2159

DOW 054864
MN073280

MIDLAND
February 15, 1967

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

William E. Dixon
Bioproducts Department
BPC

cc: W. L. Corbin, BPC
D. E. Fletcher, BPC
J. H. Gewell, BPC
W. J. McCoy, BPC
B. D. Holder, M.D., 607

THOMPSON CHEMICAL COMPANY, ST. LOUIS, MISSOURI

On February 2, 1967, W. J. McCoy informed me that a Mr. M. S. Buckley of Thompson Chemical had called Dow indicating that they had had an accident associated with the manufacture of trichlorophenol, and that they had some men with what they thought was chloracne. They wondered if we could advise them in regard to medical practice. I contacted Dr. Holder, who then called Mr. Buckley and discussed with him medical aspects of the problem. It is my understanding from Dr. Holder that Mr. Buckley then started talking about the chemistry of this material, and Dr. Holder suggested that he contact me in regard to anything along this line.

On or about February 7 Mr. Buckley called me to see what we know about chloracne caused by contact with materials associated with the manufacture of trichlorophenol from tetrachlorobenzene. 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. He indicated that they had been distilling some oils or tars containing anisoles when the operation got out of control, and the material either spilled or splashed onto a hot autoclave. He thought that the fumes and vapors of the anisoles had caused their difficulty. I told him I did not think the acne was caused by the anisoles, but rather by other materials present in the anisoles.

NOTICE: POOR COPY DUE
TO DEFICIENT ORIGINAL

16742

THE DOW CHEMICAL COMPANY 2182

420 MARKET STREET
CAMDEN 2, NEW JERSEY

January 19, 1962.

bcc: J.H.Wallberg-ACS-MY
W.J.McCoy-ACS-MID
P.H.Ritty-ACS-ATB
V.K.Rowe-D.F.L. 1701

MN0732800

Mr. John Dante,
Sordoni Construction Company
Kingston, Penna.

Dear Mr. Dente:

We have discussed your employee's claim of Tracheitis due to chemical inhalation, with our Biochemical Research Department. In our opinion, it is highly unlikely that a man spraying a Kuron-water mixture would develop tracheitis. On the other hand, one can never say that such an irritation could not occur if an individual had an excessive exposure to heavy mists. It would be our opinion, however, that even if this happened, the throat irritation would clear up very promptly upon cessation of exposure and there would be no further consequences.

It is also our opinion that if this man is a heavy smoker, particularly a cigarette smoker, that this could well account for his chronic cough. We believe there is adequate medical history to show that smoking can result in a chronic cough.

We would be pleased to be kept informed of the developments of this case. Please contact us if we can be of any further service.

Sincerely yours,

D. L. Reed,
Agricultural Chemical Sales
Industrial Products Section

mfg

RECEIVED
JAN 22 1962
Biochem. Res. Lab.

16744

T2.30-1 2201

WM. H. THIEN, PRESIDENT
WM. NIEMUEGGE, VICE-PRESIDENT

MONROE COUNTY ELECTRIC COOPERATIVE, INC.

DAVID F. HUNT, SECRETARY-TREAS. etc.
C. B. MORRISON, COUNSELOR

REA

C. M. DOUGLAS, MANAGER
Waterloo, Illinois

September 16, 1954

RECEIVED
SEP 20 1954
Biochem. Res. Dept.

DOW 05360000
MN0073280

Mr. V. K. Rowe
Biochemical Research Dept.
The Dow Chemical Company
Midland, Michigan

Dear Sir:

Thank you for your letter dated September 1, 1954 giving us information with reference to the effect of Esteron Brush Killer on skin and lung tissues.

We note that this information covers cattle, whereas our request addressed to the Dow Chemical Company in St. Louis, Missouri, dated August 24, 1954, requested the same information with reference to the effect on human beings.

We would appreciate receiving this information at your earliest convenience. Thanking you for this courtesy, we are

Yours very truly,

MONROE COUNTY ELECTRIC
COOPERATIVE, INC.

C. M. Douglas, Manager

CMD:MP

16745

Dr. V. K. Rowe, Biochemical Lab., Mid.

2203

THE DOW CHEMICAL COMPANY
3615 Olive Street
St. Louis, Missouri

August 27, 1954

Monroe County Electric Cooperative, Inc.
Waterloo
Illinois

Attention of Mr. C. M. Douglas, Manager

Dear Mr. Douglas:

This will acknowledge your letter of August 24th in which you requested information as to whether the drift of Esteron Brush Killer during application would be injurious to skin or lung tissue. It is your understanding that the spray does not injure skin or lung tissues but you would like to have a confirmation of this.

We feel quite sure that your assumption is correct in that this spray does not injure the skin or lung tissues, however, we are asking our Mr. V. K. Rowe of our Biochemical Research Lab at our Home Office in Midland, Michigan to advise you direct regarding this as he has been working with 2,4-D type products from a toxicological viewpoint and will be in a position to give you the latest information on these materials.

Very truly yours

R. A. Crandall
Agricultural Chemical Division

RAC:ave

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DOW 0055178
MN0073280

2216

THE DOW CHEMICAL COMPANY

Abbott Road Building
Midland, Michigan
February 16, 1965

F. H. Riley, Special Chemicals Sales, ARB
J. C. Tucker, Industrial Chemicals Sales, ARB
R. N. Smiley, International Sales, ARB

cc: J. W. Harris, Chemicals Sales, ARB
L. B. Grant, Sales Administration, 47 Bldg.
H. W. Feinauer, Chemicals Department, ARB
C. O. Hutchenreuther, Organic Chemicals Prod. Dept. 258 Bldg.
E. C. Staehling, Organic Chemicals Prod. Dept. 172 Bldg.
C. E. Otis, Bioproducts Dept., Bioproducts Center
L. Silverstein, Biochemicals Research Lab., 1701 Bldg.

Subject: 2, 4, 5 Trichlorophenol

The 2, 4, 5 trichlorophenol currently being manufactured has been found to contain 2, 3, 7, 8 tetra chloro dibenzo-p-di-oxin and is suspected to contain 2, 3, 7, 8 tetra chloro dibenzo furan. It is known that both the 2, 3, 7, 8 tetra chloro dibenzo-p-dioxin and the tetrachlorodibenzo furan can produce chloracne.

The concentration of these impurities has been found to be less than 0.5 ppm of the 2, 3, 7, 8 tetra chloro dibenzo-p-dioxin and approximately 20-25 ppm of the tetrachloro dibenzo furan if the present VPC analysis is correct. Analysis of retainer samples shows that these concentrations are very close to the impurity level in the trichlorophenol we have shipped in the past. Up to our recent in-depth studies of our trichlorophenol and its impurities, we did not know that they were present in our product. Consequently, we do not have animal experience which indicates this impurity level is consistant with safe handling. We do know; however, that we have had no chloracne problems in our own operations in the handling and processing of these materials, and we have not heard formally that any of our customers have. We are presently making animal studies to determine what the safe levels for these impurities are.

While the current product is essentially the same as past material, we feel it is imperative that our customers know this new impurity and concentration information. They should, if they decide to accept our

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material with this new knowledge, be cautioned to exercise care in handling and processing this material to avoid human exposure.

As I indicated before, we are carrying out animal tests to determine safe levels, and if needed, additional handling precautions. When this work is completed, we will make it available for you to pass on to your customers.

Meanwhile, your customers should be informed of this information before any material is shipped to them.

J. D. Doedens
Chemicals Department
ARB

DOW 0485516

AGRICULTURAL PRODUCTS

THE DOW CHEMICAL COMPANY
AGRICULTURAL PRODUCTS DEPART
MIDLAND, MICHIGAN 48640

2223

SPECIFICATION		SUPERSEDES		METHOD OF ANALYSIS
NUMBER	DATE	NUMBER	DATE	87523
87523	2/13/70	87523	2/27/69	

2, 4, 5-TRICHLOROPHENOXYACETIC ACID

2, 4, 5-Trichlorophenoxyacetic acid, minimum	98.0%
Freezing point, minimum	148.5°C
2, 3, 7, 8-Tetrachlorodibenzo-p-dioxin	< 1 ppm

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

THE POLICY OF THE DOW CHEMICAL COMPANY IS ONE OF CONTINUED IMPROVEMENTS BY RESEARCH AND MANUFACTURING WHEREVER POSSIBLE TO ASSURE A STILL FINER PRODUCT. HENCE, SPECIFICATIONS ARE SUBJECT TO CHANGE WITHOUT NOTICE.

FORM C-15770 PRINTED IN U.S.A. 10-68

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THE SEVESO ACCIDENT: ITS NATURE, EXTENT AND CONSEQUENCES

January, 1979

E. Homberger*, G. Reggiani**, J. Sambeth*, H. Wipf*

Introduction

In July 1976 a runaway reaction during the production of trichlorophenol in a subsidiary of the Givaudan company, the Icmesa plant in Seveso, Italy, resulted in the discharge of products containing TCDD (2,3,7,8-tetrachlorodibenzodioxin) over an area of about 2.8 km^2 (700 acres). This report covers the past two years and gives an account on the nature, the extent and the consequences of the accident.

* Givaudan Research Company Ltd.

** F. Hoffmann-La Roche & Co.Ltd.

DOW 2750917

1. Conditions of the accident

Trichlorophenol was produced in this factory only for the manufacture of hexachlorophene, a local antiseptic active against grampositive bacteria. When designing the installation for this production the chemists and engineers were aware of the previous accidents in the chemical plants manufacturing this chemical. To avoid a chemical process under pressure and the formation of dangerous amounts of TCDD, the unwanted highly toxic byproduct of the reaction of 1.2.4.5-tetrachlorobenzene with alcali especially at temperatures above 170-180° (Fig. 1) and to prevent uncontrollable exothermic reactions which can start above 230°, special attention was given to the

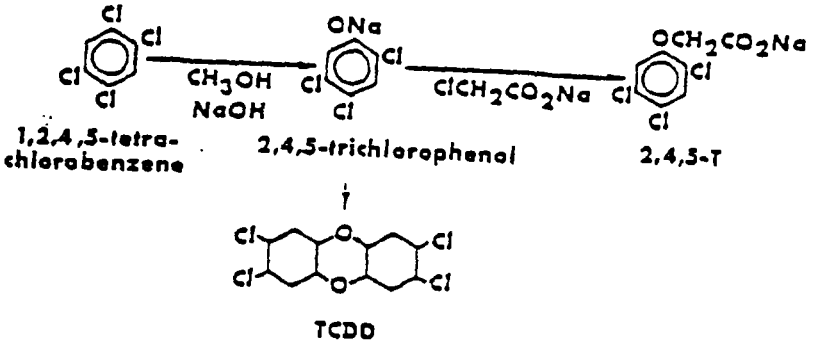


FIGURE 1 Formation of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) as a by-product in the synthesis of 2,4,5-T.

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choice of the solvents (ethylene glycol instead of methanol), of the heating system (steam instead of hot oil) and of the cooling system (flushing of cold water through the same heating coils and quenching the reaction mixture with a large volume of water in a matter of minutes). During the premanufacturing laboratory and pilot phase of production as well as during the later phase of routine manufacture no exothermic reaction which would elicit a runaway temperature rise,increased TCDD formation and explosive discharge, ever occurred.

In order to abide by the regulations of the USA, where the trichlorophenol was delivered for the production of hexachlorophene, the quantity of the TCDD formation was carefully controlled and kept within the limit of 0.1 ppm recommended by the Advisory Committee to the Environmental Protection Agency Administrator on May 7, 1971 (16). The working and handling conditions in the Icmesa TCP plant were adequate with respect to hygienics and exposure of the plant operators.

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Chloracne, the indicator of TCDD exposure, was never observed either in the workers of the Icmesa factory or in those manufacturing hexachlorophene in the USA and Switzerland.

On the day of the accident the production of sodium trichlorophenate in the reactor was completed and some 15 % of the ethylene glycol had been removed. When the heating was switched off the final recorded temperature was 158° C. The workers night shift left the plant shortly after 6.00 a.m. and nothing happened until 12.30 p.m. when the accident occurred.

2. The causes of the accident

The task of assessing the causes of the explosion has been given to several groups of scientists in- and outside our laboratories. It was assumed that the temperature increase which led to the accident was provoked by a slightly exothermical reaction proceeding very slowly already below 200° in alkaline surroundings and which had been unknown so far. Preliminary tests examining all conditions at which an exothermic reaction might have been provoked, i.e. long-term heating at

DOW 275100

critical temperatures, thermal behaviour of the reaction mix when exposed to air, accidental presence of metals, copper etc. and checking all materials used for the reaction and the operating procedures at the plant have led to the following reconstruction of the possible mechanism of the accident. At the beginning a slow exothermical reaction of as yet unknown nature may have taken place in alkaline environment raising the temperature of the reactor over several hours to approximately 250° with slow decomposition and with formation of gas. Possibly due to an obstruction of the pipe that connects the reactor with the outside, this slow formation of gas may have caused a pressure increase inside the reactor greater than the one allowed by the rupture disc, thus leading to the escape of gases together with glycol and other organic products. The chlorodioxins produced at the higher temperature in the reaction and particularly TCDD proved to be, under the conditions of the accident, much more volatile than one would have expected from known scientific data and foreseen on the basis of their physical properties. Further investigations and experiments are needed to prove that this explanation of the mechanism

DOW 2751124

of spontaneous abortions in the Seveso population for the years 1976 and 1977 (19, 20, 59, 60) was substantially similar to that found in the previous years 1973-1974 and 1975 in the same region and which fluctuated between 9.0 and 10.3 % (Table 11). For the Lombardy region, where Seveso is located, the rate of spontaneous abortions has been indicated to be in the range of 12-15 % (13) and world-wide an overall ratio of 15-20 spontaneous abortions per 100 pregnancies has been estimated (68). This rate of pregnancy wastage seems to be common for all mammalian species which are said to rarely lose less than 30 % of their fertilized eggs (8).

Table 11

Incidence of stillbirths, spontaneous and induced abortions rate per number of calculated pregnancies

Township	1973 %	1974 %	1975 %	1976 %	1977 %
Cesano	9.01	10.89	8.81	9.15	9.06
Desio	15.34	13.43	13.38	8.91	14.34
Meda	6.23	5.88	5.70	9.00	8.70
Seveso	10.79	7.84	12.83	11.14	12.09
Average	10.39	9.51	10.23	9.55	11.09
Barlassina	6.18	5.43	4.12	8.97	3.03
Bovisio	9.46	11.05	14.61	12.82	16.56
Lentate	1.82	1.85	1.87	1.59	5.85
Muggio	11.45	13.72	9.86	12.67	14.38
Nova M.	13.44	15.03	11.72	15.36	12.64
Seregno	13.28	11.09	9.85	8.75	12.07
Varedo	10.30	9.09	11.36	7.02	10.34
Average	9.41	9.60	9.05	9.59	10.69
Seveso region	9.90	9.55	9.64	9.57	10.89

(world-wide: 15 - 20 % - Lombardy region: 12 - 15 %)

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A closer analysis of the chronology of the fetal losses for the months which immediately followed the accident and in correlation with their geographical distribution in the zones with and without contamination shows that (Table 12)

Table 12

INCIDENCE OF SPONTANEOUS ABORTIONS IN THE 11 TOWNSHIPS OF THE SEVESO ZONE FROM JULY 1976 TO JUNE 1977
RATE PER NUMBER OF CALCULATED PREGNANCIES

		ABORTIONS 3rd QUARTER 1976	DELIVERIES 1st QUARTER 1977	ABORTIONS 4th QUARTER 1976	DELIVERIES 2nd QUARTER 1977	ABORTIONS 1st QUARTER 1977	DELIVERIES 3rd QUARTER 1977	ABORTIONS 2nd QUARTER 1977	DELIVERIES 4th QUARTER 1977
TOWNSHIPS COVERING ZONE A, B AND R	CESANO	15	88	21	76	14	102	10	96
	SEVESO	12	49	9	35	7	52	11	21
	DESIO	6	98	18	98	29	104	17	105
	MEDA	12	84	8	63	9	66	10	75
	TOTAL	45 (12 %)	319	56 (17 %)	272	59 (14 %)	329	48 (14 %)	297
TOWNSHIPS OUTSIDE CONTAMINATED ZONES	BARLASSINA	-	25	8	11	-	8	-	9
	BOVISIO	5	38	5	28	9	36	7	35
	LENTATE	7	35	-	35	9	41	10	42
	MUGGIO	8	65	17	64	17	64	7	54
	NOVA	14	87	21	73	15	71	13	78
	SEREGNO	12	129	7	116	23	95	16	117
	VAREDO	4	44	4	31	10	36	6	48
	TOTAL	50 (10 %)	423	62 (14 %)	358	83 (19 %)	351	59 (13 %)	394

during the third quarter of 1976 the incidence of abortions for the 4 townships embodying the contaminated zones was 12 % and for the remaining townships of the territory under health surveillance was 10 %. The

DOW 275126

incidence increased in the fourth quarter of 1976 to 17 % for the contaminated and to 14 % for the non contaminated part of the territory. At first sight the figures could be interpreted as showing a relation between incidence of abortions and degree of contamination. Yet if the analysis is extended to the following months, i.e. the first quarter of 1977, there is drop to 14 % for the contaminated townships and an increase to 19 % for the townships without contamination. In the second quarter of 1977 the values are 14 % and 13 %. The fluctuations observed are therefore likely to be related to factors other than TCDD. Besides it should be noted again that the frequency of abortions in the contaminated area remained well within the normal incidence in Europe.

b) Congenital malformations

The same can be said for the frequency of congenital malformations. For the population of the western countries, the ratio of defective children reported when no special diagnostic procedures are used is of 2-3 % (21, 58). It increases to over 7 % of malformations if the cardio-vascular system, respiratory tract, gastrointestinal tract and genitourinary system are considered (26, 66).

DOW 027521

In Seveso the number of malformations notified to the provincial health officers shows an enormous increase between 1976 and 1977 from 4 to 38. The number of malformations reported during the first quarter of 1978 is 5. However if these numbers are related to the number of live-births that occurred in the corresponding periods of time (Table 13), the only possible explanation for the discrepancy is that the notification data on birth defects are incomplete. A previous survey (17) on the incidence of malformations in the same territory based on data of better quality had revealed a ratio of 2.9 per 100 live-births.

Table 13

Frequency of malformations - Seveso Zone (11 districts)

Year	Rate of malformations per 100 live-births		
	Number of live-births	Notified	Expected at the rate of 2.5-3.5
1976 second semester	1617	4 (0.28 %)	35 - 42
1977 12 months	2648	38 (1.42 %)	66 - 80
1978 first quarter	678	5 (0.74 %)	16 - 20

16758

The polymorphism of the malformations observed (Table 14)

Table 14

Neonatal malformations in Seveso

Type and pattern	1976	1977	1978 first quarter
Pulmonar aplasia	-	1	-
Anencephalia	-	1	-
Atresia of auditory meatus	-	1	-
Congenital cardiopathy	-	8	2
Vesical ectopia	-	1	-
Gastrical exstrophy	-	1	-
Hydrocephaly	-	1	-
Hypospadia - Epispadia	2	2	1
Abdominal malformation	-	2	-
Anal malformation	-	1	-
Pedalic malformation	-	10	-
Meningocele	-	1	-
Neoplasia	-	2	-
Defect osteogenesis	-	1	-
Down syndrom	2	2	-
Syndactyly	-	3	-
Cleft palate	-	-	1
Diaphragmatic hernia	-	-	1
Total	4	38	5

in the newborns of the Seveso region is another element in favour of the assumption that there is no causal relationship between the malformations registered and the chemical. Morphological heterogenicity of anomalies scarcely supports the presence of a single causal agent. Even in the groups of congenital cardiopathy (8) and pedalic malformations (10) it corresponds to the normal distribution of congenital spontaneous anomalies. The

DOW 827528

morphological differences of these anomalies is from this point of view convincing. A further aspect examined, the geographical distribution of the mothers of the malformed children in the zones contaminated by TCDD compared with those outside the contaminated communities shows that the malformed children were equally distributed among the two groups (Table 15)

Table 15

Geographical distributions of malformations

Districts	1976 2nd Semester	1977	1978 1st quarter
Cesano Mad.	0	5	1
Desio	1	5	0
Meda	0	11	1
Seveso	0	2	1
Total	1	23	3
Barlassina	0	0	0
Bovisio	1	2	0
Lentate	0	1	0
Muggio	1	1	0
Nova Mil.	1	1	1
Seregno	0	7	1
Varedo	0	3	0
Total	3	15	2
Grand total	4	38	5

c) Neonatal growth

Growth retardation, decreased survival and smaller size at birth have been observed in experimental animals under the effect of TCDD (12, 38, 40). The examination of about

2000 newly born infants of the Seveso region have revealed no abnormalities in respect of the somatic and psychic development of the child.

DOW 2751130

d) Embryomorphological studies

Embryomorphological studies were performed in Lübeck on 34 cases of abortions. In 30 cases the pregnancy had been interrupted at the gestational age of 5/6 to 15/16 weeks. In 3 cases a spontaneous abortion followed an intrauterine death at the developmental stage of 8, 13 and 18 weeks respectively. In a 4th case of spontaneous abortion no embryo was found (49).
Direct examination and radiophotography did not detect any gross or clear signs of abnormal development. Histological examination and morphological evaluation of the lymphatic and other visceral systems did not provide any sign of damage brought about by the action of an exogenous agent. The cases of spontaneous abortion showed different morphological alterations obviously due to a variety of causative factors.

DOW 2751131

5. Cytogenetic studies

Induced abortion was sought by women of the communities most affected by the TCDD release in the second half of 1976. Chromosome analysis of maternal peripheral blood, amniotic fluid cells and fetal tissues were performed for numerical and structural chromosome variations. No significant change in the chromosome number nor an increase in the frequency of aberrations was found in the blood samples. There was a higher number of aberrations in the fetal tissues than in the blood samples or fibroblasts from adult tissues. However, the frequency of these aberrations was not greater than that expected in cultures of comparable cells (52, 57). Chromosome analysis have also been performed on the blood of people belonging to the group of acute (145) and chronic exposure (69), of the Icmesa plant workers (73), on children with (14) and without (15) chloracne and on a control group (87). The average frequency of gaps, breaks and structural rearrangements found were within the accepted standard frequency (30, 66).

DOW 275132

6. Immunological studies

Immunosuppression and decreased resistance to infections due to TCDD have been observed in several animal species (51, 61). Immunocapability was therefore examined from September 1976 to March 1978 at 4 months intervals in 45 children belonging to the zone at maximum level of exposure, of which 20 children had chloracne and concurrently on a comparable group of 44 children who had not been exposed to TCDD. The age range of the children was 3 to 7 years. The serum immunoglobulins, the circulating level of complement, the ability of the lymphocytes subpopulation T and B cells to react to non-specific mitogens were examined. No significant difference in the immunoresponse of the three groups has been so far detected.

7. Occurrence of infectious diseases

The number of notifications for infections diseases submitted in 1977 to the provincial health officers of the 11 townships looked after by the medical commission shows a clear increase compared with that of the previous year, rising from 435 to as many as 1219 (30).

DOW 275133

This fact seems to contradict the results of the immunological investigations referred to above. In fact it has to be attributed to a better compliance to the mandating notification of the prescribed diseases during 1977. Indeed (Table 16)

Table 16

Rates of incidence of infectious diseases per 10 000 population units

Infectious diseases	townships (4) covering contaminated area		townships (7) outside contaminated area		nearby community with population 220 000		Province of Milan 1 730 000		Lombardy Region 8 900 000	
	1976	1977	1976	1977	1976	1977	1976	1977	1976	1977
1) Orofecal transmission										
- Salmonella infections										
a) typhoid fever	0.67	1.07	0.68	1.29	0.22	0.22	1.79	1.09	1.14	0.79
b) other salmonellosis	1.06	1.08	1.12	1.20	3.59	3.72	1.52	1.11	1.97	1.77
- Viral hepatitis	3.09	3.38	3.76	5.26	4.59	4.09	4.42	4.57	4.72	4.62
- Poliomyelitis	0	0	0	0	0	0	0	0	0	0
2) Airborne transmission										
- Diphtheria	0	0	0	0	0	0	0.005	0.002	0.005	0.008
- Scarlet fever	3.9	3.7	0.34	0.95	9.7	6.45	5.50	6.19	4.28	3.77
- Meningococcal meningitis	0.2	0	0	0.17	0.04	0	0.07	0.10	0.05	0.08
- Pertussis	1.8	0.67	0.77	1.29	3.31	1.22	2.06	0.97	3.49	1.17

the increase affects mainly the infections for which the notification is normally made with greater frequency as for example viral hepatitis, salmonellosis, meningitis, scarlet fever, and pertussis. Furthermore, the increase

DOW 2751134

affects to a lesser extent the inhabitants of the more highly contaminated zone. Finally it does not involve poliomyelitis and diphtheria, diseases where vaccination is currently performed, thereby confirming a normal immunological reaction of the population to antigen stimulation. If compared with the incidence of a nearby community of equal population, of the Province of Milan and of the Lombardy region the infective pathology of the Seveso zones does not exceed the average of this part of Italy.

8. Birth rate and mortality

The demographic trend recorded by the health statistic in the Seveso zone is caracterized by a constant decline in births. During the period 1975-1977 in the districts under consideration the birth rate fell from 17 ‰ to 12.5 ‰. The fall was more pronounced in 1977 and affected particularly the four communities most involved by the accident (Table 17)

16765

DOW 275135

Table 17

Rate of births in the Seveso region (11 districts) 1973 - 1977

District	1973	1974	1975	1976	1977
	Births ‰	Births ‰	Births ‰	Births ‰	Births ‰
Cesano Mad.	15.47	16.34	15.41	14.57	13.92
Desio	17.50	15.70	16.47	15.99	12.56
Meda	17.00	17.74	16.35	15.17	14.21
Seveso	18.71	18.69	15.54	15.66	11.03
Average	17.17	17.36	15.46	15.34	12.18
Barlassina	16.74	15.74	16.60	12.54	11.35
Bovisio	15.03	16.50	15.08	12.06	11.54
Lentate	17.02	16.52	16.05	14.29	13.48
Muggio	19.03	17.56	18.23	13.64	13.17
Nova M.	18.60	19.25	17.90	16.40	15.51
Seregno	17.20	16.28	16.47	13.84	12.52
Varedo	15.28	16.45	16.69	14.44	12.99
Average	16.98	16.94	16.43	13.37	12.93
Seveso region	17.07	17.15	15.74	14.60	12.55

The fact may be attributed to psychological factors associated with the abortion-seeking phase of the period of time immediately after the accident; to the use of contraceptive methods recommended as a preventive measure at technical level; to the advice to abstain from sexual intercourse. It may also suggest that there is a reduction in fertility in the population although this relationship must still be regarded as hypothetical and in need of further study.

An examination of the statistical data relating to mortality shows an overall increase in the eleven districts in question, particularly pronounced for the year 1976,

when the death rate rose from 7.62 ‰ in 1975 to 8.24 ‰ in 1976. The rate went down again to the current figures in 1977 (Table 18)

Table 18

Rate of deaths in the Seveso zone per 1000 population units

District	1973	1974	1975	1976	1977
Cesano Mad.	6.26	6.66	6.82	6.56	6.32
Desio	8.84	8.18	8.30	9.02	7.68
Meda	8.44	7.65	8.28	8.17	8.59
Seveso	9.11	7.42	6.79	9.53	7.88
Average	8.16	7.47	7.67	8.32	7.61
Barlassina	6.99	10.49	7.67	7.42	7.09
Bovisio	8.18	7.67	8.33	8.85	8.69
Lentate	9.89	7.71	9.29	10.43	9.36
Meggio	6.96	5.50	5.71	6.90	8.48
Nova M.	6.36	5.84	5.87	6.66	5.78
Seregno	8.71	9.40	8.53	9.39	8.51
Varedo	6.76	8.41	7.70	7.51	7.41
Average	7.69	7.86	7.58	8.16	7.90
Seveso zone	7.92	7.66	7.62	8.24	7.75
Province of Milan		8.29	8.39	8.53	
Lombardy region		9.50	9.85	9.95	

A breakdown by the place of residence of the death cases (Table 19) shows striking high values for the district of Seveso and at first sight the increase appears to be specific to the more highly contaminated zone.

Table 19

Geographical distribution of deaths and death rate in two districts of the Seveso zone

Zone	Seveso				Cesano Mad.			
	1976		1977		1976		1977	
	Number	Rate ‰	Number	Rate ‰	Number	Rate ‰	Number	Rate ‰
A	7	10.27	4	5.87				
B	5	7.98	5	7.98	14	5.12	18	6.59
R	72	9.06	67	8.43	86	5.73	91	6.07
Outside	78	10.08	58	7.49	122	7.57	105	6.51
	162	9.34	134	7.44	222	6.14	214	6.39

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A monthly breakdown of the death rate for the township of Seveso where the increase was the highest (9.54 ‰) shows that in fact the increase occurred during the first semester of that year, i.e. prior to the accident and therefore related to other factors (Table 20)

Table 20

Rate of deaths per month in the Seveso district

Month	1973	1974	1975	1976	1977
January	18	11	13	24	18
February	11	16	9	9	8
March	16	14	12	20	12
April	12	9	7	12	10
May	14	6	7	13	9
June	11	10	9	19	5
July	13	8	4	11	10
August	13	7	10	8	9
September	10	7	10	12	12
October	5	8	13	13	14
November	12	11	6	8	14
December	14	17	15	14	13
	149	124	115	162	134

Taken as a whole the death rate has always remained within the frequency of the province of Milan and of the Lombardy region.

DOW 275138

CONSEQUENCES ON THE ANIMALS

1. The period immediately following the accident

The first deaths among domestic animals and some wildlife in the area occurred about three days after the accident. Small animals were most severely affected, particularly rabbits but also guinea pigs and domestic poultry and other birds. Whereas the birds appeared to die quickly and without specific symptoms, rabbits and other small animals showed anorexia, apathy and later also gastrointestinal hemorrhages, pulmonary oedema and wasted away with a complete depletion of the fat stores.

The first animal deaths occurred in the immediate vicinity of the factory, but the zone became progressively larger in the following days. The dying of the animals was therefore the second element, after the results of the chemical analysis of the soil and vegetation samples, which was used for completing the map of the contaminated zones, which had been set up by the Givaudan laboratories and submitted to the Italian authorities with the request of the evacuation of the population. In fact the map based

on the deaths of the animals which was later compiled by the Regional Veterinary Service, working from animal death patterns and TCDD levels in surviving animals (24) corresponded rather closely with the analytical map originally composed by the Givaudan laboratories. The analytical and veterinary data were then used in the definition of the contaminated area and in its subdivision in zones with different levels of contamination. When approximately four weeks after the accident, some animals died at a still greater distance from the factory, a further zone of protection (Zone R) was created which covered several square kilometers and had only a few sporadic spots with very low levels of TCDD ($< 5\ \mu g/m^2$).

2. Conditions two months later

a) Domestic animals

It has been reported that during the two months following the accident over 2000 animals had died, predominantly rabbits. Probably not all these animals died because of TCDD. Some emergency slaughtering had in fact taken place

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because of the evacuation and other animals had been sacrified by the Regional Veterinary Service for examination.

Table 21

Mortality of domestic animals during the first two months (position on 10th September 1976)

Zone	Animal count before 10th July 1976	Total mortality	Rabbit mortality
A	3'000	22.9 %	42.1 %
B	13'000	1.4 %	3.7 %
C	ca. 60'000	< 1 %	max. 1 %

Table 21 shows the mortality of domestic animals in the three zones up to September 10, 1976. By this time the number of spontaneous deaths had for various reasons substantially declined and it was possible to draw a first balance. It was clear that only a minority of animals had been directly affected by the aerosol cloud on the actual day of the accident with the possible exception of birds and some poultry and rabbits. The most severely and most

rapidly affected animals were the herbivorous which had ingested with the food relatively large amounts of the chemicals sprayed on the vegetation with the cloud and of TCDD as it was later confirmed by the levels found in their organs. The site where the animals were kept was obviously of lesser importance than the source of the fodder. Small animals succumbed to the toxic effect of the chemicals and of TCDD more rapidly than large ones. Sheep and goats were affected later than rabbits and cattle and horses last. Table 22 shows the deaths among large animals.

Table 22

Deaths of large animals in zones A, B and R

Animals	Animals alive on 10th July 1976	Subsequent deaths
Cattle	349	6 (1.7 %)
Horses / donkeys	49	2 (4.1 %)
Sheep	21	- (0 %)
Goats	49	1 (2 %)
Pigs	233	3 (1.3 %)
Large animal total	701	12 (1.7 %)

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It is difficult to tell how far these deaths could be related to TCDD alone. The aerosol that escaped consisted chiefly of trichlorophenolate which was also the cause of the chemical burns in human subjects. Undoubtedly there have also been harmful effects on freely moving animals. Cats and dogs for instance had inflamed sites and wounds chiefly on the extremities. Whereas some cats died of the wounds or of the systemic toxic effects caused by licking, the dogs recovered.

The chemical burns found in the pharynges of rabbits and cattle can also be explained by the caustic properties of trichlorophenolate. Animals which had from the beginning been fed on uncontaminated grass came to no harm, and many animals which had been taken off the contaminated food showed no toxic effects although some, on their subsequent slaughter, were found to have traces of TCDD in the liver.

b) Wildlife

To prevent the entry of TCDD in the food chain all the larger animals of Zone A were exterminated. Although the vegetation showed no external changes with the

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exception of minute phytotoxic damage on old acacies foliage, at the beginning of September, there was still 30 % of the total TCDD to be found on the vegetation, where virtually the entire aerosol had been deposited originally. The acute danger to herbivorous animals was past only when the old grass died down in September/ October due to the wet season. After that virtually all TCDD was to be found in the upper most layer of the soil as the new growth vegetation was practically not contaminated apart from traces resulting from dust.

In autumn some wildlife still remained in the Zone A. Many birds populated the area and behaved normally. Insects, snails, slugs and earthworms were clearly unaffected. Lizards, mice and rats were thriving without visible impairment. No dead animals were found. Dogs continued to roam and poultry and rabbits released into the wild were seen time and again.

27.5144

3. Precautionary slaughter

On our request the authorities of the Lombardy region had banned the consumption of vegetables, dairy products and meat from the Zones A and B in order to keep TCDD out of the human food chain. They also banned the use of products of the zones for animal feeding purposes. Sick animals and those which could no longer be cared for as a result of the evacuation had to be slaughtered. Slaughtering operations were later extended to all animals because officially uncontaminated feed were in short supply and it became difficult to enforce the official measures. The last animals were killed at the beginning of 1978. A few animals have been kept alive for research purposes or for the study of the effects of TCDD on the animal body.

According to the final report on the action (Table 23) the original death toll was approximately 3300, a figure which inlcudes many slaughtered under emergency conditions; the animals slaughtered as a prophylactic measure numbered nearly 78000.

Table 23

Summary of the animals of Zones A, B and R; position on 30th June 1978

Animals	Original number (10th July 1976)	Died after the accident*)	Still in the zone	Evacuated for study purposes	Slaughtered prophylactically before 30.6.1978
Small animals	80'430	3'281	-	71	77'078
Cattle	349	6	36	9	298
Horses / donkeys	47	2	-	-	47
Swine	233	3	-	3	227
Sheep / goats	70	1	-	3	66
Total	81'131 (100.0 %)	3'293 (4.1 %)	36 (0.0 %)	86 (0.1 %)	77'716 (95.8 %)

*) Spontaneous deaths or emergency slaughter

4. Analysis of tissue samples

It is known that TCDD accumulates chiefly in the liver and fatty tissues. The veterinary service of the Lombardy region secured therefore a large number of livers from animals which had died or had been slaughtered. The chemical analysis (limit of detection: 2.5 ug/kg = 2.5 ppb or 2500 ppt) demonstrated TCDD in the livers of some of the dead animals but not in all of them. TCDD has been detected in 71 out of 113 rabbits, 3 out of 3 goats, 2 out of 3 hares and 2 out of 27 chicken, but the organs of 6 ducks,

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2 hens, 1 cat, 2 guinea pigs and 1 peacock did not contain TCDD (1, 22).

Table 24

Dioxin levels in the livers of rabbits

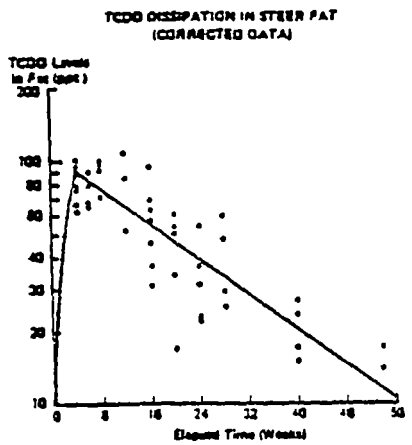
Zone / animal group	TCDD in the liver* in µg/kg = ppb
A (15 -6666 µg/m²) / slaughtered	58 ± 10 (14)
A " / died	167 ± 88 (7)
B (5 - 15 µg/m²) / died	83 ± 29 (13)
B " / died	215 ± 85 (5)
B (0 - 5 µg/m²) / died	52 ± 11 (29)
Others / died	25 ± 13 (3)
Control / slaughtered	< 2.5 (5)

* Mean ± SE; the figures in brackets represent the numbers of samples

The levels found in the rabbits' liver are shown in Table 24. The amount of TCDD detected in the animals that died ranged between 50 and 200 µg/kg in the livers, but levels of the same magnitude have also been found in clinically healthy rabbits. Of 14 rabbits, collected in the Zone A, which had rather large amount of TCDD in their liver (up to 300 µg/kg), all were apparently normal,

had normal serological, hematological and enzymatic values and only 5 showed histologically hepatic lesions when sacrified three months after the accident (1). Consequently analytically measurable amounts of TCDD in the liver or in the fat do not necesserally correspond to anatomical or functional lesions. There is certainly an accumulation of TCDD in the liver and in the fatty tissues, but there is also an elimination from the body. The half-life of TCDD in the rat (43, 50) is approximately three weeks and a steady state is reached after approximately 80 days. If doses of 0.01 µg/kg TCDD are administered daily to the rat for a life time, the steady state level in the liver and fatty tissues is 20 respectively 50 µg/kg without prejudice for the animal. As soon as the rats are withdrawn from the contaminated food, the body TCDD level falls exponentially. The same applies to other animals (47) especially cattle, for whom the elimination rate (half-life) is in the region of 100 days (Figure 5) and to smaller animals (guinea pigs,

Fig. 5



sheep, monkeys) for whom the half-life is similar to that for rats, i.e. 3-4 weeks. Animals which have grazed on or have been fed with TCDD contaminated food would therefore no longer have any measurable tissue concentrations of TCDD after a corresponding feeding time with uncontaminated food. In fact, even affected animals have been known to recover after having been exposed to levels of TCDD much higher than those found in Seveso. At least six horses of the Arena B in Missouri (10), which had been ill, had recovered. The TCDD levels in this arena as measured 3 years after the incident in the removed soil was 0.5 ppm, i.e. 100 times higher than in the zone at highest contamination in Seveso. The original contamination in the arena may well have been 10 times higher yet.

Our own measurements with liver samples from animals slaughtered in Seveso (Table 25) in the last months of 1977 have revealed levels which are at most one thousandth of those measured in rabbits in 1976.

Table 25

Contamination of animals in the B zone in Seveso
(End 1977 / beginning 1978)

Animals	Mean concentration in the liver	
	in µg/kg	in ppt
Pigs	< 0.01	< 10
Cattle	0.04	40
Horses	0.08	80
Goats	0.13	130

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This may to some extent be referred to a lower original exposure but also undoubtedly to the elimination of TCDD from the body. In due time, virtually all the liver samples would no doubt have been negative, despite the low detection limit of 10-20 ppt reached in our laboratories.

Table 25 shows also the difference between animal species in relation to the food. Swine, as non herbivorous, show no measurable traces of TCDD, whereas cattle, horses and goats appear to have been more exposed.

Table 26 represents a cross section of TCDD concentrations found in healthy and unaffected wildlife and domestic animals in the USA. The living organism examined by Young et al. (70) in Florida seem to tolerate soil concentrations of between 1000 and 1500 ppt without discernible damage. Commoner (11) shares the view that 500 ppt in the soils represents a tolerable level for the fauna. In Seveso the TCDD levels found in the soil after the vegetation had died out, i.e. in late autumn 1976 were of 150-20000 ppt for the Zone A which had been fenced in,

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of 50-150 ppt for the Zone B and 0-50 ppt for Zone R. After the Zone R and B had been ploughed in the spring 1978, the TCDD surface concentration was below 10 ppt throughout.

Table 26 TCDD levels in healthy domestic animals and wildlife in the USA

Cause of contamination	State	Animal	TCDD concentration in body tissues	Year	Lit.
Old oil treatment of soil to bind dust (suspected)	Missouri	Cattle	ca. 20- 90 ppt in the fat	1977	
Herbicide application to pasture (cattle fenced in)	Texas	Cattle	5 ppt in the fat	1978	
Chemical industry (suspected)	Michigan	Fish	10- 20 ppt	1978	
Experimental herbicidal programme of the US Air Force. Eglin AFB 1962-1970 soil contamination 10-1500 ppt	Florida	Insects	40 ppt	1974/75	
		Birds			
		Sturnella magna	100-1020 ppt in the liver	1974/75	
		Zenaidura macroura	50 ppt in the liver and fat	1974/75	
		Fish			
		Notropis hypselopterus	12 ppt in the body	1973/74	
		Gambusia affinis	12 ppt in the body	1973/74	
		Lepomis punctatus	85 ppt in the gut	1973/74	
		Reptiles			
		Chamidorus sizilineatus	360 ppt in the body	1973/74	
		Rodents			
		Peromyscus pellionetus	20-1300 ppt in the liver	1973/74	

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CONSEQUENCES ON THE CROPS AND THE LAND

1. The situation after the accident

It should be remembered that the summer of 1976 was rather hot and dry in Lombardy. This was reflected in the condition of the crops at the time of the accident. The grasslands were ready for the second cutting and the cereals which had ripened slightly prematurely due to the drought, were nearly ready for harvest. The aerosol cloud which settled down southeast of the factory after the accident had practically no effect on the flora. Phytotoxic damage (Figure 6) throughout the affected area was confined to a few broad-leaved plants in the immediate vicinity of the factory. Most of the damage was due to the high temperature and high alkalinity of the mass that escaped from the reactor and consisted in a drop like perforation and in a brownish change of the green colour of the leaves. There were no discernible changes anywhere in the remaining areas, either to crops or to shrubs in numerous little copses or to ornamental plants.

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Fig. 6



It was the sampling of the vegetation and the chemical analysis of the samples which made possible the location of the areas which had been severely or slightly contaminated and those which had escaped. The map (Figure 7)

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FIGURE 7

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represents the results of our sampling and of the chemical analysis of the Givaudan research laboratories and this map was the determinating factor for the decisions on all protective and preventive measures later taken by the Italian authorities. In respect of the crop and rangeland of the contaminated zone, an absolute ban on cultivation and grazing was issued for all three zones and the same regulation prohibited the use of plant products. At that time (August 1976), measurements showed 80 % or over of the total TCDD traced to adhere to the vegetation (foliage, grass, crops). This TCDD location would have been highly favourable for the decontamination work as will be related later. It changed however rather rapidly toward the autumn. Heavy rains flattened the standing grass and overripe cereals and pressed them with the adherent TCDD to the ground. Young grass and weeds grew up and covered what remained standing. Consequently the TCDD adhering to the vegetation was transferred to the ground and by the activity of the rain as well as of the micro- and macroorganisms living in the soil, it was shifted to the upper layer of 1 to 2 cm. This made it more difficult to take rapid and effective measures of decontamination as by that time immediate removal of the

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contaminated soil and its safe disposal were the only actions that promised a reasonable degree of success. The autumn storms, the heavy rainfalls which followed further complicated the situation created by the leaf fall rendering the TCDD penetration to deeper layers of the soil virtually inevitable.

2. The behaviour of TCDD in the environment

At the time of the accident data on the TCDD behaviour in the environment - unlike those on animal toxicology - were sparse as in previous accidents contamination had generally been restricted to the production buildings of the chemical industry. The only available findings from investigations of incidents comparable with that of Seveso were those obtained by the U.S. Air Force in connection with the use of "Agent Orange". On the basis of the references in the literature and of the data obtained by ourselves we can make the following comments on the effects of TCDD on ecology:

TCDD is not mobile in the soil. Rain at most causes TCDD to be washed out and transported with simultaneous erosion of the soil. There is accordingly no risk for the ground-water (7, 27, 29, 32, 33, 34, 36, 70).

DOW 2751155

TCDD is transported within plants in only negligible amount or not at all. There is no accumulation of TCDD in the vegetation (14, 15, 16, 27, 29, 33, 34, 70). TCDD is broken down in the soil under natural environmental conditions. Unless the breakdown is speeded up by additional measures, the half-life ranges from 200 days to one year (10, 27, 32, 33, 34, 69, 70).

3. Field and greenhouse trials

The environmental behaviour of TCDD as outlined above were confirmed by a trial under controlled conditions in a greenhouse; by a field trial in Zone A and by sampling from various areas of the three zones.

Leachability of TCDD was measured in soil columns with Mitscherlich containers using Seveso soil and showed that even at high TCDD levels and simulation of heavy rain precipitation (downpour of 200 mm in 20 minutes equivalent to an extremely heavy thunderstorm) no TCDD could be demonstrated in the percolated water.

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Systematic measurements of soil samples taken from different depths carried out in the course of a field trial in Zone A (520 µg/m^2) in spring 1977 showed that there was no leaching beyond a depth of 20 cm.

The breakdown of TCDD corresponded to the findings reported in the literature. In our greenhouse trials (Table 27) the breakdown was measured on the crops obtained from the Zone A (520 µg/m^2) and transferred to greenhouse pots. The breakdown rate ranged here from 21 to 52 % for a nine months period.

Table 27

Reduction rates measured in the greenhouse trial; means from 6 pots

Crop type (soil from Zone A) (520 µg/m^2)	TCDD in ppb		
	May 1977 before start of test	December 1977	% Reduction
I Naturally grown weeds	4.1	2.97	27.6
II Carrots	2.6	1.32	49.2
III Beans	2.5	1.62	35.2
IV Naturally grown weeds	3.0	1.55	48.3
V Naturally grown weeds	2.2	1.72	21.8
VI Barley and vetch	3.5	1.65	52.8
VII Radiance	2.9	1.97	32.1
VIII Untreated	not detectable	not detectable	-

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In the field trial (Table 28) carried out in the Zone A (62 $\mu g/m^2$) the reduction occurred during December 1976 and May 1978 ranged from 28 to 49 %.

The breakdown was therefore more rapid in the greenhouse than under field conditions. This difference may be largely attributed to the increased activity of the soil living organisms in the greenhouse where the mean temperature was approximately 20°C and there was no winter season with frost and arrest of growth.

Table 28

Reduction of TCDD in Zone A (62 $\mu g/m^2$)

Test area	December 1976	May 1978	% Reduction
1	273 ppt	138 ppt	49
2	296 "	183 "	38
3	178 "	125 "	28
Mean	248 "	149 "	40

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Examination of the crops from the three different zones showed that there was no detectable TCDD in the Zone R (Table 29) and B.

Table 29

TCDD levels measured in vegetation samples from zones B and R (autumn 1977)

Specimen	TCDD concentration in the surrounding soil	TCDD concentration in the plant specimen	Limit of detection
Grapes	ca. 200 ppt	not detectable	< 0.25 ppt
Peaches	ca. 200 ppt	"	< 2.5 ppt
Tomatoes	36 ppt	"	< 0.36 ppt
Beans	2 ppt	"	< 1.5 ppt
Rye (ears)	49 ppt	"	< 1.9 ppt
Grass	ca. 150 ppt	"	< 2 ppt
Cabbage stalks	ca. 200 ppt	"	< 0.9 ppt
Millet	2 ppt	"	< 0.9 ppt
Rosemary	36 ppt	"	< 5 ppt
Cauliflower	10 ppt	"	< 1 ppt
Cauliflower leaves	10 ppt	"	< 1 ppt
Chicory	10 ppt	"	< 3.5 ppt
Cabbage	10 ppt	"	< 0.7 ppt
Lucerne	38 ppt	"	< 1.7 ppt
Cucumbers	15 ppt	"	< 0.4 ppt

The crops collected from a highly contaminated part of Zone A (1000 $\mu g/m^2$) contained small amounts of TCDD. In this connection it was interesting to note that TCDD was contained on the surface areas of the crops, i.e. in the skins of the fruits, the spathes of the corncobs etc. (Table 30).

