist at the University of Arkansas for Medical Sciences, is one of the U.S. chemical industry's favorite expert witnesses. But critics charge that he has consistently contradicted himself in government testimony.

"The man will say whatever he's paid to say," charges Dr. Samuel Epstein, a renowned expert on hazardous chemicals at the University of Illinois Medical Center.

Environmentalists also cite another Clinton appointment as evidence of acquiescence to big business interests. Last summer the governor chose Paul Means to be the new chief of Arkansas' Department of Pollution Control and Ecology (ADPC&E). Before the appointment, Means worked for six years as an executive for the state's major utility, Arkansas Power and Light.

But now Means cannot administer his own department's National Pollution Discharge Elimination System permit program because of a federal regulation forbidding former employees of industries and municipalities holding such permits from doing any oversight in government service for two years. A subordinate has been granted the permitting authority.

Robert Blanz, deputy director of the pollution control agency, resigned when Means' appointment was announced. Blanz, who led whatever charge the state had mustered against the Vertac Chemical Corporation for

[redacted] certainly didn't give a [redacted] way or another the whole time I was there—we were just sort of winging it. He would back us once we explained things to him, but there was no real agenda."

Several other agency employees followed Blanz out the door. Many were concerned that Means, the man who had overseen lobbying on behalf of the state's nuclear power plant, would be running the entire pollution agenda.

Such moves by Clinton have angered many concerned about the Jacksonville situation. In February 1986, 30 protesters gathered with picket signs outside the governor's office, irate that he had not attended any of the local residents' public meetings. Clinton had, however, found time to attend a Jacksonville Chamber of Commerce luncheon honoring local industries, including Vertac.

The governor's disposal proposal: For several years, Clinton has been a staunch advocate of incineration of the dioxin wastes and other chemicals still leaking at the Vertac plant. The incineration plan first came from Vertac, which in 1985 contracted the job to Ensco, an Arkansas firm with financial links to the governor's campaign and family. But after Vertac last year declared itself unable to fulfill its financial responsibilities in Jacksonville, the state pushed ahead with its own incineration plan.

The EPA, along with many state governments, believes incineration is the best solution to the nation's landfill glut. And they like the fact that these "waste-to-energy" facilities generate electricity that can be sold to utilities. But the incinerators emit a host of air pollutants and generate some toxic ash (see *In These Times*, Feb. 11, 1987). No one disputes the presence of some dioxin in mass-burn incinerator emissions, and according to Barry Commoner of the New York-based Center for the Biology of Natural Systems, this makes incinerators "an inherently unacceptable technology." Opponents of garbage-burning say that preferable recycling programs are being given short shrift by the government.

Hazardous waste like Jacksonville's cannot be recycled, of course. And there is a major difference between trash incineration and the high-temperature burning methods proposed for hazardous waste disposal. Trash-burners synthesize a mixed stream of refuse in the cooler parts of the incinerator while hazardous waste incinerators feed the material directly into the furnace. But this process is not foolproof. The question is how much dioxin and other chemicals may be released into the environment?

The EPA has set a "six 9s" destruction and removal efficiency for such materials, meaning that 99.9999 percent of the waste must

[redacted] sion of the regional office in Dal[redacted] Jacksonville citizens' meeting in 1985 that although humans should not breathe as much as one part per trillion of dioxin, it was possible that as much as 100 parts per trillion could remain in the air if an incinerator burned wastes as contaminated as the local plant's.

The burning of 2,4,5-T waste itself creates dioxin, which then must also be eliminated during the combustion. Even with the "six 9s" destruction capability, dioxin is so toxic that the most minute amounts left behind can be extremely dangerous.

"Temporary operating problems could result in very serious exposure," says Commoner. "Suppose the flame goes out for a few seconds, and you are just blowing this stuff right out the stack. It is very tricky, and these things belong only in an isolated area with nobody living downwind. Doing this in a residential neighborhood makes no sense at all."

The EPA did successfully burn dioxin from contaminated soil in Missouri, but destroying contaminated barrels of such toxics in a populated area has never before been attempted. When the EPA conducted a series of dioxin test-burns at the National Center for Toxicological Research, the first four efforts failed due to mechanical difficulties. Later experimental burns in Ensco's mobile incinerator were declared a success by the EPA, but these did not include dioxin wastes. Commoner adds, "The only data I've seen on dioxin for an incinerator indicates that the emissions are on the same order as a not-too-well-operating trash incinerator."

The ash left over from the incineration process, as consumer advocate Ralph Nader points out, is so toxic that "the government doesn't know what to do with it other than declaring it 'non-hazardous' and storing it somewhere." That is precisely what Arkansas has said will happen to the tons of toxic ash from the Jacksonville plant, which will be stored on-site permanently.

Walter Hang, an incineration expert with the New York Public Interest Research Group (PIRG), adds: "Neither the EPA nor state authorities have demonstrated an understanding of the long-term hazards posed by incinerator ash. On paper, these hazardous incinerators look great; they're high-tech, state-of-the-art. But you're looking at the prospect of learning on the job, and such a facility has to operate at peak effectiveness all the time because of the extraordinary toxicity and persistence of these compounds if they're released into the environment. Any kind of fire, explosion or leakage could have extremely far-ranging implications."

The people speak: In December 1985 author Lewis Regenstein, another expert on

[redacted] to incinerate is in the middle of a neighborhood."

At this point, many residents decided to oppose the incineration plan. Alderman Gary Fletcher, representing the neighborhood adjacent to Vertac, said Gov. Clinton should be prepared "to call out the National Guard" to quell protests if incineration were allowed to proceed. Three separate actions soon followed: the Jacksonville City Council, a people's referendum and a subcommittee of the Governor's Task Force on Hazardous Waste voted to ban incineration in Jacksonville.

And upon taking office in 1987 as pollution control chief, Means made public assurances that no incineration would proceed unless local citizens agreed to it. He told Jacksonville residents that there was no scientific reason why the chemical facility's wastes couldn't be transported off-site for disposal.

But despite such rhetoric, neither Means nor the state has wavered from the incineration approach. Now Means is warning that if Jacksonville refuses to repeal its anti-incineration ordinance, his department will have to seek federal court action to force the change. By law, federal and state authority supersede local ordinances.

The last straw, as far as Frase's group is concerned, was a new law that zipped through the Arkansas State Legislature last spring, after being introduced by none other than state Rep. Mike Wilson.

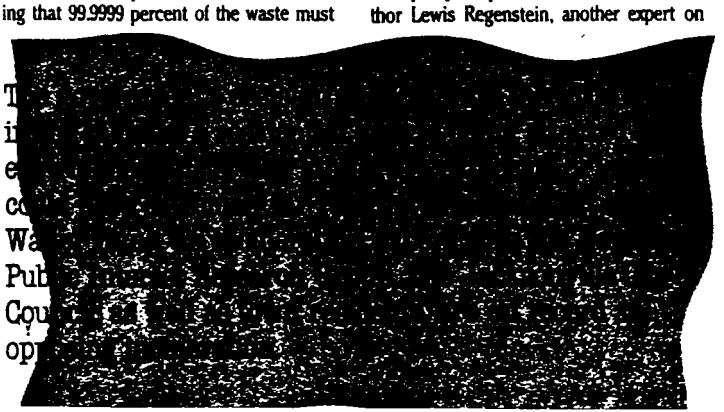
It provides that any contractor hired by the state for a waste cleanup will not be liable for injuries, damages, death or economic loss resulting from the release of hazardous substances, unless negligence or intentional misconduct can be proven. Means' pollution agency pushed for the legislation, maintaining that it was needed to get companies to bid on the incineration contract.

In mid-October, an outraged Ralph Nader paid a visit to Jacksonville and called a news conference. "I have not seen such a bill anywhere else in the country," he said, noting that there would be no standard against which to measure the company's actions, since how could any people harmed "try to prove the state of mind of the contractor?"

Returning to Washington, Nader received a letter from Clinton. In it, the governor insisted that the law protecting cleanup contractors "is modeled on federal law which gives EPA the authority to hire contractors to complete remediation of Superfund sites." Without it, Clinton said, potential contractors would justifiably fear that they might be held liable "for releases from conditions that existed before they began work at the site."

Congress had passed a similar bill in 1986, but Arkansas was the first state to follow suit. Nader wrote to Clinton on October 31 that his "concern in the statute was the deletion of any strict liability (liability without fault) in tort. What is left is a negligence standard (liability with fault) which is a greater obstacle to any community litigation."

Commenting on his visit with Jacksonville citizens, Nader concluded his letter to the governor this way: "Among other things, it is a feeling that their government is not representing them so much as it is reflecting corporate priorities and demands—some say ultimatums (e.g., either give us this or we won't do the job)."



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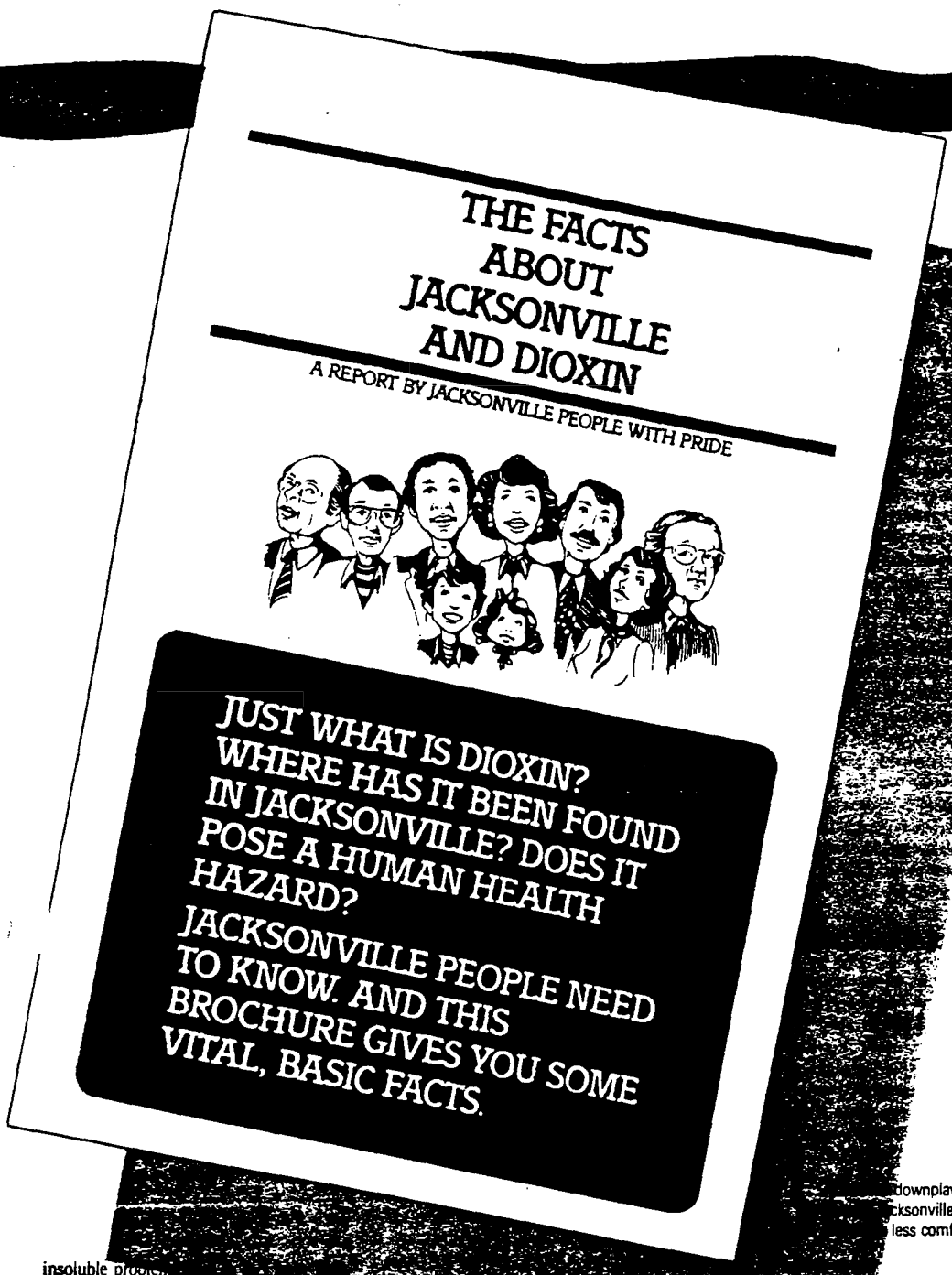

...ville to overturn its ban,

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PCBs there.

John Schofield, senior vice president of ITC, told the *Arkansas Democrat* that his company previously worked "under contract" to Vertac at the site, but would not disclose any specifics. ITC also served as an EPA contractor on some initial groundwater containment and cleanup at the plant. The same firm completed a $29 million EPA contract in 1985 for incineration of dioxin-contaminated soil and clothing at a farm site in Verona, Mo.

Yet ITC's past record is anything but encouraging. Last April it received a $20-million-plus contract from the Pentagon to burn munitions-contaminated soil and pollution from leakage at the Cornhusker Arsenal in Grand Island, Neb. Using a mobile incinerator similar to the one now slated for Jacksonville, an accident occurred during a shutdown for routine maintenance after the first test burn in October. Two workers were severely burned when hot ash fell on them from an upper chamber.

"ITC's mainstay has been land disposal of hazardous waste," says Will Collette, program director at the Citizen's Clearinghouse for Hazardous Wastes in Arlington, Va. "It has operated three landfills in California and for the past several years has had nothing but trouble at those facilities. In April 1987 it was levied the highest fine against any company in California history—$3.2 million—for violating state regulations. Even with the lax enforcement there by the Deukmejian administration, it has been ordered closed and allowed to re-open twice. I am told it has announced plans to divest its entire California landfilling operation."

A 62-year-old firm that evolved from a marine cleaning business, ITC currently has global sales of $237 million. Last May the Justice Department filed suit against the company, charging it had violated regulations on its hazardous waste storage. Also last year an ethics commission found ITC in violation of ethical standards. Citing the company for purchasing land while doing a feasibility study for an incinerator, and for hiring an employee who had worked for the state agency that awarded the contract, Louisiana's Ethics Commission ordered the company to return the $375,000 it had received from the state. ITC has challenged the finding in a state court.

"If a company has shown it can't handle its main line of business, that doesn't inspire much confidence in its ability to handle something entirely new," says Collette. "But Arkansas and the EPA say there's no cause for alarm, the situation is well in hand and anybody who says otherwise is an environmental kook or hysterical housewife."

In recent weeks Arkansas pollution officials have not been able to get ITC to agree to all the safety and testing requirements that must be met before a contract can be signed. And this is not the only problem state officials face. More than half of the $10 million needed to do the incineration was supposed to come out of a trust fund that Vertac established before transferring all of its assets into a new corporation and leaving its Jacksonville plant behind last year. But now the trust fund is tied up in federal court litigation proceedings. The state has also been unable to collect another $4 million through a letter of credit in a Swiss bank that Vertac supposedly set aside for the incineration.

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Arkansas State Rep. Doug Wood, who told the story of his efforts to enlist American Fuel and Power Corporation, the first commercial licensee of an experimental technology that would destroy the wastes under a closed system that allows no venting of chemicals into the air. A large, clay-lined trench would be dug in the ground on the plant site, the barrels placed inside it and electricity used to melt the wastes into a substance similar to boiling lava. The high temperature would destroy most of the dioxin. When it cooled, a huge black glass monolith of obsidian-like rock would be all that remains.

"Therefore, it does not have the excessive ...ck emissions of an incinerator and it does leave an ash for further treatment or disposal," wrote Wood. Though untried on dioxin wastes, the process has worked successfully on petroleum wastes at several Texas sites. And, according to Wood, an EPA lab verified that contaminated soil samples from Vertac have also been tested by the company and achieved a destruction and removal efficiency of "seven 9s"—"fully an order of magnitude greater than EPA stan...

...spokesperson ... would cost about one-third of the ... ton incineration price tag.)

In dismay, Wood added that the state and federal agencies won't "let American Fuel and Power do an on-site test at full scale because of prior commitments by EPA officials to incinerate the first phase of the project. This is absurd!" Wood later told *In These Times*, "Any new technology doesn't have a chance because the EPA's regulations are so heavily skewed toward incineration. The greatest irony is that the citizens of Jacksonville accepted this other technology but are still fighting incineration."

Wood's disposal alternative is one of several options other than incineration. Rollins Environmental Services, a company based in Deer Park, Texas, offered last year to have the waste shipped there, where it would be burned in an unpopulated area. The proposal was not warmly received by the state of Arkansas or the EPA, so the company withdrew its bid. Another largely unexplored option is a chemical solidification process that would ...

...mist at New York's St. ... and a nationally recog... expert, offered still ... when he came to Jacksonville last year. Expressing alarm about the incineration plans, Connett said the best approach would be "secure holding in concrete bunkers" that would be built until a safe disposal method can be found. "I'm scared stiff about [the incineration] being a money-making operation," Connett said in a later interview, "especially if the operators have any kind of track record that makes them dubious."

Dubious track record: Unfortunately, the company that Arkansas chose for the job has just such a record. Late last October the state, under an EPA permit procedure, selected the International Technology Corporation (ITC) of Torrance, Calif., to receive a $9.7 million contract to incinerate Vertac's wastes on-site. According to Means, once negotiations and tests are completed, the company would be able to complete incineration of nearly 30,000 drums of waste in about seven months, although environmen...

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Dioxinville

Continued from page 13

In addition, Means says Vertac kept such poor inventory records that some barrels contain unidentified solid substances that may have to be destroyed differently from the dioxin-contaminated drums. Now state officials say that not even a test burn on the waste can occur before next fall at the earliest. Meanwhile, ITC is rumored to be on the edge of insolvency due to its other environmental liabilities. So Arkansas is reportedly negotiating once again with Ensco—a firm with an equally dubious record—to eventually handle the incineration.