Table 30

TCDD levels of various plants grown in the severely contaminated zone A (ca. 1000 µg/m2)

Crops	ppt TCDD in the soil	ppt TCDD in the plants	In % of soil contamination
Maize spathes grains	10'000	< 1.3 < 0.8	< 0.013 < 0.008
Apples peel flesh	10'000	137 < 2.5	1.370 < 0.025
Pears peel flesh	10'000	79 < 0.5	0.790 < 0.005
Peaches skin flesh	10'000	102 < 0.8	1.020 < 0.008
Apricots whole fruits	10'000	9	0.09
Plums whole fruits	10'000	7	0.07

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This finding suggests that TCDD found in plants was chiefly derived from fine contaminated local dust deposited on the surface of the crops. The greenhouse trials seem to support this assumption because even where plants were grown in soil with high levels of TCDD, only 0.04 to 0.2 % - depending on the crop - of the TCDD soil level could be found in the plant (Table 31)

Table 31

Contamination of plants grown in the greenhouse on contaminated soil

Plant (Mean from 4 pots)	ppb TCDD in the soil	ppb TCDD in the plants	% Contamination
Beans	8.1	0.0106	0.13
Barley (ears)	12.6	0.0047	0.04
Weeds grown from seed present in the soil	10.4	below detectable limit	-
Radishes (Raphanus sativa)	11.6	0.0220	0.19

4. Decontamination methods

A rapid collection and storage of the vegetation under safety precautions on the basis of the analytical tests carried out during the first days would have permitted the disposal of the major part of the TCDD. A second possibility would have been the spraying of an H donor and the utilization of the UV part of the August daylight.

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The photochemical reaction would have resulted in a relatively rapid breakdown of TCDD. Corresponding experiments had been carried in our laboratories (68) shortly after the accident. Food quality olive oil was used as H donor (Table 32). Other agents proved equally active but had been shown in preliminary tests to be less tolerated by the plants than olive oil. A limited field trials carried out in Zone A confirmed the laboratory findings.

Table 32 Breakdown of TCDD after olive oil treatment

Test	TCDD level in µg/m²			
	Before treatment	24 h after treatment	48 h after treatment	Reduction in %
Olive oil emulsion 400 litres/ hectare	26.2	16.9	9.6	63.4
Olive oil - cyclohexanol 400 l oil/ha	19.5	18.8	10.7	45.1
Untreated	16.4	18.5	16.8	0

A decontamination program for the houses, gardens and land of the less contaminated part of the Zone A was worked out and operated by ourselves. The in- and outside of the houses were cleaned with special vacuum cleaners,

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washed and finally repainted. In the gardens 10 to 20 cm soil were removed, followed by a fresh layer of humus. The entire network of streets and paths was renewed and either paved with asphalt or stone slabs. Analytical tests after the cleaning operations failed to detect any TCDD and the evacuated residents were allowed to return to their houses.

The core of Zone A with TCDD levels of 150-5000 $\mu g/m^2$ is still sealed off and behind fences. Moreover, it has been used as dumping ground for waste from other zones. The natural course of the TCDD breakdown will take, in the light of our present knowledge, 6 to 8 years. The area could be make accessible by removing the contaminated soil layers and burying them in a concrete pit. The process would have the advantage of eliminating TCDD from the environment completely and rapidly.

Conclusions

Two years after the most publicized Seveso accident, when products containing the highly toxic TCDD descended on the surroundings of a chemical plant, an attempt can be made to summarize what happened.

It is still not yet possible to explain the accident. The nature of the possible exothermic reaction which should have brought about a rise in the temperature in the reactor during the production of TCP with slow decomposition of the reaction mass, formation of gas and increase of the pressure, is still unknown. Further experiments are needed to explain the mechanism of the accident.

It was the chemical analyst who supplied the data for the assessment of the amount and location of the hazard. The detection of the TCDD and the measurement of its amount in our laboratories led to the definition of the contaminated territory and of the importance of the contamination. Neither the injuries on the humans nor the effects on the animals, on the vegetation and land would have been sufficiently relevant for the preventive and protective measures taken for the population and the territory.

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The harm induced by TCDD on the health of the population either during the acute high level exposure of the first two weeks or during the lower level chronic exposure of the following 24 months shows the following main features:

Chloracne, the striking clinical feature which is suggestive of a TCDD exposure appeared in a very small percentage of the most sensitive group of the population involved. The manifestation was not limited to the first days after the accident but held on during the following months and is still lingering in the environment. The skin lesions were rarely severe, mostly mild or extremely mild and always inclined to rapid and complete healing. Recidivism of the symptomatology was rare and occurred practically only in cases with mild or very mild lesions probably originated from low level and short duration of exposure. The incidence of chloracne and its degree of severity persistently decreased and has now reached a rate which is very close to the frequency of chloracne in the surrounding provinces. This fact suggests that the level of TCDD exposure has also decreased. The TCDD contamination of the environment has not affected neither the incidence nor the degree of severity of the puberty acne nor the current skin pathology of the region. One is inclined to

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assume that in these cases the skin lesion is the manifestation of the presence of TCDD in the environment more than a sign of the toxic effect of the substance on the human organism. The systemic effects of the TCDD exposure which have been reported in over 50 % of the chloracne cases occurred after occupational exposure in the past, have not been observed here. No laboratory evidence of significant hepatotoxicity or deranged porphyrin metabolism, no abnormal neurologic findings have been observed in these cases.

As for the other samples of the population (adults evacuated from the Zone A, inhabitants of the Zone B, plant workers of the Icmesa factory, decontamination parties) no prevalence in the current neurological and hepatic pathology of the region could be correlated so far with the exposure. The rate of abortions and malformations, the growth of newly born infants, the immunoresponse, the chromosome aberrations, the reaction to infectious diseases, the morbidity and mortality have not been affected by the amount of TCDD exposure.

In the wake of the accident a number of wild and domestic animals died in the contaminated zones. Affected were mainly small herbivores, while only 1.7 % of the larger animals died. A small number of the surviving animals were evacuated for study purposes (86) while the rest (77 716) were slaughtered preventively in order to keep them out of the food chain.

Chemical analysis of liver samples from dead animals confirmed TCDD in 78 of 158 samples collected immediately after the accident, at the original detection limit of 2.5 µg/kg (highest values in the order of 300 µg/kg). However, measurable amounts of TCDD in the liver do not necessarily imply anatomical or functional lesions. Apparently healthy rabbits with normal body functions were also found to have as much as 300 µg/kg TCDD in their liver.

Many originally affected animals have recovered, consistent with other observed recoveries of horses in a Missouri mishap, where much higher TCDD concentrations occurred. This is due to the elimination of TCDD from the body. The elimination process has been studied in the laboratory. The half-life of TCDD in the body is 3-4 weeks for smaller animals (rats, guinea pigs, sheep, monkeys) and approximately

100 days for cows. If contaminated animals had been fed with uncontaminated feed sufficiently long, they would no longer have shown measurable TCDD concentrations in their tissues. Actual liver concentrations in the domestic animals slaughtered at the end of 1977 were at least three orders of magnitude less than in the rabbits in 1976. In many cases they were even below the new detection limit of 10-20 ng/kg (ppt).

The study of the effect, persistence and mobility in the environment has shown that the cloud of chemicals which settled down southward of the plant had very little effect on the vegetation of the fallout area. About 80 % of the TCDD ejected with the reaction mixture adhered to the foliage, grass and crops for several weeks until it was transferred to the soil by the rain. Our field and greenhouse trials have shown that in Seveso TCDD does not leach vertically beyond a depth of 20 cm in the soil and that it disappears slowly by a natural degradation process and half of it is lost after 9 and 12 months. Plants do not take up significant amounts of TCDD. Only fractions of the quantity in the soil can be found in the vegetation and in

DOW 2751666

the fruits growing in the contaminated area. A useful method for removing large quantities of TCDD from the area could have been applied immediately after the accident either by collecting and disposing of the vegetation or accelariting the natural process of degradation by spraying a suitable hydrogen donor. Today the remaining part of Zone A (115 acres) which is still fenced in could be made accessible by removing the contaminated soil layers and burying them in a concrete pit. The natural process of degradation would take 6 to 8 years.

Reprints to be requested at the following address:

Dr. G. Reggiani
Research Department
F. Hoffmann-La Roche & Co. Ltd.
4002 Basle
Switzerland

16799

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DOW CHEMICAL U.S.A.
AN OPERATING UNIT OF THE DOW CHEMICAL COMPANY
MIDLAND, MICHIGAN 48640

SALES SPECIFICATION

NUMBER	DATE
20683	7-9-
SUPERSEDES	
NUMBER	DATE
20683	1-17-
METHODS OF ANALYSIS	
20683a	

DOW 0248 170

2,4-DICHLOROPHENOXYACETIC ACID

2,4-Dichlorophenoxyacetic acid, minimum	99.0%

→ DENOTES CHANGE

The policy of The Dow Chemical Company is one of continued improvements by research and manufacturing wherever possible to assure a still finer product. Hence, specifications are subject to change without notice.

For a more complete description of this product, including average physical properties, please refer to the appropriate Dow technical data bulletin.

All shipments will be accompanied by minimum markings which include product identification, lot or batch number, net contents, company name and address, and such precautionary labeling and other information as seemed appropriate for this product.

FORM 30780 PRINTED R-3-74

16809

NOTED
APR 14 1965
DOW
SILVEX
FOR MANUFACTURING USE ONLY
2(2,4,5-Trichlorophenoxy)propionic acid, minimum ... 98.0%
CAUTION
DUST IRRITATING TO EYE, NOSE, AND THROAT
MAY CAUSE SKIN IRRITATION
Avoid Breathing Dust - Avoid Skin Contact
NET 175 POUNDS
LOT
THE DOW CHEMICAL COMPANY
MIDLAND, MICHIGAN
DOW 1123934

DOW CHEMICAL U.S.A.

POST OFFICE BOX 1706
MIDLAND, MICHIGAN 48640

June 27, 1973

bcc: D. D. McCollister/Action File
M. L. Leng
R. F. Flannery
L. R. McCutchen
L. Southwick
E. E. Kenaga

Mr. Richard F. Mountfort
Fungicide-Herbicide Branch
Registration Division
Environmental Protection Agency
South Agricultural Building
12th & Independence Ave., S.W.
Washington, D. C. 20460

DOW 363924
MN 053305

Dear Mr. Mountfort:

Subject: KURON® Weed and Brush Killer
EPA Reg. No. 464-162
Your letter of May 1, 1973

For convenience in review a copy of your May 1, 1973, letter is enclosed. We will discuss your comments by their numbers in that letter.

Comment No. 1.

At our May 31, 1973 meeting on Phenoxy Labels, Mr. Robert J. Taylor discussed our KURON label application of March 13, 1973. In accord with that discussion and your letter we have deleted the recommendation for a tank mix of KURON and TORDON 101 Mixture for Forest Site Preparation until we have the phytotoxicity data requested concerning planting of conifer seedlings.

To make your files more complete, we are enclosing copies of two brief research reports and a brief letter report indicating the general efficacy of such a tank mix for overall brush control.

Notes on transmission line brush control test near LaPlace, Louisiana, 1972 by H. A. Nation March 1973. Report to The Dow Chemical Company.

Notes on power transmission line brush control test near St. Francisville, Louisiana, 1972 by H. A. Nation March 1973. Report to The Dow Chemical Company.

West Tree Service Inc. Letter report of October 6, 1972 to Mr. W. G. Wright, The Dow Chemical Company.

16811

Comment No. 2.

We had previously changed the statement (page 10) to read ".... along the shorelines of ponds and similar aquatic areas ...." We believe the use of the word "of" rather than "in" is a non-substantive change and that the sentence as written expresses the idea you had in mind.

Under Comment No. 2 - a request for additional bird toxicity data, if available.

We have no additional bird toxicity data to supply. This matter was discussed between our E. E. Kenaga and your A. J. Duvall in a phone call of May 8, 1973. It is my understanding that there were no further questions raised. I also understood from Mr. J. W. Akerman at the May 31, 1973 conference previously mentioned that if he wished further information he would contact Mr. Kenaga.

Five copies of labeling for this product revised in accordance with the above comments are enclosed. We believe this label therefore is acceptable to you and look forward to receiving such official notification.

Sincerely,

Wendell R. Mullison
Registration Specialist
Ag-Organics Department

Enc.

cah

DOW3603925

2239

[redacted]

SPECIMEN LABEL

DOW

KURON

WEED AND BRUSH KILLER

FOR CONTROLLING CERTAIN HERBACEOUS WEEDS, WOODY PLANTS AND AQUATIC WEEDS

Contains 4.6 Pounds per Gallon of Low Volatility Esters of Silvex

SILVEX ACID EQUIVALENT 4.0 POUNDS PER GALLON

Active Ingredients:

Silvex[2-(2,4,5-Trichlorophenoxy) propionic Acid] propylene Glycol (Ester of 2-(2,4,5-Trichlorophenoxy) propionic Acid) 47.9%

Silvex (2-(2,4,5-Trichlorophenoxy) propionic Acid) Equivalent 42.0%

Inert Ingredients 53.1%

U.S.D.A. Registration No. 464-148

CAUTION

KEEP OUT OF REACH OF CHILDREN

Read Complete Precautions on Side Panel

1 GALLON

WEED LIST

[illegible]

KUAWAI—Continued

[illegible]

WARNING

[illegible]

CAUTION

MAY CAUSE SKIN IRRITATION

Avoid Contact with Eyes, Skin and Clothing
Keep Out of The Reach of Children

KURON FOR AQUATIC WEED CONTROL

[illegible]

THE DOW CHEMICAL COMPANY

86-1092 PRINTED IN U.S.A. IN NOVEMBER 1967

REPLACES SPECIMEN LABEL 86-1092 PRINTED IN NOVEMBER, 1965, AND JULY, 1967.

REVISIONS INCLUDE: (1) GENERIC DESCRIPTION OF THE PRODUCT NOW READS "WEED AND BRUSH KILLER." (2) NEW DISCLAIMER STATEMENT. (3) REVISED RECOMMENDATIONS FOR USE IN SUGAR CANE IN LOUISIANA.

[redacted]

16813



DOW

SPECIMEN LABEL

D BRUSH KILLER

IG CERTAIN HERBACEOUS
ANTS AND AQUATIC WEED

EPA Registration No. 464-449

CAUTION

T OF REACH OF CHILDREN

ative Precautions on Side Panel

1 GALLON

KURON FOR AQUATIC WEED CONTROL

U.S. Patent No. 3,765,868

1967

DIRECTIONS

USE RECOMMENDATIONS IN SUGAR CANE

FLORIDA

LOUISIANA

HAWAII

DOW220252477

16814

DUMZUZZ540

2301

KUR

Active Ingredients

Silvex [2-(2,4,5-Trichlorophenoxy) propionic Acid], Propylene Glycol Butyl Ether Esters 67.9%

Silvex [2-(2,4,5-Trichlorophenoxy) propionic Acid], Equivalent 45.0%

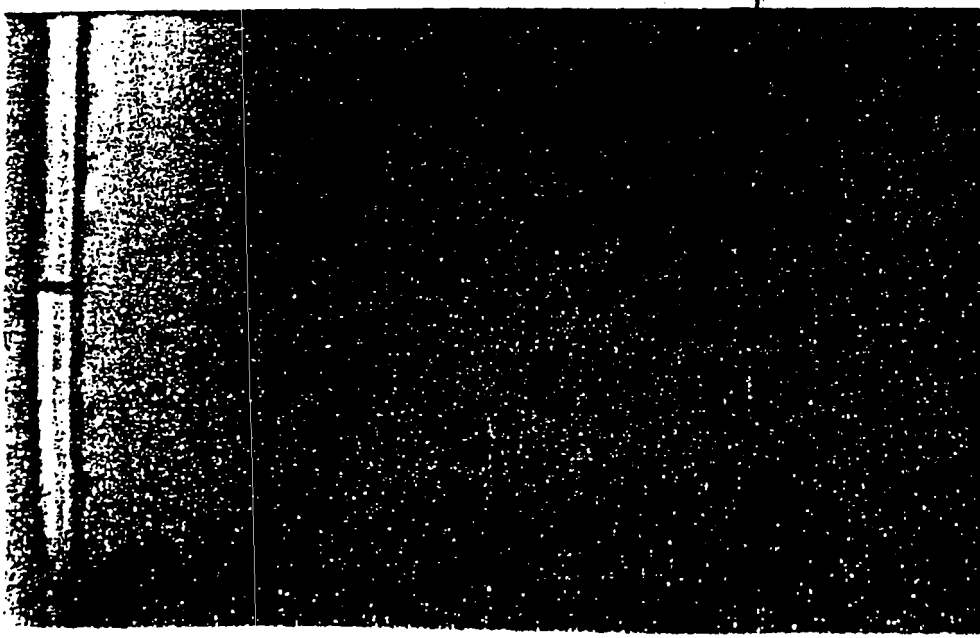
Inert Ingredients 32.1%

U.S.D.A. Registration No. 464-162

Contains 6.0 Pounds per Gallon of Low Volatility Esters of Silvex

SILVEX ACID EQUIVALENT 4.0 POUNDS PER GALLON

BRUSH



Now Recommended for AQUATIC WEED CONTROL

1615

RON®

Submergent Aquatic Weeds in Ponds and Other Still Water: To control certain submergent weeds such as water milfoil, fanwort, bladderwort and waterweed, use 5 quarts of Kuron per acre foot of water. (An acre foot of water is one acre in area and one foot deep. Thus an acre of water 5 feet deep will require 5x5 quarts of Kuron or 6.25 gallons.) Apply in early summer when water temperature is above 50° F. and weeds are approaching the water surface. To apply properly, first dilute the Kuron with enough water for uniform distribution over the water surface with the spray equipment at hand. Application may also be made with properly calibrated proportioning equipment which automatically mixes Kuron and pond water in the pump.

NOTE: Do not treat flowing water with Kuron. Ponds with a slight current can be treated if the water level can be lowered so there will be no overflow for at least 3 days after treatment. However, control will be less around spots where untreated water flows into the pond. In treating shoreline of lakes or large ponds, there will be some dilution caused by the water in the untreated center areas of the pond; therefore, it is best to treat an area at least 200 feet square.

Emergent Aquatic Weeds: To control emergent weeds such as white water lily, spatterdock, pickerelweed, arrowhead, etc., use one gallon of Kuron in 100 gallons of water. Apply as a wetting spray to leaves and stems when leaves are fully developed above the waterline. Re-treat as necessary.

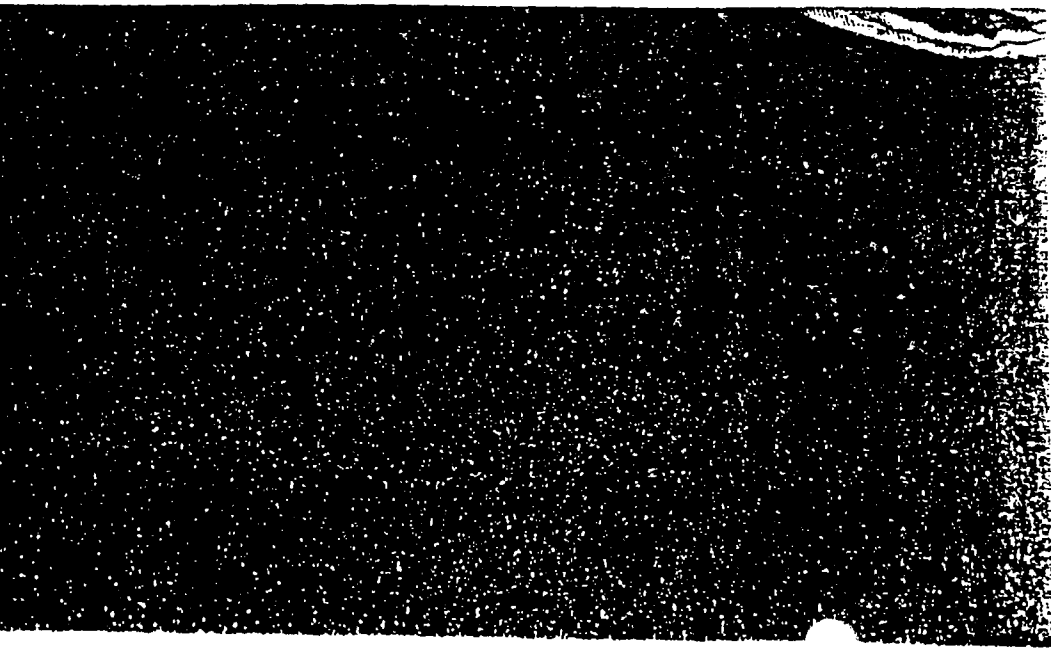
Special Precautions for Use in Aquatic Weed Control: Apply only in accordance with state and local laws and regulations governing chemical treatment of bodies of water for control of weeds. To avoid injury, do not use Kuron where pond water is being used for irrigation (including rice production), for agricultural sprays, domestic water supply or for livestock watering. When used as recommended above, Kuron is not ordinarily harmful to aquatic animals, but some fish kill may occur, especially in shallow coves where uniform application is difficult. Apply Kuron when water level is low, so as to keep at a minimum the exposure of desirable vegetation along the shoreline. Since they may cause interference with the action of Kuron, do not apply algacides such as copper sulfate for 3 days before or after applying Kuron. Note: Treat pond edges or lake shoreline first so fish will not be trapped in shallow pockets or inlets.

KILLER

CAUTION

KEEP OUT OF REACH OF CHILDREN

Read Complete Precautions on Rear Panel



DUH2UZZ541

16816

KURON® BRUSH KILLER

FOR CONTROLLING CERTAIN HERBACEOUS WEEDS AND WOODY PLANTS

Particularly Post Oak, Blackjack Oak, and Northern Oaks such as Pin Oak, Red Oak, White Oak and Scrub Oak

DIRECTIONS

Kuron foliage herbicide is used in controlling certain woody and herbaceous plants growing in pastures, rangelands, fence rows, right-of-ways, and on ditchbanks

Kuron is effective in controlling - -

blackjack oak	maples, such as red,	ground ivy	post oak
northern pin, red,	sugar, and big leaf	mesquite	sand shinnery oak
white scrub oaks	maple	poison ivy	wild blackberry
			yucca

also certain broad-leaved weeds such as —

broomweed	curly indigo	Mexican weed	ragweed
cocklebur	lamb's-quarters	pokeberry	salt cedar
croton weed			sunflower

NOTE: Do not use Kuron for the control of ash.

PREPARING THE SPRAY: Add half the required amount of water to the spray tank, then add Kuron with agitation. Kuron forms an emulsion in water and tends to settle out on prolonged standing. Provide agitation to prevent such separation and ensure uniform mixture in the spray tank.

FOLIAGE TREATMENT: Spray woody growth up to 6 or 8 feet tall after the foliage is fully developed, using a spray containing 3 to 4 quarts of Kuron per 100 gallons of water. With sensitive species, taller brush or trees may be controlled if foliage is adequately covered. On poison ivy and brambles such as wild blackberry, use 2 quarts of Kuron per 100 gallons of water. **Spray should drench all plant parts including leaves and stems.**

Delay spraying new sprouts from recently cut stumps until they have made appreciable growth. Under good growing conditions, applications made up to three weeks before fall frost are usually effective. Spraying after leaves have lost their normal green color and vigor may not give satisfactory control. Less effective control may result during hot dry weather when deep soil moisture is deficient. Usually a single application in any one year is sufficient. If new growth develops, repeat applications may be necessary in succeeding years.

AIRPLANE APPLICATION: For control of post and blackjack oaks, use 2 quarts of Kuron in 1 gallon of diesel oil and 2½ to 3½ gallons of water, or 2 quarts of Kuron in 3½ to 4½ gallons of diesel oil per acre. Apply after foliage is fully developed (usually in May or June). An additional spray using 1 to 2 quarts of Kuron may be necessary the second or third year. These applications will effectively control broad-leaved weeds in sprayed areas.

SPOT TREATMENT: For knapsack application of Kuron, mix ½ cupful in 3 gallons of water. Wet all foliage thoroughly.

WEED CONTROL IN LAWNS AND GOLF COURSES: For control of broad-leaved plantain, buckhorn, common chickweed, mouse-eared chickweed, dandelion, and legumes such as white clover and black medic in established turf, apply 1½ quarts of Kuron in 25 to 40 gallons of water per acre. Higher volumes up to 100 gallons per acre may be used to minimize drift hazard. Apply in fall or early spring at hot weather use may cause excessive damage to turf. **Do not apply to cool-season grasses such as bent, Bermuda, and St. Augustine, or to new turf of any variety.**

CAUTION: To avoid damage to turf, do not spray in any manner which will cause excessive dosages. Avoid overlapping and double coverage when backing up, and at turns. Avoid spraying when nozzles and boom are not moving, such as when cleaning or testing nozzles. Use a positive quick shut-off valve on boom spraying equipment.

WEED CONTROL IN RICE: Treat 4 to 8 weeks after emergence of the rice. Where flooded, treat between 7 and 9 weeks after seeding, when plants have emerged above water and leaves are standing erect. Use 1½ to 3 pints of Kuron in the amount of water needed for even distribution. For many situations 2 pints per acre is adequate. Where weeds tend to be resistant because of specie, age or growth condition, up to 3 pints will give better control. Treatment after flooding is usually later than before flooding. Consult your State Experiment Station or Extension Service for specific local recommendations.

FOR CONTROL OF YUCCA AND SAND SHINNERY OAK: Use 1 pint to 1 quart of Kuron in 1 gallon diesel oil, and water to make 4 gallons total per acre. Two to three applications as necessary in successive years may be needed. Apply after foliage is fully developed. Consult competent local authorities for information on best rate and best time for application.

Local conditions may affect the use of herbicides. State agricultural authorities in many states issue recommendations to fit local conditions.

USE RECOMMENDATIONS IN SUGAR CANE

FLORIDA

For post emergence control of ragweed, dog fennel, ground cherry, purslane, wild lettuce, nightshade and other susceptible broad-leaved weeds, apply 1 to 1½ quarts of KURON in 20 to 40 gallons of water per acre as broadcast spray. Make the first application after the cane emerges as spring growth and when weeds are growing vigorously, but before they send up seed stalks. A second application can be made for late emerging weeds. **NOTE:** Do not apply after the cane is 3 to 3½ feet tall.

LOUISIANA

For the control of crabgrass, barnyard grass and Johnson grass seedlings in sugar cane, apply one quart of Kuron in 15 gallons of water per acre on the row (approximately one-third of the total area) shortly before the seeds are expected to germinate. If cane is shaved and off-barred, treat immediately following this operation. Follow the early treatment when necessary with 2 pounds of Dowpon® grass killer per acre, applied over the grass in the row (approximately one-third of the total area).

To control wild lettuce, curled dock, and other weeds use one of the following procedures when the weeds are [illegible]

Ground Application: Use 1 quart of Kuron in 15 gallons of water per acre applied over the row (approximately one third of the total area). A second application can be made if needed. Do not make application after cane is 3 to 3½ feet tall. Make application at least 5 months before harvest.

Air Application: Use 1 quart of Kuron per acre in enough water for uniform coverage. Application can be made up to 5 months before harvest.

HAWAII

For pre-emergence control of hairy crabgrass, yellow foxtail, richardsonia, browntop clematis, amaranth, Elusine paniculata, jungle rice, purslane and wild grass in Hawaiian sugar cane, apply 4 to 5 quarts Kuron per acre in 20 to 40 gallons of water as a broadcast spray immediately after planting or ratooning and before cane emergence. For post-emergence control of weeds after canes have emerged add 2½ to 5 pounds Dowpon per acre to the spray of Kuron in order to control grasses and spray the interline space without spraying the cane directly. This application can be made up to the time of "closing in" but not less than 5 months before harvest. Do not make more than two applications of 5 quarts each of Kuron to any one crop.

Local conditions may affect the use of herbicides. State agricultural authorities in many states issue recommendations to fit local conditions.

WARNING

Do not apply Kuron directly to or otherwise permit it to come into contact with any crop plant or ornamental plant (including but not limited to peanuts, soybeans, beans, peas, tomatoes, tobacco, cotton, melons, okra, sweet potatoes, peppers, celery, flowers, ornamentals, grapes, deciduous and evergreen fruit trees) and do not permit sprays mist containing Kuron to drift onto them since even minute quantities may cause severe damage during both growing and dormant periods. Coarse sprays are less likely to drift. **Applications by airplane, ground rigs and hand dispensers should be carried out only when there is no hazard from drift. Do not apply by airplane in the vicinity of any desirable crops or ornamentals including those listed above.** At elevated temperatures vaporization may cause injury to susceptible plants growing nearby.

Do not use Kuron on freshly seeded lawns, pastures or range land until grass has become well established. Do not contaminate irrigation ditches or water used for domestic purposes. Do not store near fertilizers, seeds, insecticides or fungicides. To avoid injury to sensitive plants, do not store, handle or apply other agricultural chemicals with the same containers or equipment used for Kuron. Do not use Kuron in spraying equipment contaminated with 2,4-D if the 2,4-D will increase the hazard to desirable plants.

Be sure that use of this product conforms to all applicable regulations.

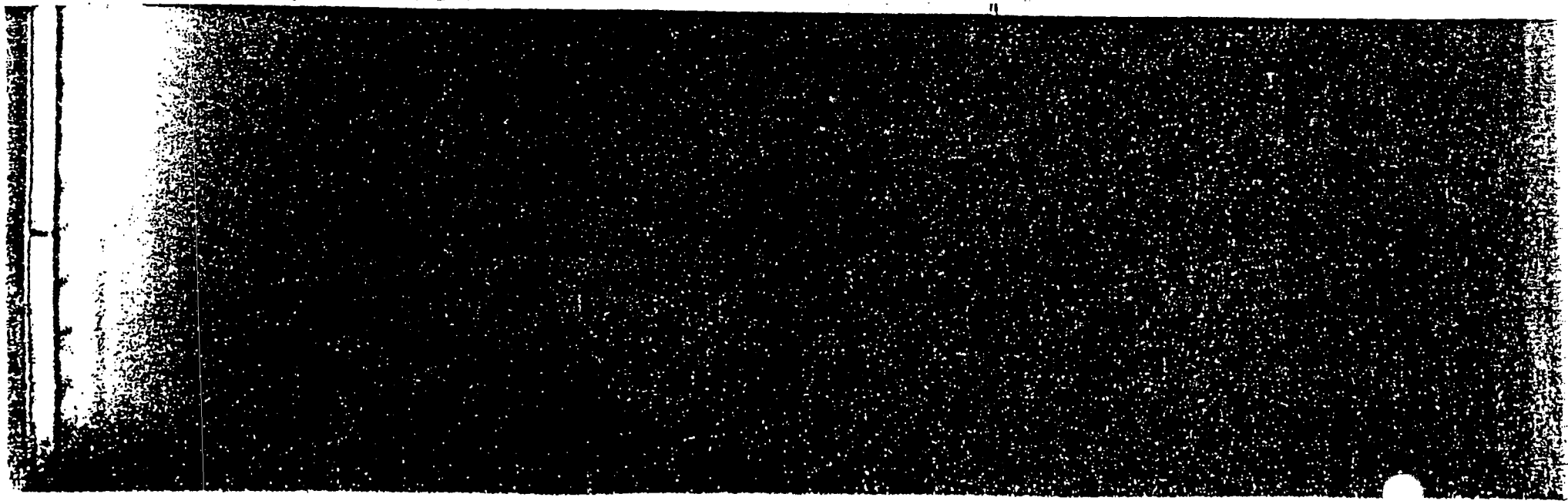
CAUTION

MAY CAUSE SKIN IRRITATION
Avoid Contact with Eyes, Skin and Clothing
Keep Out of the Reach of Children

NOTICE: Seller makes no warranty of any kind, express or implied, concerning the use of this product. Buyer assumes all risk of use or handling, whether in accordance with directions or not.

U S P [illegible]

30 and 55 gal. drums



DIRECTIONS

Kuron [illegible] is used in controlling certain woody and herbaceous plants growing on pasture [illegible] ditch banks, fence rows and right-of-ways.

Kuron is effective in controlling – post oak, blackjack oak, ground ivy, northern (pin, red, white, scrub) oak, mesquite, maples (such as red, sugar, and big leaf maple), poison ivy, sand shinnery oak, tucca, wild blackberry.

also certain broad leaved weeds such as – broomweed, cocklebur, croton weed, curly indigo, lamb's-quarters, Mexican weed, pokeberry, ragweed, salt cedar, sunflower.

NOTE: Do not use Kuron for the control of ash.

PREPARING THE SPRAY: Add half the required amount of water to the spray tank, then add Kuron with [illegible] Kuron forms an emulsion in water and tends to settle out on prolonged standing. Provide [illegible] to prevent such separation and ensure uniform mixture in the spray tank.

FOLIAGE TREATMENT: Spray woody growth up to 6 or 8 feet tall after the foliage is fully developed, [illegible] containing 3 to 4 quarts of Kuron per 100 gallons of water. With sensitive species, taller [illegible] can be controlled if foliage is adequately covered. On poison ivy and brambles such as [illegible] use 2 quarts of Kuron per 100 gallons of water. Spray should drench all plant parts including leaves and stems.

[illegible] spraying new sprouts from recently cut stumps until they have made appreciable growth. Under [illegible] conditions in humid areas, applications made up to three weeks before fall frost are [illegible] application in late summer and fall in Texas and Oklahoma is not recommended.) [illegible] after leaves have lost their normal green color and vigor may not give satisfactory control. Less [illegible] may result during hot, dry weather when deep soil moisture is deficient. Usually a single [illegible] is sufficient. If new growth develops, repeat applications may be necessary [illegible].

AERIAL APPLICATION: For control of post and blackjack oaks, use 2 quarts of Kuron in 1 gallon of [illegible] and 2 to 3½ gallons of water, or 2 quarts of Kuron in 3½ to 4½ gallons of diesel oil per acre. [illegible] foliage is fully developed (usually in May and June). An additional spray using 1 to 2 quarts [illegible] may be necessary the second or third year. These applications will effectively control broad [illegible] in the sand hill area.

SPOT TREATMENT: For basipetal application of Kuron, mix ½ cupful in 3 gallons of water. Wet all [illegible] of the [illegible].

AREA CONTROL IN LAWNS AND GOLF COURSES: For control of broad leaved plantain, hurrhorn, [illegible] prostrate knotweed, knotweed, dandelion, and legumes such as white clover and black [illegible] use 1½ quarts of Kuron in 25 to 40 gallons of water per acre. Higher volumes, [illegible] per acre, may be used to minimize drift hazard. Apply in fall or early spring as not [illegible] and may cause stunting or discoloration to turf. Do not apply to stoloniferous grasses such as bent, Bermuda and St. Augustine or to new turf of any variety.

CAUTION: Kuron is damaging to turf. Do not spray in any manner which will cause excessive drainage [illegible] and do not overspray when herbicide up, and at times. Avoid spraying when nozzles [illegible] are not spraying, such as when cleaning or testing nozzles. Use a positive quick shut off valve [illegible] to prevent.

AREA CONTROL IN RICE: From 6 to 8 weeks after emergence of the rice. Where flooded, wait between [illegible] weeks after seeding when plants have emerged above water and leaves are standing erect. Use [illegible] gallons of water in the amount of water needed for even distribution. For many situations, 2 pints per acre is adequate. Where weeds tend to be resistant because of species, age or growth condition, up [illegible] to 3 pints per acre may be used. Treatment after flooding is usually safer than before flooding. Consult [illegible] for proper control. Treatment or Extension Service for specific local recommendations.

FOR CONTROL OF TUCCA AND SAND SHINNERY OAK: Use 1 part to 1 quart of Kuron in 1 gallon of [illegible] and water to make 4 gallons total per acre. Two to three applications as necessary in successive

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years may be needed. Apply after foliage is fully developed. Consult your state weed control specialist for information on best rate and best time for application.

USE RECOMMENDATIONS IN SUGAR CANE

FLORIDA

For post emergence control of ragweed, dog fennel, ground cherry, purslane, wild lettuce, nightshade and other susceptible broadleaved weeds, apply 1 to 1½ quarts of KURON in 20 to 40 gallons of water per acre as broadcast spray. Make the 1st application after the cane emerges at spring growth and when weeds are growing vigorously, but before they send up seed stalks. A second application can be made for late emerging weeds. NOTE: Do not apply after the cane is 3 to 3½ feet tall.

LOUISIANA

PRE-EMERGENCE: For the control of crabgrass, barnyardgrass and Johnsongrass seedlings in sugar cane apply 1 quart of Kuron in 15 gallons of water per acre on the row (approximately one third of the total area) shortly before the seeds are expected to germinate. If cane is shaved and all borrow treated immediately following this operation. Follow the early treatment when necessary with 2 pounds of Dowpon grass killer per acre, applied over the grass in the row (approximately one third of the total area).

POSTEMERGENCE: To control wild lettuce, curled dock, morning glory, ragweed, cypressvine and other broadleaved weeds use one of the following procedures when the weeds are growing vigorously:

Ground Application: Use 1 quart of Kuron in 15 gallons of water per acre applied over the row (approximately one third of the total area). A second application can be made if needed.

Air Application: Use 2 to 3 pints of Kuron per acre in enough water for uniform coverage.

NOTE: Do not apply within 3 months of harvest to sugar cane to be processed for feed or seed. However, treatment can be made at any time to sugar cane to be used for planting purposes only.

HAWAII

For pre-emergence control of hairy crabgrass, yellow foxtail, richardsonia, burweed, pigeon grass, Florida's paintbrush, jungle rice, purslane and sweetgrass in Hawaiian sugar cane, apply 2 to 3 quarts Kuron per acre in 20 to 40 gallons of water as a broadcast spray immediately after planting or replanting and before cane emergence. For post emergence control of weeds after canes have emerged add 2½ to 5 pounds of Dowpon per acre to the spray of Kuron in order to control grasses and spray the intervening space without spraying the cane directly. This application can be made up to the time of closing of the rows but not less than 3 months before harvest. Do not make more than two applications of 3 quarts each of Kuron to any one crop.

Local conditions may affect the use of herbicides. State agricultural experiment stations or extension service weed specialists in many states issue recommendations to fit local conditions.

KURON FOR AQUATIC WEED CONTROL

SUBMERGENT AQUATIC WEEDS IN PONDS AND OTHER STILL WATER. To control some submergent weeds such as water milfoil, fan wort, bladderwort and waterweed, use 3 quarts of Kuron per acre foot of water. (An acre foot of water is one acre in area and one foot deep. That an area of water 5 feet deep will require 5 x 3 quarts of Kuron or 5.75 gallons.) Apply in early summer when water temperature is above 50°F. and weeds are approaching the water surface. To apply properly, first dilute the Kuron with enough water for uniform distribution over the water surface with the spray equipment at hand. Application may also be made with properly calibrated proportioning equipment which automatically mixes Kuron and pond water in the pump.

NOTE: Flowing water should not be treated with Kuron. Ponds with a slight current can be successfully treated if the water level can be lowered so there will be no over flow for at least 3 days after application. However, control will be less around spots where untreated water flows into the pond, by mixing shoreline

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years may be needed. Apply after foliage is fully developed. Consult experienced local authorities for information on best rate and best time for application.

USE RECOMMENDATIONS IN SUGAR CANE

FLORIDA

For post emergence control of ragweed, dog fennel, ground cherry, purslane, wild lettuce, nightshade and other susceptible broadleaved weeds, apply 1 to 1½ quarts of KURON in 20 to 40 gallons of water per acre as broadcast spray. Make the 1st application after the cane emerges as spring growth and when weeds are growing vigorously, but before they send up seed stalks. A second application can be made for tall emerging weeds. NOTE: Do not apply after the cane is 3 to 3½ feet tall.

LOUISIANA

PRE-EMERGENCE: For the control of crabgrass, barnyardgrass and Johnsongrass seedlings in sugar cane, apply 1 quart of Kuron in 15 gallons of water per acre on the row (approximately one-third of the total area) shortly before the seeds are expected to germinate. If cane is shaved and off barred, treat immediately following this operation. Follow the early treatment when necessary with 2 pounds of Dowpon® grass killer per acre, applied over the grass in the row (approximately one-third of the total area).

POSTEMERGENCE: To control wild lettuce, curled dock, morning glory, ivyvine, cypressvine and other broadleaved weeds use one of the following procedures when the weeds are growing vigorously.

Ground Application: Use 1 quart of Kuron in 15 gallons of water per acre applied over the row (approximately one third of the total area). A second application can be made if needed.

Air Application: Use 2 to 3 pints of Kuron per acre in enough water for uniform coverage.

NOTE: Do not apply within 5 months of harvest to sugar cane to be processed for food or feed. However, treatment can be made at any time to sugar cane to be used for planting purposes only.

HAWAII

For pre emergence control of hairy crabgrass, yellow foxtail, richardsonia, fireweed, slender amaranth, Florida pusleybrush, jungle rice, purslane and smutgrass in Hawaiian sugar cane, apply 4 to 5 quarts Kuron per acre in 20 to 40 gallons of water as a broadcast spray immediately after planting or ratooning and before cane emergence. For post emergence control of weeds after canes have emerged, add 2½ to 3 pounds of Dowpon per acre to the spray of Kuron in order to control grasses, and spray the interline space without spraying the cane directly. This application can be made up to the time of "closing in" but not less than 5 months before harvest. Do not make more than two applications of 5 quarts each of Kuron to any one crop.

Local conditions may affect the use of herbicides. State agricultural experiment stations or extension service weed specialists in many states issue recommendations to fit local conditions.

KURON FOR AQUATIC WEED CONTROL

SUBMERGENT AQUATIC WEEDS IN PONDS AND OTHER STILL WATER: To control certain submergent weeds such as water milfoil, Jan weed, bladderwort and waterweed, use 5 quarts of Kuron per acre foot of water. (An acre foot of water is one acre in area and one foot deep. Thus an acre of water 5 feet deep will require 5 x 5 quarts of Kuron or 6.25 gallons.) Apply in early summer when water temperature is above 50°F. and weeds are approaching the water surface. To apply properly, first dilute the Kuron with enough water for uniform distribution over the water surface with the spray equipment at hand. Application may also be made with properly calibrated proportioning equipment which automatically mixes Kuron and pond water in the pump.

NOTE: Flowing water should not be treated with Kuron. Ponds with a slight current can be successfully treated if the water level can be lowered so there will be no over-flow for at least 3 days after treatment. However, control will be less around spots where untreated water flows into the pond. In treating shoreline areas of lakes or larger ponds, have well the same distance covered by the water in the recommended center areas of the pond, therefore, it is best to treat an area at least 200 feet square.

EMERGENT AQUATIC WEEDS: To control certain emergent weeds such as cattail, water lily, spatterdock, pickerelweed, arrowhead, etc., use one gallon of Kuron in 100 gallons of water. Apply as a coarse spray to leaves and stems when leaves are fully developed above the water line, and plants are actively growing. Re treat as necessary.

SPECIAL PRECAUTIONS FOR USE IN AQUATIC WEED CONTROL: Apply only in accordance with state and local laws and regulations governing chemical treatment of bodies of water for control of weeds. To avoid injury, do not use Kuron where pond water is being used for irrigation (including sod production) for agricultural sprays, domestic water supply, or for livestock watering. When used as recommended above Kuron is not ordinarily harmful to aquatic animals, but some fish kill may occur, especially in shallow areas where uniform application is difficult. Apply Kuron when water level is low, so as to keep at a minimum the exposure of desirable vegetation along the shoreline.

Since they may cause interference with the action of Kuron, do not apply algicides such as copper sulfate for 3 days before or after applying Kuron.

Note: Treat pond edges or lake shoreline first so fish will not be trapped in shallow pockets or coves.

WARNING

Do not apply Kuron directly to or otherwise permit it to come into contact with any crop plant or plant part (including but not limited to peanuts, soybeans, beans, peas, tomatoes, tobacco, cotton, cucumbers, sweet potatoes, peppers, celery, flowers, ornamentals, grapes, deciduous and non-deciduous trees) and do not permit spray mists containing Kuron to drift onto them. Even minute quantities may cause severe damage during both growing and dormant periods. Coarse sprays are less likely to drift. Applications by airplane, ground rigs and hand dispensers should be carried out only when there is no hazard from drift. Do not apply by airplane in the vicinity of any desirable crops or ornamentals including those listed above. At elevated temperatures vaporization may cause injury to susceptible plants growing nearby.

Do not use Kuron on freshly seeded lawns, pasture or range lands until grass has become well established. Do not contaminate irrigation ditches or water used for domestic purposes. Do not store near food, feed, seeds, insecticides or fungicides. To avoid injury to desirable plants, do not store, handle or apply other agricultural chemicals with the same containers or equipment used for Kuron. Do not use Kuron in spraying equipment contaminated with 2,4-D if the 2,4-D will increase the hazard to desirable plants.

Be sure that use of this product conforms to all applicable regulations.

CAUTION

MAY CAUSE SKIN IRRITATION
Avoid Contact with Eyes, Skin and Clothing
Keep Out of The Reach of Children

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

12107-010 2

U.S. Patent No. 3,748,360

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U.S. DEPARTMENT OF AGRICULTURE
AGRICULTURAL RESEARCH SERVICE
PESTICIDES REGULATION DIVISION
WASHINGTON, D.C. 20250

FORM APPROVED
BUDGET BUREAU NO. 40-R1746

APPLICATION FOR AMENDED REGISTRATION OF ECONOMIC POISONS

(Under the Federal Insecticide, Fungicide, and Rodenticide Act)

1. DATE OF APPLICATION: October 17, 1973

IMPORTANT: READ INSTRUCTIONS ON REVERSE

2. NAME OF ECONOMIC POISON *(Must be same product name as on label—do not list active ingredients)*

KURON®

3. NAME & MAILING ADDRESS OF REGISTRANT *(Include Zip Code)*

Dow Chemical U.S.A.
P. O. Box 1706
Midland, Michigan 48640

Attn: Fred Hoerger

4. REGISTRATION NO.: 464-162

5. PROPOSED EFFECTIVE DATE OF CHANGE: As soon as possible.

DOW MN 0227 289300

6. NATURE OF REVISION *(Check applicable item and give details in item 7, when required)*

- ☐ GENERAL REVISION OF LABELING
- ☐ CHANGE IN FORMULATION *(Give description of exact change in item 7)*
- ☒ OTHER *(Specify in item 7)*
- ☐ ADDITIONAL USES ADDED TO LABELING *(List new recommendations in item 7)*
- ☐ CHANGE IN PRODUCT NAME *(Give old name and new name in item 7)*

7. DETAILS REQUIRED BY REVISION CHECKED IN ITEM 6 *(Attach additional sheets if more space is needed)*

For a number of years, Louisiana has recommended the use of KURON [2-(2,4,5-trichlorophenoxy) propionic acid propylene glycol butyl ether esters] herbicide in combination with dalapon, sodium TCA, and 2,4-D for control of a variety of weeds in sugarcane. Each of the herbicides is currently registered for use on sugarcaneein Louisiana, but the current labels do not bear specific directions for the combination treatments as recommended by Louisiana.

This application therefore consists of a supplemental labeling brochure to cover the combination treatments. The brochure is intended to augment the individual product labels and pepresent too much printed material to include on each product package label.

Based on state recommendations, the combination treatments have been used commercially for a number of years. We believe that Federal registration would bring these practices within the intent of the Federal Environmental Pesticide Control Act of 1972.

The attached volume "Technical Information on Tank Mixtures of Dow Herbicides for Louisiana Sugarcane" provides data supporting the practices. It also seems noteworthy that commercial field experience has been extensive with satisfactory weed control and no indication of adverse problems.

☐ CONTINUED ON ATTACHMENT

8. THE FOLLOWING MUST BE SUBMITTED WITH THIS APPLICATION

- Five (5) copies of revised labeling, including any printed or graphic matter which may accompany the sale of this product. Copies must be clearly legible and identical. Attached
- If a change in formulation is involved, five (5) copies of a statement of revised formula showing the precise name and percentage of each active and each inert ingredient. *(This information is treated confidentially)*
- When appropriate, three (3) copies of Supporting Data. Attached

IN ANY CORRESPONDENCE ON THIS PRODUCT REFER TO REGISTRATION NO. IN ITEM 4, ABOVE.