"Explosive situation": Despite the delay, the concerns of Jacksonville citizens have not abated. "If there is a malfunction out there," says Frase, "it could cause cancer through the whole community. During the incineration, they are not going to do any secondary monitoring (monitoring after the incineration takes place). Yet dioxin would show up as a secondary chemical, because it's formed in the combustion. The other terrible thing is that the turn-around period for sending in lab samples is six weeks, so if there is a problem and dioxin is pouring out, we won't know until much later."

Hazardous-chemicals expert Epstein believes "the only real way to cope with this issue is to have a high-level congressional inquiry that would investigate not only the role of the chemical industry, but also the EPA, the state and the industry's consultants. You are dealing in Jacksonville with an already tragic, and potentially explosive, situation."

Incineration expert Connett adds, "I am really distraught by the whole Jacksonville phenomenon. I believe those people; they're not giving me a song-and-dance about what they've been through. You hear story after story of health damage done to people of all ages. To me, it's outrageous that this 'anecdotal' information is dismissed as being non-scientific and therefore irrelevant, when clearly it demands an answer. If these agencies don't get their act together pretty soon, no one is going to believe anything they do."

In Jacksonville, where the people talk about "cancer alley" and wear T-shirts reading "Hostage of Vertac and Clinton," it is the 11th hour in a tragic microcosm of America's toxic time-bomb. And if the federal and state governments eventually do get their way on incineration, the people of Jacksonville can only hope that it won't cause an apocalyptic high noon. □

Dick Russell is a freelance writer whose environmental reporting regularly appears in national publications.

(Next week: In Part 3 of *In These Times*' investigation into the Jacksonville imbroglio, the interlocking ties among the chemical companies—including Dow Chemical and other multinationals—are revealed.)

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The Jackson factor in election '88

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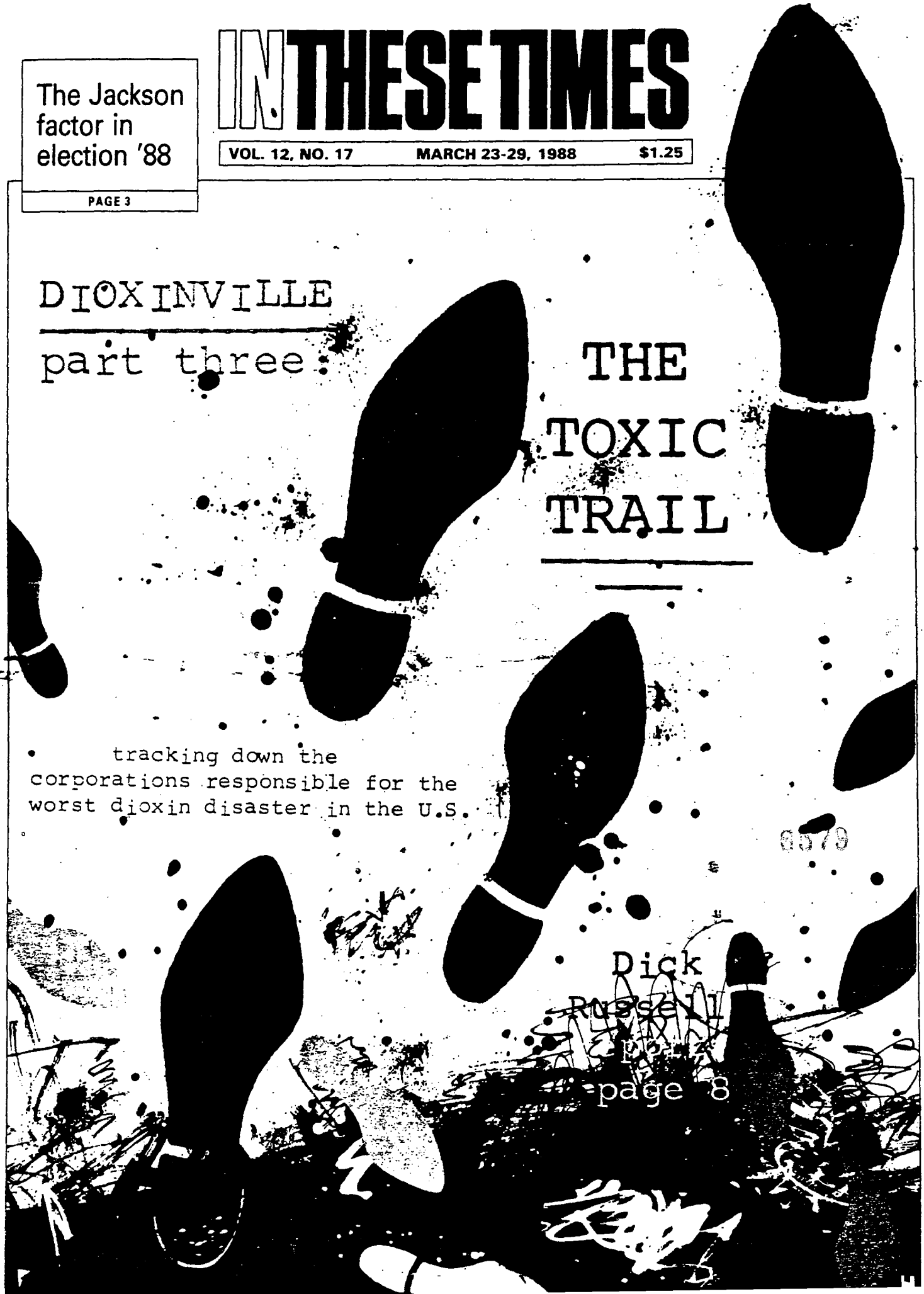

DIOXINVILLE

part three:

THE TOXIC TRAIL

tracking down the corporations responsible for the worst dioxin disaster in the U.S.

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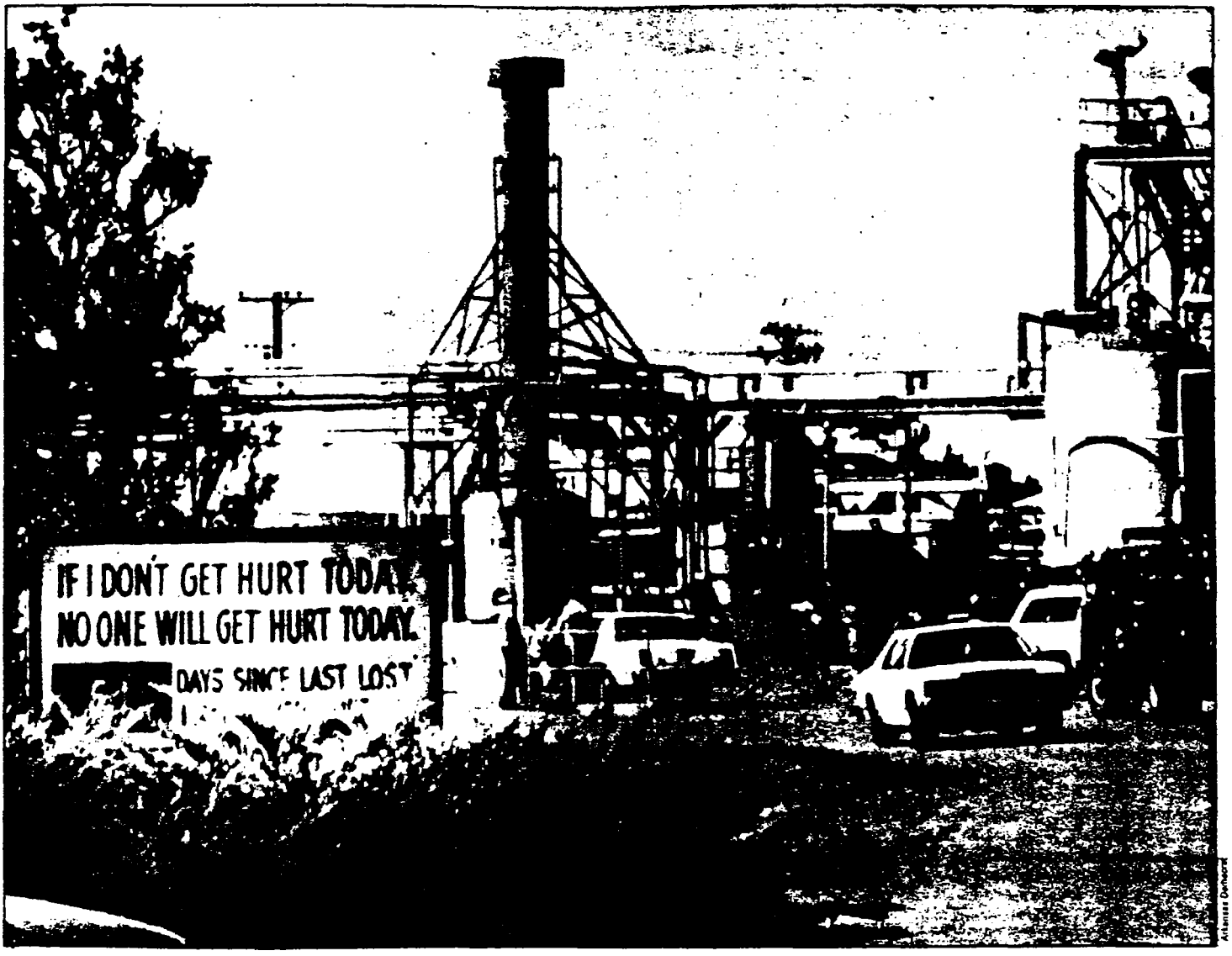
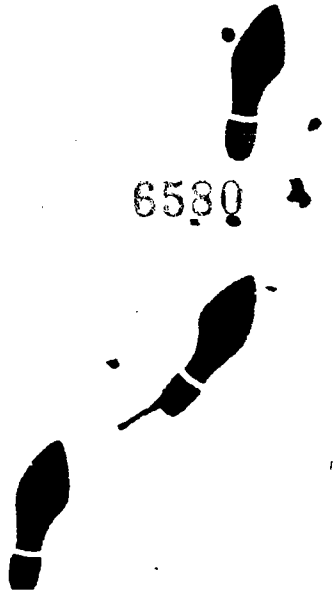
Dick Russell

page 8



Arkansas Democrat

The conclusion of In These Times' *three-part investigation into the dioxin contamination of Jacksonville, Ark., focusses on the chemical companies involved. In unveiling the hidden ownership behind Vertac Chemical Corporation, it is revealed for the first time that the city's toxic disaster extends outward to envelop two of the nation's largest multinationals. Their connections to an obscure and once quiet community pose troubling questions that go far beyond Arkansas.*



By Dick Russell

JACKSONVILLE, ARK.

THIS IS A STORY OF CORPORATE INTRIGUE and manipulation, a journey through the labyrinthine world of the makers of toxic chemicals. It attempts to answer this question: who bears the ultimate responsibility for thousands of leaking barrels of dioxin-laden chemicals and other poisons in this Arkansas community—a place that can justifiably be called the most serious hazardous waste area in the U.S.?

An *In These Times* investigation has tracked a corporate maze extending far beyond the contaminated chemical plant in Jacksonville, 12 miles from the state capital of Little Rock. It includes not only a network that stretches into five other nations—Panama, Italy, Switzerland, Sweden and Japan—but also hidden ownership and shady deals. It points to the quiet involvement of the former chief executive officer of the Diamond Shamrock Corporation and the potential liability of one of the chemical industry's giants,

The intricate maze illustrates how bigger companies use smaller ones—like Jacksonville's Vertac Chemical Corporation—to keep up production of lucrative, but potentially deadly, products. Then, when push comes to shove over liability for the toxic hazards posed by these chemicals, the companies sometimes square off to implicate each other. Although they often publicly appear to be corporate "enemies," they collude behind the scenes to tie the hands of government regulators, lawmakers and citizens. Employing small armies of attorneys, they are able to stall remedies and avoid product restrictions indefinitely. Employing sophisticated public relations staffs, they are able to stay out of the national limelight.

Legacy of neglect: Jacksonville, a city of 30,000 people, is a case study in such corporate maneuvers. Its pollution woes far surpass those of the Love Canal landfill near Niagara Falls and of Times Beach, Mo., where in both places residents were evacuated by the Environmental Protection Agency (EPA). Yet except for a 1980 story published in *Life* magazine, the major media have ignored the Jacksonville situation. A former Vertac public-relations employee, David Simmons, admits that "when inquiries came [from major media outlets], generally the local stories had enough holes in them that they were discreditable."

Yet the EPA found Jacksonville's toxic saga very credible indeed. In recent years it designated three different areas for Superfund cleanup. The agency estimates that disposal

Vertac Chemical's Jacksonville plant: "the corporate maze leading out of this dioxin-laden site spans several continents."

wastes at the chemical plant and "restoration" of off-site pollution areas may cost close to $400 million. It has detected TCDD-dioxin, a byproduct of herbicide production and the most lethal substance produced by humans, at the highest levels ever found in soil and barrels of toxic waste. Many scientists say that there is no safe human exposure level for this form of dioxin.

But Jacksonville residents were not even informed until 1979 of the pollution problems that had abounded for about 30 years. Before chemical production ceased in 1986, toxic wastes were systematically spewed into the city's waterways, sewer system and several landfills, severely contaminating the area and causing numerous health problems for local residents. During what a former plant supervisor calls "runaway chemical reactions," and an explosion in the mid-'60s, vast quantities of dioxin were released into the air.

Dozens of residents maintain that over the years they have suffered everything from miscarriages and birth defects to Sudden Infant Death syndrome and cancer. More than 100 Jacksonville residents have sued two of the three companies that since 1948 have run the chemical plant, alleging personal injury and wrongful death. Since 1986 portions of both lawsuits have been settled out of court for undisclosed sums.

The question of future liability for the con-

DIOXINVILLE III:

THE TOXIC TRAIL

tamination, however, is now tangled up in federal courts. The two companies that are supposed to share cleanup costs with government agencies are at each other's throats. Vertac Chemical, which has run the plant for the past 16 years, is suing its predecessor, Hercules, Inc., which manufactured 25 percent of the Agent Orange used to defoliate the Vietnamese jungles. Vertac is claiming that Hercules should be held responsible for all future liability. In turn, Hercules, as well as federal and state agencies, are hounding Vertac in other court proceedings.

In a seeming attempt to duck its legal obligations, Vertac last year suddenly transferred its remaining assets into a series of newly ·med corporations and left Arkansas. It ver informed government officials of these moves.

A friend in need: This is where Dow Chemical enters the narrative. Headquartered in Midland, Mich., with 50,000 employees worldwide, the multinational was for years Vertac's main supplier of herbicides and the formulas for them. In December 1986, two months before Vertac pulled out of Jacksonville, company officials held a series of meetings with Dow executives in Great Britain, Washington, D.C., and Michigan. At the time Vertac was feeling considerable heat from the government. Although it had ceased operations in Jacksonville in February 1986, the company was being sued by the Justice Department (on behalf of the EPA) for continuing to discharge contaminated waste water into a creek adjacent to the plant site. The department was seeking a $10,000-a-day fine. Vertac wanted out from under—and in a complex and back-handed way, Dow was about to provide the opportunity.

Dow, which contracted trademarks and products to Vertac, privately informed its "supply partner" that the smaller company had breeched one or more of their agreements. Thus, Dow declared Vertac in default, with a debt of $5.3 million owed Dow for goods sold and delivered.

Vertac could cover the debt, but its money was tied up in a trust fund and letter of credit; the company had earlier agreed with govern··ent agencies to set aside $11 million for al on-site cleanup at the Jacksonville plant. After consulting with Dow, Vertac quietly established three new companies in Memphis, Tenn., where Vertac's corporate headquarters were located.

Then, on Jan. 31, 1987, Vertac President J. Randal Tomblin called representatives from the EPA, the state of Arkansas and Hercules to a meeting in Dallas. Without mentioning

Jon Knowles Picture Group

Former Diamond Shamrock Chief Executive Officer William Bricker: was he linked to Vertac?

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Jacksonville News

On the road again: The EPA came to Jacksonville last year.

Continued from preceding page

Vertac's meetings with Dow or Vertac's newly formed companies, Tomblin said that the company could no longer meet its legal obligation to maintain the corroding waste drums in Jacksonville. He seemed to be implying that Vertac was broke.

But it wasn't. Nine days later Vertac transferred all of its assets (which it claimed were $12.7 million) into Inter-Ag, under the umbrella of the two other newly formed companies in Memphis.

The next day Inter-Ag gave Dow Chemical nearly $1.7 million of the money Vertac owed the chemical giant. Dow also received claim to both the interest payments from the Jacksonville cleanup trust fund and any uncontaminated equipment from the Arkansas plant. And Dow took title to the remainder of Vertac's inventory, along with all product formulas and trademarks. This was a strange turn of events, because Dow had sold those three areas of its 2,4-D herbicide business to Vertac back in 1983.

"Evidence of fraud": What was going on? The EPA and Justice Department soon hauled Vertac into U.S. District Court in Little Rock to try to find out.

Last July Vertac's lawyers argued that the company hoped its business dealings with Dow would provide it with enough money to defray "environmental expenses." Further testimony revealed that those "expenses" were hardly "environmental." They included more than $400,000 for upkeep of Vertac's Memphis office and about $500,000 for "depreciation and lawyers' fees." It also came out that a Vertac employee was seen moving documents from the plant to a private storage area. Although Judge Henry Woods did not hold Vertac in contempt of court, he ordered measures to assure no more unauthorized removal of documents.

In handing down his ruling in September 1987 Judge Woods said, "The evidence of fraud is clear and compelling. The present management of Vertac has demonstrated its willingness to manipulate numbers and corporate assets to facilitate non-performance of Vertac's environmental responsibilities under various court orders." The transfer of assets into Inter-Ag, he added, was simply "an effort to put them beyond the reach" of environmental agencies—a deal that involved "fictitious considerations" rather than fair market value.