16819

9. SIGNATURE OF AUTHORIZED FIRM REPRESENTATIVE

TITLE: Sr. Registration Specialist

11. DATE SIGNED: October 17, 1973

PR FORM 9-198
MAY 1969

EXISTING STOCK OF PR FORM 9-198 (AUG. 1968) WILL BE USED UNTIL EXHAUSTED

APPLICANT'S COPY

'EXHIBIT C' CONTINUED
KURON REGISTRATION FILE

DOW 0289000A

'EXHIBIT D'
KURON LABELS

VOL 4

'EXHIBIT E'
KURON COMPLAINTS

16820

EXHIBIT C

(CONTINUED)

Dow 02896008

:URON registration file including communications with USDA and EPA 1963 - 1974.

20. Application of July 17, 1970

21. Application of November 10, 1964

22. Application of May 15, 1963

23. Application of October 17, 1973

24. Label of September 19, 1966 and Application of July 12, 1966

25. Label of November 24, 1965

26. December 1964 revisions - Florida Sugarcane

27. Revisions of early 1964

28. Getzendaner, RESIDUES OF SILVEX AND SILVEX ESTER IN SUGAR CANE RESULTING FROM AERIAL APPLICATIONS OF KURON

29. DETERMINATION OF TRACE AMOUNTS OF 2,4,5-TP AND THE PROPYLENE CLYCOL ISOBUTYL ETHER ESTERS OF 2,4,5-TP IN SUGAR CANE PULP (April 9, 1963)

30. A RESIDUE STUDY OF KURON IN SUGAR CANE

31. DETERMINATION OF TRACE AMOUNTS OF 2-(2,4,5-T)-PROPIONIC ACID OF THE PROPYLENE CLYCOL BUTYL ETHER ESTERS OF 2-(2,4,5-T)- PROPIONIC ACID IN SUGARCANE PULP (Sept. 24, 1959)

32. DETERMINATION OF TRACE AMOUNTS OF PROPYLENE CLYCOL BUTYL ETHER ESTERS OF 2-(2,4,5-T) PROPIONIC ACID IN SUGAR CANE JUICE (August 13, 1959)

33. KURON USE RECOMMENDATIONS IN SUGAR CANE

34. COMPARISON OF SILVEX AND DCMU WITH OTHER COMMONLY-USED HERBICIDES FOR PRE-EMERGENCE WEED CONTROL

35. COMPARISON OF SIMAZIN AND OTHER NEWER HERBICIDES FOR PRE-EMERGENCE WEED CONTROL

36 RECOMMENDATIONS FOR JOHNSON GRASS SEEDLING AND JOHNSON GRASS CONTROL IN SUGARCANE by Ernest R. Stamper and S. J. P. Chilton

37. REPORT OF THE DEPARTMENT OF PLANT PATHOLOGY TO THE AMERICAN SUGARCANE LEAGUE FOR 1958

Dow 0289300 C

38. EXHIBIT D

DOW02896300D

KURON specimen labels dated:

May 20, 1974
January 21, 1974
November 16, 1971
January 12, 1971
October 3, 1969
May 29, 1969
August 1967
June 1967
August 1966

39. Miscellaneous labels

40. EXHIBIT E

Dow 02853003 E

KURON Complaints:

1. E. L. Hand - Lake Jackson, Texas
2. John Norton - Glendale, Arizona

TAYLOR V. DOW

EXHIBIT C

KURON registration file including communications with USDA and EPA 1963 - 1974.

DOW 289218
MN 022777

2307

To E Blair
R+D
2020 Bldg

DOW 1664267

MN0027509

AGRICULTURAL PRODUCTS
DEPARTMENT - 9001
Midland, Michigan 48640

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517-636-4826

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ECOTOXICOLOGY AND ENVIRONMENTAL SAFETY 4, 96–102 (1980)

DOW 1664268

PANEL REPORT

Panel to Discuss the Epidemiology of 2,4,5-T New York City, July 10–11, 1979

Chairman: DR. FREDERICK COULSTON
Rapporteur: DR. EUGENE J. OLAJOS

Received October 19, 1979

MEMBERS

DR. R. COOK, Epidemiologist, Dow Chemical U.S.A., Midland, Michigan.
DR. F. COULSTON, Professor and Director, Institute of Comparative and Human Toxicology, Albany Medical College, Albany, New York (Chairman).
DR. F. DECKER, Associate Professor, Atmospheric Sciences, Oregon State University, Corvallis, Oregon.
DR. P. J. GEHRING, Director, Toxicology Research Laboratories, Dow Chemical U.S.A., Midland, Michigan.
DR. E. C. HAMMOND, Vice President, Epidemiology and Statistics, American Cancer Society, New York, New York.
DR. R. HARBISON, Associate Professor of Pharmacology and Biochemistry, Division of Pediatric Clinical Pharmacology, Vanderbilt Medical Center, Nashville, Tennessee.
MS. M. HATCH, Division of Epidemiology, School of Public Health, Columbia University, New York, New York.
DR. J. KLINE, Research Associate, Gertrude Sergievsky Center, Columbia University, New York, New York; and Research Scientist III, New York State Psychiatric Institute.
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MR. L. MARK WINE, Kirkland & Ellis, Washington, D.C.

1. INTRODUCTION

This report contains the collective views of a group of experts who participated in a Panel Meeting to "Discuss the Epidemiology of 2,4,5-T," held in New York City on July 10 and 11. The purpose of this meeting was to discuss the epidemiologic

[1] In attendance on Day 2 only.

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methodology and data used by the Environmental Protection Agency in its recent action suspending the use of 2,4,5-T because of the possibility that spontaneous abortion rates increased in the Alsea basin area of Oregon. Dr. Coulston, in his opening comments, stated:

> The EPA is to be commended for its desire to insure the health of the public by removing any possible environmental hazard. The position of this meeting should not be forgotten. We are here not to judge whether 2,4,5-T is safe for use around man. Dr. Barbara Blum, Deputy Administrator of the EPA, in the document of March 1, 1979 presented a number of interesting points; namely, that there was a problem, that according to information the EPA has received that there was an increased incidence of spontaneous abortions in a certain area of Oregon. Dr. Blum emphasized very carefully and I quote "We are not saying that the health effects in humans are positively proven, or that 2,4,5-T should never be used again. What we are saying is that there is sufficient evidence to stop further exposure to the chemical until the issues can be resolved." What was the evidence EPA used? Was this good evidence in the sense that it follows good scientific, epidemiologic procedures? Had the EPA acted too quickly?

The Panel considered the following points: (1) Whether the Control and Study areas were indeed comparable? (2) What was the true spontaneous abortion index? (3) What was the actual individual exposure and what other contaminants may have been present in the Study area? (4) Was the analysis of the data a correlative one and if so, does this relate to causation? (5) What kind of definitive study should be done to settle this controversial problem, namely, did 2,4,5-T indeed increase the spontaneous abortion rates?

Available to the Panel were all pertinent reports from the United States as well as foreign countries on the subject of 2,4,5-T and spontaneous abortions. Most of the discussion related to Alsea I and II, but other documents were also considered in light of the experience of other epidemiologists and scientists from different geographic areas. The documents are listed in Appendix I.

2. SUMMARY OF FINDINGS

2.1. Alsea I Report

The Alsea I report was based on an extensive health questionnaire administered to nine women who had experienced 13 early spontaneous abortions in the Alsea, Oregon, area from May 1973 to March 1978.

In general, the study design was adequate; however, several flaws characterize the study: (1) A major flaw in the study was the failure to define the array of miscarriages that were distributed among the women reporting spontaneous abortions. Therefore, the possibility exists that at least a number of these miscarriages were experienced by miscarriage-prone women. (2) There was no attempt to identify specific causes for any of the miscarriages; for example, exposure to other pollutants and contaminants, advanced maternal age, prior history of abortion, heavy smoking, alcohol use, and chromosomal or morphologic abnormality in the embryo or fetus. (3) There was no documentation of exposure to 2,4,5-T.

2.2. Alsea II Report

The Alsea II report was a follow-up to the Alsea I study where it was noted that 12 of the 13 miscarriages reported by the original nine participants were for terms

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under 20 weeks. In the Alsea II report, the investigators compiled the rates of hospitalized early spontaneous abortions (less than 20 weeks term) in three areas of Oregon: (1) a Study area, which centered around the Alsea basin including additional contiguous areas; (2) a nearby Urban area (Corvallis); and (3) a Control area, a distant inland rural region located in eastern Oregon.

Although the objectives of the Alsea II study were valid, the study was poorly conceived and designed. Indeed, even taking into account the aspects of confidentiality and public pressure, the study design was still inherently very weak. Numerous shortcomings, invalidities, and biases characterize the Alsea II study. A number of the most apparent deficiencies are described below.

2.2.1. Collection of Data and Data Input

a. Only *hospitalized* spontaneous abortions were reviewed with no consideration of clinic data. This resulted in a significant bias when one compares the Urban area with the Study and Control areas. Spontaneous abortions were treated in hospitals in the Study and Control areas, whereas in the Urban area they were treated in hospitals and in clinics. The lack of data for abortions treated in the clinics in the Urban area seems to account for the notable difference in the overall spontaneous abortion rates among Study, Control, and Urban areas.

b. The investigators of the Alsea II study examined the rates of spontaneous abortions in a Study area and compared those rates in a *comparable* Control area. In no manner are the Control and Study areas comparable; the Alsea II investigators had not determined whether real differences existed in demographic and geographic characteristics that could affect the rate and seasonal pattern of spontaneous abortions. The two areas are not compatible with regard to socioeconomic and population parameters such as: (1) life-styles; (2) employment practices; (3) ethnic and racial makeup; (4) health care delivery systems; (5) medical practices; (6) environmental pollutants and infectious agents; and (7) additional background factors within the two populations. The demographic characteristics including occupation and ethnic composition may influence the use of medical services between the Study and Control areas, particularly, if related to season, may produce spurious results. More importantly, the Alsea II study had *not* analyzed the comparability of the Study and Control areas with respect to variables known to be associated with spontaneous abortion, namely, maternal age, cigarette smoking, and alcohol usage.

c. The Alsea II investigators intended to compare only those abortions occurring within the endogenous populations of the Control, Study, and Urban areas. The abortion and/or birth rates may have been significantly altered by the inclusion of abortions of seasonal residents in the Study area, which may experience an influx of population during the summer. The summer transients within the Study area coupled with the exodus of people from the Urban area would maximize the difference in the abortion rate that occurs during the summer months.

d. The documented spray areas represented only a small proportion of the Study area, which in turn was defined by zip code. The question which immediately comes to mind is where in the area did the people live in relation to the 2,4,5-T-sprayed areas? Furthermore, the unjustifiability in using zip codes is also apparent when one considers the possibility that a summer transient hospitalized for an abortion in the

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Study area could have given her summer address at the time of hospitalization, and perhaps be classified as a resident of the area. Only those women who were living in the area at the time of spraying could have provided the necessary data base relatively free of variables.

e. The Alsea II authors used two types of variables: the effect measure (hospitalized early spontaneous abortions/live births) and exposure data (acres or pounds of 2,4,5-T). As they stated in their report:

> Thus, the data from the Alsea basin illustrate a pattern which may be considered as representative of the Study area.

The above quote refers to the spray data and represents their justification for extrapolating the pattern of exposure from sampling 2,4,5-T usage in the Alsea basin to the entire Study area. The investigators of the Alsea II study have correlated exposure in a small area with outcomes in a larger area, and it is essential that they discuss how representative the Alsea basin spray data is of the use patterns in the entire Study area. One may question if the amount of 2,4,5-T acreage, and timing of the sprayings are similar; therefore one must know exactly to what extent they may differ.

f. There was no attempt by the Alsea II investigators to estimate variability.

2.2.2. Ascertaining Reproductive Effects

a. The overall incidence of spontaneous abortions as reported in the Alsea II study was as follows: (a) Study area (8.1%); (b) Control area (6.5%); and (c) Urban area (4.4%, unusually low). In a general discussion pertaining to the spontaneous abortion rate, it had been stated:

> We have estimates of the rate of spontaneous abortion (all recognized spontaneous abortions). Take the one good prospective study in Hawaii: maybe estimate that 1/4 of the pregnancies diagnosed after 4 weeks from the last period will abort. The highest we would estimate is that 1/4 of the pregnancies that you know exist at 2 weeks post-conception would abort. People estimate all the way up to 90%, but we think a sensible estimate would be that 1/4 of all recognized pregnancies will abort.

It was the consensus of the panel that the hospitalized abortion rates reported in the Alsea II study were low. Estimates of *hospitalized* spontaneous abortion rates in the United States generally range from about 8 to 15%. It is not known whether this range reflects real differences between populations in the rate of spontaneous abortion or whether it reflects differences in patterns of service use. Estimates of the rate of spontaneous abortion from obstetric histories are usually somewhat higher, ranging from about 12 to 18%. The hospitalized abortion rates reported in the Alsea II study are on the low end of the spectrum when compared to other hospital-based studies. Since spontaneous abortion indicates a strong association with maternal age, evaluation of these rates should consider the maternal age distributions of the populations as well as the possibility of differences in service use as an explanation for the somewhat low rates.

b. The study was not based on a cohort of women all conceiving at the same time. The importance in examining the outcomes in a cohort of women conceiving at the same time is that for reproductive health effects (as opposed to other types of

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effects) the timing of exposure is critical: for example, with radiation the conceptus is sensitive to particular outcomes at some stages of gestation and not at others.

c. The gestational age was determined by the date of abortion and in some cases was not well defined. One must distinguish a preconception from a postconception effect, the miscarriage must be analyzed by date of conception or last menstrual period, and not just by date of abortion. The manner in which gestation was estimated *varied* tremendously from hospital to hospital; therefore, the possibility exists that women may *not* have conceived at the time of purported exposure to 2,4,5-T.

d. The extracted hospitalized spontaneous abortions (HSA) were not identified with individual women; therefore, a small number of chronic aborters in the area could have significantly biased the results.

e. The live birth data base was collected in a differential fashion between Control, Study, and Urban areas.

f. A serious bias was introduced in the computed hospitalized abortion indices (HSAI: HSAI = spontaneous abortion data/weighted live birth data). The weighted live births were derived from gestational ages aggregated over the entire 6 years, these weights were somewhat unrelated to the gestational ages of the monthly spontaneous abortions found in the numerator. The weighted aggregate method would potentially smooth out the denominator data which would make the index more dramatic in monthly peaks. A more serious error is noted in the weighted live birth data (denominator). The authors of the Alsea II report stated, and we quote "The computed monthly births for the six-year interval were divided equally between the two periods." This assumes that the births were relatively stable for all areas over the entire 6 years. The raw data provided by the EPA subsequent to the emergency ban clearly indicate that the above assumption was not valid. The births rise slightly in the Control area during the last 3 years, but more dramatically in the Study area. The equal division of births produces an artificial rise in the HSAI of the Study area for the second period.

2.2.3. *Documentation of Exposure and Exposure Levels*

The EPA assumed a dose–response effect in the *absence* of validating exposure. The failure to examine the data with respect to exposure is unfortunate since it is absolutely critical in demonstrating that 2,4,5-T or *any* other compound was associated with or had caused an increase in the spontaneous abortion rates. Normally, one tries to establish the use pattern, occurrence, and the levels of whatever chemical agent is being examined in order to determine a correlation with a biological event. It is very disturbing that the authors of the Alsea II Study had not:

a. provided data on human and animal exposure to 2,4,5-T as well as providing an estimate of the levels of 2,4,5-T in the aborted products of conception (no attempt was made to determine the individual exposure or to ascertain whether any other contaminant(s) was present in the Study area);

b. attempted to identify an independent source of data existent, so one could cross-check exposures;

c. concentrated on the time relations of the raw number of abortions in the Study area (the time exposure is absolutely critical, the data had not been examined in the above manner).

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3. CONCLUSIONS

After reviewing all the documents and the data presented, including the Alsea I and II reports, the Panel expressed the following conclusions:

a. The new evidence (Alsea II) did not demonstrate an effect or the absence of an effect. Neither cause nor even association of the use of 2,4,5-T to the incidence of spontaneous abortion had been demonstrated.

b. There was no evidence to establish a causal relationship between 2,4,5-T exposure and spontaneous abortion.

c. There were no data of individual exposure to 2,4,5-T or to any other contaminant or pollutant in the Study area.

d. With respect to 2,4,5-T exposure and spontaneous abortions, the majority concensus of other panels and expert reviewers of the Alsea II study was that no relationship exists.

e. The overall spontaneous abortion rates reported in the Alsea I and II documents (8 to 14%) are well within the background spontaneous abortion rate of the general population.

f. The Study and Control areas of Alsea II study were too diverse to be considered comparable. The abortion data for the Urban area cannot be properly compared to the abortion data for the Control and Study areas. In fact, the data base obtained from the Urban area should be dismissed completely.

g. Only those women living in the area at the time of the spraying of 2,4,5-T should have been used for the data base in the Study area (Alsea II study).

h. The Panel could not draw valid conclusions from the cluster of 13 cases in the Alsea I study because the data base was derived from a very limited sample size.

4. RECOMMENDATIONS

a. Both the Alsea I and II studies could be made more informative by reanalysis of the data and additional data. Pivotal to such a reanalysis would be the utilization of established cohorts, the uniform definition of gestation age, and the collection of complete spray data. However, even with such improvements a crucial problem would still exist; namely, that the population in the area is too sensitized in connection with collecting additional information.

b. A comparison study in another area where 2,4,5-T is known to be used is essential.

c. To settle the controversial problem as to whether 2,4,5-T is responsible for spontaneous abortions, and following definitive study is recommended by the Panel:

One would design a prospective, long-term, dose–response epidemiological study with a clear understanding of the problem, appropriate modeling, and accessibility and control over the data. A study that goes beyond the level of an ecological study which permits hypotheses to be tested on an individual basis. The study would consist of a sufficiently large cohort of women of reproductive age, with a record of reproductive experience on every single woman in the defined cohort, utilizing reltively simple endpoints to determine reproductive effects. Also, the incorporation of reproductive history by interview of the population in the Study and Control areas that is solid, complete, and unbiased. The reproductive history is the truest estimate of pregnancy history that can provide information over and

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above that which comes to medical attention. One would also establish gestational age based on a uniform definition of gestation, establish a baseline level of abortion rate, and acquire a control population that is virtually the same without exposure. Finally, definition of the exposure areas must be established using reliable measures of dosages and exposure. Validation of exposures to 2,4,5-T must be done through blood, urine, fat tissue analyses of the human and animal populations as well as tissue analyses of abortices.

APPENDIX I:
DOCUMENTS AVAILABLE FOR REVIEW OF 2,4,5-T DATA

1. *Emergency Action to Stop Spraying of the Herbicides 2,4,5-T and Silvex*, Press Conference Statement by EPA Deputy Administrator Barbara Blum, EPA, Washington D.C.
2. *Forest Spray Miscarriage Investigations, Alsea, Oregon: Questionnaire Evaluation and Study Plan (Alsea I)*, EPA, Washington, D.C.
3. *Report of Assessment of a Field Investigation of Six-Year Spontaneous Abortion Rates in Three Oregon Areas in Relation to Forest, 2,4,5-T Spray Pesticides (Alsea II)*, EPA, Washington, D.C.
4. *Critique of "Report of Assessment of a Field Investigation of Six-Year Spontaneous Abortion Rates in Three Oregon Areas in Relation to Forest 2,4,5-T Spray Practices."* Epidemiological Studies Program, Human Health-Effects Monitoring Brands, Benefits and Field Studies Division OPD, OTS, EPA.
5. *Analysis of EPA Decision to Declare an Emergency Suspension of 2,4,5-T as Related to Studies in Animals*, Dow Chemical Co., Midland, Mich.
6. *Australian Communique*, Press Statement by the Minister of Health, Canberra, Australia.
7. *Foster Letter*, Office of Disease Monitoring and Control, Department of Human Resources, Health Division, Portland, Ore.
8. *Niswander Review*, EPA, Washington, D.C.
9. *Stenchever Review*, EPA, Wahsington, D.C.
10. *Darney Review*, EPA, Washington, D.C.
11. *Downs Review*, EPA, Washington, D.C.
12. *Labarthe Review*, EPA, Washington, D.C.
13. *Mantel Review*, EPA, Washington, D.C.
14. *Battelle Review*, EPA, Washington, D.C.
15. *Hale Review*, EPA, Washington, D.C.
16. *Raw Data Provided by EPA on 14 March 1979, Live Births*, EPA, Washington, D.C.
17. *Cook Reviews (5) with Printouts of Spontaneous Abortion Data as Provided by EPA on 14 March 1979*, Dow Chemical Co., Midland, Mich.
18. *Amended Live Birth Data Provided by EPA Witness (Duncan) on Last Day of Emergency Suspension Hearing—9 April 1979*, EPA, Washington, D.C.
19. *Cook Review of Amended Live Birth Data*, Dow Chemical Co., Midland, Mich.

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...NDUCTED ON 2,3,7,8-TETRA-
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CHLORACNE STUDY CONDUCTED ON HEXACHLORODI-BENZO-p-DIOXIN

FILE BC T36.25-84763-3
K/NO. K84763
CHG. 01212-000-029
REF. FDA-F911
SOURCE AEPohland
SUB. BY OAniline
REP'T. BY JMNorris
CHECKED BY PJGehring
DATE 12/11/70

LAB CODE LETTERS AND REPORT NO. BC T36.25-84763-3

INFORMATIVE SUMMARY WITH CONCLUSIONS BASED ON THE SAMPLE RECEIVED. ADDITIONAL INFORMATION INCLUDING THE EFFECTS OF REPEATED EXPOSURE MAY BE REQUIRED AS SPECIFIC USES AND FORMULATIONS ARE DEVELOPED OR IF PROCESS CHANGES OCCUR.

A sample of hexachlorodibenzo-p-dioxin (95% pure) was received from A. E. Pohland of the FDA and submitted to the Biochemical Research Laboratory for evaluation as a chloracnegen.

Two 0.005% solutions of the test material, one in dimethoxyethane and the other in chloroform, were prepared. Each solution was applied to the inner surface of 3 rabbit ears, 5 days per week for 4 weeks at a dose of 0.1 ml/day. Both test solutions produced chloracne responses. All skin contact with the test material should be avoided.

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March 21, 1979

STATE DEPARTMENT OF AGRICULTURE

SUPPLEMENTAL LABELING 2,4,5-T AND SILVEX PRODUCTS

The enclosed stickers are being used on DOW products that are the subject of the Emergency Suspension Orders by The Environmental Protection Agency on 2,4,5-T and Silvex. The Agency has chosen to handle this as a compliance program independent of the individual registration actions so our communication with you is to allow your files to reflect the most current labeling for these products. It is our intent that the products listed below be moved in your State with these stickers applied.

ESTERON® Brush Killer	ESTERON 245 Herbicide
VEON® 245 Weed and Brush Killer	VERTON® 2T Herbicide
KURON® Brush and Weed Killer	

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WN 053305

Since only part of the registered uses have been suspended, the use of these stickers on containers with non-suspended uses is intended to clarify the status of the remaining accepted uses for these products while the Emergency Suspension Order is in effect. This procedure has been reviewed by the Agency, is consistent with their programs, and is being implemented for compliance purposes by making stickers available to dealers who own stocks of these products and placing stickers on DOW owned stocks prior to shipment.

You are undoubtedly aware that several additional legal actions are underway regarding this Order and the implementation of this program for compliance purposes is not to indicate that The Dow Chemical Company has waived any rights or recourse to challenge this action on the part of the Administrator. It is likely that legal actions will again alter this subject in the near future.

This program would also apply to 2,4,5-T products registered to deplete stocks in your State. If you have any questions in this matter, please do not hesitate to contact me.

Sincerely yours,

A. T. Talcott

A. T. Talcott, Manager
Product Safety Compliance
Quality Assurance

jh
Enclosures: 2,4,5-T and Silvex Stickers
EPA Compliance Policy

LIFE IS FRAGILE HANDLE WITH CARE

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NOTICE

The following uses for products containing 2,4,5-T have been suspended by the United States Environmental Protection Agency.

All uses in forests, right-of-ways and pastures.

Do not apply this product on any of the areas listed above.

THE DOW CHEMICAL COMPANY, MIDLAND, MI 48640

DOW 362652

NOTICE

The following uses for products containing Silvex have been suspended by the United States Environmental Protection Agency.

1. **All uses around the home and recreation areas.**
2. **All uses in forests, right-of-ways and pastures.**
3. **All aquatic uses.**

Do not apply this product on any of the areas listed above.

THE DOW CHEMICAL COMPANY, MIDLAND, MI 48640

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Los Angeles Times Tues., June 24, 1980—Part I 3

DUW0088871

State Warning on 2,4-D Herbicide Exposure Issued

By RONALD B. TAYLOR
Times Staff Writer

In the first hazard alert of its kind, the state Department of Health Services is warning the public today that exposure to the herbicide 2,4-D may cause lasting nerve damage, as well as cancer or birth defects.

The unusual warning, based on expert examination of seven persons who suffered nerve damage, is expected to set off another controversy over the continued use of such phenoxy herbicides.

Dr. Marc Lappe, chief of the Health Services Department's hazard alert system, said six of the people were exposed while working as pesticide applicators, the seventh was a woman who knelt down in her garden on soil soaked with herbicide.

Two weeks after exposure, the seven people reportedly developed tingling or numbness in their toes and fingers, followed by weakness of their arms and legs. Some suffered "virtually complete arm and leg paralysis," Lappe said.

Herbicides like 2,4-D and the now banned 2,4,5-T have been widely used in forests, on farms and along public rights of way to kill weeds, brush and unwanted trees. In combination, these herbicides were called Agent Orange and were used to denude the jungles of Southeast Asia during the Vietnam war.

Along California's north coast, in

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HERBICIDE ALERT

Continued from Third Page

the timber country of Oregon and the rangelands of Montana, groups of concerned citizens and doctors contend, 2,4-D is causing birth defects and miscarriages among women who have been exposed to pesticide sprays.

Lappe said the hazard alert report is being sent out to workers and doctors in an effort to warn them that 2,4-D has caused cancers and birth defects in laboratory animals and nerve damage in humans.

According to Lappe, "Current work practices (in the forests and on farms) are inadequate to protect against potential neurotoxicity."

Lappe said that while officially the hazard alert system was established to warn workers of health problems, he was also concerned about home gardeners because one of the seven victims had been exposed to the herbicide in her garden.

Lappe explained the state was issuing the unusual warning because the Environmental Protection Agency had failed to act.

He told The Times, "There is a policy vacuum in EPA, an absence of leadership. So we had to move on this."

However, EPA officials told The Times the previous toxicology data was inconclusive, that it neither proved nor disproved anything and the chemical companies were being asked to do new studies. Such studies could take from one to three years to complete.

The timber harvesting companies, backed by the U.S. Forest Service, argue that the use of phenoxy herbicides are critically needed if timber harvests are to be sustained. They contend 2,4-D is a relatively mild pesticide and that there is no proof it is harmful to humans when used properly.

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Foreward.

The phenoxy herbicides, including 2,4-D, have received considerable attention during the last decade in the press, in public hearings and by groups which have campaigned against the continued use of these herbicides for controlling unwanted vegetation in forests, on rights-of-way and on certain croplands. The groups against the continued use of herbicides have spent considerable time and effort preparing literature, press releases, mailings and in participation at public hearings.

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The primary message of these groups is that the use of phenoxy herbicides will increase birth defects and cause miscarriages, cancer or other physical effects. Various scientific studies as well as articles from the press are used to support their allegations. Very frequently only those portions of the data in a given study which support the allegation are cited.

The reliance upon data from studies conducted in animals to estimate the effects in humans has also been debated. However, animals are the only species phylogenetically close to humans which can be used for testing. Therefore, it is necessary to correlate data from animal studies with the potential for human exposure under worst case conditions and define a safety factor.

In most studies on living organisms the data are neither completely positive nor completely negative but require the expertise of knowledgeable scientists for interpretation.

Herein, data and conclusions are submitted which are intended to present an unbiased review of the toxicological studies on 2,4-D which have been conducted to date.

1. What is 2,4-D?

2,4-D (2,4-dichlorophenoxyacetic acid) is an herbicide which selectively controls many broadleaf weeds, certain hardwood trees and brush on crop and rangelands, rights-of-way, and on turf and lawns. 2,4-D was first introduced in the U.S. for use by farmers in 1946 (Peterson, 1967). It performs its control function by altering the normal growth of susceptible weeds and woody plants. The major use of 2,4-D is controlling broadleaf weeds in cereal grains. It does not kill most grasses.

2,4-D is usually applied at the rate of ¼ to ½ pound active ingredient per acre for cereal grains. Higher rates are often used on rights-of way. 2,4-D is usually formulated as amine salts or esters.

2. How toxic is 2,4-D to animals?

2,4-D is moderately toxic to mammals. The three routes of possible human exposure are: ingestion, dermal contact and inhalation. The single dose oral LD50 (dose determined to be lethal to 50% of the treated species) for 2,4-D acid is greater than 350 mg/kg of body weight in rats, mice, guinea pigs and chickens (NRCC, 1978). In these same species the acute oral LD50 for various formulations of 2,4-D salts and esters ranges from 75 to 2000 mg/kg (Weed Science Society of America, 1979) (IRAC, 1977).

In a case of a suicide by a 23 year old student, the total amount of 2,4-D in the body was estimated to correspond to a dose of 80 mg/kg. (Nielson et al., 1965) No adverse effects were reported in a man who took 500 mg 2,4-D orally daily for 2 weeks (approximately 8 mg/kg/day) (IARC, 1977). When 2,4-D was used as a treatment in a patient with

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terminal stages of disseminated coccidiomycosis, no side effects were observed following 18 intravenous doses of 15-37 mg/kg of body weight over 33 days (Seabury, 1963 in IARC, 1977).

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Dermal exposure is perhaps the most frequent route by which man becomes exposed to 2,4-D. Kay et al. (1965) studied the effects of repeated skin application of the dimethylamine salt, isooctyl ester and the butyl ester of 2,4-D on intact and abraded rabbit abdominal skin. Skin application of test materials, prepared as dilutions in water or oil or both, was made 7 hours per day, five days per week for three weeks with no significant systemic effects noted.

Skin absorption studies were conducted on the shaved skin of albino rabbits. The butyl ester and the diethanolamine salt of 2,4-D were not absorbed in toxic amounts up to 3,980 mg/kg (the highest rate tested). For the butoxy ethanol ester, the acute skin absorption LD50 in rabbits was calculated to be 3980 mg/kg (Unpublished data, The Dow Chemical Co.)

There have been several cases reported in the literature in which spray applicators and production workers exhibited various symptoms as a result of exposure to the spray mixtures. [redacted] weakness [redacted] mention is made as to whether the primary route of exposure was dermal contact, inhalation or both. However, a recent report (Ott et al. 1978 and IARC, 1977) on workers exposed in a manufacturing plant to 30-40 mg/day of 2,4-D for periods ranging from 0.5-22 years indicated no differences in health parameters from a control group of workers.

Men (248) and women (44) engaged in the manufacture of the amine salt or the butyl ester of 2,4-D with exposure periods ranging from under 5 years to 6-10 years (for 194 and 98 persons respectfully); were screened and 63% of these workers complained frequently of weakness, rapid fatigue, headache or vertigo. About 20% had disturbances of the cardiovascular system (mainly hypotension and bradycardia) and of the digestive organs (dyspeptic symptoms and gastritis). The various liver dysfunctions that were found were more pronounced in workers with longer exposures to the herbicides. (IARC, 1977)

DOW 1249300

Feldmann & Maibach (1974) studied in man the absorption through the skin of 4µg/cm² ^{14}C-labelled 2,4-D dissolved in a small amount of acetone. ^{14}C activity was measured in urine over a 5-day period and compared with that in urine after i.v. administration of the compound: urinary excretion of 2,4-D after i.v. administration was 100% of the dose in 120 hours, while excretion after topical administration was 5.8% of the dermal dose.

Kohli et al. (1974) administered 5 mg/kg body weight of pure 2,4-D in a gelatin capsule with water to 6 healthy male volunteers, aged 22-30 years. None of the subjects complained of any ill-effects, no changes in blood pressure, pulse rate, hemoglobin content or total or differential white cell counts were observed. 2,4-D was absorbed fairly rapidly. The highest concentration in blood was reached in 7-24 hours. In urine, 2,4-D was present as early as 2 hours after ingestion, and more than 75% was excreted in 96 hours without undergoing transformation in the body.

In 5 male volunteers given a single oral dose of 5 mg/kg body weight, the half-life in the plasma was 11.7 hours, and elimination in the urine

occurred with a half-life of 17.7 hours. About 82% was excreted as such and 12.8% as a conjugate (Sauerhoff et al., 1976).

From the above studies it appears that 2,4-D is readily absorbed from the gut. Some absorption through the skin may occur, but appropriate precautions will adequately minimize exposure during the transferring, mixing, and application of the herbicide.

DOW 1249301

3. Does 2,4-D cause cancer?

Long term studies conducted in laboratory animals have been evaluated by several eminent scientific groups who have concluded that 2,4-D does not cause cancer. In 1969, a Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health was published (Mrak, 1969). In that report the studies conducted by Innes et al (1969) in two strains of mice receiving 46.4 or 100 mg 2,4-D/kg/day by stomach tube from day 7 to 28 of age followed by ingestion of diet containing 149 and 323 ppm of 2,4-D for 18 months were reviewed. Even under these rigorous conditions the conclusion was, "2,4-Dichlorophenoxyacetic Acid (2,4-D) and five compounds closely related to it structurally were found to be non-tumorigenic in the test circumstances".

The Food and Agricultural Organization of the United Nations World Health Organization's Working Party of experts on pesticide residues also reviewed the Innes study and concluded, "There is no significant increase in tumors between the controls and the groups given the two levels of 2,4-D". (FAO/WHO, 1971).

Hansen et al (1971) administered 2,4-D in the diets of rats for two years at 0, 5, 25, 125, 625 or 1200 ppm. While the number of rats employed in this study would not be adequate by todays standards, the authors concluded 2,4-D was not a carcinogen.

DOW 1249302

Arkipor and Kozloria (1974) state there was no significant increase in tumors in rats or mice from dietary or skin painting administration of 2,4-D.

Bjorkland and Erne (1966) administered 2,4-D in the drinking water of rats for two years at levels up to 1000 ppm and observed no increase in tumors.

4. Does 2,4-D cause birth defects in humans?

Teratological studies (study of birth defects) have been conducted with 2,4-D as the acid and as certain esters in rats, mice, hamsters and sheep. There are differences among scientists in defining teratological responses to treatments. In this discussion we will cite the definitions of the National Academy of Sciences' (1974) and their explanation of each.

"Prenatal development is divided into the embryonic stage (early) when the organs are forming, and the fetal stage (later) when the organism is maturing during gestation. However, the division is not clear-cut and the prenatal organism will be referred to in this discussion as an embryo even if it is technically known as a fetus."

"An agent or chemical is considered as teratogenic when it causes developmental disturbances in the embryo resulting in congenital malformations. If an agent kills the embryo it is said to be embryocidal, and if it

produces tissue damage (not necessarily resulting in malformation) it is embryopathic. The term embryotoxic will refer to any harmful effect on the embryo."

"The harmful effects of biochemically active compounds vary with the dose of the compound, the route by which it is given, the gestational stage at which the embryo is exposed, and the genetic constitution of the exposed mother and embryo."

DOW 1249303

"In general, the embryo is more sensitive than the mother, and teratogenic doses are likely to be lower than embryopathic doses which, in turn, are lower than embryocidal doses. However, there is a good deal of overlap, and much variation in this respect between different compounds. For instance, thalidomide is teratogenic in pregnant women at low doses but is not toxic to the mother at very high doses. For many other agents a teratogenic dose also increases the resorption (embryonic mortality) rate, but this is not always so. Still other agents may not be teratogenic even at doses that kill many of the embryos, at least in some species. Finally, the teratogenic effect may vary with the route of administration. Vitamin A, for instance, may be teratogenic when given orally, but is not when given intramuscularly. In general, acute doses are more teratogenic than chronic exposures, possibly because repeated exposure allows the formation (induction) of enzymes which degrade the potentially teratogenic compound."

"It is important to recognize that species differ widely in their susceptibility to teratogens. An outstanding example is thalidomide which is highly teratogenic in man and the New Zealand grey rabbit, but has only a very low level of teratogenicity in the mouse and rat. Cortisone

causes cleft palate in the mouse and the rabbit, but not in the rat. We still do not know if it is teratogenic in man. Thus, one cannot extrapolate with any assurance from one species to another, or even one strain to another, and one cannot rigorously prove an agent is teratogenic in man from data on experimental animals--only from data on human beings."

DOW 1249304

"It must be emphasized that a great many agents are teratogenic in experimental animals, particularly rodents. Many drugs have demonstrated teratogenicity: various antibiotics, amphetamines, antihistamines, anticonvulsants, barbiturates, caffeine, clomiphene, cyclizine, LSD, thalidomide, tolbutamide, and various tranquilizers. Metals (cadmium, calcium, lead, mercury), hormones (ACTH, adrenalin, androgenic hormones, antiovulatory compounds, estrogens, glucosteroids, insulin, serotonin), vitamin A, and several other kinds of chemical, physiological, and environmental agents (maternal dehydration, maternal stress, carbon monoxide, noise, and hypoxia) have also been shown to be teratogenic in laboratory animals. For several of these there is good evidence of low or no teratogenicity in man (e.g., cyclizine), but for most of them the possibility of low levels of teratogenicity has not been ruled out, and it would be very difficult to do so. Only five have been clearly implicated as humans teratogens (diphenylhydantoin, androgenic progestins, organic mercury, radiation, and thalidomide)" (NAS, 1974).

"Much less work has been done on the teratogenicity of 2,4-D. One study (Bionetics Study, see Mrak Report, 1969) suggested that the butyl, isopropyl and isooctyl esters of 2,4-D may be teratogens of low potency. Schwetz et al. (1971), feeding the free acid, the propylene glycol butyl ether ester and the isooctyl ester at levels up to 87.5 mg/kg/day--

the maximum tolerated level--on day 6-15 of pregnancy, found symptoms of embryotoxicity (edema, delayed ossification, etc.) but no genuine teratological effects in rats even at the highest dose. The highest levels of the esters decreased viability and lactation in the mothers but had no effect on the growth and development of the offspring. Khera and McKinley (1972), working also with rats and using four samples of 2,4-D and one each of the butyl, isooctyl, butoxyethanol, and dimethylamine derivatives, found similar abnormalities as in their experiments with 2,4,5-T and derivatives, at the same dose levels (100 mg/kg and above). Collins and Williams (1971) found in the progeny of hamsters treated with three samples of 2,4-D some increase in malformations but there was no dose-effect relationship and the differences were not statistically significant."

"An agent may be considered a potent teratogen if it has teratological levels far below the dose levels that are lethaly toxic to the mother. By this criterion 2,4-D would be considered to be a rather weak teratogen in experimental animals. In view of wide differences between species in teratogenic suseptibility, one cannot extrapolate teratological results from experimentals animals to man." (N.A.S. 1974)

DOW 1 249305

Is 2,4-D a Mutagen?

First, a mutagen is a material that is capable of producing genetic damage which can be inherited by future generations. 2,4-D has been evaluated in a number of mutagenicity studies. It has been demonstrated that 2,4-D is not a mutagen in a variety of microbial studies as well as in male fruit flies (Drosphila melanogaster). (Vogel - Chandler, 1974). Epstein et al (1972) found that a total of 75 mg of 2,4-D/kg of body weight given over a five day period did not increase dominant lethal mutations in mice.

DOW 1 249306

Treatment of in vitro cultured human lymphocytes with 0.02 mg/ml. 2,4-D increased the number of chromatid aberrations and to a lesser exstent, chromosomal aberrations. In mice, toxic concentrations (100-300 mg/kg/body weight) of 2,4-D administered as a single oral dose significantly increased the frequency of aberrant metaphases (2-4 fold) in lymphocytes; single fragments were the primary aberration (Pilinskaya, 1974, cited in IARC, 1977).

2,4-D had no effect on cultured cells nor on bone marrow after its oral administration to rats (Styles, 1973 cited in IARC, 1977). There was no increase in the micronuclei in erythrocytes of mouse bone marrow after injection of 100 mg 2,4-D/kg/body weight. Examination of chromosones of workers employed in the production of 2,4-D indicated no changes (Johnson, 1971).

The Royal Swedish Academy of Sciences arranged a conference in Stockholm in February, 1977 organized into five working groups comprising chemistry, plant physiology, toxicology, genetics, and ecology with economics. The conclusion reached by the group of international experts regarding the mutagenicity of the phenoxy herbicides was as follows.

"The only statistically significant demonstration that phenoxy acids induce mutations transmissible to the offspring was obtained in the recessive lethal test in Drosophila melanogaster. Work on microorganisms sustains the conclusion that the phenoxy acids are mutagenic under the test conditions used. Two investigations on 2,4,5-T and one on 2,4-D, both using pure acids, showed an increased number of recessive lethals in Drosophila. From a tentative comparison of the radiation dose that would give a similar effect, the mutagenic effects of 2,4,5-T and 2,4-D were concluded to be weak.

DOW 1 249307

Somatic mutations have been observed in Drosophila, and chromosomal aberrations have been shown to be induced in plants and mammals. The relevance of these latter findings to a risk of mutation from phenoxy acids (associated or not with heritable damage) requires further studies. Observation in one study of a possible role of the emulsifier and/or solvent show the necessity of including these constituents of phenoxy acid formulations in future studies." (Ramel, C. 1977).

6. Are there "dioxins" in 2,4-D?

The generic term "dioxin" is often used incorrectly to designate one member of the family, 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD). There are 75 possible polychlorinated benzo-p-dioxins with a million-fold spread in the dosage level required to kill laboratory animals. Trace amounts of polychlorinated dibenzo-p-dioxins can be formed during the manufacture of chlorophenols under alkaline conditions at elevated temperatures and high pressure. Trace amounts of the highly toxic TCDD are formed during the manufacture of 2,4,5-trichlorophenol by alkaline

hydrolysis of 1,2,4,5 tetrachlorobenzene. Any TCDD so formed can be carried through into products made from 2,4,5-trichlorophenol, such as 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and hexachlorophene. No TCDD is found in 2,4-D (Ramel, C. 1977).

DOW 1 249308

The expected 2,7-dichloroisomer is not formed by condensation of 2,4-dichlorophenate under the acid conditions used in its manufacture by chlorination of phenol. Of 28 samples of 2,4-D tested for content of chlorodibenzo-para-dioxins, one was reported to contain less than 10 mg/kg (10 ppm hexachlorodibenzo-p- dioxin. (Woolson et al 1972, cited in IARC, 1977)

7. What Effect Does 2,4-D Have on The Environment?

The environment is composed of many compartments including soil, air, water, man, birds, animals, plants and insects, etc. 2,4-D, when used as directed on the label, exerts its effect on a select portion of the plants in the environment. Application of 2,4-D by means of spraying, either by ground or air, provides the potential for contamination of the other compartments.

Fate in Soil

In soil, in the presence of moisture, even at low levels, the esters of 2,4-D are hydrolyzed to the acid form. The persistence of the isooctyl ester of 2,4-D was studied under field conditions by Burcar et al. (1966, cited in NRCC 1978) who noted the complete breakdown of the ester to the acid in two weeks. The free acids also have a relatively

short life in soil. Klingman (1961) states that when used at normal rates, from 0.5 to 3 lb/acre, 2,4-D disappears from soil in 4 to 5 weeks. Microbial degradation also plays a significant roll in 2,4-D breakdown. It has been shown that repeated use of an agricultural chemical is likely to increase the population of soil microbes which can degrade it. 2,4-D does not build up in the soil, and treatments can be applied to cropland year after year without accumulation.

DOW 1 249309

Fate in Water

Detectable residues of 2,4-D do not appear in surface waters unless it is added directly to the water or falls there incidental to spraying adjacent areas. In practice, residues in streams or lakes resulting from range and forest uses are less than 0.1 ppm (Newton and Norgren, 1977). In the United States the maximum permissible concentration of 2,4-D in water which is used for public supplies is only 0.1 ppm.

Once introduced in water, 2,4-D undergoes relatively rapid decomposition. In 1971 over 7,000 acres in the Loxahatchee National Wildlife Refuge, Florida were sprayed with the acid equivalent of 4 pounds 2,4-D per acre to control water hyacinth. The highest 2,4-D residue level measured in water was 0.037 mg/liter found on the day after treatment. The highest levels in hydrosol, 0.005 mg/kg, occurred 3 to 15 days after treatment.

Mullison (1970) has review 150 studies on the Effects of Herbicides on Water and Its Inhabitants. This review demonstrates that 2,4-D breaks down in water quite rapidly. The rate of breakdown is dependent upon

temperature, pH, presence of organic matter, sunlight and microbial flora. At the labeled rates of application, 2,4-D would not be detected in most aquatic environments 30 days after introduction.

DOW 1249310

Toxicity studies with fish have been reviewed by Mullison (1970). In general, under natural conditions most fish species can tolerate 2 ppm 2,4-D. Spraying 5 pounds 2,4-D per acre in water about one foot deep would approximate 2 ppm. Under natural conditions fish could usually swim away from areas of high concentrations.

Fate in Air

Formulations of 2,4-D are applied as aqueous emulsions or solutions in oils by ground sprayers or by aircraft. During application, some of the material may drift from the target site before being intercepted by the target. The quantity which may drift is dependent upon droplet size, wind velocity, temperature and humidity, viscosity of the formulation, distance from applicator to target, and perhaps the most important factor, the precautions exercised by the individuals performing the application according to the label.

2,4-D formulations differ in their rate of volatilization from the target surface. The amine salts are less volatile than the esters. Proper selection of the formulation and observation of the climatic conditions recommended on the label can minimize volatilization from the target site to adjacent areas where damage may occur.

required on the label. Subchronic or less than one half the lifetime studies include: 90 day dietary in rats, six month dietary in dogs, teratogenicity in two species, two generation reproduction in rats and metabolism in two species. Chronic (essentially lifetime) dietary studies are conducted in rats and mice to determine a no effect level to assist in establishing tolerance levels and possible oncogenic (tumor producing) effects. These comprehensive studies require at least four years to complete.

DOW 1249311

During this same time period samples of the target crop which has been treated with the chemical at the maximum label rate are collected from various geographical areas and analyzed for possible residues. Residue studies are also conducted in cows and chickens to determine if residues which might be present in the food of these animals is carried into meat, milk or eggs which humans might consume.

The EPA then evaluates these data together with the data which describe the fate and effects in the environment and only after detailed analysis may grant a residue tolerance. The tolerance granting procedure is very detailed and not taken lightly by the EPA nor the industry. By the time a tolerance is granted an excess of five years have elapsed since the initial data gathering.

There may be trace quantities of 2,4-D in the food we eat but an extensive review of the data assures us it is a quantity which will not cause harm. The FDA market basket samples for 1974-1975 (PEMJJAA) which are comprised of collections in 20 cities which range in populations from less than 50,000 to more than one million showed no residues of chlorophenoxyacids.