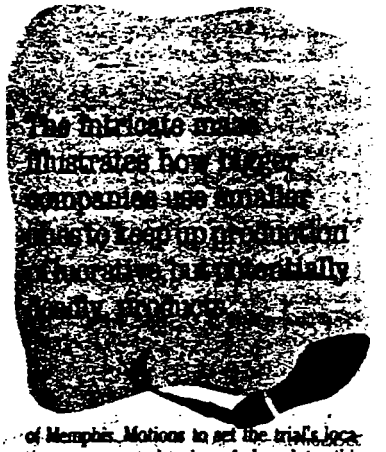
The judge agreed with the government that the state should appoint a receiver to take over Vertac, an arrangement that he ruled would extend to Inter-Ag as well. Vertac officials are currently seeking to overturn the decision in the U.S. Court of Appeals in St. Louis.

Meanwhile, the Justice Department demanded that Dow give the EPA the money it had received from Vertac, as well as assign over to the federal government the herbicide trademarks that Vertac had returned to Dow. When Dow refused, the EPA and the Justice Department filed another suit. This time, the government said that not only Vertac's top officers and successor corporations but also Dow should be held liable for Vertac's court-ordered share of the Jacksonville cleanup costs.

Dow immediately filed a countersuit in federal court in Memphis. *Dow vs. USA* maintains that any legal proceedings should be held there, not in Little Rock. In the suit, which includes Vertac and the First Tennessee Bank (where the cleanup trust fund is administered), Dow claims it is entitled to the net income from the trust fund as part of Vertac's remaining debt to it.

Enter the corporate maze: Why is Dow, with $11 billion in global revenues in 1987, quibbling so vociferously over a comparatively paltry $5.3 million? "The Vertac-Dow relationship is definitely a deep pocket to look into," says Robert Blanz, who dealt with the Vertac situation for seven years as deputy director of Arkansas' Department of Pollution Control and Ecology. "I don't think anyone understands all the dealings that went down between them. But you don't take Dow on lightly with inexperienced government lawyers, because they will come in loaded for bear."

Vertac, with its new name, Inter-Ag, continues to this day to conduct business out



of Memphis. Motions to set the trial's location are expected to be ruled on later this year. Meanwhile, under a separate ruling by Judge Woods, the government agencies have tried to collect on a $4 million letter of credit that Vertac in 1985 agreed to set aside at a

The chronology of a toxic coverup: Dow, the EPA and dioxin

1948–Secret human health tests sponsored by Dow Chemical show that extremely low concentrations of several of its compounds, including the 2,4,5-T herbicide, are capable of producing skin rashes, acne-like effects and allergic responses. 2,4,5-T is registered as a pesticide with the U.S. Department of Agriculture.

1949–The first industrial accident involving dioxin occurs at a Monsanto Chemical 2,4,5-T plant in West Virginia.

1957–Dioxin is identified by scientists as an unavoidable contaminant in 2,4,5-T.

1958–Findings point to the presence of liver damage in German chemical workers exposed to 2,4,5-T.

1962–Defoliants containing 2,4,5-T are first used in Vietnam. Dow starts making napalm, a jellied gasoline that kills in a particularly painful way, for military use in Vietnam.

1965–The Pentagon contracts with Dow and other U.S. chemical companies to manufacture Agent Orange (50 percent comprised of 2,4,5-T and 50 percent 2,4-D) for use in Vietnam. At a secret meeting at Dow's headquarters, manufacturers are told that 2,4,5-T has negative health effects.

1970–After suppressed 1966 studies are released linking 2,4,5-T to birth defects in rodents, the Pentagon suspends its use. Dow, leading producer of the chemical, expands 2,4,5-T use for weed control in the U.S.

1971–The newly formed Environmental Protection Agency (EPA) announces cancellation of 2,4,5-T use in most food crops. But Dow wins a court injunction allowing continued manufacture. In 160 communities in Missouri, dioxin mixed with waste oil is sprayed on dirt roads to keep down dust.

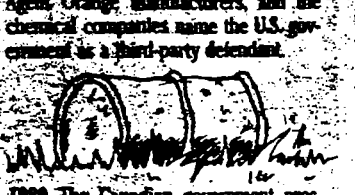
1973–A Vietnamese study lists higher incidences of liver cancer, spontaneous abortions and birth defects to Agent Orange.

1976–An explosion at a chemical plant in Seveso, Italy, releases several pounds of dioxin in a densely populated area. Local residents are not informed for eight days, after hundreds of animals have died and hundreds of people are hospitalized. Chronic health effects ensue.

1977–Soldiers who served in Vietnam begin approaching the Veterans Administration (VA) with various health problems they believe are related to Agent Orange exposure.

1978–The EPA offers evidence based on testing of laboratory animals that 2,4,5-T and dioxin cause cancer, birth defects and fetal deaths. The Love Canal area of Niagara Falls, where 21,800 tons of chemical wastes including dioxin are buried, is declared an emergency disaster area by President Jimmy Carter.

1979–Rural residents of western Oregon disturbed by health effects in their spraying area file a federal lawsuit against 2,4,5-T use in the U.S. Forest Service. It contends that the government had failed to consider the effects of dioxin. The EPA issues an emergency suspension of 2,4,5-T uses, with the exception of rangelands and "rice fields" and establishes a "no safe level of dioxin" policy. The EPA sets up a Chlorinated Dioxins Work Group (CDWG). Vietnam veterans file a massive class-action suit against Agent Orange manufacturers, and the chemical companies name the U.S. government as a third-party defendant.



1980–The Canadian government presses the U.S. to investigate the source of high dioxin levels found in the Great Lakes. The EPA considers Dow the chief suspect for dioxin contamination of fish downstream from its Michigan headquarters. The company issues a report suggesting that dioxins are a natural product of all combustion sources, present in the environment since "Prometheus stole fire

1982–When a severe contamination problem in Times Beach, Mo., comes to light—resulting from the illegal disposal of dioxin-laden waste oil 11 years before—the EPA raises its "no safe level"

Swiss bank for the Jacksonville cleanup. But the bank, citing problems with certain "procedural requirements," has so far refused to turn over the money.

For now, the EPA—which spent more than $5 million last year re-drumming leaking barrels of waste at the Jacksonville plant—and the state are left holding the bag. Under Superfund, Arkansas is supposed to provide 10 percent of the total funds to restore Jacksonville's polluted environment. But the state's economy is already one of the country's most depressed. Coming up with 10 percent of a potential $400 million cleanup tab "might well be impossible," says Phillip Deisch, a Little Rock attorney and former counsel to Arkansas' pollution agency. "Arkansas is vitally interested in getting to the private pockets who are really responsible for this mess."

Those corporate private pockets, however, so overlap each other that proving liability may be impossible. To understand why, the origins of Vertac must be examined. The real ownership behind the company has long been a mystery. Sources in and out of the government remain reluctant to discuss what they know. Even when they were simply confirming information that *In These Times* had uncovered, many of them requested anonymity.

Who owns this firm, anyway? Vertac is an acronym for the names of four chemical companies that merged in 1976 (Vicksburg, Eagle River, Transvaal and Agricultural Chemicals). At the time, Transvaal was leasing the Jacksonville site from Hercules. Vertac, according to an ex-official, was initially set up by some former executives of Union Carbide —the chemical company responsible for the 1984 disaster in Bhopal, India. In addition to its Jacksonville operation, Vertac owned

chemical plants in West Helena, Ark., and Vicksburg, Miss. But, says the source, "the Union Carbide people did not understand that there were limits to expense accounts." In 1978 Vertac declared bankruptcy.

Not long after, the company re-emerged intact, although its new owners were unknown. They had registered Vertac under the aegis of three offshore holding companies in Panama. Says Reed Newman, a former Justice Department lawyer who investigated the company for the EPA, "Panama is somewhat of a haven for people who wish to incorporate or have a significant interest in companies, but not have a lot of folks know about it in terms of [U.S. government] reporting requirements. We ran into a brick wall as far as finding out who really owned Vertac."

Over the past year or so, however, the mystery surrounding Vertac's owners has started to unravel. *In These Times* was able to trace majority ownership to a wealthy Italian named Vittorio de Nora. This was confirmed by several sources.

Now age 76 and living in Geneva, Switzerland, de Nora made his fortune in the electrochemical segment of the industry. At a Milan-based company that he and a brother established more than 50 years ago, he pioneered in the '70s a process used in making chlorine. Chlorine is the basic building block of chlorohydrocarbon herbicides produced by both Dow and Vertac.

To protect themselves from possible patent lawsuits, the de Noras "set up companies all over the place that could be financially isolated," says Colonel Dillmore, a laboratory researcher with PPG Industries, an American company that previously worked closely with de Nora's Italian firm.

Parts of the de Nora operation were registered in Panama. "Vittorio is a man of the world," Dillmore adds. "He used to have his own private jets, and spent most of his time outside Italy. He was deeply involved with the Diamond Shamrock company, and used to own a substantial block of their stock."

The Diamond Shamrock connection: Diamond Shamrock, for years one of America's "big five" chemical giants, was a major producer of herbicides, including Agent Orange, for the Pentagon. Vittorio de Nora's relationship with Diamond executives dates back to the '50s. By 1973 he sat on Diamond's board of directors. But because de Nora was trying to do business with competitors, fellow directors convinced him not to stand for re-election the next year.

He was a longtime friend of William Bricker, then in charge of bolstering Diamond's agricultural chemicals business. In 1976 Bricker was appointed chief executive officer of Diamond. That same year Diamond spent more than $50 million to acquire de Nora's Electronor Corporation that was registered in Panama. De Nora remained in Italy as chairman of Electronor.

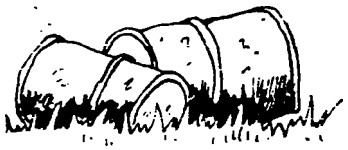
In later 1979, Bricker reportedly introduced de Nora to Vertac's owners and

Continued on following page

on dioxin to a one part per billion "level of concern."

1983–Attempting to defuse a mounting scandal surrounding misconduct and mismanagement at the EPA, the agency offers to buy the entire town of Times Beach and evacuate residents. John Hernandez becomes the EPA's acting administrator after the scandal forces two top officials to resign. Hernandez soon also steps down in disgrace after Congress uncovers that he had intervened personally to allow Dow to alter the draft report on Great Lakes dioxin contamination, at the same time that Dow was refusing to give the EPA information on dioxin problems at its plant. The altered report had also eliminated all risk information on dioxin-tainted fish, a damaging scientific appraisal of 2,4,5-T's health effects in Alsea, Ore., and any mention of Agent Orange. Congress appropriates $4 million for an EPA study of dioxin nationwide.

Reagan appoints William Ruckelshaus to restore the EPA's image. Ruckelshaus calls for "risk-benefit analysis" to replace the "margin of safety" laws. Part of an EPA study showing the severity of dioxin contamination in Alsea, Ore., is released—pages that the agency had claimed to a federal court did not exist. The EPA asserts a "mix-up," maintaining that the highly contaminated samples were not really gathered in the sediments of Oregon drinking water supplies, but inside Dow's Michigan manufacturing facility. Dow and the EPA are privately negotiating an agreement to allow wider use of 2,4,5-T, permitting resumption of some applications banned in 1979. But in the face of another potential scandal over the "mix-up," Dow and the EPA simultaneously announce the cancellation of all remaining registrations on 2,4,5-T.



1984–Interagency working groups on dioxin are now coordinated from the White House by Maj. Alvin Young, an Air Force scientist who had a key role in developing Agent Orange as a weapon. The day before the Agent Orange trial is to begin, Dow orchestrates a $180 million out-of-court "settlement"—over the vehement objections of many veterans involved—to be paid by seven chemical companies. Thus, the manufacturers avoid a precedent-setting court decision—as well as having to reveal what they knew about Agent Orange and when. Referring to the suppressed Oregon study and to "widespread fraud" in herbicide health-testing, an appeals court judge bans federal use of all herbicides in the Alsea study area until they are adequately tested for health effects.

1985–A veterans' attempt to sue the government over Agent Orange is initiated, but denied on grounds of federal immunity. All domestic uses of 2,4,5-T herbicides are finally outlawed by the EPA. Fish samples collected downstream from pulp and paper mills consistently reveal dioxin contamination.

1986–A new study of Missouri residents by the federal Centers for Disease Control (CDC) reveals that exposure to relatively small amounts of dioxin in the environment appears to lead to a higher risk of immune-system damage. A privately funded medical study finds that nursing infants in the U.S. may be imbibing dioxin in mothers' breast milk at levels 1,300 times those considered acceptable by the CDC. A group of Vietnam veterans, scientists and members of Congress announce research results showing a biological "fingerprint" left in veterans' blood by dioxin.

1987–An appeals court upholds the chemical companies' settlement in the Agent Orange case. The CDC and the Congressional Office of Technology Assessment agree that no large-scale study on the effects of Agent Orange can be conducted because too few troops were actually exposed to the chemical. The Air Force announces results of a 20-year Agent Orange study that it says has failed to uncover any unusual health problems in veterans. Over the protest of seven chemical manufacturers, the Supreme Court lets stand an appeals court order that the companies allow Vietnam veterans to see research documents on Agent Orange.

A privately funded medical study finds dioxin present in the breast milk of all 50 American mothers tested. A federal appeals court absolves Monsanto Chemical of knowingly exposing seven workers to dioxin. The paper industry reveals that traces of dioxin have been detected in a wide range of its products, but says that there is little risk to human health. The EPA announces that dioxin-contaminated soils are less prevalent than feared. The EPA unveils a new draft study sharply lowering its estimate of the cancer-causing potential of dioxin by sixteenfold. Dow Chemical, now embarked on a major advertising campaign to foster a "good-guy" image, finally shuts down the world's last 2,4,5-T production facility, in New Zealand. A Texas jury holds Dow liable for $1.5 million in the death of a forest service worker who sprayed its 2,4-D product, on grounds that the herbicide had caused his cancer.

1988–The Supreme Court denies an effort to overturn governmental immunity in the Agent Orange litigation. Dr. Barnes, who has held control of the government's dioxin information for nine years, is promoted to chairman of the EPA's Science Advisory Board. –D.R.

Continued from preceding page

the idea of acquiring the company. It must have seemed an attractive business opportunity to de Nora. After all, herbicides were a multimillion-dollar international business. De Nora could use his own electrochemical processes to make chlorine (which he did, especially at another Vertac outlet in Vicksburg, Miss.), and then save money by using the chlorine in his own herbicides. When he bought Vertac, Jacksonville's environmental problems had barely begun to surface.

In These Times could not determine whether Bricker took part ownership in Vertac, supposedly a competitor of Bricker's company, Diamond. But "if that is what happened," and if Bricker was privately involved with two competing companies, says staff attorney Robert Hausman of Trial Lawyers for Public Justice in Washington, "the lack of a technical violation of the anti-trust laws does not make it less scandalous."

This much is certain: two of Diamond's executives left the company and went to Vertac. Arne Obel, president of Bricker's International and Diversified Technology unit—which oversaw the newly acquired de Nora firm in Italy—set up the main holding company for Vertac in Panama. Obel then became Vertac's chief executive officer and was, according to company officials, "the liaison between the management and ownership" of Vertac. Ray Guidi, who had been an executive at Diamond's New Jersey chemical plant, became the Jacksonville plant's operations manager.

The relationship between Diamond's top executive Bricker and Vertac's de Nora continued over the next several years. In 1982 their companies established Eltech Systems, a new joint venture to make chlorine production equipment. Two years later Diamond sold its interest to de Nora. A Diamond attorney told *Business Week* magazine that this buyout came about because "the chemical industry was flat on its back." For a company that other sources told *Business Week* was a "guaranteed money-maker," de Nora paid $13 million less for Eltech Systems than what Diamond thought it was worth. Bricker kept his ties to de Nora as an unpaid director of Eltech.

By 1982 de Nora's Vertac venture was already coming under heavy fire in Arkansas. The EPA was suing Hercules and Vertac, trying to force the companies to split the initial cleanup costs at the Jacksonville plant. The extent of the off-site contamination, which stretched for miles across a flood plain and onto several landfills where the companies disposed of their wastes, was beginning to be discovered. Perhaps de Nora wanted to unload a potential albatross. And Bricker seemed willing to help him out.

The puzzle widens: Diamond had undertaken with a Japanese firm another joint venture in the early '80s. The U.S.-based company was called SDS-Biotech, the initials of Showa Denko/Diamond Shamrock. Besides Vertac, SDS-Biotech was America's only other major manufacturer of widely used 2,4-D herbicide products. At a board meeting in 1984, a source told *Business Week*, Bricker demanded that SDS-Biotech's Japanese partner either agree that SDS-Biotech buy Vertac or the partnership was over. But the Japanese refused.

Why was Bricker apparently so interested in incorporating Vertac into a subsidiary of his own company? Was he trying to corner the market on 2,4-D? Or was it part of a long-range plan to help de Nora dump Vertac one way or another? The latter seems an equally logical explanation. Shortly after the Japanese arm of SDS-Biotech turned Bricker down on Vertac, Diamond bought out the Japanese and took sole control of SDS-Biotech.

But someone else was interested in SDS-Biotech. In the fall of 1985 Bricker and de Nora travelled to Stockholm, Sweden, to meet with Refaat el-Sayed, owner of the Fermenta biotechnology company. El-Sayed had previous business relations with de Nora, dealing him Fermenta stock options in exchange for an Italian pharmaceutical company that de Nora owned. Now el-Sayed was interested in acquiring SDS-Biotech.

But according to Hans Lindberg, Sweden's chief prosecutor who later investigated the transaction, Diamond's Bricker and de Nora insisted on a "package deal." If el-Sayed wanted Diamond's subsidiary, he would have to buy Vertac as well. At the time, however, more and more of Jacksonville's environmental troubles were being uncovered. El-Sayed's advisers "looked into Vertac," Lindberg says, "and said he should not buy the Jacksonville plant, only the other Vertac chemical companies." Otherwise the deal was off.

Trust fund set up: In October 1985 Vertac's management called a meeting with representatives of the EPA, Justice Department and Arkansas' pollution agency. "The idea, at least as it was represented to us, was that a foreign corporation had approached the board of Vertac seeking to acquire certain of its assets," says Reed Newman, then with the Justice Department. Fermenta AB was described to the officials as "a giant holding company with a multinational participation in its capitalization."

Vertac's officials told the Justice Department that the Swedish company would acquire only the plants in West Helena, Ark., and Vicksburg, Miss. It was a "spinoff" proposal, whereby "Vertac would reincorporate those other entities as Cedar Chemical, which would then be acquired by [el-Sayed's] Fermenta through a stock deal," says Newman. Vertac's owners would get a large chunk of Fermenta stock.

According to Newman, the government was concerned about whether the deal would leave Vertac with enough capital to maintain its responsibility for the Jacksonville cleanup. The government wondered whether the deal was part of a Vertac plan to walk away from Jacksonville completely. Newman says that the Justice Department considered legal action to prevent the deal, but settled instead for what appeared a legitimate resolution.

Vertac's management proposed that the owners of the company, along with the potential buyers, establish a $7 million trust fund and an additional $4 million letter of credit to be assigned later for specific cleanup tasks at the Jacksonville plant. Vertac was also ordered to spend a dollar on environmental cleanup for every one it spent on operations. The deal was struck and the letter of credit was drawn on a Swiss bank in the Italian language. At the time the Justice Department did not know who had approved the transaction on Vertac's behalf.

On Dec. 18, 1985, the *Wall Street Journal* reported that Fermenta had purchased SDS-Biotech and a Vertac unit. Reincorporated as Cedar Chemical, the Vertac spinoff would be managed by SDS-Biotech, now owned by el-Sayed.

A shutdown and a scandal: Two months later Vertac shut down its Jacksonville plant. This move coincided with an announcement by Arkansas environmental of-

It is unclear who will eventually have to pay the cleanup costs in Jacksonville. Every company involved wants off the financial hook.

Jacksonville News

Taking soil samples in Jacksonville: the city's pollution woes are worse than New York's Love Canal.

s that the company was being fined $40,500 for violations of a 1982 court-ordered cleanup decree. Vertac, the state claimed, was still discharging levels of chemicals up to 10 times the allowable level into adjacent Rocky Branch Creek. The company was not reporting monitoring of these chemicals as required, and was also violating barrel storage requirements.

On Feb. 28, 1986, Vertac laid off 50 of its 80 Jacksonville employees, keeping the rest, it claimed, to start cleanup at the plant. Four days later, the company settled out of court with 71 nearby residents who had filed suit against it. Details of the settlement were not revealed. That same week Diamond announced plans to sell its $820-million-a-year chemical division to Occidental Petroleum.

De Nora had come out of the SDS-Biotech Vertac deal with $44 million in cash and $30 million in Fermenta stock. He had also unloaded most of Vertac, including other plants besides Jacksonville that had potential environmental liabilities.

Meanwhile, the Swedish government had launched an investigation of Fermenta's corporate dealings. The resulting scandal, one of Sweden's biggest in years, led to Fermenta's expulsion from the Swedish stock exchange and el-Sayed's resignation as chairman of the company's board.

Swedish prosecutor Lindberg did not bring any indictments in the affair. But he ' *In These Times* that he believes the SDS-ch/Vertac deal may have involved millions of dollars' in stock kickbacks from de Nora to el-Sayed. Could those kickbacks have been compensation for el-Sayed taking most of Vertac off de Nora's hands?

Following the scandal in Sweden, Fermenta's stock value dropped by 90 percent. With de Nora's investment in Fermenta nearly wiped out, and $11 million of Vertac's money bottled up in the Jacksonville cleanup trust fund and letter of credit, he needed a way out of the Jacksonville imbroglio more than ever.

A backroom deal? Late in 1986, a year after de Nora sold most of Vertac to Fermenta, Dow suddenly called in its chips on Vertac's debt for its herbicide supply contracts. The question that arises through *In These Times*' probe of the various corporate maneuvering is this: did de Nora, or perhaps Bricker, work out a behind-the-scenes deal with Dow—allowing Vertac to use the debt payment as an excuse to transfer all of its assets into Inter-Ag and bolt from Jacksonville?

In These Times was unable to determine the extent of de Nora and Bricker's possible involvement in the Vertac-Dow dealings. Neither could be reached for comment.

But *In These Times* did trace a probable de Nora connection to Dow. The chemical giant was—and still is—involved in a joint venture with the Italian electrochemical company that de Nora originally formed with ' brother Oronzio. Bricker, as head of a r chemical company like Diamond, was also likely acquainted with Dow executives.

In an unrelated incident, Bricker was forced to step down at Diamond in December 1986. He reportedly had been under pressure from Diamond's board for alleged misuse of company funds.

In telephone interviews with *In These Times*, Justice Department investigators refused to comment on their probe of Vertac's

Eben Given

ties to Bricker and Diamond. But if Bricker was aware of a government examination of his relationship to de Nora—and his own possible liability for the Jacksonville cleanup—it may have seemed a sensible idea to help unload what was left of Vertac.

The links between Dow and Vertac have always been curious. They can be traced to 1978, when Vertac was brought out of bankruptcy by de Nora and Diamond executives. In retrospect, it appears that Dow was using the smaller company as a kind of "shell" to handle some of Dow's more controversial products. On paper, the two companies were competitors. Both, for example, made substantial quantities of 2,4-D herbicides—which recent studies have linked to cancer. But even though Dow continued to manufacture 2,4-D, it sold in 1983 all of its registration rights, inventories, formulation recipes and marketing data to Vertac.

"Dow knew 2,4-D was a dirty business, with a lot of environmental hazards associated," says Vertac's former publicist David Simmons. "So they wanted Vertac to take front-line responsibility for it."

About the same time, Vertac received permission from the EPA to put some wastes that were classified as containing TCDD-dioxin back into its 2,4-D products. Some of these wastes may have come directly from Dow.

"Among Dow employees," says Paul Merrell, co-author of a report on dioxin pollution published by Greenpeace, "the scuttlebutt was that part of its dealings with Vertac involved transferring a bunch of Dow's 2,4,5-T [dioxin] waste to the Jacksonville plant."

The herbicide supply contract between Dow and Vertac has now been terminated, according to Vertac officials. Although Judge Woods found "clear and compelling evidence" of fraud in Vertac's transfer of assets into Inter-Ag, it remains an open question whether the company's move was part of a scheme between Vertac's owners and Dow Chemical. That question is, perhaps by design, now mired in the federal courts.

Passing the buck: A different court proceeding, however, may answer some other lingering questions.

Dow, along with Vertac and its Jacksonville predecessor Hercules, was named in a lawsuit filed by 183 former workers at the chemical plant and their families. They maintain that Dow, through its ongoing supply of herbicides to Vertac despite full knowledge of their potentially detrimental effects, shares the guilt for health problems that the workers have suffered. In the legal dispute over cleanup obligations among the chemical companies, Vertac is now pitted against Hercules.

Last June Vertac petitioned the court that Hercules should be held responsible for all future Jacksonville cleanup liability because no dioxin contamination was disclosed back when the plant changed hands. It was, Vertac's lawyers said, "a deliberate transfer of technology" that resulted in "continuing the manufacturing and waste disposal methods practiced by Hercules, with no disclosure by Hercules of the associated hazards and risks."

While this may seem a ludicrous exercise in buck-passing, the fact remains that the courts found Hercules, along with Vertac, equally liable for the Jacksonville cleanup. Back in 1965, at a secret meeting called by Dow Chemical at its Michigan headquarters, Hercules, Diamond Shamrock and other chemical companies learned that the Agent Orange ingredient 2,4,5-T caused adverse health effects. Dow and Hercules, using different competing formulas, then attempted to remove dioxin from the finished Agent Orange, resulting in a relatively "clean" product. Both were fairly successful in getting rid of the impurities, but in Hercules' Jacksonville operation this process left behind about three tons a week of the highly concentrated dioxin wastes.

These wastes were then placed in 55-gallon drums at the Jacksonville plant. According to former plant workers who have testified under oath, Hercules' dioxin-filled drums were either buried in unlined pits at the plant site or carted to a nearby city dump, where unwitting residents sometimes bought them from the dump's manager to burn trash in. Some of the Agent Orange waste was simply hosed into Rocky Branch Creek, which ran into a neighborhood to the south.

Then, after the Pentagon's suspension of its Agent Orange contracts and with the controversy over 2,4,5-T mounting, Hercules decided in 1971 to move on to other ventures. Today, the company is a major aerospace contractor with 26,000 employees, headquartered in Wilmington, Del.

But the Jacksonville plant still technically belonged to Hercules until 1976, although from 1971 to 1976 it was under lease to Transvaal, Inc. Transvaal then merged into Vertac, which took over the site later that year.

Vertac attorney Rick Beard recently testified in federal court that Transvaal had in the early '70s discovered dioxin on the site and reported it to the EPA and Arkansas officials. Some wastes containing dioxin were then taken at a cost to the company of $250,000 to "a place approved by the government," according to Beard.

A Herculean dilemma: But whether Hercules, as Vertac alleges in its lawsuit, is more culpable than Vertac for the Jacksonville mess is not really the point. The fact is, everyone involved wants off the financial hook.

So Vertac is suing Hercules, the state and federal governments are suing Vertac and Hercules, Dow is suing the government and Vertac, and Vertac's promised letter of credit for cleanup costs is still being held by the Swiss bank. While all this is going on, the EPA and the state—if they can retrieve the court-ordered cleanup funds—are planning to go ahead with a controversial plan to incinerate the Jacksonville wastes at the plant site (see *In These Times*, March 16).

Thus, no one currently knows for sure who will bear the Jacksonville cleanup burden. In Vertac's case, the law is unclear about

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Dioxinville

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whether a corporation that has transferred its assets can ultimately be held accountable. A recent ruling in a Michigan court found that a company can be, but most other states have been reticent about making such a determination.

Whether Vittorio de Nora can be implicated by U.S. authorities is another matter. As Vertac's apparent majority owner, he might bear responsibility for the company and its environmental liabilities. But de Nora may be out of reach, since he resides in a foreign country. The way things now stand under an international treaty, U.S. courts must rely on local courts in each country to serve any legal papers. A case currently before the Supreme Court, however, is examining whether plaintiffs in product liability cases can drag foreigners into U.S. courtrooms.

Then there are the legal questions surrounding the roles of Dow Chemical and Diamond Shamrock. Yet another corporate courtroom drama—either in Little Rock, if the government has its way, or in Memphis, if Dow wins the jurisdictional dispute—is expected to unfold later this year.

Looming questions: It is conceivable that the Dow-Vertac debt exchange could backfire on both companies. Several questions may be decided by the courts. Will Dow be forced to turn over the money and goods it retrieved from Vertac to the government agencies? Will Dow be ruled at fault in the plant workers' lawsuit for having supplied Vertac with the toxic herbicides in the first place? Finally, will possible involvement of the de Nora family or Bricker be tackled by investigators, amid the tangle of corporate shufflings?

And when it comes to big companies, are there ramifications of Bricker's possible dealings with Vertac that might also apply to Occidental Petroleum? The Armand Hammer oil giant absorbed Diamond Shamrock Chemical back in 1986. Occidental, because of its ownership of the Hooker Chemical company that polluted Love Canal, was held liable in February by a federal judge for undetermined millions in cleanup costs surrounding that situation.

Meanwhile, Diamond's ex-chief executive Bricker and Vittorio de Nora apparently remain travelling partners. A source in Dallas says the men were recently observed paying visits to several American chemical companies, looking to strike up more business ventures.

All these questions and considerations could perhaps only be unravelled by a full-scale congressional investigation into the powers behind the nation's worst hazardous waste disaster. Some of those powers may already be worried about such a possibility. Diamond is still based in Dallas, where its legal counsel—Gardere and Wynne—is conveniently located in the Diamond Shamrock Tower. The same law firm is representing Inter-Ag—and Vertac's assets—in the battle against the government.

According to Arkansas' Patty Frase—who for the past seven years has led the fight to expose the chemical companies behind Jacksonville—somebody in Dallas apparently wants to know what the environmental movement knows about the chemical companies' dealings. A few months ago Frase says she received a visit from a private investigator. He said he was with the Fred Meyers agency in Little Rock, but had been hired by a client in Dallas whom he would not identify. He brought with him a list of names of environmental activists, including one who has long battled Dow Chemical in Michigan, and wanted to know what information Frase might have about them. Frase says she refused to speak to him.

Lonely victims: But Frase will continue to speak out about Jacksonville's unprecedented toxic tragedy. So will many other residents, despite a reversal in federal court on March 1 that surprised even the judge. It was a jury trial, in which about 100 people living near the two city dump-sites had charged Vertac and Hercules with contaminating their property and damaging their health. Vertac settled with the citizens out of court, for an undisclosed sum, as the proceedings began. Then, after deliberating for two days, a Little Rock jury found Hercules innocent of negligence in its operation of the plant.

About fifty of the citizens staged a demonstration in Jacksonville three days later, gathering more water samples near the plant site in an effort to further document ongoing contamination. But unless the machinations of the chemical companies are probed further by federal investigators and environmental lawyers, the people of this small community in Arkansas are—and will remain—the lonely victims of governmental indifference and corporate manipulation.

The corporate maze leading to Jacksonville brings to mind a scene from the 1976 movie *Network*. In it, Mr. Jensen, the hitherto unseen power behind the megacorporation, stands at the end of a long conference table addressing the irreverent newscaster, Mr. Beal, informing him that there is only one "vast, interwoven, interacting, multivaried, multinational dominion of dollars," Mr. Jensen goes on about the "natural order of things today.

"There is no America. There is no democracy," he says. "There is only IBM, ITT and AT&T, and DuPont, Dow, Union Carbide and Exxon.... The world is a college of corporations, inexorably determined by the immutable laws of business."

And so it goes in Jacksonville. □

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Chapter 9

Biological Issues in Extrapolation

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Approximately 41% (26/63) of the pesticides evaluated in the chronic toxicity and carcinogenicity studies of the National Toxicology Program (NTP) showed varying degrees of carcinogenicity. Since those chemicals nominated to the NTP for carcinogenicity studies usually represent a sampling of potentially "problem" chemicals, this ratio (i.e., 41%) does not implicate the actual percentage of carcinogenic chemicals among all pesticides. In general, results from epidemiological studies are of limited value in prevention and have been done on few pesticides. Furthermore, it is impossible to conduct chronic toxicity/carcinogenicity studies in humans. Therefore, laboratory animals must be utilized as surrogates, at least for the foreseeable future. To assess potential risks of chemicals to humans, extrapolation of the findings in laboratory animals to possible health effects in humans is inevitable. Several important biological issues must be considered in such a process; these include extrapolation between doses, species (including strain and sex), routes of administration and exposure regimens (e.g., intermittent vs constant rate). While there is no perfect surrogate for humans in the evaluation of carcinogenic potential and other toxicities of chemicals and other agents, rodents still represent the best models. Any imperfection in such a process (i.e., hazard identification and risk assessment of any given chemical or other agent) must be taken into consideration during extrapolation. The state-of-the-art technique or tools, such as physiologically based pharmacokinetics/computer modeling, should be considered and utilized judiciously to minimize the

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> intrinsic imperfections in the process. The continuing refinement and improvement of the entire process (from selection of chemicals for testing, experimental design and conduct, interpretation and analysis of data, interpolation and extrapolation, to risk assessment) is essential as scientific advances are made in these areas. Other important issues related to hazard identification and risk assessment include multiple chemical exposure as well as multiple route exposure; these must be incorporated into the process as information and tools become available.

In a recent review article (1), the Council on Scientific Affairs of the American Medical Association reported their findings on the cancer risk of pesticides in agricultural workers. Their conclusions were: (a) The primary hazard of pesticide exposure is the development of acute toxic reactions as a result of dermal contact with or inhalation of a relatively large dose. The effects usually are manifested within minutes or hours of contact; (b) Epidemiological studies offer only limited evidence at best that pesticides may be carcinogenic; (c) A large number of pesticidal compounds have shown evidence of genotoxicity or carcinogenicity in animal and in vitro screening tests, but no pesticides -- except arsenic and vinyl chloride (once used as an aerosol propellant) -- have been proved definitely to be carcinogenic in man; (d) With few exceptions, the long term (e.g., carcinogenic) effects of pesticides on human health have been difficult to detect. Perhaps the health risks are sufficiently small that they are below the power of epidemiologic studies to detect. But it is also possible that there are very few effects to humans at all. While a comprehensive review of the epidemiologic studies conducted world-wide on pesticides, fertilizers, and/or agricultural practices (e.g., poultry, hog, dairy production) yielded conflicting results, the limitations of epidemiologic studies were also given (1) as shown in the following quotation.

> "Epidemiologic analysis of data in man often fails to yield conclusive results because the size of the study group is too small (statistical power is inadequate to detect a difference), exposure data are lacking, concomitant or prior exposures to other known or suspected carcinogens may interact with the compound(s) in question and confound the analysis, or a proper control group cannot be identified. Then, too, some well-defined studies in different groups under different circumstances may yield totally conflicting findings."

Even if there were no such limitations, epidemiologic analysis is retrospective study; it cannot be depended upon for the detection and prevention of potential health hazards to the public. In comparison to epidemiologic studies, animal bioassays are short in duration, relatively inexpensive, easily perfomed under controlled conditions, and are reliable predictors for known human carcinogens. Therefore, from the point of view of identifying and preventing public health hazards, animal bioassay is an invaluable tool.