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DOW 1 249312

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DOW 1 249313

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DOW 019010

BIOCHEMICAL RESEARCH DEPARTMENT

THE DOW CHEMICAL COMPANY

MIDLAND MICHIGAN

DATA SHEET OF PROPERTIES, HEALTH HAZARDS, AND PRECAUTIONS FOR SAFE HANDLING OF MATERIALS

MOLECULAR FORMULA		CHEMICAL NAME
		M-2121
MOLECULAR WEIGHT	INDUSTRIAL HYGIENE STANDARD	SYNONYMS

STRUCTURAL FORMULA - OR COMPOSITION

Silvex acid 25%
Silvex, Potassium salt 28.5%
8/15 AA RVM Attaclay to contain 50% Silvex equ. 46.5%

PHYSICAL AND CHEMICAL PROPERTIES

BOILING POINT °C / mmHg.	EXPLOSIVE LIMITS (% BY VOL. IN AIR)	FLASH POINT °F.	IGNITION TEMP. °C.	MELTING POINT °C.	VAPOR PRESSURE mm Hg 25°C

CORROSIVENESS (To Common Metals)	PHYSICAL STATE	COLOR
	solid	white

CHEMICAL REACTIVITY	ODOR (Include Concentration in Air)
	ess. none

STABILITY (To pH Change, Heat, Light)

TOXIC PROPERTIES

TYPE OF CONTACT		CLASSIFICATION OF TOXIC PROPERTIES	
EYE		[X] May cause no response or no more than very slight to slight transitory pain and/or slight transient corneal injury and/or irritation of the eyelids.	[ ] May cause some permanent loss of vision (this includes damage to cornea or internal injury which is incompletely healed in one week.)
		[ ] May cause sufficient injury to the eye to result in loss of time from work. (This includes damage to the cornea which heals or nearly heals in a week and/or considerable conjunctival irritation with edema.)	[ ] Vapor exposure may cause severe pain, lacrymation or serious injury to the eyes.
SKIN		[X] Single prolonged exposure (hours) causes no effect. Several repeated prolonged exposures may or may not cause the development of some slight irritation.	[ ] Single short exposure (minutes) may cause considerable irritation and/or single prolonged or frequently repeated short exposures cause a burn and/or may cause systemic injury, even death.
		[ ] (1) Single prolonged exposure may cause some reddening of the skin. Repeated prolonged contacts may cause appreciable irritation, possibly a mild burn and/or may cause appreciable systemic injury due to absorption.	[ ] An exposure rapidly causes severe burns and/or serious systemic injury, even death.
INHALATION	DUST OR MIST	[ ] No systemic injury expected. No irritation to nose and throat in dusty or misty atmospheres.	[ ] Dusty or misty atmosphere painful to nose and throat (intolerable to most people) and/or exposure may cause serious systemic injury.
		[ ] Throat and nose irritation in a dusty or misty atmosphere is painful but not intolerable and/or prolonged or repeated exposures may cause systemic injury.	[ ] Short exposure (minutes) may cause death or serious systemic injury.
	VAPOR	[ ] Exposures do not cause any effects other than some very slight irritation or pain to the eyes or respiratory passages at the most.	[ ] Exposures may cause extreme drowsiness, and/or serious systemic injury, and/or may cause intolerable irritation to the respiratory passages.
		[ ] Single exposures exceeding 1/2 hour, or frequently repeated exposures of shorter duration, may cause slight anesthesia and/or slight systemic injury, and/or cause appreciable, but not intolerable, irritation of respiratory passages.	[ ] Short exposures may cause unconsciousness, and/or serious systemic injury, including death.
		[ ] Even very short exposure will cause serious systemic injury or death.	
INGESTION		[X] Amounts which may be swallowed incidental to industrial handling will not cause injury. [redacted]	[ ] Amounts which may be swallowed incidental to industrial handling and use may cause serious injury.

COMMENTS

(1) Applies when wet and confined under a bandage.

16856

	DEGREES OF EXPOSURE RELATED TO TYPES OF OPERATION		PRECAUTIONS (SEE CODE BELOW)				
			EYES	SKIN (1)	INHALATION* DUST OR MIST	INHALATION* VAPOR	INGESTION
I	NO CONTACT	Characterized by remote operation with equipment isolated from the work area. The persons entering isolated areas will require the personal protection outlined for IV below.	A	A			A
II	MINOR CONTACT	Characterized by closed systems with equipment vented outside the work area; instrument control; mechanical handling of materials in bulk. Examples are: continuous reactors, stills and filters; enclosed conveyors; ventilated packaging.	A	A			A
III	OCCASIONAL DAILY CONTACTS	Characterized by manual handling of materials in packages such as bags, drums and fiberpaks. Ventilation may be provided for specific jobs. Many batch operations fall into this category.	A	A			A
IV	GROSS CONTACT LIKELY	Characterized by hand operation. Examples are: Emergency repairs, cleaning equipment, cleaning filters, taking care of spills, packaging volatile or dusty materials without ventilation, wheeling and tray drying.	B	A			A

EYE CONTACT	A No eye protection needed. B Use safety glasses without side shields. C Use safety glasses with side shields.	D Use chemical workers goggles. E Use gas tight goggles or a full face gas mask.	
SKIN** CONTACT	A A bath and clean clothes once per week along with the usual washing at mealtimes should be adequate precautions. B Grossly contaminated clothing and shoes must be removed not later than the end of the work period and must be thoroughly cleaned before re-use. C Require shower at the end of the work period and clean clothing from the skin out at the start of each work day.	D Clothing should be changed and skin washed promptly upon any detectable contact. Each use will require special consideration to determine suitable protective devices and standards of personal cleanliness. E Impervious clothing such as rubber boots, rubber aprons, and rubber gloves will be required. Specific items will be dictated as required by circumstance.	
INHALATION* DUST OR MIST	A No respiratory protection. B No protection required for exposure of thirty min. duration or less to obviously dusty atmospheres. Exposures of longer duration will require the use of a dust respirator bearing the approval of the U. S. Bureau of Mines for the use with toxic dusts.	D Any exposure to obviously dusty atmospheres will require a dust respirator bearing the approval of the U. S. Bureau of Mines for use with toxic dusts. E Any exposure to dusty atmospheres will require the use of an airline respirator, blower mask, or Chemox mask.	
INHALATION* VAPOR	A No precautions necessary. B No precautions necessary for single exposures of less than 1/2 hour. Longer single exposures, or frequently repeated exposures will require a gas mask or respirator equipped with appropriate canister.	C No precautions necessary for single exposures of no more than ten minutes. Longer exposures either single or repeated, will require gas mask or respirator equipped with appropriate canister. D Gas mask with appropriate canister required at all times. E Evacuate area at once and enter only with airline respirator, blower mask or Chemox mask.	
INGESTION	A No unusual procedures required.	E Food and tobacco should not be present in the work area. Hands and face should be washed before smoking and eating.	

COMMENTS

**GOOD PRACTICE REQUIRES THAT GROSS AMOUNTS OF ANY CHEMICAL BE REMOVED FROM THE SKIN AS SOON AS IS PRACTICAL

*SUITACLE GAS MASK CANISTER
dust respirator

(1) Avoid confining to the surface particularly if moist or wet.

DOW013011

16857

SIGNED K.J.O. F.O. CHECKED H.R.Hoyle

DATE 12-27-61 DATE

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MN055699 548974 DOW 1

HEH23.14-11-2(S) Author: R. W. Bohl

COMPREHENSIVE SURVEY OF EMPLOYEES' EXPOSURE TO AIRBORNE CONTAMINANTS IN THE MICHIGAN DIVISION 2,4-D PLANT, 489 BUILDING, OCTOBER, 1977-MARCH, 1979

INDEX NO. 9053

16858

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CAT NUMBER	9053
LABORATORY REPORT CODE	HEH23.14-11-2(8)
DATE ISSUED	June 21, 1979
ACCOUNT NO.	PROBLEM NUMBER 9084000

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OYEES' EXPOSURES TO AIRBORNE CONTAMINANTS IN THE
T, 489 BUILDING, OCTOBER, 1977-MARCH, 1979

K. F. Davey K. F. Davey

Schneider 7/10/79

clude in this space references to data books, and to earlier related
orts, patents and publications.)

...borne contaminants were evaluated during operation of
...he packaging lines. Eight-hour time-weighted average
...B, Dowanol PIB, isooctanol, ammonia, dichlorophenol
...ester, carbon monoxide and MCPA were measured for
...ith the highest potential for exposure to each. All
...le. The potential for overexposures to Dowanol EB in the
...and Dowanol PIB in the "acid" ester area was corrected
...ast high levels of DCP were lowered to acceptable
...closure through ventilation improvements made prior to
...igh ammonia excursions in the acid ester area will be

...ant, 489 Building
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... Section, 834 Building
...istration, 834 Building
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...ls Research, 1710 Building
...l Department, 607 Building
...iene Services, 607 Building
...aboratories, 574 Building
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PURPOSE

An evaluation of 2,4-D Plant employee exposures was completed as part of their active on-going industrial hygiene program. Survey work of the 2,4-D Acid operation reported by M. F. Stevenson in 1976, HEH23.14-11-2(6), found exposures to dichlorophenol in two job classifications to be in excess of health guidelines. New ventilation in the enclosure area had been installed and exposures were reevaluated. The last employee exposure data to the alcohols used in the two ester production areas were reported by G. H. Flores in 1973, in report NBH2.1-1-53(2). Process changes were made in the intervening years and new employee exposure documentation was required. Evaluations during this survey were also made in the packaging areas and when methyl chlorophenoxy acetic acid was being handled.

CONCLUSIONS AND RECOMMENDATIONS

1. New Chemical and Physical Agent Inventory sheets were prepared for all job classifications.

2. Employees' exposures while working in the 2,4-D acid enclosure area were reevaluated prior to early shutdown in 1978.

   a. The Crystallizer Operators' and Assistant Operators' 8-hour TWA exposures to dichlorophenol (DCP) and 2,4-dichlorophenoxy acetic acid (2,4-D acid) were within acceptable limits.

   b. The reaction equipment was scheduled for removal. The packaging operation of the process was started again (on 2,4-D acid) in the first quarter of 1979.

3. For the 2,4-D "acid" ester operation area:

   a. The Ester Operators' and Formulation Operators' 8-hour TWA exposures to Dowanol EB, Dowanol PIB, isooctanol and ammonia were within acceptable limits.

   b. Transient concentrations of ammonia next to the reactors, just after the Ester Operator manually added [redacted] into an open manhole, occasionally exceeded the excursion limit. Although the operator was able to avoid exposure by stepping away, this potential for exposure will be eliminated in 1979 with the installation of a direct addition method.

   c. Concentrations of alcohol next to the open slurry tank were the highest measured in the ester process area and occasionally were above recommended guidelines. This part of the process was changed to a closed system to eliminate this source of exposures.

4. For the direct ester area:

   a. The Direct Ester Operators' (two operators per shift) 8-hour TWA exposures to Dowanol EB, Dowanol PIB and Esteron 245 were within acceptable limits.

   b. Concentrations of Dowanol EB in the "high Bay" area were occasionally above the acceptable excursion limit. The potential for overexposure was reduced with the installation of an improved temperature controller at the decanter and by piping the stripper column overflow to an outside sump. (EB and water phases invert over a narrow temperature range and EB often was discharged with water into an open trench).

   c. Reevaluation of potential exposures to Dowanol EB in the "high bay" is recommended for 1979 survey work.

5. Concentrations of airborne 2,4,5-T PIB ester in the work area of the Material Handlers at the one gallon can filling machine area did not exceed 0.004 mg/m^3, which was judged acceptable.

6. The Loader/Checkers' and Material Hanglers' 8-hour TWA and peak exposures to carbon monoxide (CO) in the drum filling area and warehouse were within acceptable limits. A new continuous area CO monitor was installed. Periodic calibration is to be carried out by the Instrument Department.

7. The Clerk/Tank Car Unloaders' estimated 8-hour TWA and peak exposures to methyl chlorophenoxy acetic acid (MCPA) were well within acceptable limits. The local exhaust ventilation hood over the bag dumping hopper was acceptable for the control of dust from this lot of MCPA. An average hood face velocity of approximately 150 feet per minute is recommended if a dustier product is handled in the future.

8. Ventilation to the drum filling lines was ineffective and high transient concentrations of ammonia were noticed during the filling of drums with amine formulations. A new exhaust ventilation system will be installed in 1979.

9. No data exists for the Formulation Operators' exposure to dimethylamine, and an evaluation of these exposures is recommended for 1979.

MRI 1 5489777

PROCESS AND JOB DESCRIPTIONS

DOW 1548978

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DUKE
1548979

2,4-D "Acid" Ester Process

DOW 1548980

16364

The 2,4-D acid process was discontinued early in 1978 as the new production plant came on stream.

Packaging and Warehouse

Packaging and warehouse operations were contained on two floors with two can filling machines on the second floor and two drum filling lines on the first floor. These lines were operated by Material Handlers, Set Up Men and Loader/Checkers. Very little ventilation was installed which allowed a noticeable odor when DMA formulations were packaged. New ventilation for the drum filling line was planned for 1979. In 1978, two gasoline powered forklifts were being operated and carbon monoxide fumes were generated. A continuous analyzer was installed in the center of the drum filling area to monitor carbon monoxide. The analyzer was found to be inaccurate and was replaced in 1979.

Methyl Chlorophenoxy Acetic Acid (MCPA)

MCPA production was a formulating project for about one to two months each year. Purchased bags of solid or granular MCPA were opened by hand and manually dumped into a hopper in a room east of the warehouse. A local exhaust ventilation hood covered the hopper to control dust evolution. The rest of the work of the Clerk/Tank Car Unloaders who performed this job was located outside or in other low exposure areas.

Formulations

Formulations work was performed by the Formulations Operator. This operation, aside from when amine formulations were made, had a low exposure potential and was not extensively investigated. The Formulations Operator spent most of his time in an air conditioned control room or at outside equipment. He did have to enter the 2,4-D or "acid" ester process area and was therefore evaluated for exposures related to that process. Potential exposures to dimethylamine will be investigated in 1979 and the process described in that report.

The other job classifications listed in Appendix 1 that have work in process areas (potential exposure areas) were the Analytical Technicians, Plant Mechanics and Foremen. The Spares covered for the absence of other classifications. The remaining classifications had primarily administrative and office or clerical functions which required infrequent entry and short exposure time in the process areas.

MUM 1548981

EVALUATION CRITERIA

Dow Industrial Hygiene Guides (IHGs) are concentrations of airborne substances to which nearly all employees may be repeatedly exposed throughout a working lifetime without adverse effect. IHGs are established by the health professionals of the Dow Industrial Health Board for chemicals (raw materials, intermediates, by-products, wastes, and products) handled within The Dow Chemical Company. Published exposure criteria are available for many industrial chemicals; examples include the Threshold Limit Values (TLVs) of the ACGIH (American Conference of Governmental Industrial Hygienists), the ANSI standards of the American National Standards Institute, and the OSHA standards of the Occupational Safety and Health Administration of the United States Department of Labor. For most of these chemicals, the Industrial Health Board has adopted the published exposure criteria as the Dow IHGs. In a few instances the IHG set by the Industrial Health Board differs from the published exposure criteria. In establishing IHGs for chemicals which lack published exposure criteria, the Industrial Health Board considers toxicological information, occupational exposure data, and medical experience.

Industrial Hygiene Guides do not represent fine lines between safe and dangerous exposures. As the name indicates, IHGs are properly used as guides for plant design and for evaluating occupational exposures. IHGs for gases and vapors are usually expressed in parts per million (ppm, volume/volume); for dusts, fumes, aerosols, and mists, IHGs are usually expressed in milligrams of contaminant per cubic meter of air (mg/m^3).

Most IHGs are time-weighted average (TWA) concentrations for an 8-12 hour workday and a 40 hour workweek. Limited excursion exposures to concentrations exceeding the IHG are permitted, provided that the TWA exposure for the entire work day is acceptable and the consequences of exposure, within the excursion limit, are minimal and reversible. For most chemicals, excursion limits are calculated from the IHGs and the excursion factors recommended by the ACGIH. Ceiling IHGs are assigned to those materials which cause significant or irreversible effects at concentrations exceeding the IHG. For these chemicals, no excursion exposures are allowed. The following exposure criteria currently apply to the airborne contaminants measured during this survey:

Compound or Material	IHG	Excursion Limit
Dowanol EB	50 ppm	75 ppm
Dowanol PIB mix	25* ppm	
Isooctyl alcohol	75 ppm	110 ppm
Dimethylamine	10 ppm	20 ppm

*Not established by the Dow Industrial Health Board, 25 ppm used as a temporary guideline.

UUU 1548982

Compound or Material	IHG	Excursion Limit
2,4-Dichlorophenol	1 ppm	3 ppm
Methyl chlorophenoxy acetic acid	5 mg/m^3	10 mg/m^3
2,4-Dichlorophenoxy acetic acid	10 mg/m^3	20 mg/m^3
2,4,5-Trichlorophenoxy acetic acid	10 mg/m^3	20 mg/m^3
Ammonia	25 ppm	35 ppm
Carbon monoxide	50 ppm	400 ppm

When the results of an industrial hygiene survey indicate a need to reduce exposure, control measures should be implemented. Traditional engineering control methods include containment, isolation, substitution, local exhaust ventilation, general ventilation and change of operating procedure. Administrative control -- limiting exposure time through remote control or job rotation -- may also be effective. Personal protective equipment may be used to protect employees only as a last alternative when none of the preceding control methods is feasible or until control measures can be effected.

1548983

AIR SAMPLING AND ANALYSIS

Airborne Dowanol EB (2-butoxy ethanol) Dowanol PIB-T [mixed (mono, di, tri) propylene glycol isobutyl ether] and isooctanol were collected on commerical adsorber tubes packed with 800 mg of silica gel. Each tube was connected to portable battery operated personal monitoring vacuum pumps, calibrated before and after sampling and operated at about 0.1 liters per minute (LPM). The pumps and tubes were worn by operators to collect personal breathing zone samples or placed in specified work areas to collect area samples. The sample tubes along with tubes prepared with known concentrations were later desorbed with carbon disulfide with 1% methanol or with methanol and then analyzed by gas chromatography and flame ionization detection (GC/FID). Analytical work was performed by R. G. Melcher (AL 77-51116 and AL 78-50450), L. Nauer (AL 78-50170), J. Warren and P. Kastl (AL 79-50107).

Airborne dichlorophenol and 2,4-dichlorophenoxy acetic acid were collected with both activated alumina adsorber tubes and midget impingers containing 0.1 N sodium hydroxide. Air sampling was completed using calibrated personal monitoring pumps operating at about 0.1 LPM for the tubes and up to 0.5 LPM for the impingers. Both the tubes and the impinger solutions were extracted with a 50/50 hexane/diethyl ether solution and methylated with diazomethane. Analyses were performed by L. Nauer by GC/EC (gas chromatography/electron capture detection) (AL 78-50015).

In an attempt to document exposures to airborne 2,4,5-T Dowanol PIB ester, air samples were drawn through midget impingers containing reagent isooctane. Air flow rates and volumes in the beginning were 0.3 LPM with up to 10 liters of air collected. Breakthrough at the higher contaminant levels was common. Air flow rates were lowered to under 0.2 LPM and volumes under six liters for later samples. Impinger solutions and knowns were analyzed with GC/EC techniques by R. G. Melcher (AL 78-50449) and L. Nauer (AL 78-50170 and AL 79-50029).

Ammonia was estimated on site using Bendix Gastec No. 3L ammonia detection tubes with an expected accuracy within 25%.

Carbon monoxide was estimated on site using Bendix Gastec catalog number ILa and ILL detector tubes and Draeger 50/a-L extended time detector tubes. Analytical accuracy has been determined to be within 25%.

Airborne methyl chlorophenoxy acetic acid (MCPA) is a solid at room temperature and was collected on 0.8 micron membrane filters using calibrated air monitoring pumps operating at over 3 LPM. The weights were determined gravimetrically as total MCPA by R. W. Bohl.

MMW 1548984

DISCUSSION OF RESULTS

Table 1 is a summary of employees' exposures to chemical and physical agents by various job classifications. The degree of exposure, hazard rating and evaluation results are shown for those potential contaminants with a hazard rating of 1 to 3 for any job classification.

The four ratings for the degrees of exposure are the same as the one defined on the back of the Industrial Hygiene Data Sheets.

DOW 1548985

DEGREES OF EXPOSURE RELATED TO TYPES OF OPERATION

I	NO CONTACT	Characterized by remote operation with equipment isolated from the work area. The persons entering isolated areas will require the personal protection outlined in IV below.
II	MINOR CONTACT	Characterized by closed systems with equipment vented outside the work area, instrument control, mechanical handling of materials in bulk. Examples are: continuous reactors, stills and filters, enclosed conveyors ventilated packaging.
III	OCCASIONAL DAILY CONTACT	Characterized by manual handling of materials in packages such as bags, drums and fiberpaks. Ventilation may be provided for specific jobs. Many batch operations fall into this category.
IV	GROSS CONTACT LIKELY	Characterized by hand operation. Examples are: emergency repairs, cleaning equipment, cleaning filters, taking car of spills, packaging volatile or dusty materials without ventilation, wheeling and tray drying.

The degrees of exposure, as rated by plant supervision and reviewed by the industrial hygienist, were based on normal operating conditions. Each was based on regular observations of the operating procedures and work practices employed by operators in the specific job classification. The hazard rating found in Table 1 is defined as follows:

A numerical rating ranging from 1 (high) through 5 (low) which estimated the probability that an injury or overexposure will occur in a given situation or environment. It is based on the degree of exposure and the physical and toxic properties of the chemical. The degree of exposure is influenced by the type of process (open vs. closed system) and the type of operation required (manual vs. automatic).

The industrial hygienist has the responsibility for setting the hazard ratings based on his observations of the plant, the degree of exposure and the ability of the material (or physical stress) to cause injury. The hazard ratings were unique for each job classification. Within any given plant, the hazard rating for a chemical may be different for the various job classifications because of a varying degree of exposure.

The evaluation results may include measured TWA exposures for each job classification or a professional judgment that given exposures would be acceptable based on past exposure data or other data that would indicate a low probability of overexposure.

Tables 2 and 3 show an increase in the level of exposures by the Direct Ester Operators to Dowanol EB over a one year period. Concentration in the direct ester high bay area were, at times, irritating and occasionally exceeded the excursion limit. Water from the decanter and stripper column occasionally contained excessive Dowanol EB due to a water/alcohol phase inversion which occurred within a narrow temperature range. In 1979, a new temperature controller for the decanter and piping of the stripper overflow directly to an outside waste water sump has decreased odor levels. A reevaluation of exposures was recommended and scheduled for 1979. No other alcohols, either residual from previous runs or recycled from current operations of the "acid" ester process, were detected in the direct ester area. Table 4 shows the results of monitoring at the direct acid process for Dowanol PIB and the related 2,4,5-T ester. While IHG's had not been established for these two materials, TWA concentrations of 25 ppm for PIB and 5 mg/m^3 for the 2,4,5-T ester were conservative vaues used as interium guidelines. [The lowest IHG for any Dowanol (Dowanol EM) is 25 ppm and the IHG for 2,4-D acid is 10 mg/m^3.] Exposures were well below these values and no health ahzard would be anticipated.

Tables 5, 6 and 7 show the results of monitoring for potential Dowanol EB, Dowanol PIB, isooctyl alcohol and exposures in the 2,4-D "acid" ester process area. Eight-hour TWA exposures to all four were well within acceptable limits. The Ester Operators were potentially exposed to excessive ammonia when adding through an open manhole into the reactors. Operators were observed to step back away from the fumes to minimize actual exposures. A direct addition method is scheduled for installation in 1979. The open slurry tank also contributed a potential excursion exposure as seen in Table 6. This tank was closed to eliminate the source.

LUH / 1548986

While no hazard was expected, data on airborne 2,4,5-T esters was requested, and the results of monitoring at the one gallon can packaging area are shown in Table 8. Work area concentrations were very low, and the Material Handlers' exposures were judged to be well within acceptable limits.

Gasoline powered forklifts were in use in the warehouse and drumming areas through 1978. Carbon monoxide exposures were evaluated and found to be within acceptable limits, as shown in Table 9. The forklift traffic pattern and the air sample locations are shown in Figure 5. The future conversion to electric or liquified petroleum gas powered equipment should minimize both carbon monoxide and odor levels. Until this replacement occurs, new continuous carbon monoxide analyzer located between the drumming lines should be maintained and calibrated regularly. The new analyzer manufactured by Dynamation has operated in an acceptable manner since it was installed the first quarter of 1979 to replace an older Dynamation model which continually lost calibration.

The highest exposure to methyl chlorophenoxy acetic acid (MCPA) encountered by the Clerk/Tank Car Unloaders occurred while opening and pumping purchased bags at the hopper for the mix tank. Exposures were well under acceptable limits as shown in Table 10. Also no skin irritation was reported. The MCPA flake used was reported to be less dusty than material purchased one year ago when skin irritation was experienced. The local exhaust ventilation hood over the hopper was evaluated and the air flow measurements are shown in Figure 6. For the dust levels observed, the hood was acceptable. For higher dust levels, dependent on the condition of the purchased MCPA, the air flow into the hood should be increased to an average hood face capture velocity of at least 150 feet per minute.

The 2,4-D acid process was operating in 1977 and was to be phased out as the new 2,4-D acid plant at 948 Building was brought up to capacity. It was expected that this operation might continue well into 1978. Therefore, exposures to dichlorophenol (DCP) and 2,4-D acid were evaluated to assure that the marginally excessive concentrations of DCP measured in 1976 had been reduced through the installation of a new ventilation system in 1977. As shown in Table 11, exposures were within acceptable limits. The production process was shut down at the start of 1978 and the reaction equipment scheduled for removal. The packaging end of the process was kept on stand-by condition and was started again in 1979 to package 2,4-D acid produced at the new plant.

In developing a new Chemical and Physical Agent Inventory (Appendix 2) with exposure and hazard ratings for all job classifications, the Formulations Operators' potential hazard to amines was not well established with data, and it was recommended that exposures to dimethylamine and possibly diethylamine be evaluted in 1979.

A noise survey completed by the ACPD safety representative (D. Bugg) found employees' TWA exposures were acceptable. A report of this survey is kept at the 2,4-D plant superintendent's office and in the Industrial Hygiene Laboratory's files.

MDH 1548987

Four sealed sources used in process instrumentation and in analtyical equipment were surveyed and wipe tested twice in 1978 by J. M. Bronson and R. W. Bohl of the Industrial Hygiene Laboratory. All sources were found to be in acceptable condition. Documentation is kept at the Health Physics section of the Industrial Hygiene Laboratory with copies mailed to each plant superintendent.

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Table .. SUMMARY OF DEGREE OF EXPOSURE RATINGS, HAZARD RATINGS AND EXPOSURE EVALUATION RESULTS BY JOB CLASSIFICATION IN THE MICHIGAN DIVISION 2,4-D PLANT, 489 BUILDING, OCTOBER, 1977-FEBRUARY, 1979

Material	IHG	Direct Ester Operator			2,4-D Ester Operator			Formulations Operator			Clerk-Tank Car Unloader			Loader-Checker		
		DE	HR	EE	DE	HR	EE	DE	HR	EE	DE	HR	EE	DE	HR	EE
Dowanol EB (2-butoxy ethanol)	50 ppm	3	3	2.5	3	4	1.5	2	4	0.4	1	5	JA	1	5	JA
Dowanol PIB Mix (72% mono, 22% di, 4% tripropylene glycol isobutyl ether)	NE*	3	4	1.0	3	4	1.9	2	4	0.5	1	5	JA	1	5	JA
Isooctyl alcohol	75 ppm	3	4	JA	3	4	0.5	2	4	0.1	1	5	JA	1	5	JA
Dimethylamine (DMA)	10 ppm	1	5	JA	1	5	JA	2	3	JA**	3	3	JA**	1	5	JA
2,4-Dichlorophenol (DCP)	1 ppm	2	4	JA	1	5	JA	1	5	JA	3	3	JA**	1	5	JA
Methyl chlorophenoxy acetic acid (MCPA)	5 mg/m^3	1	5	JA	1	5	JA	1	5	JA	4	3	0.07	2	4	JA
2,4-Dichlorophenoxy acetic acid (2,4-D acid)	10 mg/m^3	1	5	JA	2	4	JA	4	3	JA***	3	3	JA***	1	5	JA
2,4,5-Trichlorophenoxy acetic ester (Esteron 245)	10 mg/m^3	3	4	0.2	1	5	JA	1	5	JA	1	5	JA	3	4	0.001
Ammonia	25 ppm	1	5	JA	3	3	0.5 (est.)	1	5	JA	1	5	JA	1	5	JA
Carbon monoxide	50 ppm	1	5	JA	1	5	JA	2	4	JA	3	4	15	3	3	15
Sodium hydroxide	2 mg/m^3	2	4	JA***	1	5	JA	1	5	JA	3	3	JA***	1	5	JA

*NE - Not established
**To be measured in 1979
***Primarily a potential skin contact hazard

DE - Degree of exposure
HR - Hazard rating
EE - Exposure evaluation
JA - Judged acceptable

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Table 1. CONTINUED

Material	IHG	Material Handler			Set-Up Man			2,4-D Enclosure Prior to Shutdown: Crystallizer Operator (Not active in 1978)			2,4-D Enclosure Prior to Shutdown: Assistant (2,4-D) Operator (Not active in 1978)		
		DE	HE	EE	DE	HR	EE	DE	HR	EE	DE	HR	EE
Dowanol EB (2-butoxy ethanol)	50 ppm	1	5	JA	1	5	JA	1	5	JA	1	5	JA
Dowanol PIB Mix (72% mono, 22% di, 4% tripropylene glycol isobutyl ether)	NE*	1	5	JA	1	5	JA	1	5	JA	1	5	JA
Isooctyl alcohol	75 ppm	1	5	JA	1	5	JA	1	5	JA	1	5	JA
Dimethylamine (DMA)	10 ppm	1	5	JA	1	5	JA	1	5	JA	1	5	JA
2,4-Dichlorophenol (DCP)	1 ppm	1	5	JA	1	5	JA	3	3	0.05	2	4	0.05
Methyl chlorophenoxy acetic acid (MCPA)	5 mg/m^3	3	3	0.07	3	3	0.07	1	5	JA	1	5	JA
2,4-Dichlorophenoxy acetic acid (2,4-D acid)	10 mg/m^3	3	3	JA**	3	3	JA**	2	3	0.09	3	3	0.07
2,4,5-Trichlorophenoxy acetic ester (Esteron 245)	10 mg/m^3	3	4	0.001	2	4	JA	1	5	JA	1	5	JA
Ammonia	25 ppm	1	5	JA	1	5	JA	1	5	JA	1	5	JA
Carbon monoxide	50 ppm	3	3	15	3	3	15	2	4	JA	2	4	JA
Sodium hydroxide	2 mg/m^3	1	5	JA	1	5	JA	2	4	JA	2	4	JA

*NE - Not established
**To be measured in 1979

Note: Exposures by all other job classifications listed on Appendix 1 to all chemicals above and listed in Appendix 2 were judged acceptable.

DOW 1548950

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Table 2. AIR MONITORING FOR DOWANOL EB AND DOWANOL PIB-T IN THE DIRECT ESTER OPERATION DURING PRODUCTION OF DOWANOL EB ESTER OF 2,4-D (DOWANOL PIB ESTER BEING PRODUCED IN 2,4-D ACID ESTER PROCESS), IN THE MICHIGAN DIVISION 2,4-D PLANT, 489 BUILDING, NOVEMBER, 1977

Description	Date	Concentration (ppm) Dowanol EB	Dowanol PIB*
Personal Samples (Approximate 8 Hour TWA Exposure)			
Personal breathing zone of the Direct Ester Operator for the high bay process area	10/24/77	0.6	ND**
Personal breathing zone of the Direct Ester Operator for the high bay process area	10/26/77	0.8	ND
Personal breathing zone of the Direct Ester Operator for the high bay process area	10/28/77	2.7	ND
Personal breathing zone of the Direct Ester Operator for the low bay area	10/24/77	0.5	ND
Personal breathing zone of the Direct Ester Operator for the low bay area	10/26/77	0.4	ND
Personal breathing zone of the Direct Ester Operator for the low bay area	10/28/77	4.5	ND
Area Sampling			
Control room, Direct Ester Process	10/26/77	0.8	ND
	10/28/77	0.7	ND
Direct Ester, high bay, first level	10/24/77	23	ND
	10/26/77	28	ND
	10/28/77	17	ND

*From acid room
**ND - Not detected at analytical sensitivity of <0.3

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154991

Table 2. CONTINUED

Description	
Area Sampling	
Direct Ester, high bay, 2nd level	
	(Odor irritating)
Direct Ester, high bay, third level	
Direct Ester, low bay, first level	
Direct Ester, low bay, second level	
Inside the 2,4-D acid enclosure	
Open area, north end of 489 Building between Direct Ester and Acid Ester rooms	
Inside 2,4-D acid ester room	
Industrial Hygiene Guide	
Excursion Limit	

*From acid room
**ND - Not detected at analytical sensitivity of <0.3
***ND - Not detected at analytical sensitivity of <0.2

1263

Date	Concentration (ppm) Dowanol EB	Dowanol PIB*
10/24/77	6.8	ND**
10/26/77	10	ND
10/28/77	16	ND
10/28/77	38	ND
10/28/77	6.3	0.4
10/24/77	0.4	ND
10/28/77	0.9	ND
10/24/77	0.6	ND
10/26/77	0.4	ND
10/28/77	1.1	ND
10/28/77	0.3	0.2
10/28/77	0.5	ND
	ND***	
	50	-
	75	-

Table 3. AIR SAMPLING FOR DOWANOL EB AT THE DIRECT ESTER PROCESS DURING PRODUCT OF DOWANOL EB ESTER OF 2,4-D, 2,4-D PLANT, 489 BUILDING, JANUARY, 1979

Description	Date	Dowanol EB (ppm, vol/vol)
Personal Samples (Approximate 8 Hour TWA Exposure)		
Personal breathing zone (BZ) of Direct Ester Operator (operating high bay)	1/18/79	5.0
	1/20/79	3.4
Personal BZ of Direct Ester Operator (operating low bay)	1/18/79	3.5
	1/20/79	2.8
Area Samples		
Control room, Direct Ester Process	1/15/79	1.8
	1/17/79	2.9
	1/18/79	1.6
High bay, first floor	1/18/79	25
	1/20/79	27
High bay, second floor	1/15/79	59
	1/17/79	5.4
(Odor very strong)	1/18/79	64
	1/19/79	26
(Odor very strong)	1/20/79	61
High bay, 3rd floor	1/15/79	47
	1/17/79	55
(Odor very strong)	1/18/79	77
	1/19/79	44
High Bay, fourth floor	1/15/79	44
	1/17/79	49
	1/19/79	44

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548993 DOW

Table 3. CONTINUED

Description
Area Samples
Low bay, first floor
Low bay, 2nd floor
Industrial Hygiene Guide Excursion Limit

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	Date	Dowanol EB (ppm, vol/vol)
(Minimal odor)	1/17/79	3.0
	1/18/79	5.5
	1/17/79	3.3
	1/18/79	5.4
	1/20/79	5.2
		50
		75

Table 4. RESULTS OF AIR MONITORING FOR DOWANOL PIB-T AND ESTERON 245 AT THE DIRECT ESTER PROCESS DURING PRODUCTION OF DOWANOL PIB ESTER OF 2,4,5-T IN THE MICHIGAN DIVISION 2,4-D PLANT, 489 BUILDING, FEBRUARY-MAY, 1978

Description	Date	Dowanol PIB-T (ppm)	2,4,5-T Ester (mg/m^3)
Personal Samples (Approximate 8 Hour TWA Exposure)			
Breathing zone of Direct Ester Operator for High Bay	2/24/78	1.0	-
Breathing zone of Direct Ester Operator for Low Bay	2/24/78	1.0	-
Area Samples - Direct Ester Area			
High bay, first floor	2/20/78	-	0.3
	2/24/78	10.0	0.6
	5/01/78	-	0.1
High bay, second floor	2/20/78	3.9	0.3
	2/24/78	4.5	0.3
	2/24/78	7.5	
	5/01/78	-	0.2
	5/01/78	-	0.2
Low bay, second floor	2/20/78	-	0.3
	2/20/78	1.9	0.4
	2/24/78	3.7	0.5
	5/01/78	-	0.6
Control room	2/24/78	0.3	-
	2/24/78	1.1	-
	5/01/78	-	0.2
Industrial Hygiene Guide		NE*	NE
Calculated 8 Hour TWA Exposures:			
Direct Ester Operator (for high bay)			0.2
Direct Ester Operator (for low bay)			0.2
(Assume both spent 70% of time in control room, 15% in process area, 15% out of area)			

*NE - Not established

16879

548995 DOW

Table 5. RESULTS OF AIR MONITORING FOR DOWANOL EB, 2,4-D "ACID" ESTER PROCESS IN THE MICHIGAN DIVISION 2,4-D PLANT, 489 BUILDING, MAY, 1978

Date	Description of Samples	Dowanol EB (ppm)
	Personal Sampling	
5/01/78	Personal breathing zone (BZ) of 2,4-D Ester Operator on regular work (loaded two reactors), sample time 6.3 hours, approximate 8 hour TWA exposure	1.5
5/04/78	Personal breathing zone (BZ) of 2,4-D Ester Operator on regular work (loaded two reactors), sample time 6.1 hours, approximate 8 hour TWA exposure	1.4
5/01/78	Breathing zone of 2,4-D Ester Operator while making up two reactor batches, 52 minutes	0.9
5/01/78	Breathing zone of 2,4-D Ester Operator while changing Sparkler filter at first floor, 20 minutes	21.0
5/01/78	Personal BZ of Formulations Operator on regular work of which one hour of his 8 hour shift was spent in the 2,4-D ester room, sample time 6.3 hours and this approximates his 8 hour TWA exposure	0.3
5/04/78	Personal BZ of Formulations Operator on regular work of which one hour of his 8 hour shift was spent in the 2,4-D ester room, sample time 6.1 hours or approximate TWA exposure	0.4
	Area Sampling	
5/01/78	2nd floor, center next to north aisle near reactors, strongest odor level in room at the time, sample time 6.3 hours	7.3
5/01/78	2nd floor, south aisle, south of reactors, sample time 6.3 hours, odor just noticeable	0.8
5/01/78	2nd floor west, sample time 52 minutes	0.9

096881

1948996

Table 5. CONTINUED

Date	Description of Samples	Dowanol EB (ppm)
	Area Sampling	
5/01/78	1st floor under reactors, sample time 53 minutes	1.0
5/01/78	2nd floor, center next to north aisle near reactors, sample time 29 minutes	2.2
5/04/78	2nd floor, center of north aisle	2.8
5/04/78	2nd floor, center of south aisle on control panel	0.7
Industrial Hygiene Guide		50
Excursion Limit		75

16881

DOW 1548997

Table 6. RESULTS OF AIR MONITORING FOR DOWANOL PIB-T AT THE 2,4-D ACID ESTER PROCESS DURING PRODUCTION OF DOWANOL PIB ESTER OF 2,4-D IN THE MICHIGAN DIVISION 2,4-D PLANT, 489 BUILDING, OCTOBER, 1977 AND FEBRUARY, 1978

Description	Date	Concentration in ppm (vol/vol) Dowanol PIB	Ammonia
Personal Sampling (Approximate 8 Hour TWA)			
Personal breathing zone of 2,4-D Ester Operator	10/24/77	1.2	
	10/26/77	2.0	
	10/28/77	3.0	
	02/24/78	1.4	
Personal Sampling (Short Term High Exposure Job)			
Personal breathing zone of 2,4-D Ester Operator while charging all four reactors (his highest potential exposure period), 56 minutes	10/28/77	4.9	
Area Sampling - 2,4-D Ester Room			
Work areas on second floor, near reactors, during production of 2,4-D PIB ester	10/24/77	0.9	~50
	10/26/77	0.9	~40
	10/28/77	1.7	~5
Work areas on second floor, near reactors during reactor changes	10/28/77	3.2	~60
	02/24/78	7.6	ND*(<0.5)
Next to slurry tank, 2nd floor (highest odor level in room)	10/28/77	83	
Wor areas on first floor	10/24/77	0.7	
	10/26/77	0.5	ND(<0.5)
	10/28/77	1.0	
	02/24/77	5.4	
North end of 489 Building between direct ester room and lunch room	10/28/77	ND(<0.20)	
Between the direct ester and acid ester rooms	02/24/78	ND(<0.30)	
Between the acid ester room and lunch room	10/26/77	ND(<0.20)	
Inside 2,4-D enclosure	10/28/77	0.2	
Industrial Hygiene Guide		NE**	25

*ND - Not detected at analytical sensitivity indicated in parentheses
**NE - Not established

138281

DOW

Table 7. AIR SAMPLING FOR ISOOCTYL ALCOHOL IN THE 2,4-D ACID ESTER PROCESS OF THE MICHIGAN DIVISION 2,4-D PLANT, 489 BUILDING, OCTOBER, 1978

Description	Isooctyl Alcohol (ppm)
Personal Monitoring	
Personal breathing zone of 2,4-D Ester Operator during production of isooctyl ester of 2,4-D, approximate 8 hour TWA exposure	0.5
Personal breathing zone of Formulations Operator, approximate 8 hour TWA exposure	0.4
Area Monitoring*	
At desk on 2nd level, west of south aisle of acid ester room	0.3
Next to No. 4 reactor, 2nd floor east	0.3
Next to slurry tank, 2nd floor about six feet from open manhole in work area	0.5
Near filters, northeast on first floor	0.5
Walkway four feet off floor and running east-west under reactor area	0.5
Industrial Hygiene Guide	75

*Noticeable odor permeated the room which was considered by operating personnel to be typical and normal.

154999

DOW

1988

Table 8. AIR MONITORING FOR AIRBORNE ESTERON 245 IN THE WORK AREA OF THE ONE GALLON CANNING LINE DURING PACKAGING OF ESTERON 245 (DOWANOL PIB ESTER OF TRICHLOROPHENOXY ACETIC ACID) IN THE MICHIGAN DIVISION 2,4-D PLANT, 489 BUILDING, FEBRUARY, 1978

Description	2,4,5-T/PIB (mg/m^3)
Next to Material Handler at can filling machine	ND*
Next to Material Handler at can filling machine	ND
Next to Material Handler at capping machine	0.001
Next to Material Handler at capping machine	0.002
Near two Material Handlers loading empty cans onto the conveyor	ND
Near two Material Handlers loading empty cans onto the conveyor	ND
Near Material Handler loading pallets with filled cans and working near canner	0.004
Industrial Hygiene Guide	NE**

*ND - Less than the lower detectable limit of 0.001 mg/m^3 with a 10 liter air sample

**NE - Not established

16884

549000 DOW

Table 9. RESULTS OF AIR SAMPLING FOR CARBON MONOXIDE (GASOLINE ENGINE FORKLIFT EXHAUST) IN THE WAREHOUSE AREA OF THE MICHIGAN DIVISION 2,4-D PLANT, 489 BUILDING, NOVEMBER, 1978

Date	Description*	Carbon Monoxide (ppm)
11/02/78	Between drumming lines, 1st floor warehouse area (one forklift operation)	35**
11/02/78	Next to east drumming (one forklift operating)	20
11/02/78	Next to west drumming line (one forklift operating as close as 20 ft away)	50
11/02/78	Between drumming lines (later in day)	10**
11/02/78	Between drumming lines about 10 minutes after all forklift operations had ceased	5
11/02/78	West of drumming lines in warehouse during forklift operation in building	5
11/08/78	Aisleway south of 5 gallon filling line	15
11/21/78	Between drum filling lines (one forklift operating in area)	25
11/21/78	Between filling lines (later) next to continuous monitor which indicated 45-75 ppm (maintenance work was ordered)	25
11/21/78	Next to forklift during drum removal from 55 gallon line (near operator of forklift)	30
11/21/78	Between drum filling lines (one forklift operating)	15
11/22/78	Between drum filling lines by analyzer with 2 forklifts operating (analyzer reading approximately 250 ppm)	45
11/22/78	Storage area (west) random times	5
11/08/78	Personal breathing zone sample of Loader/Checker while working at drum filling lines (5 hour sample)	14
11/08/78	Personal breathing zone sample of Loader/Checker while driving forklift (5 hour sample)	16
Industrial Hygiene Guide		50
Excursion Limit		400

*Area samples unless otherwise noted

**These values were over 25% lower than the continuous analyzer value. The continuous analyzer was positioned between the two filling lines and about 25 feet from the warehouse office (Instrument Department evaluation was scheduled).

15885

549001 DOW

Table 11. RESULTS OF AIR MONITORING IN THE 2,4-D ENCLOSURE DURING DICHLOROPHENOL AND 2,4-D ACID PRODUCTION IN THE MICHIGAN DIVISION 2,4-D PLANT, NOVEMBER 11, 1977

Description	Dichlorophenol (ppm)	Dichlorophenoxy Acetic Acid (ppm)	Trichlorophenols (ppm)
Personal Samples			
Personal breathing zone sample of the Crystallizer Operator (approximate 8 hour TWA exposure)	0.049	0.087	0.093
Personal breathing zone sample of the Assistant Operator (approximate 8 hour TWA exposure)	0.049	0.069	0.073
Area Samples			
2,4-D acid filter wheel area, 4th floor	0.083 0.11	0.084 0.12	0.32 0.37
South of filter wheel area, 4th floor	0.065 0.059	0.038 0.094	0.19 0.14
Packaging area, 1st floor	0.008 0.005 0.015	0.007 0.011 0.047	0.007 0.019 0.034
Next to bulk tank manhole, 3rd floor	0.014	0.013	0.036
Industrial Hygiene Guide	1.0	1.1 ($10\ mg/m^3$)	1.0

DOW 1549003

9886L

FIGURE I. DIRECT ESTER PROCESS IN THE MICHIGAN DIVISION 2,4-D PLANT, 489 BUILDING

DOW /549004

FIGURE II. ACID ESTER PROCESS IN THE MICHIGAN DIVISION 2,4-D PLANT, 489 BUILDING

DOW 5490005

FIGURE 3. 2,4-D ACID PROCESS IN THE MICHIGAN DIVISON 2,4-D PLANT, 489 BUILDING

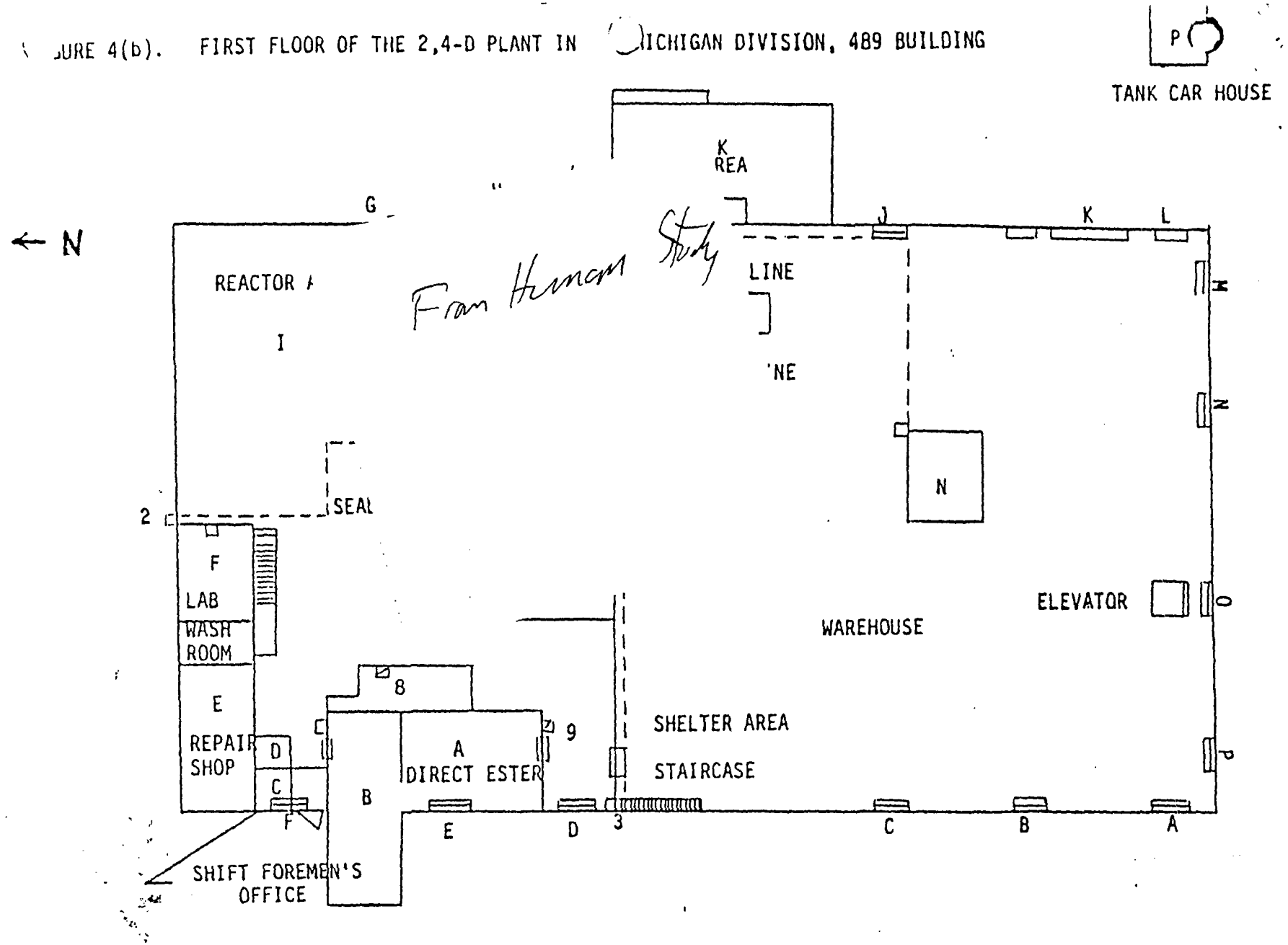
DOW 1549006

FIGURE 4(a). PLANT AREAS IN THE MICHIGAN DIVISION 2,4-D PLANT 489 BUILDING

LOCATION	FLOOR	PROCESS AREA
A	1	DE low bay
B	1	DE high bay
C	1	Shift foremen's office
D	1	Coffee room
E	1	Shop
F	1	Lab
G	1	2,4-D
H	1	2,4-D enclosure
I	1	2,4-D reactor
J	1	Acid ester
K	1	DMA
L	1	55 and 30 gallon packaging line
M	1	5 gallon packaging
N	1	Warehouse office
O	1	Warehouse
P	1	Tank car house
Q	2	De low bay
R	2	DE high bay
S	2	Lunchroom
T	2	2,4-D
U	2	2,4-D enclosure
V	2	2,4-D reactors
W	2	Acid ester
X	2	DMA
Y	2	Warehouse
Z	2	Offices
AA	3	DE high bay
BB	3	2,4-D
CC	3	2,4-D enclosure

DOW_1 549007

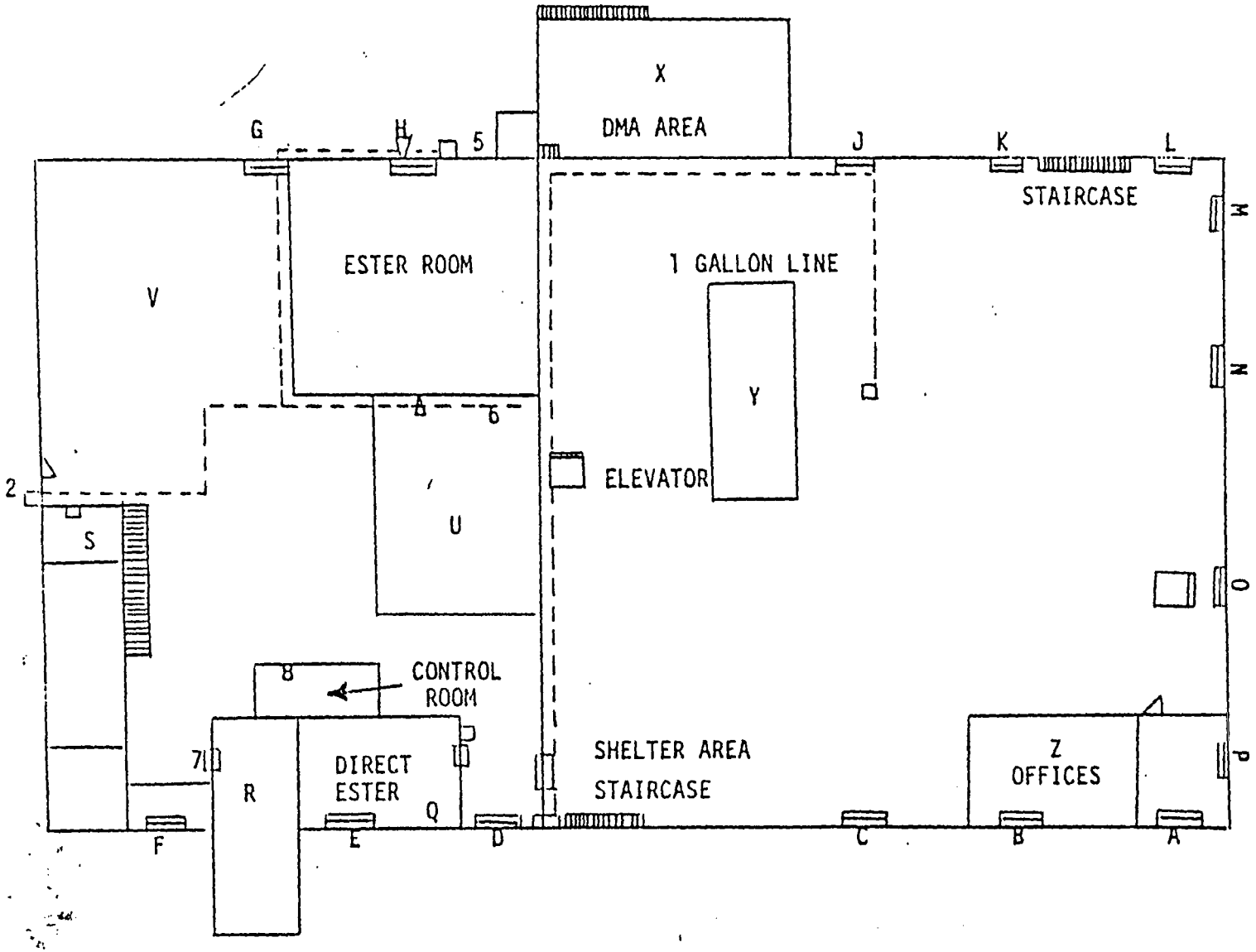
JURE 4(b). FIRST FLOOR OF THE 2,4-D PLANT IN ICHIGAN DIVISION, 489 BUILDING



16691

549008

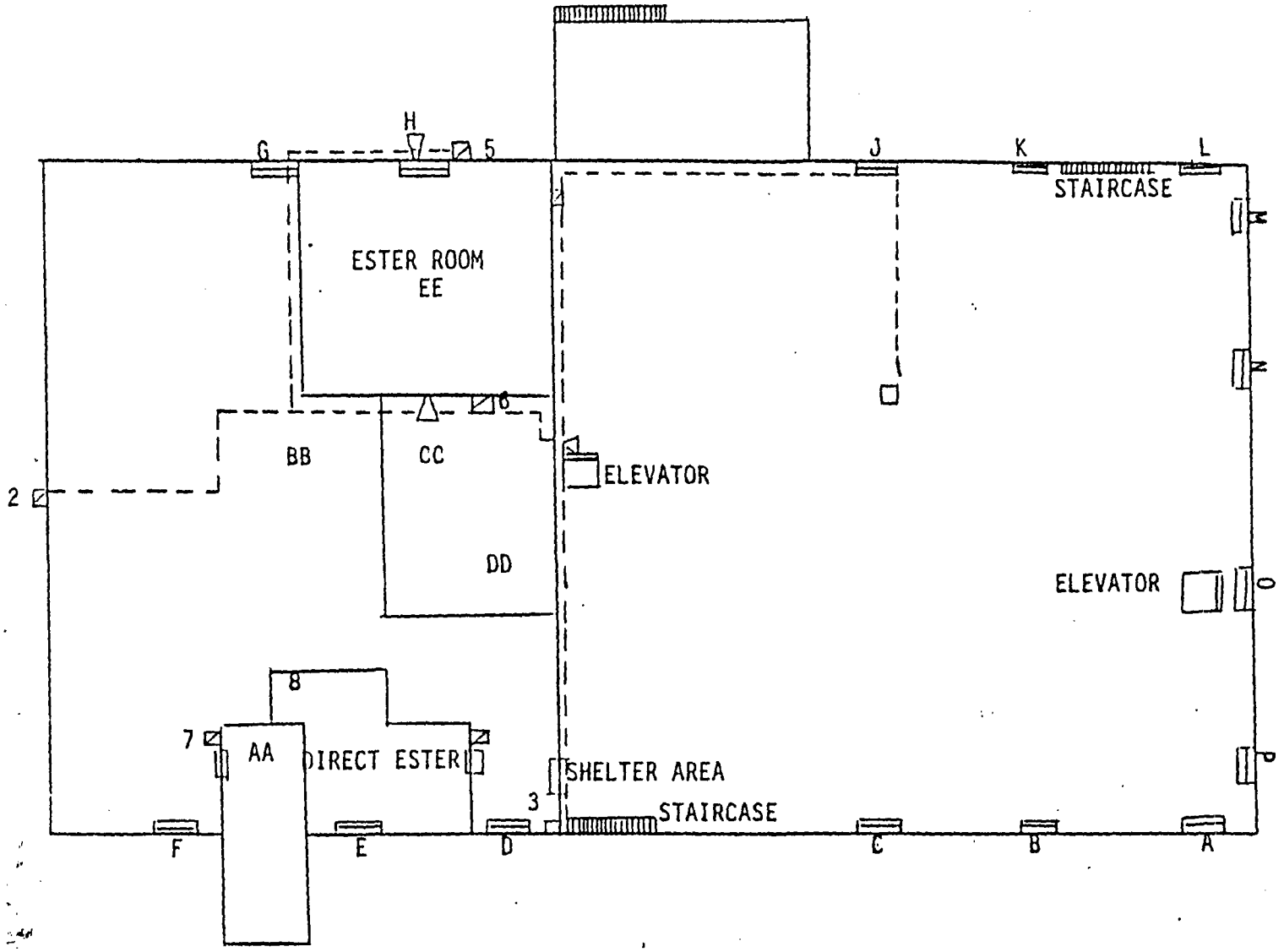
FIGURE 4(c). SECOND FLOOR OF THE 2,4-D PLANT ON THE MICHIGAN DIVISION, 489 BUILDING



26891

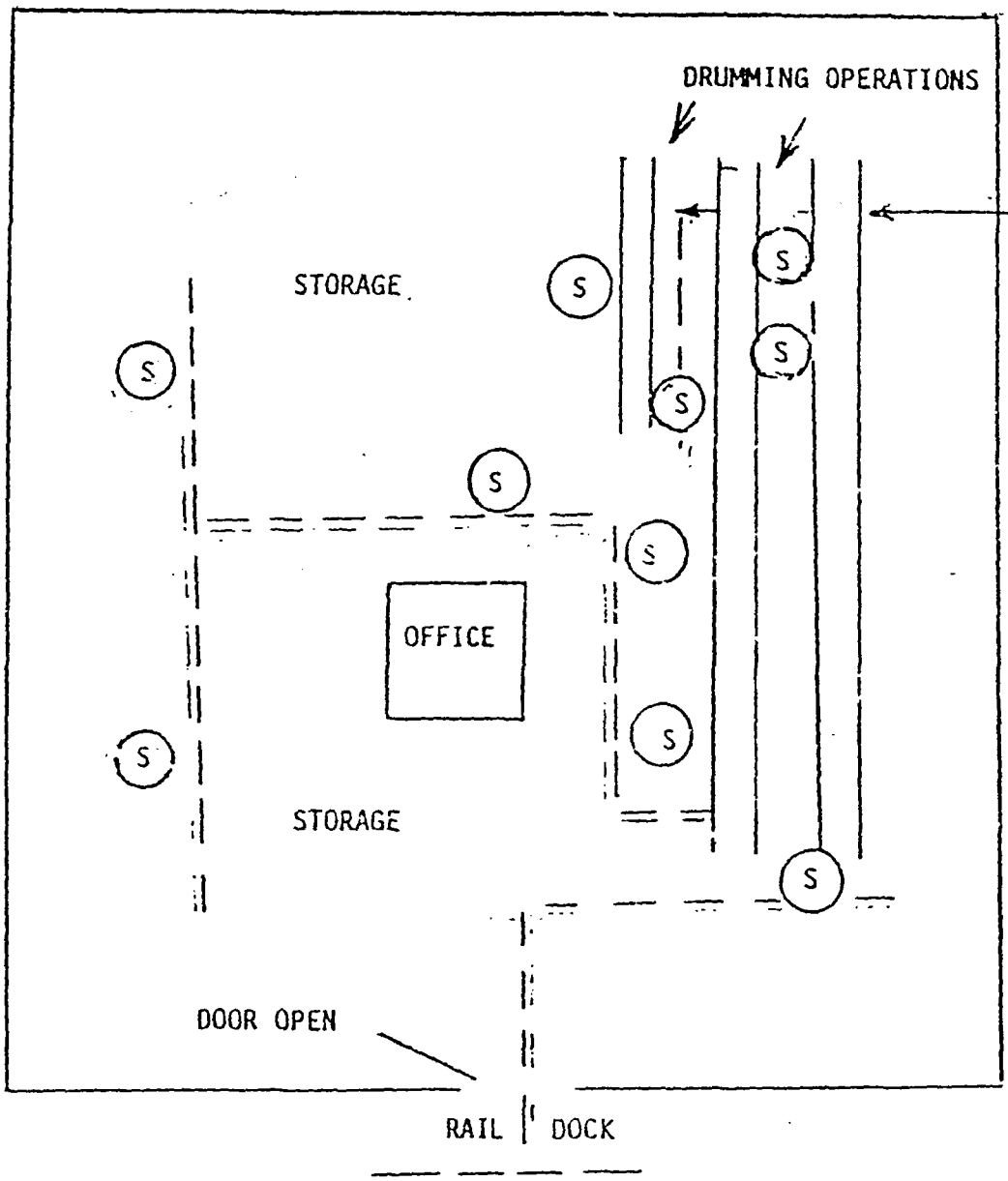
DOW 1 549009

FIGURE 4(d). THIRD FLOOR OF THE 2,..-D ANT IN THE MICHIGAN DIVISION, 489 BUILDING



549010

FIGURE V. WAREHOUSE TRAFFIC FLOW AND SAMPLING POINTS FOR CARBON MONOXIDE IN THE MICHIGAN DIVISION 2,4-D PLANT, 489 BUILDING



(S) = SAMPLE POINTS

_ _ _ _ _ = TRAFFIC PATTERN FOR GAS JEEP DURING SAMPLE PERIOD

16899

The only proposed revision to KURON label is shown on this page.

2352

DOW 239311

Kuron foliage herbicide is used in controlling certain woody and herbaceous plants growing on pasture and range lands, ditch banks, fence rows and right-of-ways.

DIRECTIONS

PREPARING THE SPRAY: Add half the required amount of water to the spray tank, then add Kuron with agitation. Kuron forms an emulsion in water and tends to settle out on prolonged standing. Provide agitation to prevent such separation and ensure uniform mixture in the spray tank.

FOLIAGE TREATMENT: Spray woody growth up to 6 or 8 feet tall after the foliage is fully developed, using a spray containing 3 to 4 quarts of Kuron per 100 gallons of water. With sensitive species, taller brush or trees may be controlled if foliage is adequately covered. On poison ivy and brambles such as wild blackberry, use 2 quarts of Kuron per 100 gallons of water. Spray should drench all plant parts including leaves and stems.

Delay spraying new sprouts from recently cut stumps until they have made appreciable growth. Under good growing conditions, in humid areas, applications made up to three weeks before fall frost are usually effective. (Application in late summer and fall in Texas and Oklahoma is not recommended.) Spraying after leaves have lost their normal green color and vigor may not give satisfactory control. Less effective control may result during hot, dry weather when deep soil moisture is deficient. Usually a single application in any one year is sufficient. If new growth develops, repeat applications may be necessary in succeeding years.

AIRPLANE APPLICATION: For control of post and blackjack oaks, use 2 quarts of Kuron in 1 gallon of diesel oil and 2½ to 3½ gallons of water, or 2 quarts of Kuron in 3½ to 4½ gallons of diesel oil per acre. Apply after foliage is fully developed (usually in May and June). An additional spray using 1 to 2 quarts of Kuron may be necessary the second or third year. These applications will effectively control broad-leaved weeds in sprayed areas.

SPOT TREATMENT: For knapsack application of Kuron, mix ½ cupful in 3 gallons of water. Wet all foliage thoroughly.

WEED CONTROL IN LAWNS AND GOLF COURSES: For control of broad-leaved plantain, buckhorn, common chickweed, mouse-eared chickweed, dandelion, and legumes such as white clover and black medic in established turf, apply 1½ quarts of Kuron in 25 to 40 gallons of water per acre. Higher volumes, up to 100 gallons per acre, may be used to minimize drift hazard. Apply in fall or early spring as hot-weather use may cause excessive damage to turf. Do not apply to stoloniferous grasses such as bent, Bermuda and St. Augustine or to new turf of any variety.

CAUTION: To avoid damage to turf, do not spray in any manner which will cause excessive dosages. Avoid overlapping and double coverage when backing up, and at turns. Avoid spraying when nozzles and boom are not moving, such as when cleaning or testing nozzles. Use a positive quick shut-off valve on boom spraying equipment.

WEED CONTROL IN RICE: Treat 4 to 8 weeks after emergence of the rice. Where flooded, treat between 7 and 9 weeks after seeding, when plants have emerged above water and leaves are standing erect. Use 1½ to 3 pints of Kuron in the amount of water needed for even distribution. For many situations, 2 pints per acre is adequate. Where weeds tend to be resistant because of specie, age or growth condition, up to 3 pints will give better control. Treatment after flooding is usually safer than before flooding. Consult your State Experimental Station or Extension Service for specific local recommendations.

FOR CONTROL OF YUCCA AND SAND SHINNERY OAK: Use 1 pint to 1 quart of Kuron in 1 gallon of diesel oil, and water to make 4 gallons total per acre. Two to three applications as necessary in successive years may be needed. Apply after foliage is fully developed. Consult competent local authorities for information on best rate and best time for application.

USE RECOMMENDATIONS IN SUGAR CANE

FLORIDA

For post emergence control of ragweed, dog fennel, ground cherry, purslane, wild lettuce, nightshade and other susceptible broadleaved weeds, apply 1 to 1½ quarts of KURON in 20 to 40 gallons of water per acre as broadcast spray. Make the 1st application after the cane emerges as spring growth and when weeds are growing vigorously, but before they send up seed stalks. A second application can be made for late emerging weeds. NOTE: ~~Do not apply after the cane is 3 to 3½ feet tall.~~ ←1

LOUISIANA

For the control of crabgrass, barnyard grass and Johnson grass seedlings in sugar cane, apply 1 quart of Kuron in 15 gallons of water per acre on the row (approximately one-third of the total area) shortly before the seeds are expected to germinate. If cane is shaved and off-barred, treat immediately following this operation. Follow the early treatment when necessary with 2 pounds of Dowpon® per acre, applied over the grass in the row (approximately one-third of the total area).

To control wild lettuce, curled dock, ~~and other~~ 2
weeds use one of the following procedures when 3
the weeds are growing vigorously.

Ground Application: Use 1 quart of Kuron in 15 gallons of water per acre applied over the row (approximately one-third of the total area). A second application can be made if needed. Do not make application ~~after cane is 3 to 3½ feet tall. Make application at least 5 months before harvest.~~ 4

Air Application: Use ~~1 quart~~ of Kuron per acre in 5
enough water for uniform coverage. Application can be made up to ~~5 months~~ before harvest. 6

HAWAII

For pre-emergence control of hairy crabgrass, yellow foxtail, richardsonia, fireweed, slender amaranth, Flora's paintbrush, jungle rice, purslane and wiregrass in Hawaiian sugar cane, apply 4 to 5

(Continued on Side Panel)

WEED LIST

Kuron is effective in controlling — post oak, blackjack oak, ground ivy, northern (pin, red, white, scrub) oaks, mesquite, maples (such as red, sugar, and big leaf maple), poison ivy, sand shinnery oak, yucca, wild blackberry,

also certain broad-leaved weeds such as—broomweed, cocklebur, croton weed, curly indigo, lamb's-quarters, Mexican weed, pokeberry, ragweed, salt cedar, sunflower.

NOTE: Do not use Kuron for the control of ash.

HAWAII — Continued

quarts Kuron per acre in 20 to 40 gallons of water as a broadcast spray immediately after planting or ratooning and before cane emergence. For post-emergence control of weeds after canes have emerged, add 2½ to 5 pounds of Dowpon per acre to the spray of Kuron in order to control grasses, and spray the interline space without spraying the cane directly. This application can be made up to the time of "closing in" but not less than ~~5 months~~ before harvest. Do not make more 7
than two applications of 5 quarts each of Kuron to any one crop.

Local conditions may affect the use of herbicides. State agricultural authorities in many states issue recommendations to fit local conditions.

WARNING

Do not apply Kuron directly to, or otherwise permit it to come into contact with, any crop plant or ornamental plant (including but not limited to peanuts, soybeans, beans, peas, tomatoes, tobacco, cotton, melons, okra, sweet potatoes, peppers, celery, flowers, ornamentals, grapes, deciduous and nondeciduous fruit trees) and do not permit spray mists containing Kuron to drift onto them, since even minute quantities may cause severe damage during both growing and dormant periods. Coarse sprays are less likely to drift. Applications by airplane, ground rigs and hand dispensers should be carried out only when there is no hazard from drift. Do not apply by airplane in the vicinity of any desirable crops or ornamentals including those listed above. At elevated temperatures vaporization may cause injury to susceptible plants growing nearby.

Do not use Kuron on freshly seeded lawns, pasture or range lands until grass has become well established. Do not contaminate irrigation ditches or water used for domestic purposes. Do not store near fertilizers, seeds, insecticides or fungicides. To avoid injury to desirable plants, do not store, handle or apply other agricultural chemicals with the same containers or equipment used for Kuron. Do not use Kuron in spraying equipment contaminated with 2,4-D if the 2,4-D will increase the hazard to desirable plants.

Be sure that use of this product conforms to all applicable regulations.

CAUTION — MAY CAUSE SKIN IRRITATION
Avoid Contact with Eyes, Skin and Clothing
Keep Out of The Reach of Children

86-1092 Printed in U.S.A. in November 1965

REPLACES SPECIMEN LABEL 86-1092 PRINTED IN APRIL 1965
THE REVISION IS IN THE SECTION "USE RECOMMENDATIONS IN SUGAR CANE." AMONG THE CHANGES WAS THE ADDITION OF THE RECOMMENDATION FOR USE IN FLORIDA.

Proposed Revisions - July 11, 1966

1. Substitute: - "within 60 days of harvest"
2. Add: - "morningglory, tievine, cypressvine"
3. Add: - "broadleaved"
4. Substitute: - "within 60 days of harvest"
5. Substitute: - "2 to 3 pints"
6. Substitute: - "60 days"
7. Substitute: - "60 days"

16895

THE GLOBE AND MAIL Thursday October 30, 1980

DOW:050479

Employers withhold truth about toxics, MD warns workers

By ROBERT STEPHENS

Workers exposed to toxic and carcinogenic substances are little more than guinea pigs, and their employers are purposely withholding information about the very real risks of industrial cancer, a expert on occupational health has warned.

Dr. Samuel Epstein, professor of occupational and environmental medicine at the University of Illinois, told a conference in Toronto yesterday that workers who are exposed to hazardous substances "are the throwaway segment of society."

He condemned the governments of the United States, Canada and Britain for failing to regulate toxic substances in the workplace. While regulations controlling the use of seven designated substances were proposed in Ontario more than two years ago, these regulations are yet to be passed.

Dr. Epstein said the incidence of cancer is increasing among the general population at an alarming rate that reflects the huge growth in the production of synthetic organic chemicals beginning 30 years ago.

He said the worker is being sacrificed by government and industry because "they believe that economic growth is paramount." And he charged that industry was engaged in a massive coverup to keep its employees ignorant of the risks of cancer in the workplace.

Dr. Epstein said one of the favorite strategies of industry was to "blame the cancer victim himself" by linking his disease to smoking, diet, and even his genetic makeup. "Industry tries to deny the evidence for occupational cancer."

He said industry also frequently resorts to the argument that the costs of complying with exposure regulations will result in plant shutdowns and higher unemployment.

He said chemical companies in the United States had fought regulations on vinyl chloride for years, and that their spokesmen had claimed the costs of compliance would be $90-billion and 2.2 million lost jobs.

"But when BF Goodrich came under the regulations in the spring of 1975 — its cost was $35-million — it actually began to make money on the recovery of vinyl chloride, and then, complaining of unreasonable government interference, it had the nerve to raise its prices," Dr. Epstein said.

One of the delegates at the conference asked what workers could do to protect themselves from exposure to dangerous substances in the absence of government regulation, and Dr. Epstein replied: "If you have an option, I'd say get the hell out of hazardous workplaces."

DOW

COMMUNICATIONS

2409

TO: CHARLTON

RE: STEVENS STUDY

I KNOW. I THOUGHT I TOLD YOU ABOUT THE KINGSLEY STEVENS PIECE.

THING IS, I CAN'T FIND AN EASY WAY TO MOVE BETWEEN PARTS PER AND mg/KG.

HAVE TO TALK WITH DAVIDSON ABOUT THAT. IT'S A SKILL I'LL BE NEEDING FOR THE NEXT TWO YEARS. ONCE I'VE LEARNED HOW TO DO THAT, I CAN REALLY MAKE USE OF THE STEVENS PIECE.

MN074379

FROM: GARRY HAMLIN
2020 Dow Center
636-1325

16897

DOW 2069496

DOW

PUBLIC AFFAIRS

9/19

G. L. HAMLIN
2020

DOW 20069407

SEE PG. 36 OF ~~ATTACHED~~ STUDY — PARTICULARLY RELEVANT TO YOUR "94%-OF- TCDD-NEVER-REACHED JUNGLE FLOOR" POSITION STATEMENT DRAFT.

ABSORPTION, UPTAKE CALCULATIONS ARE VERY SUPPORTIVE OF OUR POSITION. RETURN STUDY TO ME FOR MASTER FILE / RWC

FROM: BOB CHARLTON
636-9303

16898

Human Toxicol. (1981), 1, 31–39

Agent Orange Toxicity: a Quantitative Perspective

Kingsley M. Stevens

Department of Medicine, State University of New York at Stony Brook, Stony Brook, New York 11794, USA

1 The minimum toxic dose of tetrachloro-dibenzo-p-dioxin (TCDD) for man has been calculated from monkey and human data to be 0.1 $\mu g\,kg^{-1}$.
2 The amount of TCDD which man takes in from his environment is about 1/2050 of that present in one square metre of his immediate environment.
3 The average concentration of TCDD present in Vietnam immediately after spraying Agent Orange was 8 $\mu g\,m^{-2}$.
4 A soldier directly sprayed would attain an internal body concentration of $7 \times 10^{-5}\,\mu g\,kg^{-1}$ or 1/1750 of the minimum toxic dose; soldiers moving through previously sprayed areas would ingest much less.
5 These quantitative aspects indicate that the dioxin sprayed with Agent Orange in Vietnam cannot have caused systemic illnesses in Vietnam veterans or birth defects in their children.

Introduction

To evaluate the probable toxic effects of the dioxin in Agent Orange upon Vietnam veterans requires three steps. First, the minimum toxic dose (MTD) of 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) must be established for man. Second, the fraction of the TCDD which is actually transferred into humans, within a unit area, must be estimated. Using these figures, the known amounts of TCDD which contaminated the Agent Orange sprayed in Vietnam can be converted into fractions of the minimum toxic dose.

Minimum toxic dose of TCDD in man

The herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) composing Agent Orange have very low mammalian toxicity but the 2,4,5-T was contaminated with TCDD producing an average concentration of TCDD in Agent Orange of 2 p.p.m. (Young *et al.*, 1978). Whereas the herbicides contain a single benzene ring, the dioxins are one of a large group of polychlorinated aromatic hydrocarbons with two rings. There is a very wide range in the toxicity of these compounds but the pathology produced in a given animal species is the same once the toxic level is reached (McConnell & Moore, 1979). Hence quantitative data on poisoning by one compound can be

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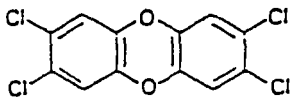
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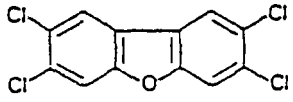
converted to TCDD equivalents if the comparative toxicity of that compound to TCDD is known.

One way to estimate the MTD of TCDD in man is by extrapolation from primate experiments. When rhesus monkeys were fed small amounts of TCDD in the daily food ration, they showed puffy eyelids, loss of facial hair and scaly skin after a cumulative ingestion of 1 $\mu g\,kg^{-1}$ (Allen *et al.*, 1977). Minimal signs must have appeared earlier, thus 0.5 $\mu g\,kg^{-1}$ should approximate the MTD. The number of monkeys was small and this value as the MTD for man must remain suspect because of basic differences unless supported by more direct data.

Human data to determine the MTD are available from the Japanese studies of Yusho or oil disease (Kuratsune *et al.*, 1972). In 1968 an oil made from rice bran was contaminated with a commercial polychlorinated biphenyl (PCB) which contained trace amounts of the highly toxic 2,3,7,8-tetrachloro-dibenzo-p-furan (TCDF), the furan analogue of TCDD. The structures of TCDD and TCDF appear below.



TCDD



TCDF

The contaminated rice oil contained between 5 p.p.m. (Nagayama, Masuda & Kuratsune, 1975) and 2 p.p.m. (Bowes *et al.*, 1978) of polychlorinated dibenzofurans of which about 30% was TCDF (Nagayama *et al.*, 1975). Taking 30% of the mean of 3.5 p.p.m. yields TCDF of 1 p.p.m. or 1 $\mu g\,ml^{-1}$ of rice oil. This oil was incorporated into a commercial chicken mash which caused illness in 2 million chickens with death in 400,000 of them. The oil was also marketed as a home cooking oil and consumed by about 2500 people over a period of several months. About two-thirds of those people who ingested the oil became ill. Frequent signs and symptoms in males were eye discharge (89%), chloracne (88%), oedema of upper eyelids (72%), asthenia (58%), and transient visual disturbance (56%). Gastrointestinal symptoms were less common with vomiting in 24%, diarrhoea in 19% and jaundice in 11%. Serum chemistries showed very few changes, the most frequent being increases in cholesterol and triglycerides. Severe cases developed anaemia and elevated alkaline phosphatase (Kuratsune, 1972). In the following decade there were 51 deaths among the 1665 patients, the first being about a year after the onset of symptoms (Urabe, Koda & Asahi, 1979). Several early deaths were associated with pericardial disease (Kikuchi & Masuda, 1976). There have been two deaths from malignant lymphomas which will be discussed later. Thirteen babies were delivered of mothers who ingested TCDF. Most babies showed some of the signs of Yusho found in adults. Some babies were small at birth and grew more slowly but later resumed normal growth rates (Yoshimura & Ikeda, 1978). There were no birth defects. Of two stillbirths, one was autopsied; it showed minor signs of Yusho but death was due to asphyxia from a twisted umbilical cord (Kikuchi *et al.*, 1969).

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Of 141 patients with Yusho whose dietary intake of oil was carefully studied, only two adults had ingested less than 200 ml of oil when they first developed signs or symptoms (Hayabuchi, Yoshimura & Karatsune, 1979). Their oil intake was 2.1 and 3.0 ml kg^{-1} respectively or 2.1 and 3.0 $\mu g\ kg^{-1}$ of TCDF. Since TCDD is 20 times as toxic as TCDF (McConnell & Moore, 1978), the minimum toxic dose of TCDF of 2 $\mu g\ kg^{-1}$ is equivalent to 0.1 $\mu g\ kg^{-1}$ of TCDD. Humans can describe symptoms while monkeys cannot, hence one would expect the true MTD for man to be lower than that obtained by extrapolation from monkey studies. The agreement between 0.5 $\mu g\ kg^{-1}$ from monkey studies and 0.1 $\mu g\ kg^{-1}$ from the Yusho studies in man is good. The value from the human studies of TCDD of 0.1 $\mu g\ kg^{-1}$ will be used as the cumulative minimum toxic dose in man.

Intake transfer factor

Chloracne can be caused by TCDD acting externally at local sites (Crow, 1971) or by systemic TCDD. The major concern of Vietnam veterans is not with chloracne but with other possible long-term systemic effects. Hence one must determine what fraction of TCDD present in a unit environmental area is introduced into a human in that environment; the intake transfer factor is the ratio of the intake of TCDD to the environmental TCDD. This factor will be estimated from two accidents which dispersed TCDD.

In May and June of 1971, TCDD contaminated waste oil sludge was sprayed for dust control on one outdoor and two indoor horse arenas in Missouri. The sludge contained waste from the purification of 2,4,5-T; its TCDD content was 330 $\mu g\ g^{-1}$ (330 p.p.m.) and a soil sample from one covered arena contained 32 $\mu g\ g^{-1}$ (Kimbrough *et al.*, 1977). TCDD does not leach into soil even from oil (Wipf *et al.*, 1978), thus most of the TCDD would remain in the top centimetre of soil. If the soil surface is equated with the top millimetre, then a square centimetre of soil would contain 3.2 μg of TCDD or 32,000 $\mu g\ m^{-2}$. Of 85 horses exercised in the arena, 58 became ill and 43 died. There were 26 known abortions in horses and many foals died young. In the second covered arena 12 out of 25 horses died; in the open arena 7 out of 40 horses died. There were hundreds of deaths of birds, many cats and a few dogs. Despite this extreme animal toxicity no human illness was associated with the open arena. Two three-year-old boys who played in the second arena developed chloracne only. A six-year-old girl played daily on the floor of the arena with 32,000 $\mu g\ m^{-2}$ of TCDD from May 26 until mid-August when she developed mild chloracne (Reggiani, 1978), nosebleeds, headaches, diarrhoea and bloody urine. Examination revealed an acute nephritis and haemorrhagic cystitis. Within a week after removal from contact with the arena her symptoms had disappeared. Cystoscopy 3 months later revealed punctate haemorrhagic areas of the bladder but no haematuria. Her ten-year-old sister and her mother also entered the arena frequently. They developed very mild chloracne (Reggiani, 1978), abdominal pain, diarrhoea and intermittent headaches, all of which promptly subsided when arena contact stopped. Five years later, extensive examinations of all three revealed only normal findings (Beal *et al.*, 1977).

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This six-year-old girl had an unparalleled opportunity to take in TCDD from her daily environment. It was during summer so her clothing was light. Systemic toxicity can occur from TCDD applied to large skin areas (Schwetz *et al.*, 1973). She played on the floor where TCDD was easily available to hands and thence to mouth and yet she became less ill than the average case of Yusho. That average case ingested 688 ml of oil (Hayabuchi, Yoshimura & Kuratsune, 1979), equivalent to 34 μg of TCDD or 0.7 $\mu g\,kg^{-1}$. Hence the symptoms shown by this girl would be consistent with a cumulative intake of not more than 0.7 $\mu g\,kg^{-1}$ of TCDD; for her 20 kg weight this would be 14 μg. The ratio of 14 μg to 32,000 $\mu g\,m^{-2}$ is 1:2300, the intake transfer factor based on this incident.

About noon on July 10, 1976, a factory north of Milan which produced trichlorophenol had an explosion which released boiling reagents into the atmosphere. Most of the cloud settled on a 110 hectare (1 ha = 2.47 acres) area in the town of Sevaso where it deposited about 2 kg of TCDD. This area was designated Zone A and a larger, more distant area of 269 ha which received only 20 g of TCDD was designated Zone B. The 733 residents of Zone A were evacuated 2 weeks after the explosion. The 4800 residents in Zone B were not evacuated but were prohibited from raising or using produce from either Zone B or the surrounding 1430 ha Zone R. These amounts of TCDD would produce average concentrations of 1800 and 7 μg of TCDD per square metre in Zones A and B respectively. Analyses carried out days to weeks after the explosion showed a very spotty distribution with a range in Zone A from 5447 μg per square meter to not detectable (Pocchiari, Silano & Zampieri, 1979). Actual concentrations on vegetation and soil shortly after the explosion were undoubtedly higher than these recorded values. Birds began dying in Zone A a few days after the explosion. Birds preen their feathers regularly. The surface area of the feathers is many times that of the skin surface so even a small bird must have at least 0.1 m^2 of feather surface. If the feathers held the average concentration of 1800 $\mu g\,m^{-2}$, then 180 μg would be present on a bird weighing only 30 to 100 g. Thus the bird could ingest 1000 $\mu g\,kg^{-1}$, about ten times the acute LD_{50} for birds (Young *et al.*, 1978). Rabbits which ate fresh vegetation from local fields died next. A 1 kg rabbit consuming vegetation from an area of one square meter would take in at least 1800 μg, over ten times the LD_{50} for rabbits. More cats than dogs died since cats both groom frequently and eat birds. Later a number of sheep and cattle died; most livestock in Zone A was destroyed. In Zone B, however, birds and rabbits would consume TCDD in the order of 7 $\mu g\,kg^{-1}$ (below the acute toxic dose) and here few of these animals were found dead.

The early toxic effects in man were not due to TCDD but to other chemicals, for example sodium hydroxide. Chloracne has been the only prominent effect found to be caused by TCDD; 193 cases have been diagnosed with 50 cases in residents of Zone A. The diagnosis in the 143 cases outside Zone A is confused because these were found by screening 49,000 people for an incidence of 0.3% and this percentage is reported to be the incidence of chloracne in more northern industrial Italian cities not involved in the accident. However, in Zone A the incidence of chloracne was 7%: 23 times this base rate. In addition, about 10% of the Zone A population showed either minor clinical signs of polyneuropathy or laboratory

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evidence of slowed nerve conduction times. Transient changes in liver enzymes were noted in a few cases. There have been no deaths, no serious disease, no immunological changes, no birth defects, no increase in spontaneous abortions and no chromosomal changes attributable to TCDD (Pocchiari *et al.*, 1979; Rehder *et al.*, 1978; Reggiani, 1978, 1979; Tenchini *et al.*, 1979; Tuchmann-Duplessis, 1977). Cases of chloracne outside Zone A were probably due to external contact with transported TCDD. The overall pattern indicates that the mean concentration of TCDD in Zone A was below the minimum toxic dose but the spotty distribution produced minimal signs and symptoms in about 10%. Since most clinical findings were in children under age 12, 30 kg will approximate the average weight. To reach the MTD of TCDD of 0.1 $\mu g\,kg^{-1}$ would require an intake of 3 μg. The mean concentration of TCDD was 1800 $\mu g\,m^{-2}$ which must have been considerably lower than the level needed to provide the MTD. It will therefore be assumed that the 10% affected were exposed to about three times this mean value or 5400 $\mu g\,m^{-2}$. The intake transfer factor for Seveso would then be 5400/3 or 1:1800.

TCDD is most toxic for guinea pigs and least for dogs. The acute toxicity for chickens, mice, rats, cats and monkeys are all within a proportional order of magnitude, and chronic toxicity in man, monkeys and rats is not very different (Young *et al.*, 1978). Hence the reason that human toxicity was low in Missouri and Seveso while animal toxicity was high, related not to innate differences in sensitivity but to a very much lower intake of the environmental TCDD. Humans wear shoes and clothing, they do not groom with their mouths, they wash themselves and their food and they do not eat vegetation in bulk. These features account for the intake transfer factors of 1:2300 calculated from a single individual for whom accurate measurements of environmental TCDD and of the duration and type of exposure were known, and of 1:1800 calculated from the signs and symptoms of about 75 individuals with less accurate TCDD measurements and of their exposure. The agreement is good and the average value of 1:2050 will be used for the intake transfer factor.

Industrial cases and animal studies

There have been at least eight industrial accidents which would have released TCDD (Young *et al.*, 1978). The explosion at Seveso differed from the others in that the reagents were released to the atmosphere instead of within the plant. Although TCDD levels were not measured in earlier accidents, it is obvious that the plant levels attained would have been much higher than those found in Zone A at Seveso (Reggiani, 1978). About 800 cases of chloracne which developed from explosions and other industrial contact have been followed, some up to 30 years. The largest group, consisting of 121 workers who developed chloracne after an explosion in 1949, have been followed for 30 years and showed no increase in overall mortality rates nor in cardiovascular or neoplastic death rates (Zack & Suskind, 1980). From the rather sparse details available, persisting morbidity from Yusho appears greater than that from industrial poisoning by TCDD.

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TCDD produces fetal deformities and cancer in rodents in cumulative doses over 1 $\mu g\,kg^{-1}$. It has not produced either of these effects in monkeys (Young *et al.*, 1978). TCDD caused abortions in monkeys after 7 months of daily feeding, and depression of spermatogenesis after a year (Allen *et al.*, 1979). Treatment of male mice with doses of TCDD which caused fetal abnormalities in pregnant mice (Lamb, Moore & Marks, 1980), caused no changes in the libido of the fathers nor abnormalities in their offspring.

Vietnam

Agent Orange is an oily liquid composed of equal volumes of the *n*-butyl esters of 2,4-D and 2,4,5,-T. TCDD, present in Agent Orange in an average concentration of 2 p.p.m., is extremely insoluble in water but readily soluble in Agent Orange. The herbicide was delivered as a coarse spray with droplets of 320–350 μm diameter (Young *et al.*, 1978). While gases readily enter the lungs, only droplets which are less than 10 μm can enter (Walton, 1971), thus Agent Orange could not be absorbed from the lungs. Each gallon of Agent Orange contained 10.7 lbs (4.9 kg) of total herbicide (Young *et al.*, 1978). One acre is 3660 m^2 so the spraying rate of three gallons per acre converts to metric mass units of 4.1 $g\,m^{-2}$. Since the mean TCDD concentration in Agent Orange was 2 p.p.m., the delivered amount of TCDD would be 8 $\mu g\,m^{-2}$. The average concentration of TCDD in Zone B in Seveso, where the people were not evacuated, was 7 $\mu g\,m^{-2}$ (Pocchiari *et al.*, 1979).

The conditions for destruction of TCDD in Vietnam were almost ideal. TCDD is very stable in the dark but is photodechlorinated in position eight. The resulting 2,3,7-TriCDD is 10,000 times less toxic (McConnell & Moore, 1979). Photodechlorination requires light, an organic hydrogen donor (Agent Orange works well) and the reaction proceeds three times faster at 30°C, the mean annual daytime temperature in Saigon, than at 23°C (Liberti *et al.*, 1978). When Agent Orange is applied to leaves in full sunlight, the half-life of the contaminant TCDD is only 2 h (Crosby & Wong, 1977). Grass receives less light and some TCDD reaches the soil; the half-life of TCDD applied to turf is about 6 days (Young *et al.*, 1978). Since spraying was done in early morning (Young *et al.*, 1978), a single day of full sun would decrease the TCDD on the leaves from 8 to 0.3 $\mu g\,m^{-2}$. About 90% of Agent Orange was sprayed on forests and only 6% of that reached the forest floor (Young *et al.*, 1978) to yield 0.5 $\mu g\,m^{-2}$ of TCDD. Hence under forest cover, troops passing through, even under direct spraying, would receive less than 1 $\mu g\,m^{-2}$ in their environment. For the 10% not sprayed on forests, the early morning concentration of 8 $\mu g\,m^{-2}$ would be less than half of that by evening. For most soldiers who had any exposure to Agent Orange, that exposure would consist of walking through vegetation which contained no more than 1 $\mu g\,m^{-2}$ of TCDD. Using the transfer factor of 1:2050, the soldier would take in 5×10^{-4} μg of TCDD. For a 70 kg soldier this represents 7×10^{-6} $\mu g\,kg^{-1}$ or 1/14,000 of the minimum toxic dose of 0.1 $\mu g\,kg^{-1}$. On rare occasions soldiers were probably exposed to direct spraying from aeroplanes. The intake would still be only 1/1750

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of the MTD. Even if a soldier were exposed to 8 $\mu g\ m^{-2}$ each day of his one year tour in Vietnam and each day was treated as a new exposure, his cumulative intake would be only 1.4 μg or 0.02 $\mu g\ kg^{-1}$ of TCDD.

Since it would take about 5 years of daily close contact with Agent Orange to reach toxic levels of TCDD, claims that illnesses in Vietnamese (Tung *et al.*, 1971, 1973) and Americans (Bogen, 1979) were due to Agent Orange are without merit. However, certain workers in forest industries have been exposed to 2,4,5-T over many years. Although the present concentration of TCDD in 2,4,5-T is <0.1 p.p.m., it was considerably higher than 2 p.p.m. before the 1960s. Commercial spraying rates were usually less than 3 gallons per acre but higher TCDD concentrations could lead to toxic cumulative intakes after several years. Two patients with Yusho have died from lymphomas and recently six cases of lymphoma of histiocytic type were reported in patients who had an average of 8 years exposure to 2,4,5-T in years past (Hardell, 1979). Hence the possibility that cumulative intakes of TCDD above the MTD may have increased the incidence of lymphoma must be further investigated.

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AN EVALUATION OF 2,4-D DATA

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Foreward.

The phenoxy herbicides, including 2,4-D, have received considerable attention during the last decade in the press, in public hearings and by groups which have campaigned against the continued use of these herbicides for controlling unwanted vegetation in forests, on rights-of-way and on certain croplands. The groups against the continued use of herbicides have spent considerable time and effort preparing literature, press releases, mailings and in participation at public hearings.

The primary message of these groups is that the use of phenoxy herbicides will increase birth defects and cause miscarriages, cancer or other physical effects. Various scientific studies as well as articles from the press are used to support their allegations. Very frequently only those portions of the data in a given study which support the allegation are cited.

The reliance upon data from studies conducted in animals to estimate the effects in humans has also been debated. However, animals are the only species phylogenetically close to humans which can be used for testing. Therefore, it is necessary to correlate data from animal studies with the potential for human exposure under worst case conditions and define a safety factor.

In most studies on living organisms the data are neither completely positive nor completely negative but require the expertise of knowledgeable scientists for interpretation.

Herein, data and conclusions are submitted which are intended to present an unbiased review of the toxicological studies on 2,4-D which have been conducted to date.

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1. What is 2,4-D?

2,4-D (2,4-dichlorophenoxyacetic acid) is an herbicide which selectively controls many broadleaf weeds, certain hardwood trees and brush on crop and rangelands, rights-of-way, and on turf and lawns. 2,4-D was first introduced in the U.S. for use by farmers in 1946 (Peterson, 1967). It performs its control function by altering the normal growth of susceptible weeds and woody plants. The major use of 2,4-D is controlling broadleaf weeds in cereal grains. It does not kill most grasses.

2,4-D is usually applied at the rate of ¼ to ½ pound active ingredient per acre for cereal grains. Higher rates are often used on rights-of way. 2,4-D is usually formulated as amine salts or esters.

2. How toxic is 2,4-D to animals?

2,4-D is moderately toxic to mammals. The three routes of possible human exposure are: ingestion, dermal contact and inhalation. The single dose oral LD50 (dose determined to be lethal to 50% of the treated species) for 2,4-D acid is greater than 350 mg/kg of body weight in rats, mice, guinea pigs and chickens (NRCC, 1978). In these same species the acute oral LD50 for various formulations of 2,4-D salts and esters ranges from 75 to 2000 mg/kg (Weed Science Society of America, 1979) (IRAC, 1977).

In a case of a suicide by a 23 year old student, the total amount of 2,4-D in the body was estimated to correspond to a dose of 80 mg/kg. (Nielson et al., 1965) No adverse effects were reported in a man who took 500 mg 2,4-D orally daily for 3 weeks (approximately 8 mg/kg/day) (IARC, 1977). When 2,4-D was used as a treatment in a patient with

Men (248) and women (44) engaged in the manufacture of the amine salt or the butyl ester of 2,4-D with exposure periods ranging from under 5 years to 6-10 years (for 194 and 98 persons respectfully); were screened and 63% of these workers complained frequently of weakness, rapid fatigue, headache or vertigo. About 20% had disturbances of the cardiovascular system (mainly hypotension and bradycardia) and of the digestive organs (dyspeptic symptoms and gastritis). The various liver dysfunctions that were found were more pronounced in workers with longer exposures to the herbicides. (IARC, 1977)

Feldmann & Maibach (1974) studied in man the absorption through the skin of 4µg/cm^2 ^{14}C-labelled 2,4-D dissolved in a small amount of acetone. ^{14}C activity was measured in urine over a 5-day period and compared with that in urine after i.v. administration of the compound: urinary excretion of 2,4-D after i.v. administration was 100% of the dose in 120 hours, while excretion after topical administration was 5.8% of the dermal dose.

Kohli et al. (1974) administered 5 mg/kg body weight of pure 2,4-D in a gelatin capsule with water to 6 healthy male volunteers, aged 22-30 years. None of the subjects complained of any ill-effects, no changes in blood pressure, pulse rate, hemoglobin content or total or differential white cell counts were observed. 2,4-D was absorbed fairly rapidly. The highest concentration in blood was reached in 7-24 hours. In urine, 2,4-D was present as early as 2 hours after ingestion, and more than 75% was excreted in 96 hours without undergoing transformation in the body.

In 5 male volunteers given a single oral dose of 5 mg/kg body weight, the half-life in the plasma was 11.7 hours, and elimination in the urine

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Hansen et al (1971) administered 2,4-D in the diets of rats for two years at 0, 5, 25, 125, 625 or 1200 ppm. While the number of rats employed in this study would not be adequate by todays standards, the authors concluded 2,4-D was not a carcinogen.

Arkipor and Kozloria (1974) state there was no significant increase in tumors in rats or mice from dietary or skin painting administration of 2,4-D.

Bjorkland and Erne (1966) administered 2,4-D in the drinking water of rats for two years at levels up to 1000 ppm and observed no increase in tumors.

4. Does 2,4-D cause birth defects in humans?

Teratological studies (study of birth defects) have been conducted with 2,4-D as the acid and as certain esters in rats, mice, hamsters and sheep. There are differences among scientists in defining teratological responses to treatments. In this discussion we will cite the definitions of the National Academy of Sciences' (1974) and their explanation of each.