As of April 1989, the National Toxicology Program (NTP) and the National Cancer Institute (NCI; up to 1981), have completed chronic toxicity/carcinogenicity studies on 385 chemicals (2). Of the chemicals studied, 63 were considered pesticides (General or Unclassified) (Tables I and II). Approximately 41% (26/63) of the pesticides eva-

Table I. NCI/NTP Carcinogenicity Study Results for Pesticides: Carcinogenic Pesticides Under the Experimental Conditions

Chemcial Name	TR No.	Route	Carcinogenicity Results MR	FR	MM	FM
Aldrin	021	Feed	E	E	P	N
Captan	015	Feed	N	N	P	P
Chloramben	025	Feed	N	N	E	P
Chlordane	008	Feed	N	N	P	P
Chlorobenzilate	075	Feed	E	E	P	P
3-Chloro-2-methylpropene	300	Gav	CE	CE	CE	CE
Chlorothalonil	041	Feed	P	P	N	N
Daminozide	083	Feed	N	P	E	N
1,2-Dibromo-3-chloropropane	028	Gav	P	P	P	P
(DBCP)	206	Inh	P	P	P	P
1,2-Dibromoethane (EDB)	086	Gav	P	P	P	P
	210	Inh	P	P	P	P
1,4-Dichlorobenzene	319	Gav	CE	NE	CE	CE
1,2-Dichloropropane	263	Gav	NE	EE	SE	SE
1,3-Dichloropropene (Telone II)	269	Gav	CE	SE	IS	CE
Dichlorvos	342	Gav	SE	EE	SE	CE
Dicofol	090	Feed	N	N	P	N
Ethylene oxide	326	Inh			CE	CE
Heptachlor	009	Feed	N	E	P	P
Mirex	313	Feed	CE	CE		
Monuron	266	Feed	CE	NE	NE	NE
Nitrofen	184	Feed	N	N	P	P
	026	Feed	IS	P	P	P
Piperonyl sulfoxide	124	Feed	N	N	P	N
Sulfallate	115	Feed	P	P	P	P
Tetrachlorovinphos	033	Feed	N	P	P	P
Toxaphene	037	Feed	E	E	P	P
2,4,6-Trichlorophenol	155	Feed	P	N	P	P
Trifluralin	034	Feed	N	N	N	P

TR = NTP Technical Report; Gav = Gavage; Inh = Inhalation; MR = Male rats; FR = Female rats; MM = Male mice; FM = Female mice
For experiments evaluated by the NCI or the NTP prior to June 1983, results are reported as "positive" (P), "negative" (N), "equivocal" (E), or "inadequate" (IS). In June 1983, the NTP adopted the use of "categories of evidence": two of the five categories correspond to positive results ["clear evidence" (CE) and "some evidence" (SE) of carcinogenicity], one is for uncertain findings ["equivocal evidence" (EE)], one is for negative studies ["no evidence" (NE)], and one is for studies that cannot be evaluated because of major flaws ["inadequate studies" (IS)].

Table II. NCI/NTP Carcinogenicity Study Results for Pesticides: Non-carcinogenic Pesticides Under the Experimental Conditions

Chemcial Name	TR No.	Route	Carcinogenicity Results MR	FR	MM	FM
Aldicarb	136	Feed	N	N	N	N
Anilazine	104	Feed	N	N	N	N
Azinphosmethyl	069	Feed	E	N	N	N
Calcium cyanamide	163	Feed	N	N	N	N
2-Chloroethyltrimethylammonium chloride	158	Feed	N	N	N	N
Chloropicrin	065	Gav	IS	IS	N	N
Clonitralid	091	Feed	N	E	IS	N
Coumaphos	096	Feed	N	N	N	N
Diazinon	137	Feed	N	N	N	N
Dichlorvos	010	Feed	N	N	N	N
Dieldrin	021	Feed	N	N	E	N
	022	Feed	N	N		
1,2-Dichlorobenzene	255	Gav	N	N	N	N
Dichlorodiphenyldichloroethane (TDE)	131	Feed	E	N	N	N
Dichlorodiphenyltrichloroethane (DDT)	131	Feed	N	N	N	N
Di(p-ethylphenyl) dichloroethane (DDD)	156	Feed	N	N	N	E
Dimethoate	004	Feed	N	N	N	N
Dioxathion	125	Feed	N	N	N	N
Endosulfan	062	Feed	IS	N	IS	N
Endrin	012	Feed	N	N	N	N
Fenthion	103	Feed	N	N	E	N
Fluometuron	195	Feed	N	N	E	N
Lindane	014	Feed	N	N	N	N
Malaoxon	135	Feed	N	N	N	N
Malathion	024	Feed	N	N	N	N
	192	Feed	N	N		
Methoxychlor	035	Feed	N	N	N	N
Methyl parathion	157	Feed	N	N	N	N
Mexacarbate	147	Feed	N	N	N	N
Parathion	070	Feed	E	E	N	N
Pentachloronitrobenzene	061	Feed	N	N	N	N
	325	Feed			NE	NE
o-Phenylphenol	301	SP			NE	NE
Phosphamidon	016	Feed	E	E	N	N
Photodieldrin	017	Feed	N	N	N	N
Picloram	023	Feed	N	E	N	N
Piperonyl butoxide	120	Feed	N	N	N	N
Rotenone	320	Feed	EE	NE	NE	NE
2,3,5,6-Tetrachloro-4-nitroanisole	114	Feed	N	N	N	N
Triphenyltin hydroxide	139	Feed	N	N	N	N

SP = Skin paint; For all other abbreviations, see Table I footnotes

luated showed varying degrees of carcinogenicity in animal studies (2); these carcinogenic pesticides and those found to be non-carcinogenic in the test systems are presented in Tables I and II, respectively. The criteria used to determine whether a pesticide is carcinogenic are according to the NTP or NCI convention; that is: one or more of the four experiments (i.e., male rats, female rats, male mice, female mice) showed "clear evidence", "some evidence" of carcinogenicity, or was ruled to be "positive" for carcinogenicity (3,4). A caution must be made here that the percentage (i.e., 41%) for pesticides tested positive as carcinogens does not mean that the same percentage will hold true for all pesticides or all chemicals. The fact that these chemcials were nominated to the NCI or NTP for testing means there was concern that these chemicals could be potentially troublesome; thus the sampling is slanted toward potential carcinogens.

As shown in Figure 1, the primary efforts of the NTP center on chemical nomination, evaluation of the existing information, study design and conduct, data analysis and interpretation, and finally the preparation, public peer-review, and publication of technical reports. However, the information presented in the NTP Technical Report is frequently used world-wide for hazard identification and risk assessment, often leading toward regulatory decisions and actions. Even though the NTP is not directly involved in the regulatory processes, the data generated at the NTP play an important role in these processes.

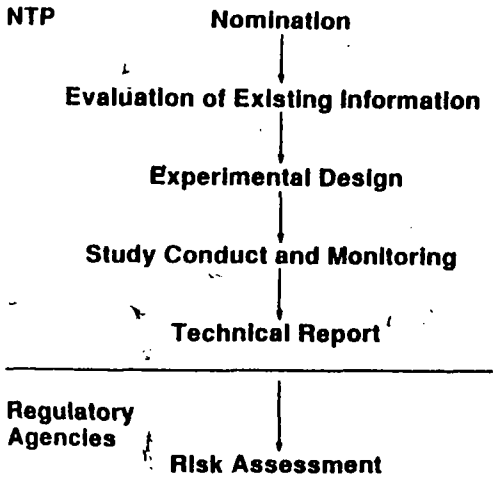

Figure 1. Flow chart of the functions of the NTP in the toxicologic characterization of chemicals and its role in relation to regulatory agencies.

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Once a chemical is demonstrated to have carcinogenic activity in laboratory rodents, extrapolations from "animal carcinogen" to "human carcinogen" and from "high dose" (i.e., the dose used in animal studies) to "low dose" (i.e., the dose humans are exposed to) are inevitable in the risk assessment process. Many biological issues are automatically brought into the limelight. At least some of these issues had been "locked in" as early as the experimental design stage. Those issues most often discussed are species, strain, sex, dose, route, and to some extent exposure scenario. Though important in the risk assessment process, the issues of toxicological interactions and the health effects of chemical mixtures have received comparatively little attention. In this paper, we will only discuss the current thoughts on a few selected issues with a special emphasis on toxicological interactions and chemical mixtures.

Species Extrapolation

Are rats and mice good models for humans toxicologically? This is an age-old question and opinions continue to be varied. But "Is a human a good model for humans?" Assuming there are no ethical and moral considerations and we, as a society, could perform toxicological studies including carcinogenicity bioassays in humans, would there be arguments? The answer is most likely a yes!, because there are so many environmental and life style differences (e.g., dietary preference, smoking, coffee drinking, alcohol indulgence, exercise, etc.) among individuals that the outcome of the results may easily be influenced. Assuming further that we built "human cages" with exercising machines, formulated "NIH-07 Human Chow," and completely eliminated all environmental and life style variables, would we then be more comfortable? The answer is no because there are known human pharmacogenetic differences such as fast acetylators and slow acetylators, and other biochemical and physiological diversities. There will always be arguments such as "Why didn't you use a different subpopulation?"

The point is that there is not and will never be a perfect system and that we have to settle for less than perfect. The right question to ask then is "Given the fact that there is no perfect system, how good are rats and mice as models for humans in toxicology?" Reviewing the literature regarding the development of the carcinogenicity bioassay, one finds such discussion as the one given by Shimkin (5) who proposed a general set of criteria for the selection of test animals in carcinogenicity studies: (a) availability; (b) economy; (c) sensitivity to carcinogens; (d) stable as to response; (e) similarity to human in regard to metabolism; (f) similarity to human in regard to pathology responses. When all these criteria are considered realistically, not too many laboratory animal species may be used for carcinogenicity studies. Other examples in the literature on the selection of species for carcinogenicity bioassay include Sontag (6) and Weisburger and Weisburger (7). On the basis of certain criteria, Sontag (6) suggested that the only

species suitable for large scale, long term carcinogenicity bioassays are the rat, mouse, and hamster. Weisburger and Weisburger (7), on the other hand, indicated that when specific questions are asked of the bioassay rather than the simple endpoint of the increases of neoplasms, a variety of species can be used. Thus, the NTP Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation suggested examples where the specific relationship of a highly defined genetic background and the induction of neoplasms in animals harboring few oncogenic viruses may lead to the use of fish or insects (8). In our opinion, considering the scientific as well as practical issues, laboratory rodents are still the best models available to provide information regarding the potential toxicological consequences of chemicals in question. As responsible scientists in the public health arena, we do not have the luxury to ignore the results from animal studies even if they are less than perfect models for humans. For instance, in recent years, there has been higher prevalence of fin rot, tumors and other lesions in Winter Flounders caught in the Boston Harbor (9). Are we to take such findings as a valid warning from nature and consider them as the results of a "natural bioassay" on the pollution in the area, or simply ignore it on the basis that a fish is not a human?

There is abundant debate in the literature about the use of laboratory rodents as models for humans; a recent example appeared in Statistical Science (10-16). Some scientists considered rodents very good surrogates for humans in predicting carcinogenicity; for instance, of the known human carcinogens, 86% to 100% (depending on the data base used) were shown to be animal carcinogens (12,17-19). Others (10), apparently using the same data base but only the "sufficient evidence" category as defined by the International Agency for Research on Cancer (IARC) (18) in their calculation, considered rodents to be poor models for humans because the concordance was poor (59%). At issue though is not whether or not the concordance is 100% or 59% between human and animal models because even a selected sample of humans probably do not have 100% concordance with the rest of the human population. We know laboratory rodents are not perfect surrogates for humans but they definitely provide valuable scientific information regarding the intrinsic biological activities of chemicals.

It is important for scientists in toxicology to recognize the imperfection of the animal bioassays and to try to continually develop better scientific methods to minimize the differences in the extrapolation between species and between high and low doses. As a case in point, the incorporation into the risk assessment process of physiologically based pharmacokinetics/computer modeling which takes into consideration physiological constants (e.g., body size, organ and tissue volumes, blood flow, and ventilation rates), biochemical constants (e.g., metabolic constants, partition coefficients for blood, tissues and air), and mechanistic factors (e.g., target tissues and metabolic pathways) of various species, including human, represents a major scientific advance in recent years (20).

The importance of continuing refinement and improvement of the hazard identification and risk assessment process based on newly developed scientific information may be illustrated by another example using a pesticide, EDB or ethylene dibromide. Critics of cancer risk assessment based on animal bioassays frequently make reference to a paper by Ramsey et al. (21). In that paper (21), Ramsey and coworkers questioned the validity of the EPA's estimate of 100% lifetime incidence of cancer to be expected in humans exposed to a concentration of 0.4 ppm (3.1 mg/m^3) of EDB for 40 years. As pointed out by Ramsey et al. (21), the reliability of such a prediction is dependent upon the validity of the carcinogenesis model (one-hit model in this case) as well as its extrapolation from rat bioassay data to human population. To test these hypotheses, Ramsey et al. (21) compared the incidence of cancer predicted by the EPA one-hit carcinogenic model with that observed in a group of 156 workers employed in the production of EDB. While the one-hit model predicted a total of 85 tumors above the normal background incidence (2.2 tumors expected based on a comparison with the U. S. white mal mortality rates) in this group of workers, the actual tumor incidence rate of 8 tumors was observed (21). Ramsey et al. concluded that u of the one-hit model appears to result in "highly exaggerated" risk estimates. Their results and conclusions have been cited as evidence that extrapolations from animal bioassays to human real-world exposures are implausible. A more recent attempt by Hertz-Picciotto et al. (22), however, has provided counter arguments. When cancer risk for EDB among the cohort of workers used by Ramsey et al. (21) were estimated by fitting several linear nonthreshold additive models to data from gavage and inhalation animal bioassays (22), the predicted upper bound risks were within a factor of 3 of the observed cancer deaths (Table III). Thus, Hertz-Picciotto et al. (22) concluded that the previous overestimate of risk to workers occupationally exposed to EDB was due to failure to consider their age at start of exposure when extrapolating from an animal bioassay with an exceedingly short latency period. In the quotation from Hertz-Picciotto et al. (22) below, the spirit of continuing improvement and refinement of the hazard identification and risk assessment process is elegantly reflected:

> "The field of carcinogenic risk assessment is in its infancy. The primitiveness of methodology echoes the lack of a clear theory of carcinogenesis. However, the gaps in knowledge and the uncertainties in methods do not constitute sufficient justification for abandoning efforts to provide the public with plausible upper bounds for cancer risks due to environmental chemical exposures. For a large number of such exposures, these estimates will necessarily be based on animal data. When quantified human exposure data are available and are related to cancer risk, these data can be useful either as a basis for extrapolation or as a standard for assessing the plausibility of risk estimates based on animal data alone."

Table III. Total Cancer Deaths Predicted by Several Models for EDB-Exposed Workers

	Observed cancer deaths	Models fitted to gavage data: One-hit	Proportional hazards: Stomach	Proportional hazards: Lung	Multistage with time-to-tumor	Multistage with variable dosing	Model fitted to Inhalation data: One-hit: terminal sacrifice tumors Omitted	Model fitted to Inhalation data: One-hit: terminal sacrifice tumors Included
				0.9 ppm Exposure				
Texas	3	38.6	10.4	31.4	7.7	7.1	3.8	4.0
Michigan	5	21.2	5.9	13.0	3.5	4.5	2.3	2.4
Overall	8	59.8	16.3	44.4	11.2	11.6	6.1	6.4
				3 ppm Exposure				
Texas	3	56.6	21.4	50.4	15.5	14.0	4.2	4.9
Michigan	5	34.2	11.7	24.3	6.1	7.7	2.5	2.9
Overall	8	90.8	34.5	74.7	21.6	21.7	6.7	7.8

Condensed from Hertz-Picciotto (22)

Maximum Tolerated Dose (MTD)

Since quantitative risk extrapolation is presented in another chapter, we discuss briefly here the issue of maximum tolerated dose (MTD). Actually "maximum tolerated dose" is a rather nebulous term without specific qualifiers. A generally accepted definition does not exist. The definition for MTD, given in one source (8), is "...this dose is determined by prechronic studies which aid in the identification of a dose level which, when given for the duration of the chronic study as the highest dose, will not impair the normal longevity of the treated animals from effects other than the induction of neoplasms. Such dose should not cause morphologic evidence of toxicity in organs other than mild changes such as slight hypertrophy or hyperplasia, inflammation or slight changes in serum enzymes..." In a second source (23), MTD is attributed to be the result of "...the simplistic approach of the National Cancer Institute's Bioassay Program, which is to conduct a 3 month range finding study with enough doses to find a level which suppresses body weight gain slightly, i.e., 10%. This dose is defined as the maximum tolerated dose (MTD) and is selected as the highest dose." In a third source (24), MTD is defined as "...a predictive dose obtained from analysis of subchronic study doses. In the oncogenicity study, the MTD should elicit toxicity without substantially altering the normal life span of the test species from effects other than tumor formation." In this case, it is of course really an exercise after the fact (i.e., after the completion of the chronic toxicity study) to evaluate if the doses selected were reasonable. Examples in such an evaluation for determining a MTD include body and organ weight effects as well as clinical and anatomic pathology (24). Thus, MTD must be considered in the context of the toxicological endpoints measured.

In the estimation of MTD and setting doses for chronic toxicity/carcinogenicity studies, one often hears advice against selecting any dose within the range of "saturation kinetics" (or "nonlinear kinetics"). The underlying reason for such advice is that we, the experimenters, should not "overwhelm" the animals' capacity of handling chemical insults. This is once again debate or argument resulting from nebulous terms. If one considers that any toxicity or toxicological response(s) is a manifestation of the disruption of homeostasis, then somewhere in the body there must be a system(s) (e.g., sites of action, transport mechanisms, metabolic pathways, binding sites, repair mechanisms, etc.) being overwhelmed. In fact, it has been suggested that toxicology is nonlinear pharmacokinetics (25). Therefore, at the stage of selecting doses for chronic toxicity studies based on prechronic toxicity data, it is very difficult to talk about nonlinear pharmacokinetics or saturation kinetics without defining precisely what parameters are involved.