Don't like these definitions

"Prenatal development is divided into the embryonic stage (early) when the organs are forming, and the fetal stage (later) when the organism is maturing during gestation. However, the division is not clear-cut and the prenatal organism will be referred to in this discussion as an embryo even if it is technically known as a fetus."

"An agent or chemical is considered as teratogenic when it causes developmental disturbances in the embryo resulting in congenital malformations. If an agent kills the embryo it is said to be embryocidal, and if it

causes cleft palate in the mouse and the rabbit, but not in the rat. We still do not know if it is teratogenic in man. Thus, one cannot extrapolate with any assurance from one species to another, or even one strain to another, and one cannot rigorously prove an agent is teratogenic in man from data on experimental animals--only from data on human beings."

"It must be emphasized that a great many agents are teratogenic in experimental animals, particularly rodents. Many drugs have demonstrated teratogenicity: various antibiotics, amphetamines, antihistamines, anticonvulsants, barbiturates, caffeine, clomiphene, cyclizine, LSD, thalidomide, tolbutamide, and various tranquilizers. Metals (cadmium, calcium, lead, mercury), hormones (ACTH, adrenalin, androgenic hormones, antiovulatory compounds, estrogens, glucosteroids, insulin, serotonin), vitamin A, and several other kinds of chemical, physiological, and environmental agents (maternal dehydration, maternal stress, carbon monoxide, noise, and hypoxia) have also been shown to be teratogenic in laboratory animals. For several of these there is good evidence of low or no teratogenicity in man (e.g., cyclizine), but for most of them the possibility of low levels of teratogenicity has not been ruled out, and it would be very difficult to do so. Only five have been clearly implicated as humans teratogens (diphenylhydantoin, androgenic progestins, organic mercury, radiation, and thalidomide)" (NAS, 1974).

"Much less work has been done on the teratogenicity of 2,4-D. One study (Bionetics Study, see Mrak Report, 1969) suggested that the butyl, isopropyl and isooctyl esters of 2,4-D may be teratogens of low potency. Schwetz et al. (1971), feeding the free acid, the propylene glycol

DOW 1 551090

Is 2,4-D a Mutagen?

First, a mutagen is a material that is capable of producing genetic damage which can be inherited by future generations. 2,4-D has been evaluated in a number of mutagenicity studies. It has been demonstrated that 2,4-D is not a mutagen in a variety of microbial studies as well as in male fruit flies (Drosphila melanogaster). (Vogel - Chandler, 1974). Epstein et al (1972) found that a total of 75 mg of 2,4-D/kg of body weight given over a five day period did not increase dominant lethal mutations in mice.

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

2,4-D had no effect on cultured cells nor on bone marrow after its oral administration to rats (Styles, 1973 cited in IARC, 1977). There was no increase in the micronuclei in erythrocytes of mouse bone marrow after injection of 100 mg 2,4-D/kg/body weight. Examination of chromosomes of workers employed in the production of 2,4-D indicated no changes (Johnson, 1971).

The Royal Swedish Academy of Sciences arranged a conference in Stockholm in February, 1977 organized into five working groups comprising chemistry, plant physiology, toxicology, genetics, and ecology with economics. The

hydrolysis of 1,2,4,5 tetrachlorobenzene. Any TCDD so formed can be carried through into products made from 2,4,5-trichlorophenol, such as 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and hexachlorophene. No TCDD is found in 2,4-D (Ramel, C. 1977).

1551092

of dibenzo-p-dioxin? but what is formed?

The expected 2,7-dichloroisomer is not formed by condensation of 2,4-dichlorophenate under the acid conditions used in its manufacture by chlorination of phenol. Of 28 samples of 2,4-D tested for content of chlorodibenzo-para-dioxins, one was reported to contain less than 10 mg/kg hexachlorodibenzo-p- dioxin. (Woolson et al 1972, cited in IARC, 1977)

Does this mean that the answer to question 6 is, yes?

7. What Effect Does 2,4-D Have on The Environment?

The environment is composed of many compartments including soil, air, water, man, birds, animals, plants and insects, etc. 2,4-D, when used as directed on the label, exerts its effect on a select portion of the plants in the environment. Application of 2,4-D by means of spraying, either by ground or air, provides the potential for contamination of the other compartments.

Fate in Soil

In soil, in the presence of moisture, even at low levels, the esters of 2,4-D are hydrolyzed to the acid form. The persistence of the isooctyl ester of 2,4-D was studied under field conditions by Burcar et al. (1966, cited in NRCC 1978) who noted the complete breakdown of the ester to the acid in two weeks. The free acids also have a relatively

...pH, presence of organic matter, sunlight and microbial flora. ... rates of application, 2,4-D would not be detected in most ... environments 30 days after introduction.

... studies with fish have been reviewed by Mullison (1970). In ... natural conditions most fish species can tolerate 2 ppm ... 5 pounds 2,4-D per acre in water about one foot deep ... 2 ppm. Under natural conditions fish could usually ... areas of high concentrations.

... 2,4-D are applied as aqueous emulsions or solutions in ... sprayers or by aircraft. During application, some of the ... from the target site before being intercepted by ... quantity which may drift is dependent upon droplet ... temperature and humidity, viscosity of the formu- ... from applicator to target, and perhaps the most important ... exercised by the individuals performing the ... to the label.

... differ in their rate of volatilization from the target ... salts are less volatile than the esters. Proper ... and observation of the climatic conditions ... can minimize volatilization from the target ... where damage may occur.

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MUW 1 551096 ROM 1

required on the label. Subchronic or less than one half the lifetime studies include: 90 day dietary in rats, six month dietary in dogs, teratogenicity in two species, two generation reproduction in rats and metabolism in two species. Chronic (essentially lifetime) dietary studies are conducted in rats and mice to determine a no effect level to assist in establishing tolerance levels and possible oncogenic (tumor producing) effects. These comprehensive studies require at least four years to complete.

During this same time period samples of the target crop which has been treated with the chemical at the maximum label rate are collected from various geographical areas and analyzed for possible residues. Residue studies are also conducted in cows and chickens to determine if residues which might be present in the food of these animals is carried into meat, milk or eggs which humans might consume.

The EPA then evaluates these data together with the data which describe the fate and effects in the environment and only after detailed analysis may grant a residue tolerance. The tolerance granting procedure is very detailed and not taken lightly by the EPA nor the industry. By the time a tolerance is granted an excess of five years have elapsed since the initial data gathering.

There may be trace quantities of 2,4-D in the food we eat but an extensive review of the data assures us it is a quantity which will not cause harm. The FDA market basket samples for 1974-1975 (PEMJJAA) which are comprised of collections in 20 cities which range in populations from less than 50,000 to

NRCC, 1978. Phenoxy Herbicides - Their Effects on Environmental Quality. National Research Council Canada No. 16075.

PEMJJAA - 1977, Pesticide and Other Chemical Residues in Total Diet Samples (XI) Pesticide Monitory Journal, Vol. II, No. 3.

Peterson, G.E. 1967. The Discovery and Development of 2,4-D. Agric. Hist. 41: 243-253.

Ramel, C. 1977, Chlorinated Phenoxy Acids and Their Dioxins, Ecological Bulletins No. 27. Report from a conference arranged by the Royal Swedish Academy of Sciences, Stockholm, Sweden, 7-9 February 1977.

Sauerhoff, M.W. et al. 1976. The Fate of 2,4-Dichlorphenoxy Acid (2,4-D) Following Oral Administration to Man. Toxicol. Appl. Pharmacol., 37, 136-137.

Schwetz, B.A., Sparschu, G.L. & Gehring, P.J. (1971) The effect of 2,4-dichlorophenoxyacetic acid (2,4-D) and esters of 2,4D on rat embryonal, foetal and neonatal growth and development. Fe Cosmet. Toxicol., 9, 801-817.

Weed Science Society of America, 1979, Herbicide Handbook, 4th ed.

MRID 00151098

ANALYTICAL REPORT

MIDLAND ANALYTICAL LABORATORIES

DOW CHEMICAL U.S.A.

RESTRICTED REPORT

AL 78-50668

ACCT. NUMBER: 8004 | SUB FUNCTION:

LAB. NO. | PROBLEM NUMBER:

DATE: July 28, 1978

TO: M. B. Chenoweth, 607; E. L. Garfield, 607; M. L. Leng, 9008; W. H. Braun, 1803; L. P. McCarty 1701 & 607; J. H. Saunders, 607; W. B. Crummett, 574

TITLE: DETERMINATION OF PHENOXY HERBICIDES IN URINE AND BLOOD SAMPLES FROM 2,4,5-T PLANT PERSONNEL - II.

DOW 1512708

MN422246

INTRODUCTION

Human urine and whole blood samples were obtained from personnel working at the 2,4,5-T production facility for a determination of 2,4-dichlorophenoxy acetic acid (2,4-D), 2-(2,4,5-trichlorophenoxy) propionic acid (Silvex), and 2,4,5-trichlorophenoxy acetic acid (2,4,5-T).

EXPERIMENTAL

The samples were prepared by extraction, hydrolysis, methylation with diazomethane, and silica gel column clean-up prior to analysis by gas chromatography-mass spectrometry (GC-MS). The experimental procedure used is detailed in Report ML-AL 78-50252.

The silica gel column used was changed slightly. The column used was packed with 1.5 grams dry silica gel (~ 11 cm x 6 mm i.d. glass). The column was eluted with 60/40 methylene chloride/hexane. The first 2 ml were collected and discarded (waste fraction). The next 13 ml of eluent were collected for analysis. Then an additional two ml were collected to check for recoveries, (extra fraction). The collected fractions were evaporated to dryness. Prior to analysis, the sample residue was dissolved in 50 µl benzene.

Validation data for this procedure are detailed in ML-AL 78-50252.

RESULTS AND DISCUSSION

Results are detailed in Table I. Figure 1 shows a typical standard ion chromatogram and GC-MS conditions. Figure 2 shows typical GC-MS data for a urine sample from a 2,4,5-T plant worker.

16918

SIGNATURE	PHONE	BUILDING	DATE FINISHED	HOURS	RESULTS PHONED	REVIEWED BY
Marsha L. Langhorst Marsha L. Langhorst Data Book AL 1207 p. 118	6-6207	574	7/13/78	37		

FORM M-50540

Figure 3 shows typical GC-MS data for a blood sample from a 2,4,5-T plant worker.

The presence of Silvex was asked to be confirmed. It was questioned whether Silvex could have an interfering compound by GC-MS six-ion monitoring or whether Silvex or an interference could be created from 2,4,5-T during the sample preparation or analysis.

DOW 1512709

To check the creation of an interference during sample preparation, a urine and blood sample were spiked with high levels (1.85 µg/gm sample) of 2,4,5-T. The sample was processed through the usual procedure and analyzed. No peaks were found other than 2,4,5-T. See Figure 4.

To check if the ethyl ester of 2,4,5-T might interfere with the methyl ester of Silvex, (both have parent ions by MS at m/e = 282) by GC-MS. A sample of 2,4,5-T was ethylated with ethanolic HCl. The sample was analyzed by GC with electron capture detection and found to elute at a different retention time than Silvex. Therefore, it could not interfere by GC-MS and produce a response interpreted as Silvex.

In addition, to check if any ethyl ester of 2,4,5-T is formed during methylation, a relatively high concentration of 2,4,5-T was methylated. No peaks were detectable except the methyl ester of 2,4,5-T. This evidence is shown in Figures 5 and 6.

The identify of Silvex in urine and blood samples is confirmed by retention time, ions in the mass spectra, and ion abundance ratios (282/198).

REFERENCES

1. Marsha L. Langhorst, "Determination of Phenoxy Herbicides in Human Urine and Blood Samples - (Validation Data)", ML-AL 78-50252.

2. Marsha L. Langhorst, "Determination of Phenoxy Herbicides in Human Urine and Blood Samples (RESTRICTED REPORT)" ML-AL 78-50405.

3. Marsha L. Langhorst, "Determination of Phenoxy Herbicides in Human Urine and Blood Samples from 2,4,5-T Plant Personnel, (RESTRICTED REPORT)" ML-AL 78-50489.

DOW 1 512710

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July 28, 1978 AL 78-50668

TABLE I

RESULTS

PHENOXY HERBICIDES IN 2,4,5-T PLANT PERSONNEL

No.	Person	Sample Type	Concentration found (ng/gm Sample) 2,4-D	Silvex	2,4,5-T
U-1	Amble	Urine	380	21	540
U-2	Crivac	Urine	520	4.1	220
U-3	Falkowski	Urine	510	23	310
U-4	Swogger	Urine	270	11	170
B-1	Amble	Blood	2.0	N.D.(1)	8.7
B-2	Crivac	Blood	8.6	N.D.(1)	5.6
B-3	Falkowski	Blood	9.3	N.D.(1)	7.9
B-4	Swogger	Blood	3.8	N.D.(1)	2.4

SPIKED SAMPLES FOR RECOVERIES

No.	Sample Type	Spiked with 2,4,5-T	Conc found (ng/gm) 2,4-D	Silvex	2,4,5-T	% Recovery
U-1	Urine	1850 ng/gm urine	N.D.(1)	N.D.(0.5)	1540	83
B-1	Blood	1850 ng/gm blood	N.D.(2)	N.D.(1)	1400	76

NOTES: N.D. = Not detected with minimum detection limits shown in parentheses.

Minimum detection limits (MDL's) are:

Compound	in ng/ml	in ng	in ng/gm urine	in ng/gm blood
2,4-D	200	10	1	2
Silvex	100	5	0.5	1
2,4,5-T	100	5	0.5	1
		assuming 50 µl final volume	assuming 10 gm urine sample	assuming 5 gram blood sample

Methods are validated down to 3 ng/gm urine and 5 ng/gm blood.

DOW 1512711

...NOW ON TAPE. MAXIMUM AVAILABLE = 10

FIGURE 1. STANDARD GC-MS DATA

...APPROXIMATELY 70.3 MINUTES OF STORAGE AVAILABLE FOR RUN# 0

INSTRUMENT: Hewlett-Packard 5992 GC-MS

COLUMN: 9'x 2mm i.d. glass, 3% SP-2401 on 100/120 Supelcoport

...Calibrations for SAMPLE # 0.00 STD Um'

TEMP1	TIME1	RATE	TEMP2	TIME2	PORT	SOLVT	OVEN MAX	RUN TIME	E.M. VOLTS.
190.0	isothermal		190.0	50.0	210.0	2.0	210.0	20.0	1000

...ACQUISITION ... CONSISTING OF STANDARD OCTOLUME RESOLUTION.

ION	234.00	236.00	198.00	282.00	233.00	268.00
DWELL TIMES	350.0	350.0	350.0	350.0	350.0	350.0

S.I.M. WINDOW SIZE = 0.30

AMOUNT INJECTED = 2.00

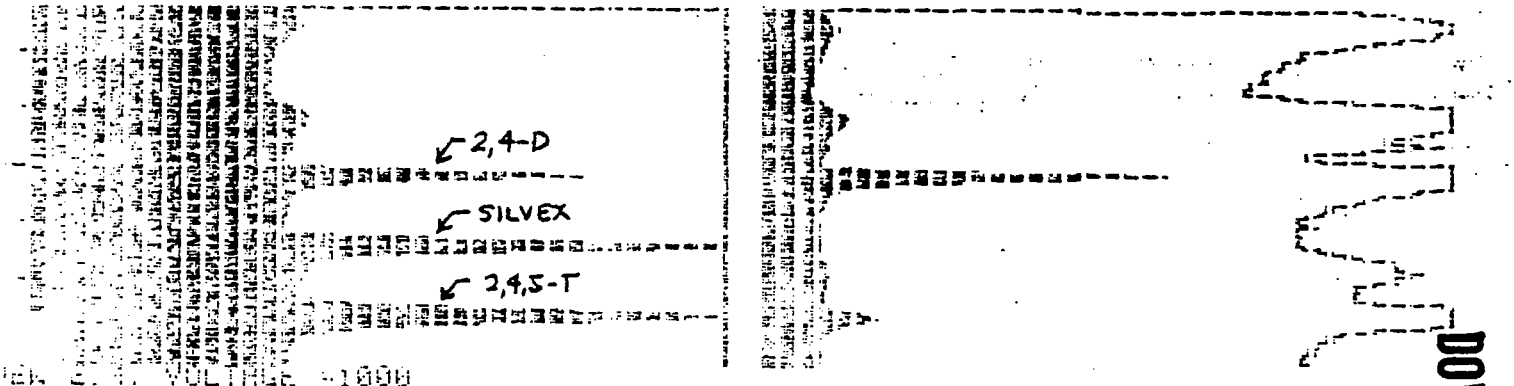
STANDARD Um'

2.36 µg/ml 2,4-D
1.98 µg/ml SILVEX
2.13 µg/ml 2,4,5-T
(as methyl esters)

SUM OF MONITORED ION ABUNDANCES
Full Scale = 100

ION 234.00
Full Scale = 50

MEM E.M. VOLTAGE =2800



MEM E.M. VOLTAGE =1000

ION MASSES	234.00	236.00	198.00	282.00	233.00	268.00
MAXIMUM ABUNDANCE	292.73	197.16	619.56	175.85	555.37	202.26

DOW 1512712

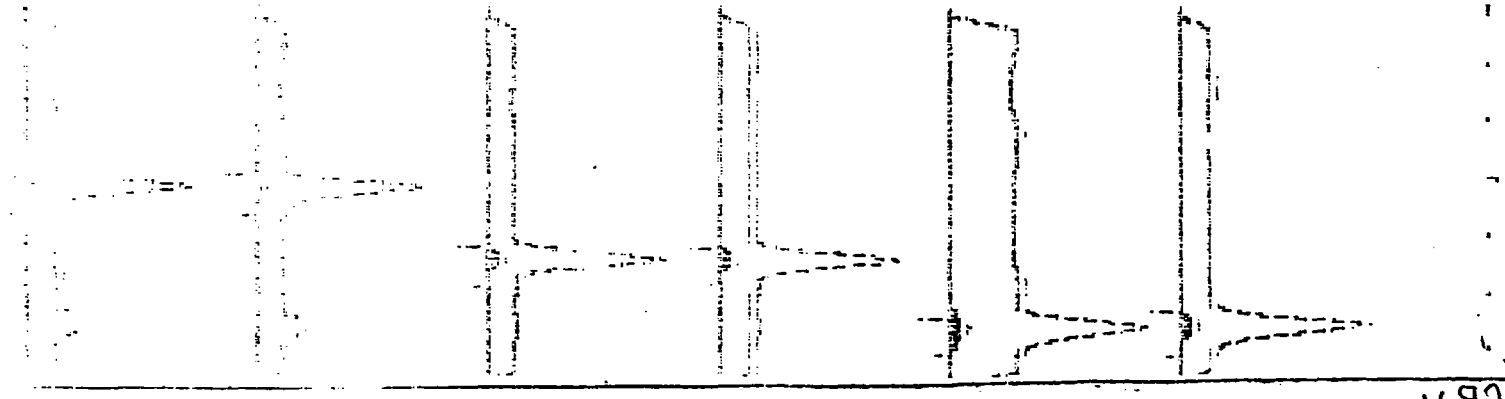
SCAN COMPLETE. Data stored in RUN 0

...SAMPLE IDENTITY # 0.00 dated ... 7/1978 Friday

ION MASSES	234.00	236.00	198.00	282.00	233.00	268.00
DWELL TIMES (msec)	350.00	350.00	350.00	350.00	350.00	350.00
MAXIMUM ABUNDANCE	292.73	197.16	619.56	175.85	555.37	202.26

RUN TOTAL RUN TIME = 0.6 AMOUNT INJECTED = 2.00

ION =234.00 ION =236.00 ION =198.00 ION =282.00 ION =233.00 ION =268.00
FS = 293 FS = 197 FS = 619 FS = 176 FS = 555 FS = 202



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FIGURE 2 : URINE SAMPLE - FALKOWSKI

Urine Falkowski 2nd

4.00

		RATE	TEMP1	TIME1	FO	SOLVT DYEN MAX	RUN TIME	E.M.VOLTS
			150.0	50.0	0.0	2.0	210.0	20.0	1000

MASSES	234.00	236.00	196.00	282.00	233.00	268.00
TIMES	350.0	350.0	350.0	350.0	350.0	350.0

E.M. WINDOW SIZE = 0.30

AMOUNT INJECTED = 2.00

SUM OF MONITORED ION ABUNDANCES — Full Scale = 100

ION 234.00 — Full Scale = 50

DOW 1512713

TEMP E.M. VOLTAGE =2800

TEMP E.M. VOLTAGE =1000

MASSES	234.00	236.00	196.00	282.00	233.00	268.00
SUM ABUNDANCE	283.35	192.47	93.44	32.96	404.12	144.14

RUN COMPLETE, Data stored in RUN 5

SAMPLE IDENT # 4.00 Date 7/1978 Friday

MASSES	234.00	236.00	196.00	282.00	233.00	268.00
TIMES (sec)	350.00	350.00	350.00	350.00	350.00	350.00
SUM ABUNDANCE	283.35	192.47	93.44	32.96	404.12	144.14

RUN 5 TOTAL RUN TIME = 0.0 AMOUNT INJECTED = 2.00

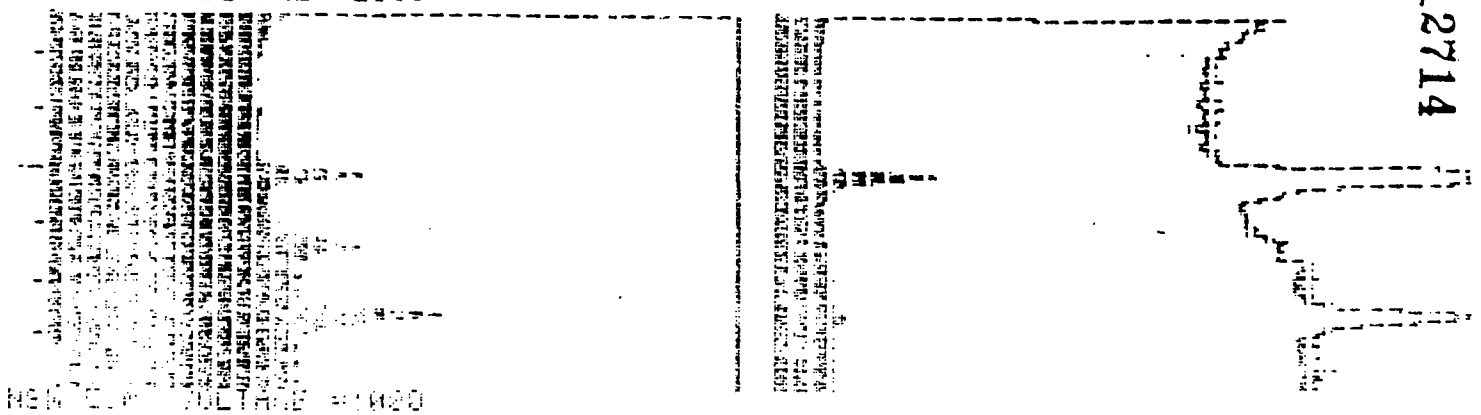
ION =234.00 ION =236.00 ION =196.00 ION =282.00 ION =233.00 ION =268.00
FS = 283 FS = 192 FS = 93 FS = 33 FS = 404 FS = 144

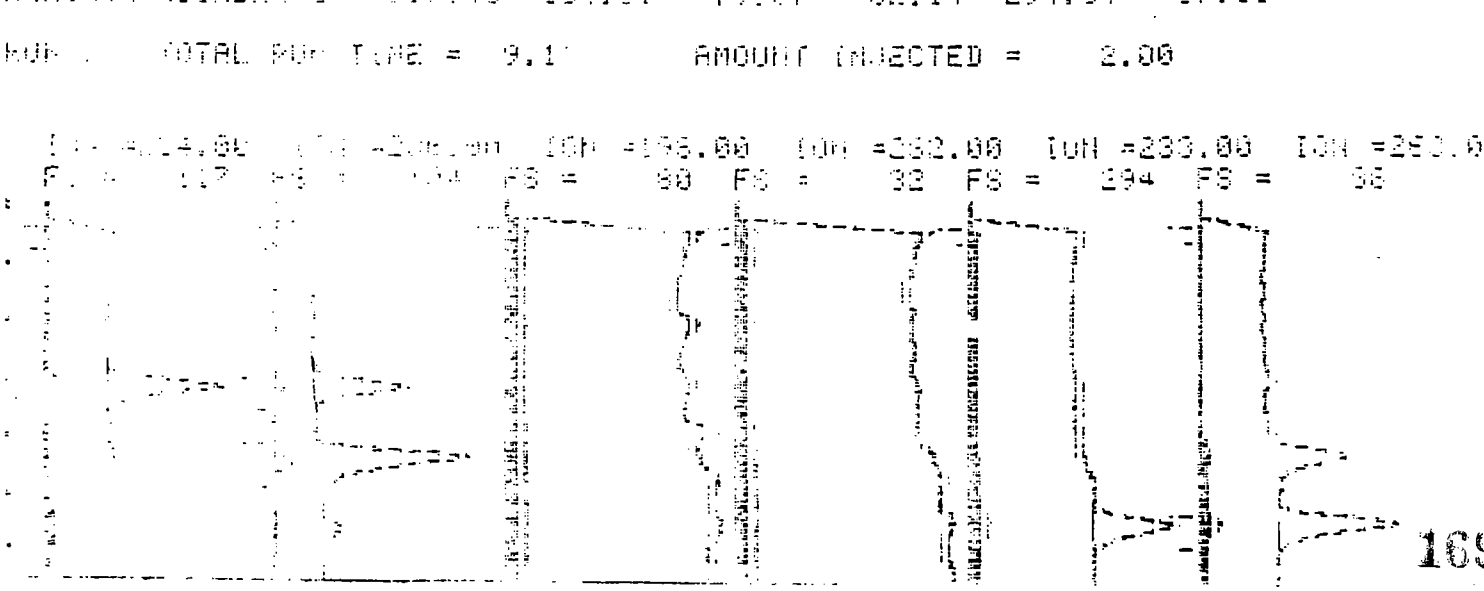
16923

FIGURE 3 BLOOD SAMPLE – FALKOWSKI

#B-4 Blood Falkowski in Spec benzene

DOW 1512714





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APPROXIMATELY 78.8 MINUTES OF STORAGE AVAILABLE FOR RUN# 3

FIGURE 4 CONTROL URINE SPIKED WITH 2,4,5-T

#1 Urine + 245T in 1ml benzene

Mass spectral conditions for SAMPLE # 1.00

FILAMENT	TUNE	RATE	TEMP2	TIME2	PORT	JET	OVEN TMP.	RUN TIME	E.M.VOLTS
300.0	Electronic	190.0	00.0	210.0	1.0	310.0	20.0		1300

Mass spectrometer operating at standard Autotune resolution.

ION MASSES	234.00	236.00	198.00	282.00	233.00	268.00
DWELL TIMES	350.0	350.0	350.0	350.0	350.0	350.0

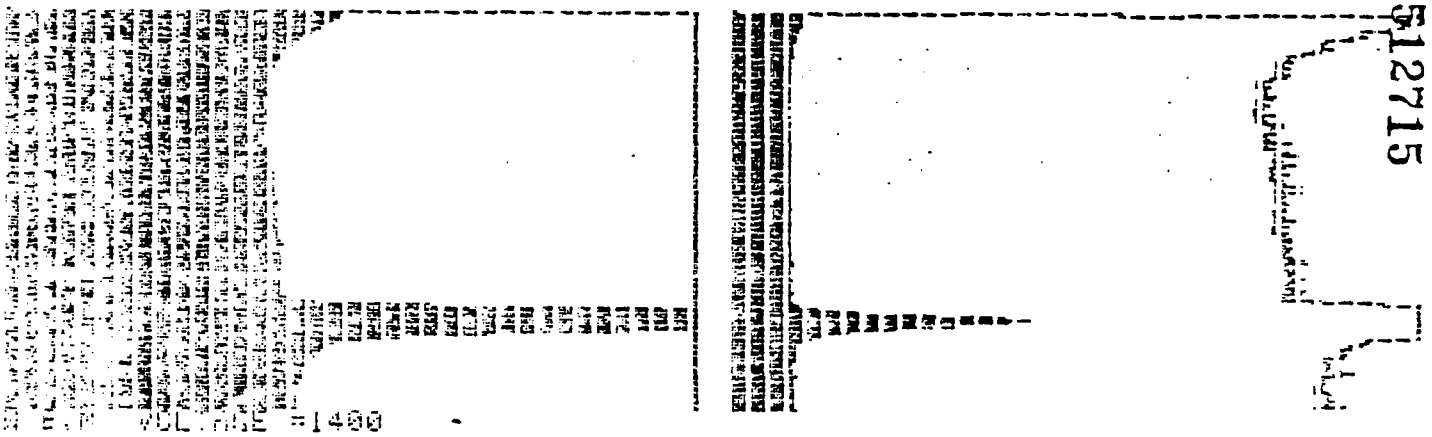
S.I.M. WINDOW SIZE = 0.30

AMOUNT INJECTED = 2.00

SUM OF MONITORED ION ABUNDANCES
Full Scale = 100

ION 234.00
Full Scale = 50

NEW E.M. VOLTAGE =2300



NEW E.M. VOLTAGE =1400

ION MASSES	234.00	236.00	198.00	282.00	233.00	268.00
MAXIMUM ABUNDANCE	216.78	140.14	140.37	42.60	1784.42	752.52

DOW 1 512715

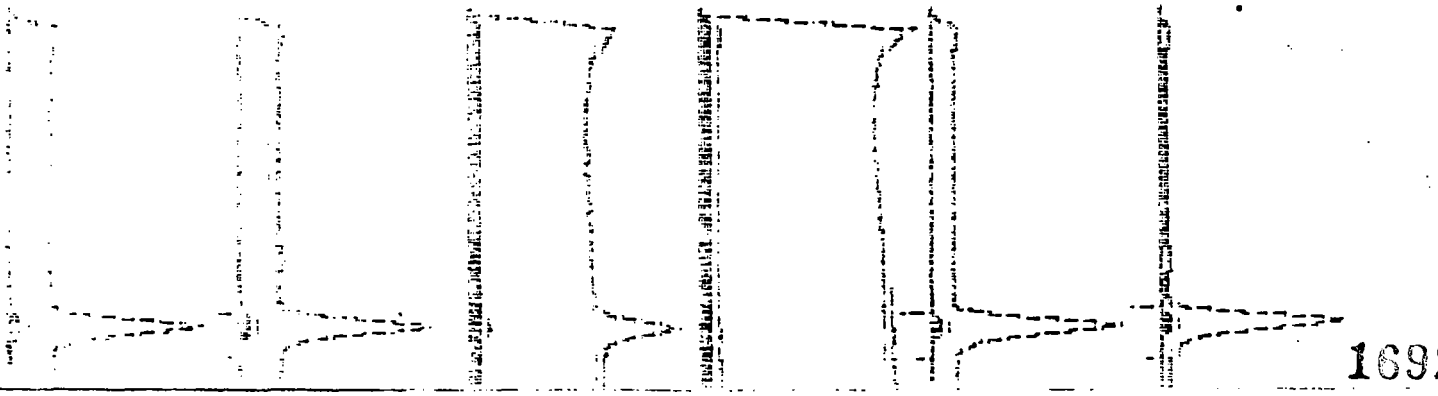
DATA RUN COMPLETED, Data stored in RUN 3

SAMPLE IDENTITY # 1.00 dated 7 F 1978 Friday

ION MASSES	234.00	236.00	198.00	282.00	233.00	268.00
DWELL TIMES (msec)	350.00	350.00	350.00	350.00	350.00	350.00
MAXIMUM ABUNDANCE	216.78	140.14	140.37	42.60	1784.42	752.52

RUN 3 TOTAL RUN TIME = 9.4 AMOUNT INJECTED = 2.00

ION =234.00 ION =236.00 ION =198.00 ION =282.00 ION =233.00 ION =268.00
FS = 217 FS = 140 FS = 140 FS = 43 FS = 1785 FS = 753



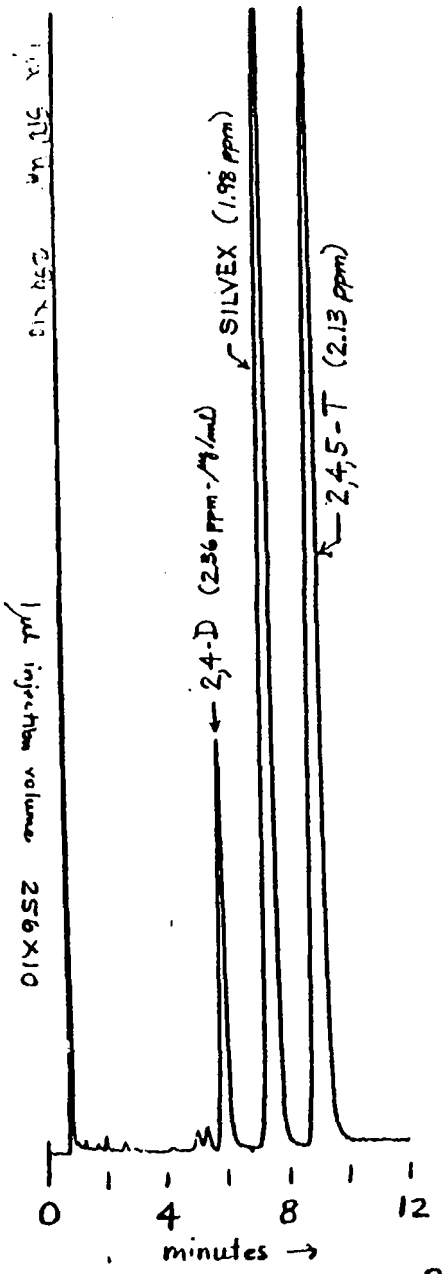
16925

FIGURE 5 RETENTION TIMES OF PHENOXY HERBICIDES STANDARD CHROMATOGRAMS AND GC CONDITIONS.

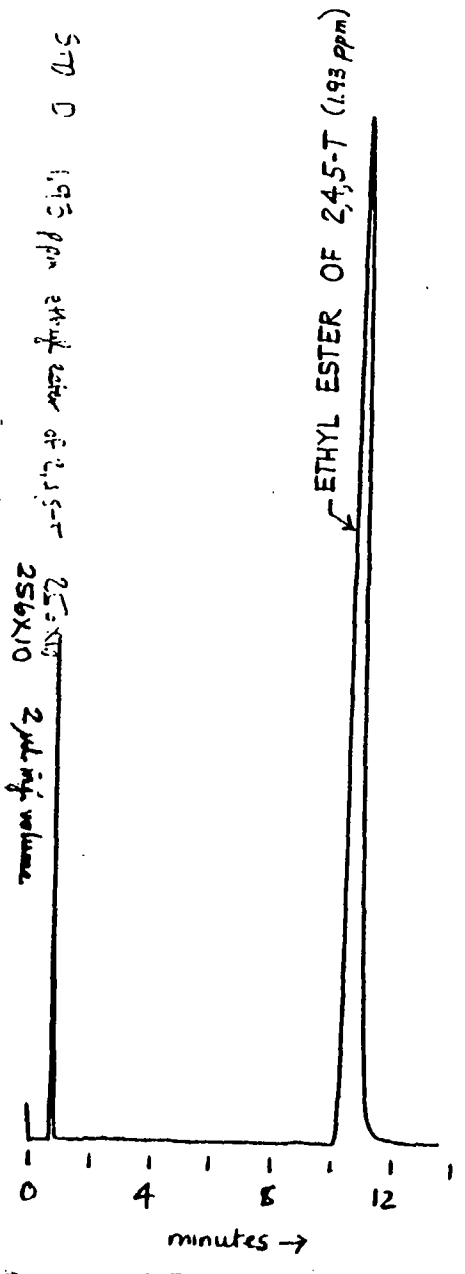
INSTRUMENT: Varian 3700 Gas Chromatograph

Operator	M.L. LANGHORST	Date	7-3-78		
Column No.	Glass	Length	9 feet	Dia.	2mm I.d.
Coating	SP-2401	Concn	3%		
Support	Supelcoport	Mesh	100/120		
TEMP: Col: Init	175°	°C Final			°C
Rate	°C/min.	Det.	340 °C	Inj.	210 °C
CARRIER GAS	Nitrogen	Rate	30		ml./min.
Pressures: Inlet		Outlet			
Hydrogen	ml./min.	Air			ml./min.
DETECTOR	E.C. Ni 63	T.C.		F.I.D.	
Scavenger		Rate			ml./min.
Sens.	As labeled	Rec. Range	1		mv.
SAMPLE	As labeled	Size	As labeled		
Solvent	benzene	Concn			

STANDARD - PHENOXY HERBICIDES AS METHYL ESTERS



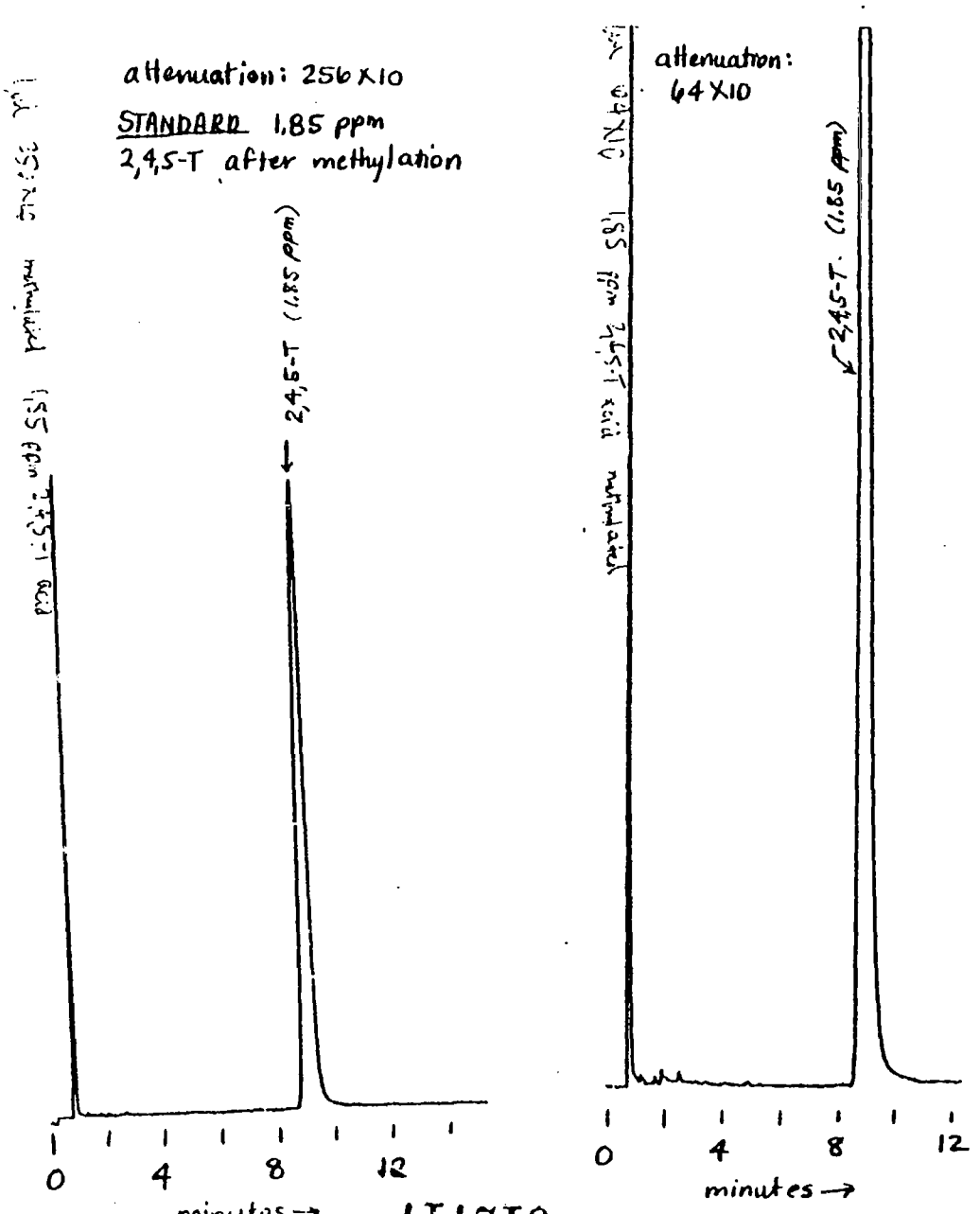
STANDARD - 2,4,5-T AS ETHYL ESTER



DOW 15127216

92831

FIGURE 3 CHROMATOGRAMS OF 2,4,5-T AFTER METHYLATION – SHOWING THAT NO ETHYL ESTER IS FORMED DURING METHYLATION



DOW 1 5127127

12891

2418

DOW 1 456152

A LONGEVITY SURVEY OF EMPLOYEES EXPOSED TO 2,4,5-TRICHLOROPHENOXYACETIC ACID

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Medical Department
The Dow Chemical Company
Midland, Michigan

RECEIVED
MAR 21 1978
REGISTRATION

16928

DOW 1 456153

A B S T R A C T

A LONGEVITY SURVEY OF EMPLOYEES EXPOSED TO 2,4,5-TRICHLOROPHENOXYACETIC ACID

Ott, M.G., Holder, B.B., Olson, R.D.

There have been few published reports regarding epidemiologic surveillance of individuals occupationally exposed to 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). The present study examined the mortality experience of 204 persons exposed to 2,4,5-T during its manufacture. Exposure durations ranged from less than one year to a maximum of approximately 10 years over a period from 1950 to 1971.

Within the scope of this mortality survey, no adverse effects were observed with respect to occupational exposure to 2,4,5-T.

16929

DOW 1456154

A LONGEVITY SURVEY OF EMPLOYEES EXPOSED TO 2,4,5-TRICHLOROPHENOXYACETIC ACID

Introduction

In 1976 Muranyi-Kovacs et al published results of a bioassay of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) for carcinogenicity[1]. The 2,4,5-T, which contained less than .05 ppm of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), was found to produce a significant increase in non-incidental tumors (diagnosed during life or causing the death of the animal) in C3HF mice, but not in XVII/G mice. Both groups of mice had been fed 80 ppm 2,4,5-T on a daily basis until death. Previously, considerable variation had been demonstrated in the kinetics of excretion of 2,4,5-T between species[2]. An earlier screening bioassay study by Innes et al was not positive for tumorigenicity in two hybrid strains of mice fed 60 ppm 2,4,5-T in their diet[3]. The authors of the 1976 bioassay article, aware of the kinetic studies and paper by Innes, suggested that additional testing of 2,4,5-T was needed. A two year feeding study in rats is currently underway at The Dow Chemical Company Toxicological Laboratories in Midland, Michigan.

Only limited epidemiological investigations of workmen exposed to 2,4,5-T have been conducted[4,5]. In 1971, Poland et al

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reported results of a health survey of 73 male employees in a 2,4,5-T and 2,4-dichlorophenoxyacetic acid (2,4-D) manufacturing plant[5]. This survey was a followup of studies published by Bleiberg et al in 1964 on 29 employees in the same plant[6]. An important finding in the followup was evidence of varying degrees of acne in 48 of the 73 employees. The term "chloracne" was employed to describe the moderate to severe lesions observed for 13 (18%) of the individuals. Evidence of abnormal excretion of uroporphyrins was not found in the followup study in contrast to the original work. Also, the authors in their summary stated that markedly less evidence of toxicity was found in other organ systems, such as the liver, than was reported in previous studies. It was noted, though not judged to be explanatory of differences in toxicity seen from the earlier work, that six months prior to the second survey, contamination of the process starting material, 2,4,5-trichlorophenol (TCP), with TCDD had been reduced from 10 to 25 ppm to 1 ppm. No detailed industrial hygiene measurements of 2,4,5-T or TCDD levels in the work environment were provided.

The present study examines the mortality experience of a cohort of 204 employees engaged in the manufacture of 2,4,5-T. A review of health exam findings of phenoxy herbicide workers in this plant was discussed in a paper by Johnson[7]. The current survey compares mortality due to specific causes, with the corresponding U.S. white male population and with reference to other mortality studies conducted at this company location.

DOW 1 456155

DOW 1 456156

The commercial production of 2,4,5-T in the company began in March, 1950, with the original process being operated continuously until May, 1971, when it was permanently shut down. In 1967, a second operation was developed that utilized different personnel and which has continued in production. Personnel from the second process were not included in the present study, because of the shorter latency period and because this more recent process produces esters of 2,4,5-T without isolation of the acid. The departmental unit under which the original process was first organized also was responsible for manufacturing a variety of other products ranging from styrene butadiene latex to herbicides such as 2,4,5-trichlorophenoxy propionic acid and 2-methyl-4-chlorophenoxyacetic acid. Thus, many of the individuals included in the present study were potentially exposed to numerous other substances during their employment with this unit.

The 2,4,5-T was manufactured by reacting sodium monochloracetate with the sodium salt of TCP, the salt being prepared by adding caustic to TCP. This was followed by conversion to the acid. An additional step not considered part of the process, but taking place in the same building, was esterification of 2,4,5-T with propylene glycol butyl ether or isooctyl alcohol. Continuing efforts were made to minimize TCDD contamination in the 2,4,5-T plant by proper control of a separate

plant which produced the TCP later used in the 2,4,5-T process. Wipe testing in 1970 failed to detect TCDD in the 2,4,5-T work area using a combined gas chromatography, mass spectrometry method sensitive to approximately 1 µg/sample depending upon interferences. The 2,4,5-T process was specifically run by a crew of four operators: a reactor operator, a salt wheel operator, an acid wheel operator, and a dryer operator.

DOW 1 4561157

The reaction portion of the process in which the sodium salt of 2,4,5-T was produced was nearly a closed system. During the subsequent wheeling operations, the sodium salt was converted to the acid. The 2,4,5-T dust levels found in the plant were believed to have resulted primarily from finishing operations where the end product was dried and fed through a hammer mill.

An industrial hygiene survey of the process was conducted in 1969 at which time 50 area and breathing zone samples were collected using a midget impinger containing isooctane at a flow rate of 2.2 liters per minute. The samples were subsequently analyzed by gas chromatography for TCP, 2,4,5-T, and 2,4-D. Concentrations of 2,4,5-T or its sodium salt ranged from <.1 mgs/m^3 to 6.21 mgs/m^3. Estimated time-weighted-average (TWA) concentrations for the three compounds by job classification are shown in Table 1. Concentrations of these substances were relatively similar for three of the job

classifications: reactor operator, dryer operator, and salt wheel operator. The acid wheel operator was exposed to lower 2,4,5-T levels and higher TCP concentrations. The 2,4-D measurements are maximum levels. This product was dried occasionally in the building where 2,4,5-T was made.

DOW 1 456158

Often dust levels in the finishing area were high enough to be noticeably irritating. Sensory responses such as nasal irritation, sneezing, and a bitter taste were reported by unacclimated industrial hygienists to result from exposure levels of approximately .1 mg/m^3 2,4,5-T and/or less than 4 mg/m^3 of TCP. A review of medical visits from 1954 to 1970 revealed 19 episodes associated with acute exposure to 2,4,5-T or its esters among the 204 men in this study. All reported exposures involved eye or skin contact, with the mild to moderate responses apparently resulting from the irritating effects of the materials. Six of the exposure episodes occurred while the men were working as ester operators rather than directly on the 2,4,5-T process. The esters of 2,4,5-T are believed to exert similar toxicological effects as the acid after adjustments for the molecular weight of the ester itself.

Method of Analysis

The employees included in the study were determined by a two-stage procedure. In the first step all persons working

in the department under which the process was organized were identified from annual census lists covering the period January, 1951, through January, 1971. The second step was a review of the complete work history for each individual to determine those who had experience on any of the four jobs of interest. These employees constituted the population of concern. This method of selecting the exposed population insured that all employees who worked continuously for at least one year with the 2,4,5-T work area were included, but could have missed some personnel who worked in the exposure area for shorter periods of time.

DOW 1456159

A crew of 8 to 12 men operated the 2,4,5-T process on a daily basis. The flow of employees in and out of the department over the 21 year period resulted in 204 men having worked for 1+ months on at least one of the four jobs involved. The mortality experience was compared with the U.S. white male experience (5 year age intervals) for the years 1952, 1957, 1962, 1967 and 1971 by the indirect method. The vital status of former employees was initially traced through the Social Security Administration. Subsequently, verification of vital status has been obtained through contact of the individual or relatives who could account for the former employees's vital status.