As to the debate on the use of estimated MTD in chronic toxicity/carcinogenicity studies, recent information may be found in two letters by Abelson (26) and McConnell (27). Abelson suggests that the public has been misinformed through "a media barrage" by the results of chemical carcinogenesis studies in animals, particularly in rodents (26). One of the criticisms from Abelson was the use of "massive doses" (i.e., MTD) which, in his opinion, "vastly exceed those to which humans are likely to be exposed" (26). McConnell

(27), on the other hand, pointed out that, in at least three important instances (asbestos, benzene, and 1,3-butadiene), past occupational exposures are not different from the levels used in laboratory experiments. Further, McConnell (27) defended the use of MTD in carcinogenicity studies because animals are able to detoxify chemicals much faster than humans do, and to get an equivalent dose to the target tissue in such a case would require much more of the chemical in animals. He illustrated his point by using cigarette smoke as an example; it takes an unusually high exposure of cigarette smoke to cause cancer in laboratory aniumals as compared to humans (27). McConnell asked that if cigarette smoke were an "unknown," would one assume tobacco was safe because the dose to animals was higher than the average human receives? (27).

Toxicologic Interactions

Toxicologic interaction has been defined as "a circumstance in which exposure to two or more chemicals results in a qualitatively or quantitatively altered biological response relative to that predicted from the actions of the single chemicals independently. The multiple-chemical exposures may be simultaneous or sequential in time, and the altered responses may be greater or smaller in magnitude" (28). While most if not all of the known examples of toxicologic interactions concerning pesticides (29) involve respective chemicals at concentrations far above levels of environmental contamination, recent findings have uncovered toxicologic interactions at low enough concentrations to be relevant to environmental pollutions. Table IV illustrates an example of toxicologic interaction other than the classical instances of insecticide synergism (e.g., pyrethrin and piperonyl butoxide). Klingensmith and Mehendale (30) and Mehendale (31) reported probably the first case where a pesticide, Kepone, at an environmentally realistic level (i.e., 10 ppm) caused a dramatic increase (67-fold) in the acute toxicity of carbon tetrachloride. Although this synergistic effect of Kepone is rather specific in that close structural analogs such as mirex and photomirex do not share this property (31), one wonders whether other chemical(s) or chemical mixtures, at environmentally low levels, might cause similar synergistic toxicity. Indeed, the NTP has obtained some preliminary experimental results (presented later) which may shed light upon this question.

Toxicologic interactions may occur in chronic toxicity and carcinogenicity studies. For instance, Wong and colleagues (32) demonstrated a profound enhancement of mortality, tumor incidences and the shortening of latency period for neoplasms of a well-known fumigant, EDB, by disulfiram (antabuse) in a chronic toxicity study. As shown in Table V, the numbers and the types of tumors increased significantly when EDB and disulfiram were given together. Of course, the reason for such a synergistic effect was due to the interference of metabolic degradation of EDB by disulfiram (32). The relevance of this study, as was the original purpose for the investigation (32), is the concern of the potential synergistic hazard for people occupationally exposed to EDB (e.g., production workers, pest control applicators) who might be simultaneously participating in an alcohol control program using antabuse as a therapeutic agent.

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Table IV. Enhancement of Acute Toxicity of Carbon Tetrachloride by Low Level Dietary Pretreatment of Kepone

Dietary Pretreatment	48-hr LD_{50} (ml CCl_4/kg)	Increase in Mortality
Control diet	2.8	--
Kepone (10 ppm) diet	0.042	67-fold

Condensed from Klingensmith and Mehendale (30) and Mehendale (31)

These examples above demonstrate yet another area of uncertainty in the extrapolation of animal toxicity studies to the hazard identification and risk assessment of humans. Since the data base in this area is extremely limited, particularly at chemical concentrations which are environmentally realistic, major endeavours in this area are urgently needed.

Table V. Major Histopathological Findings in Rats Exposed to EDB or EDB/Disulfiram (EDB+DS) in the EDB/Disulfiram Interaction Study

	EDB		EDB+DS	
	Male	Female	Male	Female
No. of Animals Examined	46	48	48	45
Liver hepatocellular tumors	2	3	36*	32*
Mesentary or omentum hemangiosarcoma	0	0	11*	8*
Kidney adenoma and adenocarcinoma	3	1	17*	7*
Thyroid follicular epithelial adenoma	3	1	18*	18*
Mammary all tumors	---	25	---	13*
Lung all tumors	3	0	9*	2
No. of Rats with Tumor	25	29	45*	45*
No. of Rats with Multiple Tumors	10	8	37*	32*

* $P<0.05$

Condensed from Wong et al. (32). Disulfiram was given in diet at 0.0 and EDB inhalation exposure was at 20 ppm. The control and DS alone groups (not shown here) had, in general, very low or no tumor incidence with respect to these organs; the only exception was that the DS alone group had statistically higher incidence in mammary tumors than did the control group.

Toxicology of Chemical Mixtures

Human exposure to chemicals, be it occupational or environmental, is rarely limited to a single chemical. Even in a strictly controlled situation such as a production plant for a single chemical, the exposure of workers to a variety of other chemicals in food, drink, personal hygiene, etc. is part of daily life. As illustrated very clearly in a recent government publication on human health and the environment (33), "...Each of us is exposed daily to multiple chemical substances in our environments. The food we eat is a complex mixture of chemical substances. Our drinking water contains hundreds of chemicals, even when it is obtained from a municipal "purification" facility. The air we breathe and the things we touch likewise contain a variety of chemicals with an almost limitless range of compositions. Moreover, our habits and lifestyle may add other chemical exposures. Tobacco smoke, for example, contains thousands of substances. Additionally, the American public spends between $4 billion and $8 billion per year on self prescribed and self-administered drugs for self-diagnosed illness..."

In the last few years, the NTP has been interested in the toxicology of a mixture of 25 frequently occurring groundwater contaminants derived from hazardous waste disposal sites. The diagram in Figure 2 is a summary of the projects completed or ongoing at the NTP and neighbouring institutes. The genesis of such a program, the formulation of a 25-chemical (19 organics and 6 inorganics) mixture in deionized water, and the analytical and initial animal toxicology work have been reported (34-41). In most of our animal studies, the highest dose level, as shown in Table VI, contains individual chemical concentrations close to those detected in the groundwater samples near hazardous waste disposal sites. When this mixture is given to female B6C3F$_1$ mice for 14 or 90 days, suppression of immune function was seen in 3 of the parameters examined (38); the results are summarized in Table VII. First, the suppression of bone marrow stem cell proliferation, as expressed by the number of colonies formed of the granulocyte-macrophage progenitor cells is presented. Note the lack of response in the paired-water control group in the 14-day study; this finding suggests that the immunotoxic responses seen had little, if anything, to do with the reduction of water consumption in the treated groups. A clear dose-response relationship was demonstrated in the 90-day study results on the suppression of bone marrow stem cell proliferation. The second immunological endpoint affected is the suppression of antigen (sheep red blood cell)-induced antibody forming cells (Table VII); similar results as discussed above for the stem cell suppression are also evident for this endpoint. Three host resistance assays following challenge with infectious agents (Listeria monocytogens, PYB6 syngeneic tumor cells, or Plasmodium yoelii) were investigated (38). Altered resistance, as expressed by % parasitemia, occurred in the group challenged with Plasmodium (Table VII). These results collectively suggest that long-term exposure to heavily contaminated groundwater may represent a risk to the immune system (38).

In another experiment (Figure 3), a collaborative effort between the EPA and the NTP, we examined the effects of pretreatment with the 25-chemical mixture of groundwater contaminants for 14 days on the hepatotoxicity of carbon tetrachloride in male Fischer 344 rats (39).

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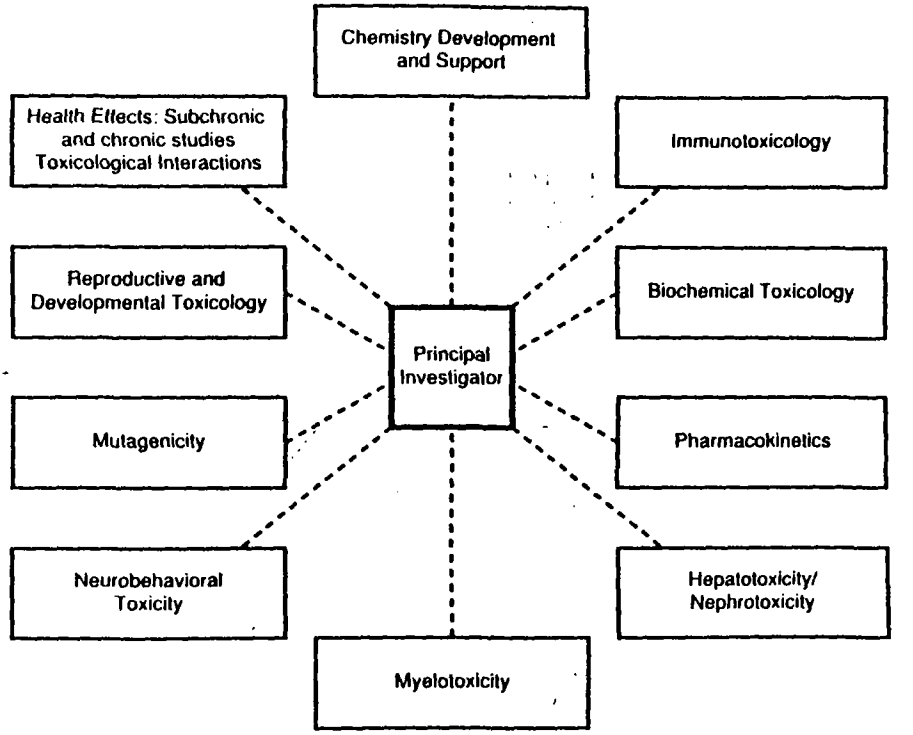

Figure 2. A program of toxicology of complex chemical mixtures of groundwater contaminants at the NTP.

Table VI. Comparison of Concentrations of the Components of the 25 Chemical Mixture Dosing Solution with EPA Survey Results

	A	B	
	Ave EPA Survey ppm	High Dose Concentrations (ppm)	Ratio B/A
Acetone	6.9	53	7.7
Arochlor 1260	0.21	0.01	0.05
Arsenic	30.6	9	0.29
Benzene	5.0	12.5	2.5
Cadmium	0.85	51	60
Carbon tetrachloride	0.54	0.4	0.74
Chlorobenzene	0.1	0.1	1
Chloroform	1.46	7	4.79
Chromium	0.69	36	52.2
DEHP	0.13	0.015	0.12
1,1-Dichloroethane	0.31	1.4	4.52
1,2-Dichloroethane	6.33	40	6.32
1,1-Dichloroethylene	0.24	0.5	2.08
1,2-trans-Dichloroethylene	0.73	2.5	3.42
Ethylbenzene	0.65	0.3	0.46
Lead	37.0	70	1.89
Mercury	0.34	0.5	1.47
Methylene chloride	11.2	37.5	3.35
Nickel	0.5	6.8	13.6
Phenol	34.0	29	0.85
Tetrachloroethylene	9.68	3.4	0.35
Toluene	5.18	7	1.35
1,1,1-Trichloroethane	1.25	2	1.6
Trichloroethylene	3.82	6.5	1.7
Xylenes	4.07	1.6	0.39

3 chemicals > 10X Average EPA Survey Concentration
14 1X - 10X
8 < 1X

As Table VIII demonstrates, the deionized water control group and the drinking water chemical mixture alone group showed no histopathological changes in the liver. While the CCl_4 alone group showed a mild centrilobular vacuolar degeneration at the dose level applied (0.075 ml/kg), the mixture/CCl_4 group showed, in addition to the mild centrilobular vacuolar degeneration, minimal centrilobular hepatocellular necrosis (Table VIII). The necrotic changes in the liver in the mixture/CCl_4 group also coincided with the elevation of serum aspartate aminotransferase (177% of controls) and alanine aminotransferase (273% of controls). We are currently conducting an experiment to determine the effect of prior exposure to the 25-chemical mixture on the CCl_4 dose-response curve and to determine the influence of the observed decrease in water and feed consumption on the apparent enhancement of CCl_4 hepatotoxicity.

Table VII. Immune Functions in B6C3F1 Mice Affected by Exposure to a Chemical Mixture of Groundwater contaminants

Exposure Level (% Stock)	CFU-GM /10^5 cells1	PFC/Spleen (X 10^3)2	P. yoelii % parasitemia3
		14-day study	
0	59.8 ± 6.0	172 ± 16	14.2 ± 1.2
0.2	57.2 ± 1.3	231 ± 16	9.2 ± 1.0
2.0	55.4 ± 3.2	157 ± 24	19.8 ± 2.9
20.0	37.8 ± 0.4**	96 ± 16**	22.1 ± 2.9*
Paired water	50.5 ± 1.3	172 ± 17	N.D.
		3-month study	
0	55.3 ± 2.1	189 ± 49	10.1 ± 1.5
1.0	52.6 ± 2.9	120 ± 19	9.4 ± 2.9
5.0	43.5 ± 4.6*	144 ± 21	12.7 ± 1.9
10.0	29.6 ± 1.7**	93 ± 15	20.8 ± 2.9*

1 The CFU-GM, granulocyte-macrophage colonies, were assayed by incubating femoral bone marrow cells in the presence of mouse lung conditioned medium as a colony stimulating factor at 37°C 5% CO_2 for 7 days. Colonies of >50 cells were enumerated using stereomicroscope. Values given represent mean ± SE of CFU-GM p 10^5 cells for at least five mice per group.

2 The antibody response to sheep erythrocytes was determined by enumerating plaque-forming cells (PFC) in splenic lymphocytes 4 days after primary immunization. Values given represent mean ± SE of PFC per spleen for at least five mice per group.

3 Infection with the malarial parasite P. yeolli was determined b quantitating the percent parasitemia on days 10, 12, and 14 following injection of 10^6 parasitized erythrocytes. Only peak day, day 12, of infection is shown. Values given represent mea ± SE of eight mice per group.

N.D. = not done;
** Significantly different from control at $P < 0.01$;
* Significantly different from control at $P < 0.05$

SOURCE: Data are from ref. 38.

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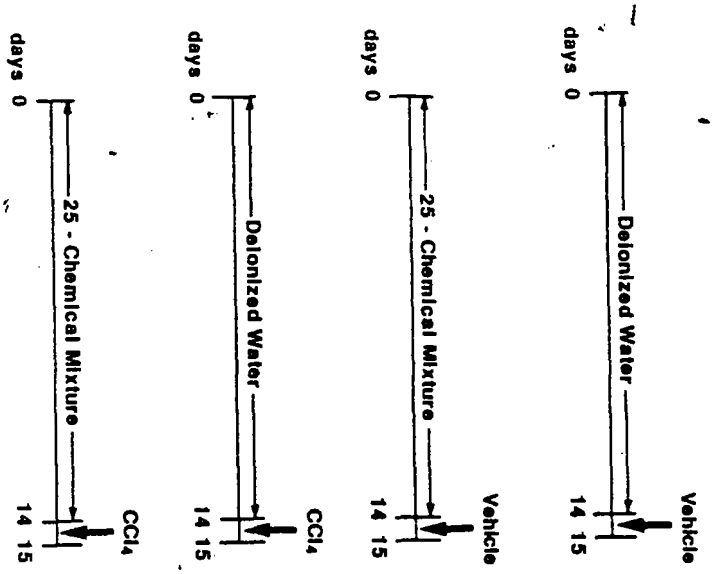

Figure 3. Experimental design of the toxicologic interaction study between a chemical mixture of 25 groundwater contaminants and carbon tetrachloride.

Table VIII. Enhancement of Carbon Tetrachloride Hepatotoxicity in Male Fischer 344 Rats by Prior Exposure to a Mixture of 25 Groundwater Contaminants

Treatment[1] Groups	No. Animal Examined	Clinical Chemistry Parameters		Liver Histopathology (No. Rats with Lesion)		
		AST2	ALT2	Normal	Vacuolar Degeneration	Cellular Necrosis
Control/ Control	4	52.8 ± 4.3	35.0 ± 4.1	4	0	0
Low Mixture/ Control	4	46.5 ± 2.6	32.8 ± 1.7	4	0	0
High Mixture/ Control	4	53.8 ± 6.2	39.0 ± 2.2	4	0	0
Control/ CCl_4	4	55.0 ± 3.9	47.0 ± 7.5	0	4	0
Low Mixture/ CCl_4	4	52.5 ± 4.0	41.2 ± 7.4	0	4	0
High Mixture/ CCl_4	4	93.5 ± 36.5**	95.5 ± 49.7**	0	4	3

1 The rats were given deionized water (Control) or 1% (Low Mixture) or 10% (High Mixture) mixture stock for 14 days and then dosed by gavage a single dose of corn oil (Control) or CCl_4 at the rate of 0.075 ml/kg in corn oil; the animals were then sacrificed 24 hours later.

2 AST = Aspartate aminotransferase; ALT = Alanine aminotransferase

**Significantly different from the Control/Control group, the High Mixture/Control group, and the Control/CCl_4

The primary hazard of pesticide exposure is acute toxicity resulting from dermal contact with or inhalation of a relatively large dose (1). However, the toxicology of chemical mixtures at the level of environmental contamination will probably not involve acute toxic responses. It is most likely an insidious effect(s) disrupting the homeostasis of the organism. The exposed animals may appear totally "normal" clinically or based on conventional toxicological endpoints. However, such a subclinical state may provide a basis for enhancement or potentiation of otherwise mild toxic responses from an acute exposure(s) of chemical, physical, and/or biological agents. In this sense, the concept of a generic "promotor" or "enhancer" for any possible toxicity may be advanced for the potential toxicologic consequence of a mixture of environmental pollutants. These findings also raise the possibility for synergistic interaction between a background long-term, low-level chemical mixture exposure and an subsequent acute dose resulting from accidental exposure or drug intake including alcohol abuse. All these issues are not only relevant but very important in the extrapolation between animals and humans.

Concluding Remarks

Two years ago, in the ACS symposium on "Pesticides: Minimizing the Risks", the utilization of physiologically based pharmacokinetics/computer modeling for dealing with the complex issues of extrapolation, toxicological interaction, and chemical mixtures was suggested (42,43). As shown in Figure 4, the Stage I effort has already been

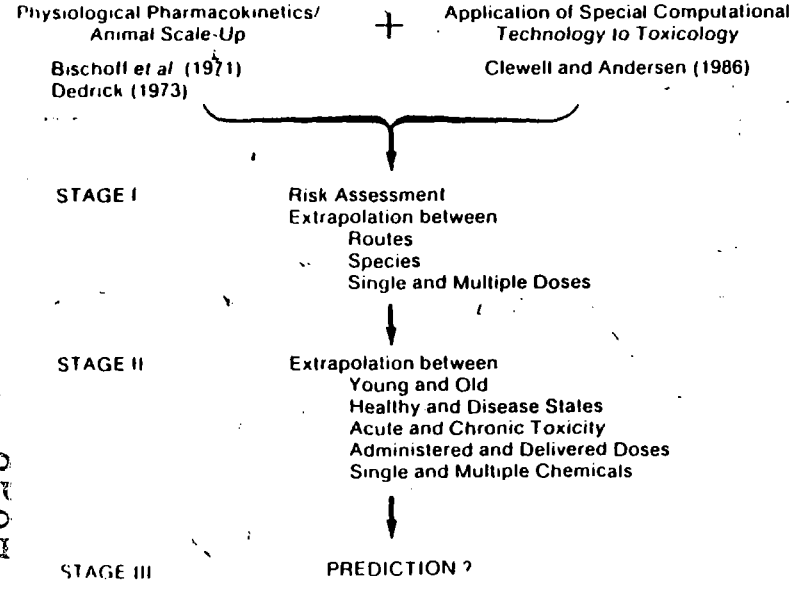

Figure 4. A suggested approach utilizing physiologically based pharmacokinetics and computer technology for the extrapolation and prediction of various situations in toxicology. (Reproduced from ref. 42. Copyright 1987 American Chemical Society.)

in progress. Some scientific activities are also evident for the effort of Stage II and beyond (44-49). In the last two years, a great deal of progress has been made in this area including a Workshop on "Pharmacokinetics in Risk Assessment" organized by the National Research Council which resulted in the publication of volu 8 of the Drinking Water and Health series (20). However, like any other new technique, the computer modeling of physiologically based pharmacokinetics and its application to risk assessment is going through an evolutionary phase. Much debate and controversy have be appearing in the literature. As a case in point, EPA's adoption of physiologically based pharmacokinetics in their risk assessment process and the related criticisms and debate reflect the current state of flux (48,49). Nevertheless, all these activities and debates wi inevitably help to improve and refine this approach. Eventually, th scientific community and the public at large will have a better risk assessment method.

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Disclaimer

The research described in this article has been reviewed by the Health Effects Research Laboratory, U. S. Environmental Protection Agency and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Agenc nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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KEISTER v. DOW - Attachment to Memo of 11/28/91 (Exhibit List of Documents)

[redacted]

ATTACHMENT TO MEMORANDUM OF NOVEMBER 28, 1991
(KEISTER V. DOW)

EXHIBIT LIST

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1. 3/20/47: United States Patent 2,509,245 "PREPARATION OF 2,4,5-TRICHLOROPHENOL" by the Givaudan Corporation of New Jersey.

Comment: This describes a process where 1,2,4,5-tetrachloro-**benzene** is subjected to alkaline hydrolysis in the presence of ethylene - or propylene glycol. This is accomplished by stirring in the ingredients at elevated temperatures between 160 C and 200 C. The reaction mixture is cooled and then acidified with hydrochloric acid. **NOTE:** It is this heating above 160 C that produces the deadly dioxin 2,3,7,8-TCDD. The benzenes are the key to all this.

2. 1/24/55: United States Patent 2,799,713 "METHOD OF MAKING TRICHLOROPHENOLS FROM TETRACHLOROBENZENES" by The Dow Chemical Company od Midland, Michigan.

Comment: Dow changes the process in exhibit #1 where they can do the same thing faster and less expensively on a mass production scale by further heating the above mixture to between 225 C and 300 C under a pressure of 400 to 1500 PSI. **The result is more dioxin contaminant** since any temperature above 160 C will produce it. These higher temperatures and pressures later led to several chemical plant explosions around the world, thus releasing the deadly dioxin into the atmosphere and exposing workers in the plant with high concentrations of dioxin. But, Dow made more money faster with this process!

3. 8/2/62: Hercules Powder Company Jacksonville, Arkansas Operations Booklet. This booklet gives information on the chemistry, equipment, method of manufacture, etc. for 2,4-D and 2,4,5-T.

Note: Hercules later made these herbicides for Dow Chemical under contract and distributed them under the Dow Label, including Agent Orange. This particular plant was especially contaminated with the TCDD dioxin impurity.

4. 1962: "Toxicology of Herbicides" by Mikkelsen et al of the Dept. of Pharmacology and Toxicology, Royal Veterinary and Agricultural College of Copenhagen, Denmark.

Comment: This report reviews the acute effects of 2,4-D and 2,4,5-T mostly in animals and shows CNS disorders. It states "Many of the toxicological data underlying assessments of the

risk involved by using them in practice originate from confidential, non-published reports placed at the disposal of the authorities concerned. Such data has not been included in the present survey."

5. 5/2/63: Confidential inter-office correspondence between Diamond Shamrock employees on Chloracne being a potential hazard to anyone working with chlorophenoxy herbicides, especially 2,4,5-T. They point out it is an inherent danger with all companies 2,4,5-T products.It states " Dow has had this problem on and off in their plants in past years." A handwritten note at the bottom says "This problem is more likely to occur when using 2,4,5-T than when using 2,4-D. **In fact, some people cannot work with 2,4,5-T."**

Note: Other literature shows that a person with chloracne is a proven exposure to the dioxin 2,3,7,8-TCDD. Dow Chemical knew 2,4,5-T had the TCDD dioxin since at least 1957 based on correspondence they received from their German chemical company friends as BASF. The literature first identified chloracne in 1897! All these chemical companies know that a person with chloracne is a walking advertisement of dioxin exposure.

6. 2/24/65: File memo from R. Kelly, M.D. on his talk (phone?) with V.K. Rowe of Dow stating that Dow has 20 cases of Chloracne in the plant. Dow found a contamination level of 3 - 10 ppm in a sample of 2,4,5-T sent to them by Dr. Kelly. Rowe says "Dow has been receiving complaints from their customers . . . on chloracne problems" Dow says "The PMS is looking into this problem and has contacted some of Dow's customers concerning the occurrence of chloracne." Rowe wants to have a "crash meeting with all the producers to try to reach some specification level in order to eliminate this particular contaminant before the PMS got into the act."

7. **3/24/65: ***** Dow Chemical Company confidential internal letter from L.Q. Silverstein to V.K. Rowe of Dow's Biochemical Research Laboratory on "Report of the Chloracne problem meeting on 3/24/65". They talk of 60 to 70 cases of individuals at Dow with chloracne and the emphasis of clinical studies on liver function tests in these individuals. Hooker Chemical related chronic exposures that are there 30 years after exposure! They showed slides of TCDD tests run on the ears of rabbits and discussed the pathology in detail at the meeting. They said if exposure occurs for very long, washing does little good. The group said no level of TCDD is safe, but they are trying to hold it to less than 1 ppm in their products. They admit the significant factor is the dose, the number of exposures and the days on exposure to the subjects. The tested level of response ranges from: none to extremely severe! It then states " the group then proceeded to the Toxicology Laboratory to view some of the test animals. They were shown responses of varying intensity and these were described. **This demonstration appeared to have considerable impact**."

8. **6/24/65:** ** Dow confidential letter from V.K. Rowe to Ross Mulholland of Dow Canada on "2,4,5-Trichlorophenol, the T Acids, and Associated Acnegens." Rowe says "as you well know, we had a serious situation in our operating plants because of contamination of 2,4,5-trichlorophenol with impurities, the most active of which is 2,3,7,8-tetrachloro-dibenzodioxin. **This material is exceptionally toxic; it has a tremendous potential for producing chloracne and systemic injury. If it is present in the trichlorophenol, it will be carried through into the T acid and into the esters and hence into formulations which are to be sold to the public. One of the things which we want to avoid is the occurrence of any acne in consumers. I am particularly concerned here with persons who are using the material on a daily, repeated basis such as custom operators may use it. If this should occur, the whole 2,4,5-T industry will be hard hit and I would expect restrictive legislation, either baring the material or putting very rigid controls upon it."** (Note: Systemic means to affect the entire organism or bodily system!) The letter ends with a P.S that says **"Under no circumstances may this letter be reproduced, shown, or sent to anyone outside of Dow."**

9. 11/18/65: Hercules internal memo from their medical department to their synthetics department of "The investigations we contemplate on chloracne possibly associated with 2,4,5-T esters." They discuss various ways to test their products for dioxin (TCDD) contaminants before they reach the customer.

10. 6/13/66: Hercules internal memo from their analytical division to their medical department on "DIOXIN FORTIFIED SAMPLES FOR BIOASSAY TESTS." Most are "spiked" samples of added dioxin from 2 to 20 ppm. One sample is a plant grade 2,4,5-T with known dioxin of 3 ppm contamination. It states they are storing their contaminated batches used in tests at the rate of 2-3 drums per day.

11. 2/15/67: Dow letter from V.K. Rowe to M.S. Buckley, Technical Director of Thompson Chemical Company on "How to deal with their chloracne problem that resulted from a chemical accident during production." Rowe refers him to an article called "Clinical Observations About The Origin of Chloracne" by W. Braun published in Germany in 1959. Rowe then writes an internal memo to Dixon in the Dow Bioproducts Department on this conversation (See attached memo of 2/15/67) where he refers to a phone conversation he had with Mr. Dixon on 2/7/67 and says **"I told him that under certain circumstances, which I did not describe, the caustic insoluble oils could contain considerable amounts of a very highly toxic substance which we had identified as 2,3,7,8-tetrachlorodibenzodioxin. I indicated to him that this material was not only extremely toxic systemically, but it was also an extremely potent chloracnogen."** Rowe later states **"Dr. Holder (of Dow) indicated to him (Mr. Dixon) that he must take extreme precautions, including the use of rubber suits and gloves and respirators."** (i.e. to clean up their chemical spill at the Thompson plant) NOTE: No one at Dow ever told a user of their

product to do this! They certainly never told a user their product was contaminated with a known deadly dioxin called 2,3,7,8-TCDD!

12. 6/30/67: Hercules confidential memo to their Jacksonville plant saying their were 5 cases of chloracne in Columbia from contaminated 2,4,5-T that entered the sales channels in 1963 and 1964. "No prior cases of chloracne outside of manufacturing operations have come to our attention . . be on the alert for abnormal operating conditions"

13. 9/26/67: Dow letter to the USAF Directorate of Air Force Aerospace Fuels from A.P. Beutel, Dow's Director of Government Affairs on "Request for Dow's Bid on the Design, Conversion, and Operation of an 8,000,000 Gallon per Year "Orange" Plant at the Government Owned Chemical Plant at Weldon Spring, Missouri." Dow asks to be withdrawn from this process because they consider it too high of a risk for them due to the location of the Air Force Plant near the University of Missouri Experimental Farm and the August Busch Reserve. Dow says any accidental release of these products into that particular environment is a risk Dow will not take. "The chloracne problem is one of human health which Dow has had to combat in the design of its own plants at its Midland operations." Dow says they are already engaged in the production of 2,000,000 gallons per year of "Orange" at their own plant.

14. 10/16/68: From Industrial Hygienist Emil Christofano to V.K. Rowe of Dow on "Hercules attempts to develop a bioassay technique to simplify detection of dioxin in herbicide formulations." He states they have not been successful on the tests that measure liver function changes after feeding their rabbits with 2,4,5-T.

15. Late 1960's: Abstract on "Influence of Dioxin on Liver Functions in the Rabbit" by M.L. Keplinger et al of Industrial Bio-Test Laboratories in Northbrook, Illinois and Hercules, Inc. which simply states that some rabbits show liver damage when fed 2,3,7,8-TCDD and some don't. Hence this test is not a positive indicator of proving contamination levels.

16. 3/17/70: Dow Press Release on "DOW RESEARCH ON 2,4,5-T BLAMES BIRTH DEFECTS ON IMPURITY." Here Dow tries to convince the public that it is a contaminant in 2,4,5-T and not 2,4,5-T itself that caused birth abnormalities in a recent test animal study by Bionetics Laboratories, under contract to the National Cancer Institute. Dow says they analyzed the Bionetics sample used and found a contamination of 27 ppm dioxin TCDD. Dow says they have kept their contamination to 1 ppm of TCDD since 1965 and hence their product is safe to users. V.K. Rowe of Dow says we simply proved again what we already knew. 2,4,5-T is a material of low toxicity while the dioxin is highly toxic."

Comment: Dow has already told other chemical manufactures that any level of TCDD dioxin is too much, but a contamination of

1 ppm is what they try to maintain at Dow. Only a few companies in the world could even test for a contamination below 1 ppm at this time. It was very expensive to test even one sample and Dow knows that few people outside of the major chemical companies can afford to do this, even if they have the equipment. It has later been proven that 1 ppm is an acute dose level, and not even Dow admits testing for long term chronic exposures to users. Private studies have shown that even a few parts per billion on a chronic basis are deadly to certain people.

What Dow does in this press release is what they have continued to do until this day - namely claim that 2,4,5-T is safe and focus on levels above 1 ppm on TCDD which are readily detectable at many labs today. The point is, no one's 2,4,5-T can be produced without the TCDD contaminant, and long term chronic exposures will cause serious health effects, including many forms of cancer! Don't forget that Hercules and Vertac made these herbicides under the Dow label for years and had a hard time keeping their TCDD contamination at 1 ppm.

17. 3/19/70: Hercules internal memo from J. J. Ford, Analytical Division to Dr. M. A. Taves, Synthetics Research Division on "ANALYSIS OF 2,4,5-T ACID FOR "DIOXIN" CONTENT." Here they say samples of their 1965 production yielded "dioxin" values of 1.3 to 3.5 ppm. They claim a dioxin level of less that 0.2 ppm from their 1967 to 1970 production.

18. **3/24/70:** ** National Agricultural Chemicals Association letter from K. K. Krausche, Director of Technical Services to J.O. King of Diamond Shamrock Chemical. ""Possible Industry Public Relations Value in Publicizing The Full Dioxin Story." They say that the consensus of the member companies most closely involved with this problem is that they will handle it on their own, but the next time the " Phenoxy Herbicide Task Force" gets together, he will bring it up again.

Comment: They handled it like Dow did in their press release and later advertisements - namely that 2,4,5-T is perfectly safe, it is only the dioxin that will kill you!

19. 4/27/70: Article entitled "GOVERNMENT STEPS UP PRESSURE ON PESTICIDES", C&EN publication. The government suspended and cancelled consumer and food crop uses of 2,4,5-T and halted its use in Vietnam. The order specifically suspended use of liquid formulations of 2,4,5-T around the home, near lakes and ponds, and on ditch banks and cancelled use of non-liquid formulations around the home and on apples, blueberries, barley, corn, oats, rye, rice and sugar cane. Not restricted were uses for weed and brush control on range, pasture, forest, rights-of-way, and nonagricultural land. Use of a 2,4-D and picloram were allowed to continue (agent white).

This action all came about because of a dioxin contamination of between 16 and 27 ppm in a Diamond Shamrock sample of 2,4,5-T taken in 1965 and found to cause birth defects (teratogenic) in rats by Bionetics Research Laboratories. A joint Agriculture-

Interior-HEW announcement said that **"nearly pure 2,4,5-T was reported to cause birth defects when injected at high doses into . . . pregnant mice, but not in rats. No data on humans are available."** Further evidence was presented by the FDA that **chick embryo studies and preliminary hamster data indicate that current production 2,4,5-T with 0.5 ppm of TCDD was teratogenic and embryotoxic.**

20. 1972: J. Agr. Food Chem.,Vol 20, No 2., 1972 by Woolson, E. et al, "Survey of Polychlorodibenzo-p-dioxin Content in Selected Pesticides." The article explains that dioxin TCDD occurs when the reaction temperature for making 2,4,5-Trichlorophenol from tetrachlorobenze exceeds 160 C. If too much heat is applied, these various dioxins will form, including 2,3,7,8-TCDD, **It is important to note that the other dioxins formed can be just as deadly as TCDD, it just takes more heat to produce them and their impurity levels can be combined to be just as deadly as the TCDD.** Of 129 samples of the 17 different pesticides derived from chlorophenols that were examined for PCDD, 9% contained seriously toxic levels of this dioxin (PCDD).

Comment: **There is just as much hazard in the other forms of dioxins as there is in TCDD, it just takes a higher manufacturing temperature and more of them to kill you!** Remember the Dow patent to produce their 2,4,5-T at temperatures between 225 C and 300 C under pressures of 400 to 1500 PSI because it was faster and cheaper that the earlier patent by their competitor! This makes for major dioxin contamination, but it doesn't show up as readily in acute doses, which is the only regulated area that is tested. It is the long term chronic exposures that kill most workers.

21. 11/72: Chemical manufacturing process of 2,4-D and 2,4,5-T in their "technical acid" and "technical Butyl Ester" forms as produced at the Jacksonville, Arkansas plant by Transvaal, Inc. (Contained in the Vertac Operations Manual).

22. **7/8/74: **** Confidential Dow memos where D.D. McCallister tells Marguerite Leng that Dow must not send to the EPA certain of Dow's residue tolerances on TCDD levels, and she tells him that **"it seems to me that our not informing the government about TCDD in 2,4,5-T is what got us in all this trouble in the first place. Withholding information at this time (which they know we have) can only make them think we are still trying to hide something from them."**

23. Jun-Nov 1976: Chemical manufacturing process of 2,4,5-T from the Vertac Operations Manual on its various "technical ester" forms.

24. 10/15/79: Presentation by Marion Moses, M.D. of the Mt. Sinai School of Medicine Environmental Sciences Laboratory at CUNY on "2,4,5-T, Agent Orange and Tetrachlorodibenzo-p-dioxin : Evolution of the Problem." This presentation was made by slides which give a well rounded picture on this whole problem to

include contamination levels of TCDD in Vietnam of between 1 and 50 ppm of TCDD. It shows all the chemical formulas and health effects of these exposures.