In this analysis exposure is expressed only in terms of length of employment on the four jobs of primary concern. Exposure

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durations do not take into account the unmeasured exposures to 2,4,5-T or esters of 2,4,5-T encountered on other jobs within the production department. One job did involve exposure to esters of 2,4,5-T and several other jobs may have required filling in on a day-to-day basis for the operators in the four classifications of interest, as well as other duties with minimal exposure. Since many of the employees in the 2,4,5-T study worked on a number of jobs within the department, the durations of exposure are conservatively estimated. Sixty of these employees are also known to have worked in a styrene/butadiene latex plant organized within the production department. Thus, the persons included in the present study have been exposed during their employment to a variety of chemical compounds.

DOW 1456160

Results

The vital and employment status of the 204 workers exposed to 2,4,5-T and its sodium salts are shown in Table 2. Fifty-three of the 56 former employees have been traced through personal contact of the man himself or someone who currently knows him. For three persons vital status was verified at least through 1973, but not through 1976, by personal contact or social security checks. Two of the former employees had died as of the end of 1976. Nine deaths were observed among individuals followed through employment and retiree records.

The distribution of employees by duration of exposure and date first exposed is shown in Table 3. More than 75% of the men had worked for less than 12 months in jobs involving defined exposure. None of the men were exposed to 2,4,5-T over a working lifetime.

DOW 1 456161

Medical records of employees were reviewed for evidence of chloracne or porphyria cutanea tarda, which might indicate exposure to TCDD. No case of chloracne or porphyria cutanea tarda was found.

Tables 4 and 5 summarize mortality by duration of exposure and interval since first exposure. In Table 4 observed deaths were increased over expected only for the cause of death category "External Causes" (6 observed vs. 3.7 expected deaths). Three deaths in this category were due to separate automobile accidents, none of which took place while the individuals were employed on jobs involving 2,4,5-T exposure. One death was the result of a nonindustrial fire, and the remaining two deaths were suicides among former employees that occurred more than 10 years after exposure had ceased. The single observed malignancy death in the cohort to date was a respiratory malignancy which was discovered in a 63 year old retiree who had been exposed to 2,4,5-T for 8 years and had a past history of cigarette smoking of up to two packs per day.

The trend of deaths with respect to interval since first exposure follows a pattern which we have observed in other studies at this company location[8]. The most favorable mortality experience occurs in the early years after first exposure followed by a relative increase compared to general population mortality. We have interpreted these findings to indicate a preselection effect due to initial employment or transfer of individuals in a state of good health which becomes less important both as the interval since employment increases and as the employees become older.

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Comment

At the exposure levels experienced by the workmen in this study, no adverse mortality effects have been observed in association with the work environment. Within the scope of this limited survey, mortality has been favorable compared with the U.S. white male population and also compares well with the background mortality experience at this manufacturing location[8]. Because of questions raised by recent animal toxicological studies, mortality surveillance of this limited employee population will be continued. We recommend the initiation of mortality surveillance of other populations which have had past exposure to 2,4,5-T.

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DOW 1456163

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Table 1. Time-Weighted-Average Exposure Estimates for 2,4,5-T Process Based on 50 Samples of Up To Five Minutes Duration and Time Studies for Each Job, 1969.

Job	TCP (mg/m^3)	2,4,5-T[1] (mg/m^3)	2,4-D (mg/m^3)*
Reactor Operator	2.1	0.8**	<0.4
Salt Wheel Operator	2.1	0.5**	<0.4
Acid Wheel Operator	9.7	0.2	<0.4
Dryer Operator	1.6	0.5	<0.4

*Highest possible values using levels of detection as real values.
**Present in work environment as sodium salt.

[1]Product specifications for 2,4,5-T in 1966 called for a maximum of 1ppm TCDD, the sensitivity of the method of detection. In 1972, the maximum was lowered to .1ppm TCDD.

0.8 mg/m³ T
→ 0.000000,8 mg/m³
0.8 ng/m³

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Table 2. Vital and Employment Status of 204 Workers Exposed to 2,4,5-T as of 12/31/76.

Vital and Employment Status	Number of Workers
Total Group	204
Still Employed	121
Retired	18
Deceased (Company Records)	9
Left Employment Other Than Through Retirement	56
Deceased	2
Known Alive	51
Followup Through 1976 Incomplete	3

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Table 3. Duration of Exposure by Date First Exposed Among 204 2,4,5-T Exposed Employees.

Date Exposure Began	Duration of Exposure*				
	Total	<1 Year	1-2 Years	3-4 Years	5+ Years
TOTAL	204	157	30	9	8
1950-1954	58	30	17	5	6
1955-1959	45	36	6	2	1
1960-1964	51	44	4	2	1
1965-1969	35	32	3	0	0
1970+	15	15	0	0	0

*Fifty-nine of the 204 employees worked as ester operators for from <1 up to 77 months (11 of these employees had worked for at least one year as ester operators). The exposure durations as ester operators, or while employed in other capacities within the production department, were not included in the table since exposure intensities had not been estimated.

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Table 4. Observed and Expected* Deaths Among 204 Employees Exposed to 2,4,5-Trichlorophenoxy Acetic Acid, by Cause and Duration of Exposure, 1950-1976.

Cause of Death Category	Duration of Exposure					
	Total Exposed Group		<1 Year Total Exposure		1+ Years Total Exposure	
	Observed	Expected	Observed	Expected	Observed	Expected
All Causes	11	20.3	6	13.3	5	7.0
Total Malignant Neoplasms	1	3.6	0	2.3	1	1.3
Diseases of Cardiovascular System	4	9.1	1	5.6	3	3.5
External Causes (Accidents and Suicides)	6	3.7	5	2.8	1	0.9
All Other Causes	0	3.9	0	2.6	0	1.3

*Expected numbers of deaths based on U. S. white male mortality rates.

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Table 5. Observed and Expected* Deaths Among 204 Employees Exposed to 2,4,5-Trichlorophenoxy Acetic Acid by Cause and Interval Since First Exposure, 1950-1976.

Cause of Death Category	Internal Since First Exposure							
	<10 Years		10-14 Years		15-19 Years		20+ Years	
	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
All Causes	3	6.6	0	4.7	4	4.6	4	4.4
Total Malignant Neoplasms	0	1.0	0	0.9	0	0.8	1	0.9
Diseases of Cardiovascular System	0	2.3	0	2.2	3	2.3	1	2.3
External Causes (Accidents and Suicides)	3	2.0	0	0.8	1	0.5	2	0.4
All Other Causes	0	1.3	0	0.8	0	1.0	0	0.8

*Expected numbers of deaths based on U.S. white male mortality rates.

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FROM: JOHN H. DAVIDSON
636-4826

ASSESSMENT OF HAZARDS ASSOCIATED WITH USE OF 2,4,5-T, 2,4-D, AND SILVEX IN REFORESTATION PRACTICES

In such a report as this it would be highly desirable to prepare a hazard analysis for each compartment or trophic level in the potentially affected ecosystem. This is at least very difficult and perhaps impossible to develop in a single document with the complexities of inter-level dependence and ultimate dependence on many target plant species. There is an extensive literature on such effects, but in this report a decision has been made to concentrate on potential human impact. In that process, essential information on lower species appears to the extent necessary.

There is an extensive literature on persistence, physical transport, and degradation mechanisms of the phenoxy herbicides in the environment and their behavior is well established. These areas are discussed only in sufficient detail to establish essential facts. The section on TCDD is an exception and includes as complete a treatment as possible because of the unique character of the chemical. Furthermore, the author is not competent to critically analyze the entire literature on physical and chemical behavior.

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Problems Associated With Assessment of Human Health Hazard Associated With Use of Phenoxy Herbicides

There are fundamental differences of opinion in philosophy of herbicide usage. A significant segment of the population consider insertion of any synthetic chemical into the environment as fundamentally wrong, regardless of benefits, however well documented. There are as well groups and individuals who are unable to accept any suggestion that some chemicals, as used successfully and with apparent impunity for decades, might constitute a hazard which is only now becoming evident.

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This issue is no more clouded by those viewpoints than is any other debate over chemical usage, and we are best served by dealing with the problem without those extremes.

Without question, the issue of phenoxy herbicides use has evolved to concerns about the contaminant TCDD in 2,4,5-T and silvex. Though 2,4-D has no such impurity, it has become tarred with the same brush, and it is not unrealistic to devote more space to the contaminant than any of the primary chemicals.

Because of the extremely low environmental levels and enormous intrinsic toxicity of TCDD, the most critical technical question about that chemical centers on analytical methodology. There are few laboratories with the sensitivity to deal with concentrations on the order of 10 ppt or less, and there is real disagreement about reliability of detection or measurement at such low levels. When the data are considered, some samples in which TCDD was undetectable had high detection limits, some areas with no spray history were found to have measurable TCDD. Also, many samples of similar origin differed widely. Nonetheless, the data appear to be telling us clearly that some TCDD is present in some segments of the environment, that the amounts are uncertain, and that existing residue information must be augmented if we are to understand the behavior of TCDD. With any effort presently imaginable, however, it will probably not be possible to directly monitor the amount of TCDD in the physical environment.

A proper analysis of hazard requires consideration of chemical behavior and ambient levels of the potential intoxicant, but in the case of TCDD we must rely on indirect assessment. The extent of uptake in

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organisms that might concentrate TCDD, as compared with residues following known laboratory exposures is of some value, but is still inadequate.

There is a pervading argument over the problem of a specially sensitive or idiosyncratic individual who responds to much lower doses than the surrounding population, or who responds in a highly exaggerated manner. Such cases are so rare that usually no field association with the causative event can be made. The effect is virtually impossible to find experimentally because it may have never been identified, and if it had, the genetic and species factors probably prevent any useful modeling. The argument about idiosyncracy follows every chemical in commerce, and society has not learned how to cope with it, or even whether it wants to try. In the context of excessive sensitivity there seems to be no reason to treat the present group of chemicals differently from any others. That is to say, every reasonable attempt must be made to locate or predict adverse effect, but it does not seem possible to anticipate the extremely rare response in areas not supported by research findings.

A hazard analysis dealing with TCDD may or may not be strengthened by a position that EPA will apparently take; i.e., that 80-200 ppt TCDD in beef fat is an "effect level." The EPA document in question is as yet in draft form and will not be specifically attributed or referenced in this report. If the figures indicated are correct, any levels in beef thus far detected are within levels which will not do harm. The conclusions were reached with the assumption that beef fat will constitute no more than 2.5% of the human diet. The concern in present forestry usage is primarily with deer which browse on treated foliage, and there is no clear indication of TCDD levels which might be expected in these animals.

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The most difficult problem of the several that are a part of the task of hazard assessment is, again, part of the decision pattern for any chemical, the risk-benefit analysis. Risk benefit analysis is an excellent basis for conversation but nearly useless in decision making. In the present case there seems to be a general conviction that herbicide application is a highly useful tool in forest production. At the same time, estimates of differences in actual relative costs of tree production or retail materials, either near-term or long-term, are difficult to find. Technically, economic benefit should be an accessible factor, but it seems elusive.

Risk, on the other hand, is not quantifiable unless major and obvious effects occur; such situations make the decisions for us. If we are able to show any human illness resulting from environmental practices of chemicals, almost certainly they will be disqualified. An exception may be in effects which are certainly reversible.

As a society we have yet to learn a usable method of determining whether, or how much, human injury can be considered acceptable.

The assessments of hazard in this report are therefore opinions by one person about the potential for human harm resulting from distribution of the chemicals at minimum levels that will achieve the forestry objective. This document should be taken as a working base enabling incorporation of other opinions, and it should be subject to periodic updating, based on new findings, existing papers inadvertently missed in review, and existing papers which may become more pertinent in the light of other new findings.

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Assessment of Human Hazard Resulting from TCDD as a Contaminant of Phenoxy Herbicides

Two arguments emerge frequently in discussion of TCDD. One is that the manifest injuries to workers and citizens in or near sites where trichlorophenol plants have had run-away reactions or explosions dictates a cessation of use. The several such accidents, some near catastrophic are certainly unique because of the enormous toxicity of TCDD. The argument has merit but the issue here is whether specified uses are hazardous. There is little doubt that industrial safety often lags far behind existing capacity for safety, but specific industrial hygiene and health problems should be dealt with on the basis of their own weaknesses. In other words, solving the factory and community exposure problem by plant shut down may make sense, but solving it by stopping use of the agent does not.

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Another argument is that laboratory data is unrealistic and not useful if it doesn't duplicate potential human exposure. Nothing fills that criterion except accidental human exposure, which we do not need. Experience has given us considerable (albeit not perfect) confidence in our ability to estimate field consequences from laboratory findings. The concept of dose dependent response has been proven valid, although there are admittedly possible discrepancies at the very low dose range. In any case, without the expenditure of enormous amounts of time and money, we cannot have studies that precisely duplicate field exposure.

It is possible to estimate a TCDD exposure rate that will not cause effect in the most sensitive parameters now known to be affected by TCDD. In rats, 0.001 µg/kg/day 5 days a week for 13 weeks, totalling 0.065 µg caused no detectable effect. Guinea pigs given 0.008 µg/kg/weekly for eight weeks also were not affected. Existing data from monkey

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experiments has not produced a "no observed effect" dose because the detailed analyses available only through interim sacrifice have not been made in primates. The group of monkeys studied in Allen's laboratories first showed clinical symptoms after three months of exposure to about 0.01 µg TCDD/kg/day, or a total dose of somewhat less than 1 µg/kg, but there is no way of knowing whether pathologic examination would have detected changes at the more than 10-fold lower dose found ineffective in the rat and guinea pig. The existing literature also does not provide access to a useful single dose no observable effect level. There is no useful data that relates specifically to human effects.

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It therefore seems reasonable to accept 0.06 µg/kg as a subchronic total dose over a short term, say, one year below which no effect can be detected. From this point it follows that some attempt must be made to judge potential human exposure levels. It is clearly impossible to directly evaluate acquisition by surface contact with treated foliage. Direct analytical methods for TCDD are probably more sensitive than for any other organic compound, but measurement of foliar distribution cannot be made at field application levels.

In my opinion significant TCDD exposure by inhalation is highly improbable. An intake of 0.02 µg of TCDD would require inhalation of one g 2,4,5-T containing 0.02 ppm TCDD, along with 10 g of diluent at usual dilution rates. The volume of air in which the spray is distributed is very large. Such an intake for a 50 kg person would constitute 1/150 of the assumed no observable effect dose. The potential for inhalation of TCDD formed during combustion of 2,4,5-T is infinitely less, because of the enormous dilution in air.

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Oral exposure in drinking water is also extremely unlikely because TCDD partitions from water to sediment very efficiently. With dilution in flowing water, TCDD at levels deposited during spraying disappears quickly. Furthermore, TCDD deposited on soil and surfaces binds tightly, and while some material can wash off of leaves, once on soil it remains, neither leaching downward or migrating toward water courses.

An acute spill of large amounts of undiluted spray formulation into a water course could present an isolated hazard but 2,4,5-T and its carriers are objectionable enough in taste and smell that such an accident provides its own alarm. However, a theoretical but remote possibility in such an accident is the selective extraction of TCDD onto sediment, followed by very slow loss of TCDD from sediment to water over a sustained period.

Probably the only way such an accident can occur is through a vehicular accident resulting in loss of herbicide drums into a water course.

Oral intake through consumption of meat or milk presents at least theoretical possibility that an individual might consume enough deer meat containing, say, 10 ppt TCDD to acquire a significant burden of the dioxin. The question then becomes one of the probability that such a circumstance can come to pass. TCDD in concentrations of this order have been found in cattle grazing on 2,4,5-T treated range land; we may assume that an occasional deer can accumulate similar amounts if forage is poor and the animals must eat forage that they have been observed to discriminate against. If uniformly distributed in all edible tissues the amount of TCDD in a pound of meat would be about 4.5 ng. The no observed effect level in a 50 kg human is assumed at 3.0 µg. To reach that amount would require nearly 666 meals of one pound of meat, or the meat from 5-10 deer,

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and assumption of perfect retention of TCDD or its effect. In point of fact, the high TCDD concentrations are in liver and fat and such a hypothetical whole animal concentration would not be approached.

A slightly different approach by Dr. George Streisinger makes assumptions about fat concentration and the percentage of fat in, as an example, ground meat. He has concluded that either 78 or 408 (depending on different no-effect assumptions) half-pound meals would exceed the danger barrier. Dr. Streisinger included a 100/1 safety factor, however, and the specified number of meals would bring a person to within 1/100th of a possibly harmful intake.

2,4,5-T is applied on a given forest area only 1-3 times in a timber growth cycle. While it is possible for a deer to acquire significant residues in a single year, the likelihood of a long-term continuous exposure of deer would require migration among sprayed plots, or repeated treatment of a single area, and is therefore remote. Even range land is not usually treated annually.

The significance of TCDD in mothers milk is considerably greater than consumption in meat. The analyses by Dr. Meselson's group indicate the possibility that TCDD on the order of 1-2 ppt may be present in human milk. Dr. Meselson has been careful to state that while he has great confidence in the individual analyses, they are close to detection limits, and the data really asks rather than answers the question.

For the sake of discussion, a sustained output of 1 ppt in human milk could provide an infant dose approaching the no observed effect level. Assuming a liter of milk consumed daily at 100 days, total intake would be 0.1 µg. If the average weight of the infant were 6 kg, the 100 day

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dose would be 0.016 µg/kg, or about 1/4 of the no observed effect level. Exposure for 200 days would produce a somewhat lower dose per unit weight because infant weight increases but milk output may not.

It is appropriate to inquire how a human mother can acquire enough TCDD to excrete 1 ppt or 1 ng/L in milk. If a constant input by consumption of one pound of meat daily is assumed, the individual will take in 4.5 ng daily.

Almost all ingested TCDD is excreted in feces, with a minor component excreted in urine. Most chlorinated hydrocarbons emerge in milk to a limited extent, and it is not unexpected that TCDD should be found at low levels in milk. A pound of meat containing 10 ppt TCDD ingested daily would bring into the body 4.5 ng daily. As with any chemical, an equilibrium will eventually be reached where excretion and metabolism of the chemical will equal intake. In the case of TCDD, metabolism to other forms is minimal. There are not data on the fraction of TCDD excretion in milk, but it may be expected to be quite small. If we assume a high figure of 20%, however, an output of about 1 ppt is at least possible. The possibility of such sustained intake of TCDD is remote, however, requiring consumption of 2-3 deer over a 6 month period.

An alternative is a more massive exposure over a short period. We have no knowledge of the distribution into milk of, for example, 1 µg TCDD/kg as a single dose. We do know, however, that TCDD has a half-time of residence in the body of no more than 30 days, and probably closer to 20 days. Milk concentrations will decrease at the same rate as tissue residues, if not faster, and a 200 day nursing period covers more than 6 half-times. A one ppt concentration in milk arising from a single exposure will dwindle to 0.5 ppt in 20-30 days, to 0.25 ppt in 40-60 days, and

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0.12 ppt at 60-90 days. Exposure of a nursing infant will therefore be minimal.

It appears to me therefore that the potential for harmful exposure of infants through human milk should be negligible. This route is nonetheless the most probable of the several potential means of contact, and demands a thorough analysis of human milk in exposed populations.

The data on TCDD carcinogenic potential suggest that it is not a carcinogen. It has been suggested that TCDD is a promoter of carcinogenic activity on the basis of a wide variety of tumor types developed over a long exposure period by the Wisconsin group. The recently completed Dow Chemical Co. study indicates that tumor incidence changed only at doses that were lethal to many animals over the two-year test period. The data base exists for one and probably several human epidemiological studies which could answer the question of influence on human cancer incidence. A recommendation is made later for such studies.

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Of the toxicological data evaluated, perhaps the most disturbing is that of Allen et al. (1977) suggesting that the lethal dose in monkeys is similar whether the agent is administered over a short period or over several months. Time independence of dosage has never been demonstrated for a chemical. If it truly exists for TCDD, there is implication that the compound leaves permanent damage, even though it has departed from the body. In this situation, continual low level impact would cause gradually accumulating injury until clinical illness would prevail. In that sense, the idea of a no-effect level would not be applicable, and no exposure would be permissible. As with radiation, however, a small intake is possible without endangering health over a lifetime. In the case of TCDD this amount is not known, but it is finite. In view of a

long history of use without apparent injury and an apparently rapidly improving data base, it seems justifiable to allow use of 2,4,5-T and silvex under conditions that will permit virtually no inadvertent or unknowing exposure. It appears to be practical to diminish ambient contact to levels which will have no significance, accepting minor one-time defects in the system which should also have no consequences, and to allow individuals the informed opinion of exposure.

Such a stringent condition is not necessarily incompatible with use of a necessary herbicide. It seems possible to design application methods and associated policies that would prevent involuntary and inadvertent exposures of humans to TCDD.

The present knowledge of dioxin effects and behavior is not sufficient to make an unqualified statement of reasonable safety. Several areas of needed research, suggested in a later segment of this report, should improve our level of confidence. Nonetheless, it is my opinion that 2,4,5-T containing less than 0.02 ppm TCDD can be used safely in reforestation if certain protective practices listed later are instituted. In brief, these involve absolute avoidance of spray intrusion across property lines, identification and protection of dwellings and water supplies reentry discipline and adequate public information programs.

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Hazard Assessment--2,4,5-T

The acute toxicity of 2,4,5-T is quite low and in itself is not a factor in the environmental hazard potential of the herbicide. This segment is concerned only with 2,4,5-T; the implications of the dioxin contaminant have been considered earlier. A wide variety of specific toxic changes have been found in experiments with acute or short-term repeated administration of high doses of 2,4,5-T.

2,4,5-T is teratogenic, but again, only at high doses. The dose response to 2,4,5-T is such a large fraction of the maternal lethal dose is required to produce birth defects.

There are substantial differences in effective teratogenic doses among strains of mice. The lowest effective dose is still substantial, however, and the kind of teratogenic response remains the same. The differences among the genetically very specific mouse strains do raise the possibility of high individual sensitivity in the heterogeneous human population. This question applies to any potential effect in humans by any chemical and really constitutes a common social question that we have not learned to handle.

The excretion of 2,4,5-T by mammals is rapid, with relatively little conversion to other compounds. Initial residues after application are high enough to possibly cause some temporary slight tissue deposition of 2,4,5-T in tissues of grazing animals, if sustained for a period of more than two weeks, but environmental degradation of 2,4,5-T is rapid and the chemical does not migrate extensively, once deposited. For these reasons and because general toxic responses to the herbicide only occur at high doses, I do not consider that 2,4,5-T as used properly in forestry procedures represents a general toxic or teratogenic hazard to the human population.

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The bulk of evidence available at this time indicate that 2,4,5-T is not carcinogenic or mutagenic. It must be emphasized that this evidence really assures us only that the herbicide is not highly carcinogenic. An epidemiological study of humans occupationally exposed has also been negative, although other herbicides were found in the same study to be possibly associated with an increased incidence of tumors.

Mutagenic assessment in a number of experimental systems has shown no evidence of such change, and epidemiological study of 2,4,5-T production employees has shown no evidence of cytogenetic change.

I do not believe the issue of carcinogenesis by 2,4,5-T can be arbitrarily closed yet, although at this time it appears that there is not a carcinogenic or mutagenic hazard at exposure levels encountered following typical application. I have made recommendations relating to needed investigations which should establish a more specific level of confidence in that opinion, or possibly cause it to change. An industrial study of carcinogenic effect of a two-year treatment of rats with 2,4,5-T is almost complete and should also shed more light on the issue.

I do not believe that 2,4,5-T per se as used in forestry constitutes a human health hazard.

Hazard Assessment--2,4-D

The acute toxic dose of 2,4-D is quite high, but a number of individuals occupationally exposed to 2,4-D have suffered severe neuromuscular and gastrointestinal effects. These incidents have been the result of gross mishandling of the chemical and are not a part of the environmental health issue.

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The reproductive effects of 2,4-D do not appear until doses approaching the lethal level are reached, and there seems to be no reason for concern in this province.

As a potential carcinogen, 2,4-D has had very little study. The only evaluation of which I am aware was negative, in one species, which indicates that the compound is not highly carcinogenic. This finding of course can give no confidence about low level carcinogenicity. Several studies of mutagenic potential have been negative, adding some confidence.

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Perhaps the key information lies in the rapid excretion of intact 2,4-D in the urine. This process is rapid and relatively complete. In some species a portion of the compound is converted to other forms for excretion, but the process is rapid. Rapid excretion probably is the factor that prevents 2,4-D or its products from reaching the detectable margin in milk after field exposure. It is possible experimentally to overload an animal to the extent that the material will appear in milk.

Because of its short persistence in the environment and the absence of toxic responses at any doses that might be found in the field, I believe the uses of 2,4-D in practices presently considered standard is not hazardous.

There are, as with any chemical, some open questions, which are addressed in the section on recommendations. These relate primarily to epidemiological needs and clinical surveillance.

Hazard Assessment--Silvex

The general considerations applicable to 2,4,5-T may also be applied to silvex. There are some minor differences between the compounds, but the ranges of toxicity, the manner of biological disposition, and the

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environmental behavior are similar enough that similar standards should apply. In the absence of data on silvex, findings from studies of 2,4,5-T should be considered applicable.

As with 2,4,5-T, the issue of TCDD contamination overshadows the characteristics of silvex itself. The one mitigating circumstances is the more limited distribution of silvex and therefore less extensive distribution of TCDD.

It is my opinion that present uses of silvex do not constitute a hazard, from silvex itself. The issue of the TCDD contaminant is separately addressed. There is, however, further information needed to increase confidence in that opinion, and recommenations have been made in the appropriate section.

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RECOMMENDATIONS OF STEPS WHICH SHOULD BE CONSIDERED TO ASSURE THAT EXPOSURE TO TCDD IS MINIMIZED OR PREVENTED

I have stated my opinion that 2,4,5-T can be used safely, with certain additional safeguards. I believe that opinion should be reviewed as new data emerges. A number of clinical questions now being asked have accessible answers, and these must be obtained. In addition, the toxic nature of TCDD and our inability to measure it satisfactorily in the environment dictates a very conservative attitude about its distribution. I see no inconsistency in accepting its presence in small quantities and recommending unique steps to prevent those quantities from reaching people.

To assure public protection and a more compatible relation with the public, I suggest the following considerations in designing a spray program.

1. With the consideration of health hazard, there is a political reality that needs more attention. Every treatment operation must be designed to prevent intrusion of spray onto premises not under control of the agency or firm using the chemical, as a matter of principle. I would not be surprised if Forest Service policy includes that concept, but I would also be surprised if its application is somewhat less than perfect. Personal rights are becoming more and more clearly defined, and it seems to be time to decide where such rights begin and end, and take a visible public position on the issue.

2. As a means of preventing any involuntary exposure, there should be assurances that every residence is identified, with any water sources that may be in the Forest. Non-legal residents should also be identified.

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Questions of liability and informed consent and other relationships with the Forest Service ought to be clearly laid out.

3. Present buffer procedures should be examined in detail and publicly shown to be adequate. If a 100-foot zone cannot be proven certainly safe, it should be expanded.

4. An intensive posting and advertising program should be used to notify the public where herbicide treatments are located. The information should be directed toward special users of the area, such as hunters, as well as the adjacent population.

5. There is definite need for documented assurance that applied herbicides arrive only at the intended target area. If this requires a spot monitoring program during and after application it should be instituted. Here again is an issue of public confidence; precision of application may be very high, but no one outside the industry knows about it, if it is so.

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RESEARCH NEEDS TO MORE CERTAINLY ESTABLISH THE SAFETY OF PRESENT USES OF PHENOXY HERBICIDES

1. During discussions of herbicide use issues we are confronted by innumerable allusions to people made ill by application of the agents. These incidents range from word of mouth descriptions of a neighbor's experience to an extensive series of carefully constructed interviews with Vietnamese who were subjected to herbicides as chemical warfare. As they appear in the context of our forestry practices, these anecdotal descriptions of illness cannot be documented and are of little value in assessing toxic hazard. They are of concern, nonetheless.

A clinical surveillance team should be commissioned to evaluate immediately any alleged herbicide contact incidents. There is no doubt

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in my mind that people complaining of physical injury are in fact affected. I am skeptical that the application of herbicide causes these effects in more than a few incidents, but it is possible. Of more importance, there may be some other public health hazard operant in the area which causes the symptoms. It is even possible that other illness is brought to the attention of the victims by their immediate concern about improper herbicide intrusion on their private property.

2. The opinion of Van Miller et al. (1977) that TCDD is a promoter of carcinogenic effect by other compounds seems reasonable according to their evidence. If the forest application of 2,4,5-T containing TCDD is inserting effective levels of TCDD into the human environment, epidemiological evaluation should disclose higher than normal incidence of various forms of cancer in 2,4,5-T use areas. Lane County, Oregon, has a very effective tumor registry program, with virtually all pathology of human cancer examined by a single consortium of specialists. These data should provide evidence of any existing difference in cancer patterns from other areas. A more definitive study should be possible in rangeland or rice-growing areas where the herbicide is used annually. Epidemiological studies such as these may settle the persistent question of cancer latency, because on an area basis, the pattern of past use of herbicides should be reasonably accessible.

3. A thorough health surveillance should be made of all herbicide applicators and others with industrial or agricultural exposure to 2,4,5-T or silvex. Cytogenetic evaluation through several seasons of the year should be an integral part of the study. Design of the medical components of the survey should be by a nationally constituted panel.

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4. Environmental degradation of TCDD is still inadequately understood. Photodegradation by light reflected from or transmitted through foliage must be measured, as must reaction in shade and under cloud cover.

5. With present sensitivities of analysis, translocation of TCDD in plants should be restudied.

6. Affinity of TCDD to plant surfaces should be examined directly, to determine how efficiently the chemical can be removed by surface contact and by animal digestion of forage.

7. Augmentation of industrial efforts to eliminate TCDD from trichlorophenol derivatives seems to be a legitimate governmental concern, and should be encouraged. Elimination of the contaminant would obviously eliminate the issue.

8. A search should be made for chemical additives that would react with TCDD or accelerate its breakdown.

9. The human milk and fat biopsy program being developed by EPA should be encouraged.

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In such a report as this it would be highly desirable to prepare a hazard analysis for each compartment or trophic level in the potentially affected ecosystem. This is at least very difficult and perhaps impossible to develop in a single document with the complexities of inter-level dependence and ultimate dependence on many target plant species. There is an extensive literature on such effects, but in this report a decision has been made to concentrate on potential human impact. In that process, essential information on lower species appears to the extent necessary.

There is an extensive literature on persistence, physical transport, and degradation mechanisms of the phenoxy herbicides in the environment and their behavior is well established. These areas are discussed only in sufficient detail to establish essential facts. The section on TCDD is an exception and includes as complete a treatment as possible because of the unique character of the chemical. Furthermore, the author is not competent to critically analyze the entire literature on physical and chemical behavior.

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Problems Associated With Assessment of Human Health Hazard Associated With Use of Phenoxy Herbicides

There are fundamental differences of opinion in philosophy of herbicide usage. A significant segment of the population consider insertion of any synthetic chemical into the environment as fundamentally wrong, regardless of benefits, however well documented. There are as well groups and individuals who are unable to accept any suggestion that some chemicals, as used successfully and with apparent impunity for decades, might constitute a hazard which is only now becoming evident.

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Long-Term Hazards of Polychlorinated Dibenzodioxins and Polychlorinated Dibenzofurans*

by J. E. Huff,† J. A. Moore,† R. Saracci,‡ and L. Tomatis‡

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During January 10-11, 1978 in Lyon, France, a joint National Institute of Environmental Health Sciences/International Agency for Research on Cancer *ad hoc* Working Group considered and discussed the feasibility of coordinating epidemiological studies on the long-term hazards associated with the chlorinated dibenzo-*p*-dioxins and chlorinated dibenzofurans (PCDDs and PCDFs). Nineteen invited scientists from eight countries presented introductory working papers summarizing the most up-to-date and relevant information available from their individual programs. This report represents the collective views and scientific opinions of the Working Group. The greater part of this document comprises epidemiological studies related to episodes of human exposure. The review begins with a brief section concerning possible routes of human exposure, an overview of the pertinent chemical characteristics, and the salient toxicological properties of the structurally similar PCDDs/PCDFs. The Working Group report ends with recommendations for future activities.

Introduction

Human exposure in the workplace can occur when chlorinated dibenzo-*p*-dioxins (PCDDs) are formed during the production of certain compounds such as the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), the fungicide pentachlorophenol, and the germicide hexachlorophene (*1*). The dioxins, impurities/contaminants associated with these end-products, result most often from treatment of chlorinated benzenes at elevated temperature and pressure under alkaline conditions. Via the widespread use of these commercial products (*1, 2*) the general population may also become exposed.

In recent years, out-of-control chemical reactions during the production of 2,4,5-trichlorophenol have proceeded to the explosive

* This report was prepared by the NIEHS/IARC Working Group and the full proceedings were printed in June 1978 as IARC Internal Technical Report 78/001. References cited in this report reflect in general those published prior to June 1978. Participants of the NIEHS/IARC Working Group: A. U. Arstila, University of Jyvaskylä, Finland; O. Axelson, Regional Hospital, Linlöping, Sweden (Vice Chairman); H. Bartsch, IARC, Lyon, France; P. J. Baxter, Employment Medical Advisory Service, London, England; F. Berrino, Instituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy; L. Bisanti, Uffici Regione, Milano, Italy; R. Frentzel-Beyme, Deutsches Krebsforschungszentrum, Heidelberg, Federal Republic of Germany; A. Hay, University of Leeds, United Kingdom; J. E. Huff, IARC, Lyon, France; L. Jiràsek, Universita Karlova FVL, Prague, Czechoslovakia; T. Kuroki, IARC, Lyon, France; G. May, Derbyshire, United Kingdom; R. Montesano, IARC, Lyon, France; J. A. Moore, National Institute of Environmental Health Sciences, Research Triangle Park, N.C., U.S.A., (Chairman); J. Parizek, WHO, Geneva, Switzerland; G. F. Peruzzo, Uffici Regione, Seveso, Milano, Italy; F. Pocchiari, Istituto Superiore di Sanità, Rome, Italy; A. Poland, University of Wisconsin Medical School, Madison, Wisc., U.S.A.; C. Rappe, University of Umeå, Umeå, Sweden; V. Riihimäki, Institute of Occupational Health, Helsinki, Finland; R. Saracci, IARC, Lyon, France; I. J. Selikoff, Mount Sinai School of Medicine, New York, N. Y., U.S.A.; R. R. Suskind, Kettering Laboratory, University of Cincinnati Medical Center, Cincinnati, Ohio U.S.A.; L. Tomatis, IARC, Lyon, France; J. G. Vos, Rijks Instituut voor de Volksgesondheid, Bilthoven, The Netherlands; N. Wald, University of Oxford, Oxford, United Kingdom; J. Wilbourn, IARC, Lyon, France.

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stage thereby exposing persons to toxic levels of PCDDs. From certain of these accidents, moreover, not only did those occupationally involved receive dangerous exposure but also those inhabiting the surrounding areas received uncommon risk.

The structurally-related chlorinated dibenzofurans (PCDFs) are contaminants found in some polychlorinated biphenyl compounds: Aroclor, Clophen, Phenoclor (*3*).

These impurities are more toxic and represent a greater environmental hazard than the compounds they contaminate (*1, 3–9*). For instance, 2,3,7,8-tetra-CDD has been recently found in beef fat from cattle grazed on 2,4,5-T-treated rangeland and in breast milk from women living in areas where 2,4,5-T is used on rangeland or in forest areas (*10*). Various investigators (*11–14*) have also discovered PCDDs and PCDFs in fly ash and flue gas from municipal incinerators, and in dust from fungicide-treated wood (*15*).

Chemical Aspects

The PCDDs and PCDFs are two series of tricyclic aromatic compounds which exhibit similar chemical and physical properties (*1, 3, 4*). The basic two-dimensional structures (I, II) have eight possible points of chemical addition. From the monochloro to the octachloro derivatives, a variety of positional isomers are possible: 75 PCDDs and 135 PCDFs (Table 1).

The extreme toxic potency of some of these compounds, as well as the large number of potential isomers, warrant analytical methods exhibiting high sensitivity and specificity to monitor the environment. A desirable detection limit of one part per trillion (ppt, 1 picogram/gram sample) is being reached with current methodology. Essential requirements included efficient clean-up, good separation and selectivity, ultrasensitive quantification, and validation (*16, 17*).

Toxicological Aspects

Animals

The prototype and most extensively studied isomer of the PCDDs and PCDFs is the 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-tetra-CDD), perhaps the most potent man-made toxin presently known. The comparative oral lethal dose values for various PCDDs in mice and guinea pigs (Table 2) show clearly that the 2,3,7,8-tetra-CDD and the 1,2,3,7,8-penta-CDD isomers are the most toxic (*18*).

Toxic effects induced by PCDDs and PCDFs vary quantitatively and qualitatively among different species; however, within a single species the untoward consequences are markedly similar for all PCDDs and PCDFs that have been studied. For example, the toxic effects induced by 2,3,7,8-tetra-CDD which are most often observed in mice, guinea-pigs, and monkeys, are illustrated in Table 3 (*20*). In a brief report, daily oral intake (12-61 days) of <1 μg/kg body weight 2,3,7,8-tetra-CDD was stated as being lethal to young male rhesus monkeys (*21*), whereas McConnell et al. (*22*) reported an LD_{50} in female rhesus monkeys as <70 μg/kg body weight.

A preliminary report on 2,3,7,8-tetra-CDF concerning the toxicity of PCDFs (*23*), and a report on PCDFs (*24*) have been published.

The toxic syndrome produced by PCDDs and PCDFs may be divided into seven categories:

Chloracne. 2,3,7,8-Tetra-CDD and the tri-PCDF and tetra-PCDF were found to be active skin irritants and to induce acneform lesions in the skin of rabbit ears (*25*).

Classical chloracne is a hallmark of PCDD exposure in humans and an analogous hyperkeratosis and the modulation of sebaceous structures to keratin cysts have been observed in monkeys, rabbits, and hairless mice.

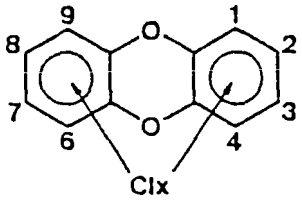
Chloracne or acneform dermatitis is a common occupational dermatitis characterized by comedones, keratin cysts, pustules, papules, and abscesses. In 1957, Kimmig and Schulz (*26*) found that 2,3,7,8-tetra-CDD was the agent responsible for causing occupational chloracne in employees of chlorophenol-producing factories. Further, in 1971 PCDDs were implicated as causing chloracne in male workers in a plant producing 2,4-D and 2,4,5-T (*27, 28*). Chloracne may appear weeks or months after the initial exposure to PCDDs and PCDFs.

Hepatoxicity. The degree of hepatic involvement appears to be dose-dependent, and the severity of the changes produced varies between species (*29*). Hepatic necrosis produced by 2,3,7,8-tetra-CDD is probably a contributing cause of death in rats and rabbits, while hepatic necrosis and liver insufficiency are less extensive in mice and are minimal in comparison in guinea pigs and monkeys (*22, 30–37*). Hepatic porphyrin accumulation has been observed in mice, rats, and chickens.

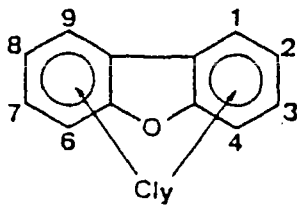
Hypoplasia of the Lymphoid Tissues. Particularly involved are the cortical cells of the thymus and this hypoplasia has been observed in mice, rats, guinea-pigs, and monkeys. The most significant findings in both mice and

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guinea-pigs treated with sublethal doses of 2,3,7,8-tetra-CDD were in the lymphoid system, resulting in suppression of cell-mediated immunity, particularly in young animals (*36, 38*). Low levels of 2,3,7,8-tetra-CDD that did not produce overt clinical or pathological changes still reduced host defences: 1 μg/kg bw given orally once weekly for 4 weeks to mice before infection with Salmonella increased mortality and decreased the time from infection to death (*39*). The increased mortality may be caused by the endotoxin content of these gram negative bacteria, since 2,3,7,8-tetra-CDD markedly increases the susceptibility of mice to endotoxin (lipopolysaccharide of *Escherichia coli*) (*40*). Treatment of female mice and rats with 2,3,7,8-tetra-CDD during the latter half of gestation and in the postnatal period resulted in a severe depletion of lymphocytes in the thymic cortex of the offspring (*41*). Cellular immunity was impaired.

Hematological changes in mice, rats, and guinea pigs treated with 2,3,7,8-tetra-CDD include lymphopenia and thrombocytopenia (*42, 43*); manifest also is an increased susceptibility to infection concomitant with the suppression of cell-mediated immunity. For 9 months, female rhesus monkeys received a diet containing 500 ppt 2,3,7,8-tetra-CDD; within 6 months, the monkeys became anemic and after 9 months pancytopenic

Table 1. Possible number of isomers for polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans.

Chlorine atoms	PCDD isomers[a]	PCDF isomers[b]
1	2	4
2	10	16
3	14	28
4	22	38
5	14	28
6	10	16
7	2	4
8	1	1
Total	75	135

[a] Chlorinated dibenzo-dioxins: empirical formula $C_{12}H_{7-0}Cl_{1-8}O_2$; molecular weight ranges, 218–460.

[b] Chlorinated dibenzofurans: empirical formula. $C_{12}H_{7-0}Cl_{1-8}O$; molecular weight ranges, 202–444.

(*44*). The marked thrombocytopenia was associated with widespread hemorrhage. Death occurred in five of the eight monkeys between months 7 and 12 of the experiment at total exposure levels of 2,3,7,8-tetra-CDD of 2-3 μg/kg body weight. At autopsy, in addition to extensive hemorrhage, there was a distinct hypocellularity of the bone marrow and lymph nodes. Hypertrophy, hyperplasia, and metaplasia of the epithelium in the bronchial tree, bile ducts, pancreatic ducts, salivary-gland ducts, and palpebral conjunctivae were observed. Squamous metaplasia and keratinization of the sebaceous glands and hair follicles were present in the skin. Death was attributed to complications from the severe pancytopenia (*44*).

General Debilitation and Wasting. Animals that receive a toxic or lethal dose of PCDDs or PCDFs exhibit a chronic and progressive weight loss with parallel mobilization of peripheral fat, increased serum triglyceride levels, and development of a fatty liver. Death due to PCDDs or PCDFs intoxication is delayed, as exemplified by an elapsed time period of 6 to 8 weeks following administration of a lethal dose and eventual death (*18, 22, 44*).

Embryotoxicity and Teratogenicity of 2,3,7,8-tetra-CDD. In repeated or single doses of 2,3,7,8-tetra-CDD to mice, as little as 1-10 μg/kg cause increased frequencies of cleft palate and kidney abnormalities (*45-48*) (see Table 4). In rats, embryo-lethal effects occur under experimental conditions (*49, 50*), and kidney anomalies (*45*), intestinal hemorrhages, and general edema can be produced in the fetuses (*51*). Few follow-up studies of the effects of prenatal exposure on postnatal functions have been published. In mice, fetal kidney abnormalities caused by 2,3,7,8-tetra-CDD may progress into a hydronephrosis during the postnatal period (*52*).

Chick Edema Disease. Hydropericardium, ascites, subcutaneous edema, liver necrosis, and death were described in 1957 following the accidental administration of toxic fats in the feed of broiler chickens (ascites have been observed also in mice) (*1*). The toxic material was later identi-

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Table 2. Estimated single oral LD50-30 values of certain polychlorinated dibenzo-*p*-dioxin isomers.[a]

Chlorine isomer	Guinea pigs		Mice	
	μg/kg	μmole/kg	μg/kg	μmole/kg
2,8	>300,000	>1,180	—	—
2,3,7	29,444	120.41	>3,000	>10
2,3,7,8	2	0.006	283.7	0.88
1,2,3,7,8	3.1	0.009	337.5	0.94
1,2,4,7,8	1,125	3.15	>5,000	>14
1,2,3,4,7,8	72.5	0.185	825	2.11
1,2,3,6,7,8	70-100[b]	0.178-0.255	1,250	3.19
1,2,3,7,8,9	60-100[b]	0.153-0.255	>1,440	>3.67
1,2,3,4,6,7,8	>600	>1.400	—	—
1-NO_2-3,7,8	>30,000	>90	—	—
1-NH_2-3,7,8	>30,000	>99	—	—
1-NO_2-2,3,7,8	47.5	0.129	>2,000	>5.4
1-NH_2-2,3,7,8	194.2	0.576	>4,300	>14.2

[a] Data from McConnell et al. (*18*). The LD_{50-30} was calculated by the Spearman-Karber method (*19*).
[b] Estimated range due to variability in replicates.

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fied in commercial oleic and stearic acids produced from inedible tallow recovered from animal hides; trichlorophenols and pentachlorophenols had been used in the curing of the hides. The edema causative was termed toxic fat and more specifically chick edema factor and was characterized by x-ray crystallography as 1,2,3,7,8,9-hexa-CDD (*53*). 2,3,7,8-Tetra-CDD, hexa-CDD, and octa-CDD have been also identified in several commercial fatty acids (*54*). Daily doses of 10 or 100 μg hexa-CDD/kg bw, or of 1 or 10 μg 2,3,7,8-tetra-CDD/kg bw, produced a positive response in the chick edema bioassay; 0.5% octa-CDD in the diet had no effect (*35*). Similar edematous effects were observed in rats, pigs, dogs, and monkeys, but not in guinea pigs (*55*). Decreased serum albumin may be associated with the edema; edema has been also shown to occur in chicks dosed orally with 2,3,7,8-tetra-CDF (*56*).

Table 3. Summary of the toxic effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.[a]

	Mice	Guinea pigs	Monkeys (female)
Thymus involution	+++	+++	+++
Spleen reduction (white pulp)	+	+	+
Bone marrow hypoplasia	±	++	+
Liver megalocytosis/generation	+++	−	−
Bile duct hyperplasia	±	±	+++
Testicular degeneration	++	+++	NA
Renal pelvis hyperplasia	−	++	+
Urinary bladder hyperplasia	−	++	−
Adrenal cortical atrophy (*zona glomerulosa*)	−	++	−
Hemorrhage			
Intestinal	+	+	−
Adrenal	−	++	−
Ascites	++	−	+
Cutaneous lesions	−	−	+++

[a] Data from Moore (*20*).

Other Effects. In one or more species of laboratory animals, bone marrow hypoplasia, testicular degeneration, renal pelvis and urinary bladder hyperplasia, and hemorrhage in the intestines and adrenals have been observed.

Enzyme Induction. 2,3,7,8-Tetra-CDD and other halogenated dibenzo-*p*-dioxins and dibenzofurans stimulate a number of enzyme activities, most notably in the liver (*1*). 2,3,7,8-Tetra-CDD is a potent inducer of hepatic and renal microsomal drug metabolizing enzymes (*57-69*). Intoxication with 2,3,7,8-tetra-CDD results in a marked increase in the cellular smooth endoplasmic reticulum content of hepatic and renal cells (*60,69*). 2,3,7,8-Tetra-CDD can simultaneously activate and suppress certain microsome-associated foreign-compound and steroid-hormone-metabolizing enzyme systems (*63*) as well as increase the activity of both renal and hepatic glutathione-S transferase (*70*).

2,3,7,8-Tetra-CDD is the most active of the PCDDs in inducing hepatic δ-aminolevulinic acid (ALA) synthetase and aryl hydrocarbon hydroxylase (AHH) in chick embryo liver preparations (*71, 72*).

The PCDDs that induce ALA synthetase in chick embryo have two common properties: (1) halogen atoms occupy at least three of the four ring positions (2,3,7,8), and (2) at least one free, nonhalogenated carbon atom is unoccupied (*71*). The available toxicological data (*35*) indicate that those PCDDs that are lethal at low doses, teratogenic, or produce acne also induce ALA synthe-

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Table 4. Evaluation of reported embryotoxic and teratogenic effects induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxins in rats and mice[a]

Species	Strain	Embryotoxic/ teratogenic effect	Dose, μg/kg		Period of dosing, days	Route	Reference
			Lowest Tested[b]	ED_{50}[c]			
Rat		Intestinal hemorrhage	0.125	0.5?		Oral	(*50*)
	CD	Kidney abnormality	0.5	>1	6-15	S.C.	(*45*)
Mouse	CD-1	Cleft palate	1?				
			3	>3	6-15	S.C.	(*45*)
		Kidney abnormality	1	1-3	6-15	S.C.	(*45*)
	DBA/2J	Cleft palate	3	>3	6-15	S.C.	(*45*)
		Kidney abnormality	3	>3	6-15	S.C.	(*45*)
	C57BL/6J	Cleft palate	3	>3	6-15	S.C.	(*45*)
		Kidney abnormality	3	<3	6-15	S.C.	(*45*)
	NMRI	Cleft palate	3	6.5	6-15	Oral	(*46*)
			9	<9	9-13	Oral	(*46*)
			15	40	13	Oral	(*47*)
			5	15	11	Oral	(*47*)

[a] Data from Neubert et al. (*47*).
[b] The lowest dose with which an embryotoxic or teratogenic effect detectable at birth has been produced is indicated. Since sometimes only one dose level was tested, this does not necessarily represent the lowest dose from which an effect could result.
[c] ED_{50}-dose required to produce an embryotoxic effect in 50% of animals.