25. 12/15/79: Research Paper on "DETERMINATION OF TCDD RESIDUES IN HUMAN MILK, BEEF LIVER, FISH, WATER, AND SEDIMENT." This study confirms that it is the **high temperature, high pressure conditions of 2,4,5-T manufacturer that produce the condensation which causes a reaction that results in the formation of TCDD.** It says that for chemical companies to even discover the presence of TCDD, the detection technique used must be **ultra sensitive and also highly specific because of the required low ppt (parts per trillion) detection limits.** EPA laboratories have had to be able to detect TCDD in the 0.02 - 100 ppt concentration to isolate and confirm the presence of TCDD in our human milk, beef liver, fish, water, and sediment extracts. Under a section entitled SAFETY PRECAUTIONS, it is stated **"TCDD is toxic and can pose grave health hazards if used improperly. TECHNIQUES FOR HANDLING RADIOACTIVE AND INFECTIOUS MATERIALS ARE APPLICABLE TO TCDD.** Only qualified individuals who are trained in laboratory procedures and familiar with the dangers of TCDD should handle this substance. Females of childbearing age should not work with this material. A good laboratory practice involves routine physical examinations and blood checks of employees working with TCDD. Also, facial photographs using oblique photoflood lighting should be periodically taken **to detect chloracne, which is an early sign of overexposure."**

26. April 1980: Dow Chemical Publication Booklet on "PUBLIC CONCERNS ABOUT 2,4,5-T", by Wendell R. Mullison, Ph.D. He is a retired Dow employee of 32 years experience in agricultural research with a degree in botany. With these "qualifications", he has been asked by Dow to tell the public that 2,4,5-T is safe. Dr. Mullison states that "Human cancer generally develops over a latency period of many years and usually is a disease of old age!" He discredits testimony of Dr. Ton That Tung of Vietnam on the horrors observed there as a result of spraying agent orange and says the Vietnamese have poisonous molds in their jungles which cause their problems of liver cancer. He further debunks all other claims regarding actual human experience and relies instead on "nine long-term carcinogenic studies with rats and mice where the authors conclude that 2,4,5-T was not a carcinogen." This kind of twisted logic reveals the whole thrust of Dow's defense on their product. **They misdirect everyone by boldly claiming that 2,4,5-T is safe and fail to add that it is the deadly 2,3,7,8-TCDD is all 2,4,5-T herbicides which is a carcinogen!** Since few labs in the world can detect the presence of TCDD at levels below 1 ppm, Dow further states that their 2,4,5-T has less that 1 ppm dioxin and hence must surely be safe! **Then Dow privately tells their fellow manufacturers that any level of TCDD is deadly and you have to wear rubber suits, rubber gloves and respirators to even be around it.** The final logic presented to the public is that "SINCE THIS CHEMICAL HAS BEEN IN PRODUCTION AND USE FOR OVER 30 YEARS, THERE HAS BEEN AMPLE TIME

FOR CANCER TO APPEAR IF IT WERE A PROBLEM. THUS, THE LIMITED HUMAN DATA AVAILABLE ARE IN AGREEMENT WITH THE EXTENSIVE ANIMAL DATA AS TO THE NON-CARCINOGENIC EFFECTS OF 2,4,5-T." Maybe people like Greenhill, Davis, Moyer, Rice and all the cancer cases around Jacksonville, Arkansas would like to dispute this claim by Dow with their double-speak about 2,4,5-T being so safe, while failing to mention the TCDD that all these herbicides contain. Dow later contradicts themselves and admits that **chloracne is the first visible symptom of human over-exposure to TCDD!** In a forum where punitive damages are awarded, this one booklet by Dow could be used as a basis for proving criminal liability on the public at large. If you want to see how Dow will currently defend its herbicide litigation, this booklet is their blueprint. They conclude their booklet by stating **"2,4,5-T is a safe, efficient, and selective herbicide to control weeds and brush and its use has not caused cancer, birth defects, or miscarriages. 2,4,5-T with its trace contaminant TCDD can be and has been used safely and effectively without harm to people, animals, or the environment."**

27. Jan-Feb 1981: Pazaderova-Vejlupkova', Jana M.D. et al, "The Development and Prognosis of Chronic Intoxication by Tetrachlordibenzo-p-dioxin in Men", Archives of Environmental Health, Vol. 36, No.1, pp. 5-11. The authors were on the Faculty of General Medicine at Charles University in Prague, Czechoslovakia. This report states that during 1965 to 1968, 80 workers who had been engaged in the plant production of 2,4,5-T became ill due to exposure to 2,3,7,8-TCDD. These doctors observed 55 of these 80 patients on a long-term basis over 10 years. It is an excellent study and shows that these patients ended up with a wide variety of health affects including almost all patients having had chloracne. The others varied from combinations of medical lesions, neurological lesions, psychiatric changes, skin lesions, and 1/3 had liver lesions. Two patients died of bronchogenic lung carcinoma. This study contradicts almost all claims made by Dow on how safe 2,4,5-T is to humans.

28. 5/81: Vertac Operations Manual on "PROCEDURE FOR DETERMINATION OF MONO-,DI-,TRI-, AND TETRACHLORO DIBENZO-P-DIOXINS IN 2,4,-D ESTERS." **NOTE: THIS IS TCDD IN THE HERBICIDE 2,4-D!** All manufacturers claim it cannot be present in 2,4-D because the heating mixtures of production do not exceed 160 C.

Comment: These tests were done by the Mass Spectrometry Laboratory in the Food Production and Inspection Branch at Agriculture Canada. It finds significant quantities of several different dioxins in 2,4-D including 2,3,7,8-TCDD! It took a very sophisticated piece of test equipment in a governmental lab in Canada to find this, but it resulted in the banning of 2,4-D in Canada.

29. 1/82: EPA Handbook on "Recognition and Management of Pesticide Poisonings." This is a good overall reference book by

Donald P. Morgan, M.D., Ph.D. at the University of Iowa Medical School under contract with the EPA. It is a general listing of all pesticide products including the herbicides 2,4-D and 2,4,5-T (see Ch. 6) that lists all manufactured brand and trade names of these products and gives their chemical formulas and a brief reference on their toxicity. While not an in-depth study on herbicides, it does serve as a good overall resource.

30. 3/83: Article by Dunagin, Wm. G. , M.D. on "Dioxin Effects on Human Health", Vol. 80, No. 3, pp. 127-131 at Columbia University. This paper concludes that the evidence on long-term health effects is conflicting and seems to depend on the dose received. It admits to some people dying of cancer, but states others do not. It says "the thymus is particularly susceptible, and the problem may be decreased immune surveillance."

Note: Based on several hundred studies I have looked at, the reason why some people get cancer and others don't is because the dioxin is really attacking the immune system of the body and creating different reactions with different degrees of exposure. These studies say that the dioxin is soluble in the fat cells of the body through skin absorption and breaks down the immune system so as to allow all kinds of disease to enter the body undefended by the natural immune process.

31. Summer of 1983: "The Agent Orange Case: An Overview." This is mostly for information on how the whole case was started and developed by the various lawyers. It is good background on this subject. The author is obviously one of the lead attorneys, by no specific name is given.

32. 7/6/83: *** News article from "The Arkansas Democrat", an Associated Press release dateline Uniondale, N.Y. entitled **"FIRMS KNEW DIOXIN EFFECT, MEMOS SHOW."** This article summarizes the key memos which show the collusion between these chemical companies, especially Dow in attempting to cover-up the known problems they had with their contaminated products. A 1957 document to Dow from a German chemical manufacturer (BASF) refers to a 1955 accident at their plant where there were **"severe cases of chloracne, including some suspected facilities."** That document includes among the entries for effects in humans: **"Usually not disabling, but may be fatal,** "liver injury" and **"long-term - two to five years to recover."** The news article also states "According to the federal Centers for Disease Control at Atlanta, **a maximum safe exposure to humans is just one part per billion."**

NOTE: This document is a continuous quote of all the damaging memos found by plaintiff's attorneys, many I have copies of, but not all of them. Read in its entirety for the story it tells, this is a major smoking- gun document.

33. 8/3/83: A Business Newsletter Article in Chemical Week publication entitled "VERTAC BEEFS UP IN HERBICIDES." This states that "Last week, the privately-held firm acquired the U.S.

rights to Dow Chemical's 2,4-D trademarks." It further states "Vertac gets the registration rights, inventories, formulation recipes and marketing data for the phenoxy herbicides."

Comment: This was in the time-frame when the EPA had formally banned 2,4,5-T for domestic uses and several countries either had banned or were considering banning both 2,4,5-T and 2,4-D. Reading between the lines here, it appears Dow is doing this partly to escape future legal liability for their 2,4-D herbicide. The Greenhill v. Dow litigation had just gone all the way to the U.S. Supreme Court and they upheld the verdict which said that 2,4-D caused cancer in Greenhill.

34. 8/10/83: Article in Chemical Week entitled "DOW SELLS ITS 2,4-D TRADEMARKS." This article says that while Dow has sold its trademark to Vertac, they will still supply technical 2,4-D to herbicide formulators, including Vertac, and that Dow is not reducing its capacity to produce 2,4-D. They have simply decided not to take it all the way to the distributor. The only other remaining U.S. maker of 2,4-D is SDS-BioTech, a 50-50 joint venture of Diamond Shamrock and Japan's Showa Denko that has taken over Diamond's 2,4-D production and marketing.

35. 1/21/84: News article entitled "International Study Is Urged of Agent Orange in Vietnam" by Phillip M. Boffey, Special to The New York Times Congress is calling for this study to determine whether Agent Orange had caused harm to the Vietnamese who were exposed to it. Congressman Don Edwards just returned from Vietnam and said "We can't resolve the problem here, . . It just doesn't make sense not to go where the living laboratory is." While there he was told of a high rate of cancer of the uterus and of abnormal births among these women.

Note: Attached to this news article is a Fall 1982 publication entitled "BULLETIN: U.S. COMMITTEE FOR SCIENTIFIC COOPERATION WITH VIETNAM", Vol. 1, No. 2. See page 5 on "In Memoria: Professor Ton That Tung (1912-1982)" and the article written by him on page 6 entitled "Vietnam, Seen From America", on his 1979 visit to the United States. Page 8 has an article entitled "The Question of Dioxin Levels in Vietnam, Then and Now."

36. 2/84: EPA Study entitled "Ambient Water Quality Criteria for 2,3,7,8-Tetrachloro-dibenzo-p-dioxin." This document was prepared under contract at several research locations in the U.S. **This study shows that TCDD is only one of many trace contaminants found in chlorinated industrial products, especially the herbicide 2,4,5-T.** It names the others including the polychlorinated dibenzofurans (PCDF's) found in 2,4-D.

37. 2/27/84: Expanded summaries of key Plaintiff's Government Causation Witnesses in the Agent Orange litigation on their: Qualifications; Subject Matter; Scientific Principles; Substance of Opinions; and Grounds for Opinions. These experts are:

A. Dr. Deborah A. Barsotti, a toxicologist expert.

B. Dr. Alastair W.M. Hay, a lecturer on Chemical Pathology.
C. Dr. Herbert Kaye, an expert psychologist.
D. Dr. Alan Scott Levin expert on the immune system.
E. Dr. Marvin A. Schneiderman an expert statistician and epidemiologist, particularly in the area of the determination of cancer causation.

Comment: All these experts have made a special study of the health effects of 2,4,5-T in humans. This gives a good summary on how to present a logical presentation of the proof of causation from these herbicide's exposure.

38. 3/16/84: Letter from attorney Margie T. Searcy to attorney Tom Henderson with copies to lead Agent Orange counsel. She presents suggested posters to show scientific causation for the Agent Orange case. These posters depict the: NERVOUS SYSTEM; NERVE CELL; HOW DIOXIN IS FORMED;HOW DIOXIN ATTACKS THE LIVER AND CREATES HARMFUL ENZYMES; THE MAJOR STEPS IN MANUFACTURING AGENT ORANGE; WAYS OF EXPOSURE; and HOW DIOXIN TRAVELED IN THE ENVIRONMENT.

Comment: This presentation, or something like it would be very good for large trial exhibits to a jury.

39. **Spring 1984: ** PLAINTIFF'S MEMORANDUM ON CAUSATION**, In re: "Agent Orange" Product Liability Litigation, MDL #381, U.S. Dist.Court Eastern District of New York. This document gives the whole line of Medical Causation and concludes on how it caused an array of adverse health effects in the nine representative Plaintiffs, including cancer.

40. **Spring 1984: ** Key Plaintiff's expert witness Dr. Lennart Hardell** summary of his QUALIFICATIONS; SUBJECT MATTER; SCIENTIFIC PRINCIPLES; SUBSTANCE OF OPINIONS; and GROUNDS FOR EACH OPINION.

Comment: This testimony is primarily based on Dr. Hardell's epidemiological studies he conducted in Sweden plus personal cancer patients he has seen in his own clinical practice regarding herbicide exposure. Since this time in 1984, he has gone on to become a world authority in this field and Dow Chemical in particular has done everything possible to find ways to discredit his studies, including manufacturing "rigged" studies on their own.

41. **Spring 1984: ** Key Plaintiff's expert witness Dr, John A. Garofalo** summary of his QUALIFICATIONS; SUBJECT MATTER; SCIENTIFIC PRINCIPLES; SUBSTANCE OF OPINIONS; and GROUNDS FOR EACH OPINION.

Comment: This testimony pertains to the field of immunology and the effect dioxin has on the human immune system.

42. 5/84: Proceedings from the "First National Agent Orange Medical Symposium", hosted by the Illinois Agent Orange Study

Commission with cover letter from the Chairman John T. O'Connell. The purpose of the symposium was to allow physicians and researchers familiar with herbicide exposure and its physiological ramifications to have a forum which they could speak. Dr. Bertram Carnow, a professor and then current director of Great Lakes Center for Occupational Safety and Health of the University of Illinois School of Medicine was a key speaker. He pointed out that 2,3,7,8-TCDD **is the most potent toxic agent ever produced by man. It has shown that it will kill a young guinea pig at a concentration of approximately five parts per trillion.** This symposium was filled with experts telling how and why this dioxin was so deadly to humans and is excellent reading for preparing a trial in this field of law.

42a. Jan-Feb 1984: Article from American Health on "Environmental Toxin: The Dioxin Syndrome" by Drs. Carnow and Conibear. This article is very strong on the health effects of TCDD dioxin and says "Once the poison is in the system, there's no way known to counteract it." (Note: a better copy should be ordered for a trial exhibit by calling 212-242-2460 who is the publisher of this magazine)

43. 1984: Encyclopedia Britannica, "The World of Medicine:Environmental Health - What is Dioxin?" written by Dr. Bertram W. Carnow, M.D. The publication says that "animal studies have shown dioxin's potency as a cancer promoter and its ability to suppress the immune system."

Comment: This is an excellent overview and easy to understand summary in six pages of what dioxin is all about.

44. 12/12/85: Letter from Dr. Bertram W. Carnow, M.D. to attorney Phillip McMath on the results and findings of his examination of the twelve clients that were done in October and November of 1985. All 12 had abnormalities to their immune system functions. This was due to 2,3,7,8-TCDD exposure detected in the patients bodies and the conclusions were that "they are all suffering from chronic chemical poisoning involving multiple organs and organ systems with damage to them of a permanent and irreversible nature."

45. 7/29/86: Memo from attorney Alison Pettiette re: "LIABILITY ISSUES CONCERNING THE VERTAC CHEMICAL PLANT IN JACKSONVILLE, ARKANSAS" The memo refers to Dow's liability in Keister v. Dow and explains the horrors found at the Vertac Plant in Jacksonville. It is an overview of Dow's attempt to hide or cover-up any evidence of their involvement.

46. 9/11/87: Fifth Circuit Opinion of Viterbro v. The Dow Chemical Co., at pp. 6357-6361. Here Dow won on appeal because plaintiff's expert admitted that the symptoms of Viterbro could have numerous causes and simply picked the cause that was most advantageous to the plaintiff Viterbro's claim. The doctor failed to specifically link the herbicide used to the plaintiff's

medical condition and admitted on cross examination that the symptoms could have a number of causes.

Comment: This case shows how not to try a toxic tort exposure case in the courtroom!

47. October 1987: Curriculum Vitae of Dr. Marvin S. Legator who has been the key expert witness in several successful cases on herbicides. He is Professor and Director of the Division of Environmental Toxicology at the University of Texas Medical Branch in Galveston, Texas. He was the expert in Davis v. Dow; Keister v. Dow; and Newman v. AT&T. All of these cases settled just prior to trial.

48. March 1988: Lead news articles from In These Times telling the entire story of the dioxin exposures in Jacksonville, Arkansas and labeled "The Site of America's Worst Toxic Contamination."

A. March 9-15, 1988 edition: "WELCOME TO DIOXINVILLE, ARKANSAS" part one of three parts.

B. March 16-22, 1988 edition: "DIOXINVILLE,ARKANSAS: PASSING THE BUCK AND BURNING THE EVIDENCE" (part two of three parts).

C. March 23-29, 1988 edition: "DIOXINVILLE III: THE TOXIC TRAIL." (Part three of three parts).

49. 1989: American Chemical Society Symposium Series No. 144, "Biological Issues in Extrapolation", Chapter 9 by Yang, Raymond S. H., et al National Institute of Environmental Health Sciences, Research Triangle Park, N.C. This report debates the issue of: "Given the fact that there is no perfect system, how good are rats and mice as models for humans in toxicology?" They conclude that "The field of carcinogenic risk assessment is in its infancy. The primitiveness of methodology echoes the lack of a clear theory of carcinogenesis." They claim that "it is impossible to conduct chronic toxicity/carcinogenicity studies in humans.... While there is no perfect surrogate for humans in the evaluation of carcinogenic potential and other toxicities of chemicals and other agents, rodents still represent the best models."

Comment: This is the kind of industry supported logic that one faces when trying to show that any given person got cancer from a particular chemical or in this case 2,4-D and 2,4,5-T. Until someone admits the causes of cancer and defines what it is, the game will go on!