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tase; those PCDDs that are not toxic generally do not induce ALA synthetase. The structure-activity relation of PCDDs to induce AHH in chick embryos was identical to that in inducing ALA synthetase (*71*).

Mixed-function oxidase enzyme systems of mouse strains "non-responsive" to other aromatic hydrocarbons were induced by single doses of 2,3,7,8-tetra-CDD, as evidenced by increases in hepatic monooxygenase activities and in concentrations of cytochrome P-448 (*73-76*). Genetic resistance to induction of AHH by 3-methylcholanthrene in DBA/2J mice was overcome by treatment with 2,3,7,8-tetra-CDD. This result conflicts with the hypothesis that induction of AHH activity is a consequence of the formation of cytochrome P-448 (*77*). A component that has a high binding affinity for 2,3,7,8-tetra-CDD was found in mouse liver cytosol (*78*).

2,3,7,8-Tetra-CDD induces AHH even in 'poorly responsive' strains of mice (*79*), not only in liver but also in lung, kidney, and colon. The DBA/2N strain, which responds only weakly to the sarcomatogenic action of 3-methylcholanthrene, becomes highly susceptible after treatment with 2,3,7,8-tetra-CDD (*74, 80*).

2,3,7,8-Tetra-CDD is approximately 30,000 times more potent than 3-methylcholanthrene in inducing AHH activity in rat liver (*81*).

McConnell et al. (*18*) reported that the comparative toxicity of 13 PCDDs in mice and guinea-pigs (see Table 2) supports the idea that the relative potency (or rank order) of a congener to produce one toxic response is a good indicator of its relative potency (or rank order) to produce other toxic manifestations.

Hepatic Cytosol Binding Protein. A macromolecular binding species has been characterized in the hepatic cytosol fraction of mouse and rat liver which has the *in vitro* binding properties predicted for the receptor for the induction of AHH activity based on the *in vivo* biology (*78*): namely, (1) ^{3}H-2,3,7,8-tetra-CDD binds to this cytosol protein reversibly with a high affinity (K_d = 0.27 *nM*) comparable to the ED_{50} for hepatic AHH induction (ED_{50} in mice = 1 nmole/kg); (2) the binding affinity of halogenated dibenzo-*p*-dioxins and dibenzofurans for this protein *in vitro* corresponds to their potency to induce hepatic AHH activity in the chicken embryo; and (3) other compounds, such as the polycyclic aromatic hydrocarbons, which induce AHH activity and cytochrome P_1-450 also compete for this cytosolic binding protein, but compounds which induce other types of microsomal monooxygenase activities (e.g., phenobarbital) and steroids fail to bind. Thus, this cytosolic binding protein may be the receptor for the induction of AHH activity.

Structure-Activity Relations. The pathologic effects produced by the toxic PCDD and PCDF isomers are similar to those of 2,3,7,8-tetra-CDD for a given species, differing only in the intensity of the toxic effect produced by a given isomer. The toxic PCDDs have chlorine atoms in at least three of the four lateral ring positions (2,3,7, and 8) with at least one unsubstituted ring position (the octa-CDD is comparatively inactive). To the extent that the toxicity has been determined, a

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similar structure-toxicity relation has been observed for the PCDFs.

The structure-activity relation established for PCDDs and PCDFs for the induction of hepatic aryl hydrocarbon hydroxylase (AHH) activity and for binding to the hepatic cytosol binding species has been extended to other classes of chlorinated aromatic compounds. 3,4,3'4'-Tetrachloroazoxybenzene (TCAOB) and 3,4,3',4'-tetrachloroazobenzene (TCAB) are potent acnegens formed as trace contaminants in the synthesis of 3,4-dichloroaniline or herbicides based on this compound (*82*). At high doses in animals, TCAB is reported to produce thymic involution and liver damage similar to 2,3,7,8-tetra-CDD (*83*). Both TCAOB and TCAB are potent inducers of hepatic AHH activity and bind to the hepatic cytosol binding protein with a high affinity. Congeners such as 3,5,3'5'-tetrachloroazoxybenzene and 3,5,3',5'-tetrachloroazobenzene fail to induce AHH activity, fail to bind to the hepatic cytosol species, and fail to produce chloracne.

Of 16 halogenated biphenyl compounds tested, only 3,4,3'4'-tetrachloro-, 3,4,5,3'4'5'-hexachloro- and 3,4,5,3'4'5'-hexabromobiphenyls induced hepatic AHH activity and bound to the hepatic cytosol binding species (*84*). The 3,4,3'4'-tetrachlorobiphenyl has been reported to produce chloracne. McKinney et al. (*56*) found that of five hexachlorobiphenyls tested in chickens, 3,4,5,3'4'5'-hexachlorobiphenyl was by far the most toxic, and the only one that induced significant chick edema and involution of the thymus.

Pharmacokinetics. In the rat, following acute or chronic administration, 2,3,7,8-tetra-CDD is accumulated primarily in the liver and to a lesser extent in the fat, and is largely eliminated unmetabolized in the feces with a whole body half-life of about 3 weeks. Some pharmacokinetic experiments suggest the formation of a polar metabolite appearing in the urine, but direct attempts to demonstrate metabolism with hepatic microsomes *in vitro* have been negative (*1*).

Mutagenicity. Only four dioxin isomers have been evaluated for mutagenicity: the 2,7-di-, 2,3,7,8-tetra, and octa-CDDs as well as the unsubstituted dibenzo-*p*-dioxin (*85*).

2,3,7,8-Tetra-CDD increased the reversion frequency to streptomycin independence in *Escherichia coli* Sd-4. In *Salmonella typhimurium*, frameshift mutations in strain TA1532, but not base substitutions in strain TA1530, were induced by toxic concentrations of 2,3,7,8-tetra-CDD (*86*). In plate assays, the response was positive with *S. typhimurium* TA1532, doubtful with TA1531 and TA1534, and negative with G46 and TA1530 (*87*). McCann (*88*) tested 2,3,7,8-tetra-CDD in *S. typhimurium*, both with and without metabolic activation, using a spot-test and the standard plate test with strains TA1532, TA1535, TA1537, and TA1538; all these tests were negative.

Octa-CDD was nonmutagenic in *S. typhimurium* strains G46, TA1530, and TA1531, and doubtful results were obtained with strains TA1532 and TA1534 (*87*). Metabolic activation systems were not included in any of these microbiological assays.

Inhibition of mitosis and chromosomal abnormalities (dicentric bridges and chromatin fusion with formation of multinuclei or a single large nucleus) were observed in endosperm cells of the African blood lily (*Haemanthus Katherinae* Baker) treated with 2,3,7,8-tetra-CDD in the presence or absence of 2,4,5-T (*89*).

No chromosomal aberrations were observed in bone marrow cells of male rats treated with 2,7-di-CDD, 2,3,7,8-tetra-CDD, or dibenzo-*p*-dioxin by oral intubation, with 2,3,7,8-tetra-CDD by intraperitoneal injection or orally (*90*). However, when Osborne Mendel rats of both sexes were treated twice weekly for 13 weeks with 2,3,7,8-tetra-CDD, a significant but weak increase in the number of chromosome aberrations in bone marrow cells was reported (*91*).

2,3,7,8-Tetra-CDD did not induce dominant lethal mutations in Wistar rats after oral administration to males for 7 days (*51*).

Carcinogenicity. Two reports indicate that chronic administration of low levels of 2,3,7,8-tetra-CDD to rats is associated with an increased incidence of neoplasia (*1*, *92*, *93*).

Groups of 10 male Sprague-Dawley rats were fed a diet containing 2,3,7,8-tetra-CDD for 78 weeks in the following amounts (figures in parentheses are approximate weekly doses): 0, 1 ppt (0.0003 μg/kg body weight) 5 ppt (0.001 μg/kg), 50 ppt (0.01 μg/kg), 500 ppt (0.1 μg/kg), 1 ppb (0.4 μg/kg), 5 ppb (2.0 μg/kg), 50 ppb (24 μg/kg), 500 ppb (240 μg/kg), and 1000 ppb (500 μg/kg). The three highest dose levels (50, 500, and 1000 ppb) were toxic and killed all animals by the fourth week. Of the six remaining test groups, the overall incidence of neoplasms was 23/60 (38%); none occurred in the 1 ppt group. In the 5 ppt group, 5/10 animals had 6 neoplasms [earduct carcinoma, lymphocytic leukemia, adenocarcinoma, malignant histocytoma (with metastases), angiosarcoma, Leydig-cell adenoma]; the following groups also showed neoplasms: 50 ppt, three observed in 3/10; 500 ppt, four 4/10; 1 ppb, five observed in 4/10; 5 ppb, ten observed in 7/10. Neoplasms were not observed in the controls (*92*).

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Groups of 100 Sprague-Dawley rats (50 males and 50 females) received for two years diets containing 0, 22, 210, and 22,000 ppt, equivalent to 0.0, 0.001, 0.01, and 0.1 μg 2,3,7,8-tetra-CDD/kg/day. Continuous ingestion of 0.001 μg/kg/day did not cause any chemically related changes in tumor incidence or toxicity; feeding with 0.01 μg/kg/day induced an increased incidence ($p < 0.05$) of hepatocellular hyperplastic nodules (female: 18/50 versus 8/86 controls), of focal alveolar hyperplasia in the lungs, and of urinary excretion of porphyrins (female). Dietary intake of 0.1 μg/kg/day caused an increased incidence ($p < 0.05$) of hepatocellular carcinomas (female: 11/49 versus 1/86) and squamous-cell carcinomas of the lung (female: 7/49 versus 0/86), of the hard palate/nasal turbinates (male: 4/50 versus 0/85; female: 4/49 versus 0/86), and of the tongue (male: 3/50 versus 0/85). Further increased were adenoma of the adrenal cortex (male) and hepatocellular hyperplastic nodules (female). At this dose, certain age-related lesions were reduced (males: acinar adenoma of the pancreas; females: granulosal cell neoplasm of the ovary, benign and malignant tumors of the mammary gland, pituitary adenoma, and benign tumors of the uterus). Also, chronic administration of 2,3,7,8-tetra-CDD caused multiple toxicologic effects, including increased mortality, decreased body weight gain, slight depression of certain hematologic parameters, increased urinary excretion of porphyrins and δ-aminolevulinic acid, increased serum levels of alkaline phosphatase, glutamyl transferase and serum glutamic pyruvic transaminase, and morphologic changes primarily of the hepatic, lymphoid, respiratory, and vascular tissues of the body (*93*).

These two reports show that chronic administration of 2,3,7,8-tetra CDD causes an increased incidence of neoplasms, but not whether 2,3,7,8-tetra-CDD acts as an initiator or promoter. This consideration is particularly important because unequivocal evidence is lacking that 2,3,7,8-tetra-CDD is a mutagen or is metabolized, and no evidence is available that 2,3,7,8-tetra-CDD and/or metabolite(s) bind covalently to macromolecules.

As summarized in Table 5, at least 24 long-term carcinogenicity studies on mice and rats are in progress (*94*).

Humans

Toxic Effects in Humans. Toxicity due to 2,3,7,8-tetra-CDD has been reported after occupational exposure during the industrial synthesis of 2,4,5-trichlorophenol (TCP) and 2,4,5-T, after exposure in factories and in the surrounding environment due to accidents occurring during the synthesis of TCP, and after exposure to herbicides and other materials containing 2,3,7,8-tetra-CDD. Exposed subjects have been found to develop a wide variety of lesions and symptoms (Table 6). For instance, a typical exposure victim experiences a number and a variety of clinical signs and symptoms: early exposure symptoms may include a burning sensation of the eyes, nose, and throat followed by headache, dizziness, nausea, and vomiting. Some days later, severe itching, redness, swelling of the face, more marked over the eyelids, nose and lips, may develop. Within the initial weeks after exposure, inflamed nodules as well as pustules appear on the face, forearms, shoulders, neck, and trunk, leading then to comedones and cysts. After a month or two, acneform eruptions emerge and the skin becomes hyperpigmented. At about the same time, aching muscles, mainly in the thighs and chest area, become manifest and aggravated on exertion. Insomnia, extreme irritability, and loss of libido also occur during this stage.

Other than the consistently found clinical feature of acne, other findings in humans may include: neuromuscular symptoms (weakness and pain with nerve conduction abnormalities), porphyria cutanea tarda, hepatic dysfunctions, hyperlipidemia, cutaneous hyperpigmentation and hirsutism, chronic eye irritation, emotional disorders, and neuropsychiatric syndromes.

Chloracne, one of the most constant and prominent features of 2,3,7,8-tetra-CDD exposure, has been described as a refractory acne characterized by inclusion cysts, comedones and pustules, with eventual scarring of the skin, more frequently originating on the face and sometimes spreading to other parts of the body. Many patients also have blepharoconjunctivitis and irritation of other mucous membranes. Sometimes the chloracne is preceded by erythematous and edematous skin lesions. The latent period between exposure and the appearance of clear signs of chloracne ranges from a few weeks to several months (*106*).

An important and unique episode revolves around three scientists who were self-exposed to 2,3,7,8-tetra-CDD: one heated trichlorophenol in an alkaline solution, a second heated potassium trichlorophenate, and a third worked in the same laboratory as the second and used a diluted solution of the synthesized dioxin (*107*). The first two scientists developed chloracne eight weeks after exposure, whereas the third showed no evidence of the characteristic acneform lesions. Delayed symptoms, probably due to 2,3,7,8-tetra-CDD, developed approximately two years later, and the second two scientists showed personality changes

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Table 5. Ongoing long-term carcinogenicity testing of chlorinated dibenzo-*p*-dioxins.[a,b]

Compound	Number of studies	Route	Species
Dibenzo-*p*-dioxin	4	Oral (diet)	Mouse, rat
		Skin	Mouse
			Mouse (with DMBA)[c]
2,7-Di-CDD	4	Oral (diet)	Mouse, rat
		Skin	Mouse
			Mouse (with DMBA)[c]
2,3,7-Tri-CDD	3	Oral (gavage)	Mouse, rat
		Skin	Mouse
2,3,7,8-Tetra-CDD[d]	5	Oral (diet)	Rat
		Oral (gavage)	Mouse
		Oral (gavage)	Mouse, rat
		Skin	Mouse
1,2,3,6,7,8-Hexa-CDD[d]	3	Oral (gavage)	Mouse, rat
		Skin	Mouse
1,2,3,7,8,9-Hexa-CDD[d]	2	Oral (gavage)	Mouse
		Skin	Mouse (with 1,2,3,6,7,8-hexa-CDD)
1,2,3,4,6,7,8,9-Octa-CDD	3	Oral (diet)	Mouse, rat
		Skin	Mouse

[a] Data taken from Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity, No. 7 (*94*). Details of these studies as well as the authors/institutes are available in this source reference document.

[b] As of October 1979, carcinogenesis bioassay testing within the National Toxicology Program included unsubstituted dibenzo-*p*-dioxin (UDD; CAS 262-12-4; NCI Tech. Rept. No. 122), considered not carcinogenic to Osborne-Mendel rats and B6C3F1 mice when administered in feed at dose levels of 5 and 10 ppb, and 2,7-dichlorodibenzo-*p*-dioxin (DCDD; CAS 22857-26-0; NCI Tech. Rept. No. 123), considered not carcinogenic to Osborne-Mendel rats and female B6C3F1 mice but suggestive of a carcinogenic effect in male B6C3F1 male mice when fed concentrations of 5 and 10 ppb. Studies are in progress on 1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin (HCDD, CAS 57653-85-7) and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD: CAS 1746-01-6) by gavage to Osborne-Mendel rats and B6C3F1 mice and by skin painting on Swiss mice. Testing on 2,3,7,8-tetrachlorodibenzofuran (TCDF; CAS 51207-31-9) is to begin in fiscal year 1980. For chemical disposition studies octachlorodibenzo-*p*-dioxin, 2,3,7,8-tetrachlorodibenzofuran, and the stereochemically related 2,4,3',4'-tetrachloroazobenzene are also proposed.

[c] DMBA = dimethylbenzanthracene.

[d] The National Toxicology Program has completed and reported the results for the long-term carcinogenesis bioassay studies on 2,3,7,8-tetrachlorodibenzo-p-dioxin and 1,2,3,6,7,8-/1,2,3,7,8,9-hexachlorodibenzo-p-dioxins, with the following results.

2,3,7,8-tetrachlorodibenzo-p-dioxin—gavage, carcinogenic for Osborne-Mendel rats (increased incidences of follicular-cell thyroid tumors in males and of liver tumors in females) and carcinogenic for B6C3F1 mice (liver tumors in both sexes and thyroid tumors in females); dermal, carcinogenic for female Swiss-Webster mice (fibrosarcoma in the integumentary system) and although not shown carcinogenic for male Swiss-Webster mice, an increase in the same tumor type was observed. Mixture of hexachlorodibenzo-p-dioxins—gavage, carcinogenic for female Osborne-Mendel rats (hepatocellular carcinomas or neoplastic nodules), carcinogenic for male and female B6C3F1 mice (hepatocellular carcinomas and adenomas), and not demonstrated as carcinogenic for male Osborne-Mendel rats; dermal—not considered carcinogenic for male and female Swiss-Webster mice.

(mainly loss of energy and drive); impairment of vision, taste, and muscular coordination; sleep disturbances; gastrointestinal symptoms; and hirsutism. The first of the three experienced none of these adverse effects. All three exhibited hypercholesterolemia (>300 mg/100 ml).

Human Exposure to PCDDs and PCDFs

Major sources of human exposure to PCDDs and PCDFs include: exposure in the workplace; exposure in factories and in the surrounding environment from industrial accidents; exposure to contaminated materials, wastes, or food in the general environment; and exposure in Vietnam and other intensive herbicide spraying operations. (Prior and subsequent to use as a defoliant, 2,4,5-T was used in weed-killing and forest-thinning operations in the United States of America and elsewhere).

Occupational exposure may occur in manufacturing plants producing chlorinated phenols (tri-, tetra-, and pentachlorophenols), or phenoxy acid herbicides (2,4-D, 2,4,5-T), or PCBs; in factories utilizing these chemicals for the production of other substances (hexachlorophene from 2,4,5-trichlorophenol); in factories manufacturing or repairing transformers and capacitors or having heat exchange or heat hydraulic systems containing PCBs; and in the use processes of these chemicals under various occupational conditions such as spraying of herbicides, using chlorinated phenols for a variety of applications (especially wood preservative), sawing, or otherwise processing treated wood, and using hexachlorophene in sanitary occupations.

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Table 6. Toxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxins in humans.

Effects	References
Dermatological	
Chloracne	(*25, 28, 95-108*)
Porphyria cutanea tarda	(*27, 104, 105, 109*)
Hyperpigmentation and hirsutism	(*27, 28, 107*)
Internal	
Liver damage[a]	(*27, 95, 98, 101, 102, 104-106, 110*)
Elevated serum hepatic enzyme levels	(*27, 28, 96, 104-106, 110*)
Disorders of fat metabolism	(*28, 104, 107*)
Disorders of carbohydrate metabolism	(*28, 101, 102, 104, 105*)
Cardiovascular disorders	(*101, 102, 104, 105*)
Urinary tract disorders	(*97, 101, 102*)
Respiratory disorders	(*95, 101, 102*)
Pancreatic disorders	(*101, 102*)
Neurological	
Polyneuropathies (peripheral neuritis)	(*101, 102, 104, 105*)
Lower extremity weakness	(*28, 95, 99, 101, 102, 104, 105, 108*)
Sensory impairments (sight, hearing, smell, taste)	(*28, 101, 102, 107, 110*)
Psychiatric	
Neurasthenic or depressive syndromes	(*28, 95, 99, 101, 102, 104, 105, 107*)

[a] Mild fibrosis, fatty changes, hemofuscin deposition and parenchymal-cell degeneration were observed in a few cases.

The burning of materials impregnated with commercial 2,3,4,6-tetrachlorophenates yielded 150-1000 μg of mixed PCDDs/g chlorophenate. Although only found as a minor constituent, 2,3,7,8-tetra-CDD has been quantified at levels exceeding 10 μg/g chlorophenate (*111*).

Pyrolysis of a technical grade PCB mixture yielded many PCDF isomers; the total yield could be as high as 3-25%. One of the main constituents is 2,3,7,8-tetra-CDF, the most toxic PCDF-isomer. Consequently, uncontrolled burning of PCBs can be an important environmental source of the hazardous PCDFs, and operations such as welding or soldering electrical equipment containing PCBs, or using casting waxes in foundries, may possibly entail a significant exposure (*112*). A PCB used in a heat exchange system for two years contained approximately 1.25 ppm of 2,3,7,8-tetra-CDF and a total of 15 ppm of PCDFs (*113*).

Apart from accidents such as the one which occurred in Seveso in 1976, general environmental exposure may originate from herbicide spraying and waste disposal.

An outbreak of PCDDs poisoning in humans, horses, and other animals occurred in Missouri in 1971 (*97, 114*) following the spraying of contaminated oil for dust control in horse arenas.

Another possible source of exposure to PCDDs and PCDFs pollution are waste oils, and possibly other waste, when burned both in industrial and municipal incinerators. Under simulated environmental conditions, the combustion of a standard 2,4,5-T formulation led to formation of small amounts of PCDDs and PCDFs (*115*). Buser and Bosshardt (*11*) quantified the total amount of PCDDs and PCDFs in fly ash from an industrial incinerator heating facility as 0.2 and 0.1 ppm, and in the fly ash from an industrial heating facility in Switzerland as 0.6 and 0.3 ppm. More than 30 individual PCDDs can be identified in the fly ash, but the known highly toxic PCDD isomers are only minor constituents (*12*). The number of PCDF isomers was larger; but, in this case, the known highly toxic isomers are major constituents (*13*).

An additional potential source of human exposure has been revealed: beef fat taken from cattle grazed on 2,4,5-T-treated rangeland contained 2,3,7,8-tetra-CDD; of the 11/14 positive samples, the four with the highest levels had 12, 20, 24, and 70 ppt (*10*). In another study, 3 of 24 samples of beef fat contained 3-4 ppt 2,3,7,8-tetra-CDD (*116*). Moreover, in a preliminary report of an ongoing enlarged study of women living in areas where 2,4,5-T is used on rangeland, 4/18 breast milk samples each contained approximately 1 ppt (*10*).

Workers in wood processing industries are exposed to wood dust containing preservatives as well as accompanying impurities and degradation products. Wood dust from a saw-mill in which a 2,3,4,6-tetrachlorophenol formulation was used as a fungicide was found to contain 1-10 ppm PCDFs and <0.5 ppm PCDDs (*15*).

In 1968, more than 1200 persons in South-west Japan were intoxicated by consuming a commercial rice oil contaminated with 1000 ppm PCBs. Nagayama et al. (*117*) analyzed the rice oil (Yusho oil) and found 5 ppm PCDFs, the major constituents of which were tetra- and penta-CDFs. Buser et al. (*113*) recently showed that 2,3,7,8-tetra-CDF was the main PCDF in the Yusho oil (0.45 ppm). The high level of PCDFs was caused by leakage from heat exchangers containing PCBs contaminated with PCDFs.

Workers manufacturing 2,4,5-trichlorophenol (TCP) or 2,4,5-T during normal production operations, and/or following explosions taking place in these plants, may have been exposed to a variety of polychlorinated chemicals whose type and

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quantity depends on the particular chemical processes in use and on the phase of the reaction in which the accident took place. Apparently, for instance, PCDFs are produced in the earlier stages when mainly tetrachlorobenzene is present and PCDDs are produced nearer the end of the reaction when primarily trichlorophenol is extant. The concentration of chlorophenols and chlorobenzenes, for example, was probably higher in the 1963 episode in The Netherlands, where the accident took place at the beginning of the reaction, then in the 1968 episode in the United Kingdom, or the 1976 accident in Italy, where the explosion took place at the end.

A thorough description of the reported industrial accidents and other cases of intoxications observed in exposed workers is given in the IARC Monograph (*1*). In this present report, only those episodes specifically discussed at length by the NIEHS/IARC *ad hoc* Working Group will be considered. (A sequential perspective of known accidents is given in Table 7).

In 1949, the first reported cases of industrial poisoning due to the formation of 2,3,7,8-tetra-CDD in uncontrolled exothermic reactions occurred during the manufacture of 2,4,5-trichlorophenol at a 2,4,5-T-producing factory in Nitro, West Virginia; 288 persons were affected (*99, 118*). In November 1953, an accident occurred in Ludwigshafen, Federal Republic of Germany, during the manufacture of TCP (*101,102,119,120*); 53 workers were affected by chloracne.

Five cases of chloracne were reported following an industrial accident in an Italian TCP-producing factory (*121*). In 1963, an accident occurred at the 2,4,5-T-producing factory in The Netherlands; approximately 50 persons were affected by chloracne (*122, 123*). In 1966, Dugois et al. (*98*) observed 21 cases of chloracne after an accident in a French factory producing TCP in the Grenoble region. In 1968, an accident occurred at the TCP-producing factory at Bolsover, Derbyshire, United Kingdom (*103, 106*). Within the next 7 months, 79 workers developed chloracne. In 1971, 2,3,7,8-tetra-CDD contaminated waste oil caused an outbreak of poisoning in humans, horses, and other animals (*97, 124*). In July 1976, an accident at the TCP-producing factory in Meda, Italy (*96*) resulted in the contamination of a large, densely populated area, including the towns of Seveso, Meda, Cesano Maderno, and Desio.

Key information concerning the effects of human exposure to herbicides in Vietnam, especially to the so-called "Agent Orange" (a 50:50 mixture of the *n*-butyl esters of 2,4-D and 2,4,5-T, containing up to 30 mg/kg or more 2,3,7,8-tetra-CDD), may be found in the literature (*1, 110, 125-127*).*

Exposure Episodes Considered in Detail by the NIEHS/IARC *ad hoc* Working Group

The text below is a condensed version of the discussions which took place during the two-day NIEHS/IARC *ad hoc* Working Group Meeting.

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Phenoxy Acids Exposure

Cohort studies on herbicide sprayers have been conducted or are being planned in Scandinavian countries. The more advanced of these concerns Swedish railroad workers with exposure to a variety of herbicides. These people exhibited a significantly increased tumor incidence (apparently dose-dependent) and tumor mortality (*129*). The excess of tumors was found particularly among workers with exposure to amitrole (aminotriazole), whereas those exposed to phenoxy acids (2,4-D and 2,4,5-T) showed only a slightly increased excess of cancers. The study was small-sized, comprising 2978 person-years at observation in the total cohort and with 18 deaths *versus* 20.54 expected. The original conclusion from this study was that amitrole exposure may have caused an excess of tumors, whereas there was probably no pertinent increase in tumor incidence associated with exposure to phenoxy acids. The study has been recently reanalysed using a case-control approach, and through stratification on amitrole when considering the effect from phenoxy acids, and *vice versa*. The results show a possible and previously masked tumor-inducing effect also from phenoxy acids.

Another retrospective cohort mortality study, conducted in Finland on workers of five companies involved in spraying 2,4-D and 2,4,5-T on brushwood, did not show any increase in mortality. During 1955-1971, in the younger group of workers (under 45 years of age), however, four cancer deaths were observed versus less than two expected (no statistically significant difference). A prospective follow-up study for the period 1972-1976 revealed fewer cancer-related deaths than expected in all age groups. Clinical and anamnes-

* More than 2,000,000 gallons of Agent Orange remaining from military defoliant operations were destroyed by incineration on board ship in the Pacific Ocean, 120 miles from Johnston Island. Temperatures not lower than 1250°C were used. The steel containers were melted (*128*).

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tic investigations were also performed showing a picture of acute complaints during and following the spraying operations: headache, transient dizziness, fatigue, abdominal complaints, skin and mucous irritations, and a few cases of persistent papulae.

Interestingly, some samples of 2,4,5-T used in Finland for spraying operations contained from 0.04 to 0.07 ppm 2,3,7,8-tetra-CDD. This may imply that the 2,4,5-T produced before 1965 contained lower levels of 2,3,7,8-tetra-CDD impurities than has been observed subsequently from 2,4,5-T used elsewhere. However, the analytical methods used in the determination of 2,3,7,8-tetra-CDD in the Finnish samples were antiquated in view of the rapid advancements made in analytical methodology and thus a confirmatory analysis of the samples using modern techniques was made by Rappe et al. (*130*). Five samples of 2,4,5-T ester dating from 1962 to 1967 were analysed for PCDDs and PCDFs; levels of 0.1-0.95 ppm 2,3,7,8-tetra-CDD and 0.1-0.15 ppm tetra-CDF were found.

A second feasibility study was designed and conducted in Finland to determine whether one could obtain anamnestic, clinical, hematological, and immunological information on Finnish railway and forestry workers who had been exposed for several years to herbicides containing 2,3,7,8-tetra-CDD. The exposed group consisted of 30 men who were control-matched to persons of the same age coming from the same district with similar job backgrounds and living conditions. Of the tests made, including liver and immunofunction studies, no differences were observed between the exposed and control groups. Although the population study is too small to permit any general conclusions as to the potential adverse health effects from long-term exposure to phenoxy acids, the investigation shows that follow-up is possible on the health status of persons exposed for several years to 2,3,7,8-tetra-CDD-containing phenoxy acids, and then to compare the exposed group results to carefully matched controls. The study is in progress.

Hexachlorophene Exposure

An excess of malformations, some severe, has been reported among children whose mothers were employed as nurses in a hospital. The mothers were exposed to hexachlorophene soap during early pregnancy, and the hypothesis of a causal relation between such an exposure and the occurrence of the malformations has been advanced (*131*); five severe and six slight malformations were observed in 65 children in the exposed group, whereas only one slight malformation was observed in the 68 children of the unexposed group. This report has been followed by another study (to be published) of a similar group of children of exposed mothers in comparison to children of unexposed mothers. Again a high frequency of malformations among the offspring of exposed mothers was reported (*132*). From these studies, however, it is not clear if exposure to other hazardous chemicals could be excluded. A retrospective-prospective study is being initiated among long-term workers of an United States' factory which used Seveso-produced 2,4.5-trichlorophenol in the manufacture of hexachlorophene. However, in the case of hexachlorophene, polychlorinated xanthenes have been also identified as contaminants at a higher level than 2,3,7,8-tetra-CDD (*133*).

Phenoxyacids and Chlorophenols Exposure in Forestry and in Wood Industry Workers

At the Regional Hospital in Umea (Northern Sweden), Hardell (*134*) observed that several patients suffering from mesenchymal tumors reported occupational or other exposures to phenoxyacids. More specifically, 87 mesenchymal tumors were diagnosed during the years 1970 through 1976. Of these cases, 55 were men (more than expected) and 43 of these 55 men were known by profession: 19 were either forestry workers, farmers and forestry workers, or workers in sawmills and papermills where exposure to chlorophenols is common. Based on the official statistics of Sweden, one can calculate approximatively the expected fraction of tumors within these trades, resulting in an expectancy of approximately 11 cases versus the 19 observed.

The Mount Sinai School of Medicine in New York is currently planning a field survey on long-term health effects on wood-preservative workers in Arkansas and Oklahoma in the United States of America.

Exposure to 2,3,7,8-Tetra-CDD during Production of 2,4,5-T or Polychlorinated Phenols and Following Industrial Accidents

The following cases, as well as others not considered at the meeting, have been described in IARC Monographs Volume 15 (*1*), and only some

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of the previously available information will be given here. The ongoing epidemiological studies on these cohorts are summarized in Table 7.

As each individual cohort has a relatively small number of person-years, a study has been proposed in which all the cohorts would be pooled and the mortality compared to that expected from the national statistics.

The first reported cases of industrial poisoning due to the formation of 2,3,7,8-tetra-CDD in uncontrolled exothermic reactions occurring during the manufacture of TCP were seen in 1949 at a 2,4,5-T-producing factory in Nitro, West Virginia, USA; 228 persons were affected. These individuals were studied by Suskind and Ashe (*135*) and followed up for a period of four years. Symptoms included chloracne, nausea, vomiting, headaches, severe muscular aches and pain, fatigue, emotional instability, and intolerance to cold. Laboratory findings showed raised total lipids and raised prothrombin time. Among those affected were not only workmen, but also laboratory personnel, medical personnel, and even the Safety Director who visited the areas of exposure. Several wives who had never visited the plant also developed acne, usually at the same time as their employee husbands.

It is important to note that information on the toxicity as well as on the stability (long persistence and slow degradability) of 2,3,7,8-tetra-CDD was not available at the time the first reports of acute toxicity were observed, and no measures were taken to decontaminate the factories and control the residue levels of 2,3,7,8-tetra-CDD. In fact, the presence of 2,3,7,8-tetra-CDD or other PCDDs and PCDFs was not even suspected. Workers, therefore, were probably exposed for a considerable time to 2,3,7,8-tetra-CDD following the first observations of acute toxic effects.

In November 1953, an accident occurred at a TCP factory in Ludwigshafen, Federal Republic of Germany; 75 workers were exposed to the reaction products during the accident and the subsequent cleaning work; most were affected by chloracne, 42 severely: 21 of the 42 suffered consequent damage to internal organs or disturbances of the nervous system. The most relevant features were polyneuritis, sensorial impairments, and liver damage. The son of one of the workers developed chloracne following contact with his father's work clothes. An additional case of poisoning occurred 5 years later in a worker who was involved in repair work (welding one of the auto-claves) at the contaminated site; subsequently this worker died with necrotic pancreatitis.

All the 75 workers could be traced in a cohort study 25 years later; mortality was compared both with the regional and national mortality and with a control group of workers from the same factory. In the exposed group, 17 deaths were observed (11 to 25 expected depending on the control population); six from cancer (four or less expected), five from cardiovascular diseases (as expected), two from suicides (0.2-0.6 expected), one from liver cirrhosis, one from a urogenital tract disease, and two from traffic accidents.

Of the six cancer deaths, three were from stomach cancer and occurred in the age group of 60-69, which is significantly more than expected. This effect was more pronounced when a minimum observation period of 10 years was considered, and more so for stomach cancer after a 20-year observation period. (Use of a long observation period permits a better estimation of the relation between exposure and disease when long "latency" periods are involved, as for cancers).

A similar accident occurred at the 2,4,5-T-producing factory in The Netherlands in 1963; 106 men are likely to have been exposed to 2,3,7,8-tetra-CDD (and possibly PCDFs) as they were in the building where the accident occurred during the subsequent period, March-July 1963. These workers may be divided into three groups: (A) factory employees (exposed during all phases of the cleaning and reconstruction activities), 44 men; (B) clean-up crew (nonfactory personnel, exposed during the months May-July), 18 men; and (C) plumbing, painting, and insulating personnel (nonfactory workers, exposed during the months May-July), 44 men.

During the explosion in Amsterdam, two operators were present in the building. With the exception of these men, who were probably exposed primarily by the inhalation route, all other workers used safety masks and were probably exposed by dermal contact. Chloracne was the most common and prominent lesion observed following 2,3,7,8-tetra-CDD exposure (26/44 examined in group A, 10/16 in group B, and 8/16 in the group C). Liver function tests (thymol turbidity and serum glutamic pyruvic transaminase and serum glutamic oxaloacetic transaminase) did not indicate liver damage. A few men complained of fatigue. The latent period between exposure and the appearance of chloracne, characterized by comedones, pustules, and cysts on the face and sometimes on other parts of the body, was approximately 4-6 weeks. Sometimes, erythematous and edematous skin lesions, possibly due to phenolic compounds, were noted one day after exposure. No skin lesions (chloracne) were reported

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in family members of the employees. Of group A, 3/44 workers died, one of pancreas carcinoma in 1964, one of myocardial infarction at the age of 69, and one of a traffic accident. Of the 17/18 traced individuals in the B group, four have died (three from sudden death, probably of myocardial infarction, at ages, 41, 53, and 65, and one of ill-defined pulmonary or cardiac cause at age 44). Only 32/44 of the C group were traced, and one of them died of sudden death, probably myocardial infarction, at age 50.

Jirásek et al. (*104, 105, 109*) studied 55 subjects from a cohort of 78 workers from a factory in Czechoslovakia producing 2,4,5-T and pentachlorophenol, who were affected by chloracne. The workers were probably exposed during the years 1965-1968 to unknown levels of 2,3,7,8-tetra-CDD. A significant symptom was the disturbance in porphyrins metabolism with signs of porphyria cutanea tarda. Many workers also suffered severe hepatic and neurological damage and had raised blood levels of cholesterol and total lipids. In the first years of follow-up, five deaths were observed, two from bronchogenic carcinoma at age 47 and 59 (only 0.12 lung cancer deaths were expected from national mortality statistics), one from atypical atherosclerosis at age 57, and one from the acute occupational intoxication. One further death, probably from liver cirrhosis, has recently been observed and 50 workers are still being followed. Many workers continue to show lipemia and hypercholesterolemia and have developed prediabetic changes and hypertension. The workers lost to follow-up are mostly foreigners who returned to their country of origin.

In July 1976, an accident in a TCP-producing factory in Meda, Italy resulted in the contamination of the towns of Seveso, Meda, Cesano Maderno, Desio, Nova Milanese, and possibly others of a large, densely populated area called the Brianza di Seveso with a total population of about 220,000 inhabitants. A retrospective health survey conducted on the workers of the ICMESA factory revealed that two workers among those directly involved in the production of 2,4,5-trichlorophenol suffered from skin lesions previous to July 1976. These facts may be indicative of a previous 2,3,7,8-tetra-CDD exposure.

A large and intensive follow-up program is in progress in the Seveso area; data were presented about the first dermatological, neurological, clinical, and laboratory findings, as well as about fetal damage. Dermatological examinations, including the screening of 32,000 children, resulted in the finding of hundreds of children with skin lesions, 135 of which were eventually identified as chloracne; 59 cases were from the more contaminated area (Zone A). However, precise description of diagnostic criteria and accurate anamnestic information, including, among others, data on places of residence, were not included. This information is needed before evaluating the meaning of the chloracne incidence data by territorial areas and efforts should be made obtain it. Chloracne cases were not systematically searched for in adults. Neurological examinations showed both signs of subclinical neurological damage and cases of clinically detectable polyneuropathy in adults (34/338 persons from zone A and 8/185 from the surrounding areas).

In about 30% of 1654 adults from both A zone and nearby zones, hepatomegaly was reported to be present on clinical investigation. No information, however, is given on the criteria by which the hepatomegaly was evaluated. The same percentage of abnormalities was observed in one or more liver tests (mainly glutamyl transferase and serum glutamic pyruvic transaminase and serum glutamic oxaloacetic transaminase). Extensive monitoring of various hematological parameters from 25,000 persons is now in progress and the data are expected to become available during 1978. Results of this investigation should allow a better understanding as to whether or not these alterations are caused by exposure to 2,3,7,8-tetra-CDD and PCDDs.

So far, immunological investigations, cytogenetic research, and embryomorphology analyses on cases of therapeutical abortions have not given abnormal results. However, the study of the frequency of congenital malformations and spontaneous abortions seems to be very difficult to accomplish. The importance of a systematic study on this subject has been stressed by the Working Group, because the questions on the teratogenicity of 2,3,7,8-tetra-CDD in humans cannot be solved by any other study.

A preliminary mortality study has been possible in 2 of the 11 towns of the Seveso area. The 1975-1977 mortality rates from liver cirrhosis and leukemia in these two limited zones of the Seveso area were compared to that of a nearby area (province of Varese). Within an overall mortality which did not appear different, an increase of deaths from liver cirrhosis and from leukemia was noted. The validity and significance of these observations should be carefully evaluated.

Recommendations

A chemical analytical program should be encouraged to identify and standardize analytical

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Table 7. Epidemiological studies on 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; human exposure episodes caused by accidental or occupational exposure occurring in factories producing 2,4,5-trichlorophenol and/or 2,4,5-trichlorophenoxyacetic acid.

Town and country	Year of exposure	Number of exposed persons	Clinical follow-up and cohort studies	Observations to date	Proposed actions	Comments and recommendations of the NIEHS/IARC Working Group
Accidental exposures						
Nitro, West Virginia, (U.S.A.)	1949	228	Only 36 individuals were followed, for a period of 4 years	No significant long-term observations are yet available (some followed-up individuals had symptoms of severe intercostal neuritis	Mortality cohort study being planned	Efforts should be made to trace the individuals who were exposed, possibly through the employment compensation files.
Ludwigshafen/Rhein, Federal Republic of Germany	1953	75	A mortality cohort study has conducted 24 yr after the accident; all exposed workers were traced for a total of 1525 person-years of observation	6 Cancer deaths were observed: 3 of stomach cancer in the age group 60-69 (significantly higher than expected), 2 of oat-cell carcinoma of the lung, and 1 of colonic adenocarcinoma	Follow-up to be continued	The results of the continuing follow-up study should periodically be made available.
Amsterdam, The Netherlands	1963	106	Preliminary observations on mortality are available; 93 exposed workers have been traced up to 1977	Of 8 deaths, 5 or 6 were from cardiovascular diseases, 5 probably from myocardial infarctions; the myocardial infarction death rate seems higher in the most heavily exposed workers affected by chloracne. One worker, who did not develop chloracne, died from pancreatic carcinoma 14 months after the accident; however, he complained of abdominal pain prior to the accident	Full report planned for 1978	Efforts should be made to trace all the workers who were exposed.
Bolsover, Derbyshire, United Kingdom	1968	90	Of the workers belonging to the original cohort, 50% are still employed and routinely undergo clinical and laboratory investigations	One worker is known to have died from coronary thrombosis	Epidemiological cohort study to be planned when the results of the present clinical follow-up investigation become available	Efforts should be made to trace all the workers who were exposed.

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Meda, Brianza di Seveso, Italy	1976	?*	A clinical follow-up of the inhabitants from the more contaminated areas is being carried out. At the time of the accident, living in Zone A was a population of 730 people, with 200 of those being between 0-14 years of age. Of these 730 persons, 623 (125 between 0-14 years of age) were followed-up. Zone B contained a population of 4732 inhabitants with 1293 between the ages 0-14 years. An accurate count of those followed in Zone B is not available, but 943 youngsters between 0-14 years of age are included in the follow-up	Initial clinical observations showed a high incidence of 2,3,7,8-tetra-CDD-dependent skin lesions among children living in the more contaminated area. Also, a number of persons residing in the zone surrounding the more contaminated areas had skin lesions, but with poorly defined, clinical features; these lesions may be the result of 2,3,7,8-tetra-CDD exposure. Moreover, both clinical and laboratory findings suggest an increased incidence of hepatic sufference among adults living in the highly contaminated areas. A preliminary mortality study suggests that although the overall rates from 2 Seveso towns are not different from a nearby area, an increase of deaths from liver cirrhosis and leukemia was noted	Among other ongoing investigations, a long-term morbidity study has been initiated	Possible teratogenic and other adverse reproductive and developmental effects from 2,3,7,8-tetra-CDD exposure should be investigated. A mortality register and population files, suitable for adequate descriptions of morbidity data, should be established. Further, the cancer registry that already covers a nearby province, should be extended to include the Seveso area.
Occupational exposure Czechoslovakia	1965-1969	80	A follow-up has been made regularly on 55 workers of the original cohort. The workers lost to follow-up are mainly foreigners who left the country	Five patients died during the first 5 year-follow-up period: 2 died from bronchogenic carcinoma and 1 from a rapidly developing atypical atherosclerosis. One further death, probably from liver cirrhosis, has recently occurred. Many of the workers are now suffering from hypertension and show signs of hyperlipidemia and hypercholesterolemia as well as prediabetic symptoms and signs	Follow-up to be continued. A 10-year report will be prepared during 1978	The results of the continuing follow-up study should periodically be made available.

* No reliable information was available to the Working Group about the actual number of exposed persons; the entire area has a population of approximately 200,000 people.

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methods used, to catalogue products contaminated with PCDDs and PCDFs, and to establish a register of known PCDD and PCDF standard samples.

The Working Group unanimously recommended that a system be developed for an international exchange of information and research coordination on the health effects of chlorinated dibenzo-*p*-dioxins/chlorinated dibenzofurans. Further, and in particular, the following three areas were indicated as deserving special attention:

1. Development of sensitive and reliable measurements of body burden; improved, more sensitive, and less expensive analytical technology should be generated. Standardized sampling (air, water, soil, tissues and body fluids, environmental), preparation, clean-up, and analysis should be promoted;

2. Development of common protocols for clinical examinations (including reproductive experience) and, in particular, design of a protocol for basic core information;

3. Development of an international registry of exposed persons to serve as a basis for long-term follow-up: this was considered especially important because the relatively small size of populations involved in individual exposure episodes are an obstacle to risk assessment and thus pooling of data is almost a necessity.

The Working Group recommended that IARC explore the technical and financial feasibility, possibly in cooperation with other national and/or international organizations, of setting-up such a permanent mechanism which could include as a minimum starting program: (a) a periodical, perhaps biennial, meeting to up-date the progress of ongoing studies, and to identify needed developments; (b) an exchange of relevant information accruing during the interval between meetings; and (c) a register of chloracne cases, containing simple, essential information in a standardized form. This PCDDs/PCDFs exposure-related sign may help to better define an exposed cohort population suitable for long-term follow-up.

This report represents the views and opinions of the U.S. NIEHS/IARC (National Institute of Environmental Health Sciences/International Agency for Research on Cancer *ad hoc* Working Group which met January 10-11, 1978 in Lyon France to review the history of human exposure to these chemicals, to collate current information, and to plan and forecast needed new directions. The meeting was funded jointly by NIEHS and IARC.

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National
Farmers Union

January 28, 1980

RESOLUTION on
The Consolidated Hearings on Cancellation of the E.P.A. Registration of 2,4,5-T and Silvex Herbicides.

FIFRA Docket #415 et al

To: Douglas Castle, Director
Environmental Protection Agency

WHEREAS, The National Farmers Union, a national farm organization which represents over two million stockmen and farmers throughout the United States, together with one thousand three hundred local cooperatives who serve them, and

WHEREAS, the action by the Environmental Protection Agency has been started to cancel the registration of the herbicides 2,4,5-T and Silvex because eight women in Alsea, Oregon reported a coincidence of abortion and spraying the forest. Activist groups who are opposed to spraying pesticides in the U.S. forests have forced EPA to hold this public hearing, and

WHEREAS, reputable physicians and scientists have now refuted the Alsea conclusions and have reported on the long time study of mother's milk from the area; the milk does not contain TCDD, the dioxin of 2,4,5-T herbicide, and

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2-National Farmers Union
Resolution
FIFRA Docket #415 et al

WHEREAS, currently, EPA registers the labelled 2,4,5-T and Silvex uses as safe and efficacious. On this basis, the herbicides and their use are highly beneficial to the stockmen, ranchers, foresters, rights-of-way users, rice growers and others, and

WHEREAS, further benefits include the future of the timber industry, which depends on vegetation management, and a reduction in the losses of livestock to poison weeds. As much as 5% of some herds die a violent death, and as much as 8% of some herds have early abortions and deformed fetus' caused by eating poison weeds. The poison weeds have been kept under control by using 2,4,5-T and Silvex. Their use is not toxic to the livestock or wild animals, and

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THEREFORE, BE IT RESOLVED,

that the National Farmers Union join the other national farm organizations in requesting the U.S. Environmental Protection Agency to stop pursuit of its hearings with intent to cancel the registered uses of 2,4,5-T and Silvex, for the management of vegetation in forests, range forage improvement, rights-of-way, poison weed control, rice production and other prudent uses.

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3-National Farmers Union
Resolution
FIRFA Docket #415 et al

This request is based on findings from data available from universities, research institutions, industry, and the fact that there is no documented report of damage to applicators, the users of 2,4,5-T, throughtout the area.

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A Mortality Analysis of Employees Engaged in the Manufacture of 2,4,5-Trichlorophenoxyacetic Acid

M. G. Ott, M.S.; B. B. Holder, M.D.; and R. D. Olson, B.S.

There have been few published reports regarding surveillance of individuals occupationally exposed to 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). The present study examined the mortality experience of 204 persons exposed to 2,4,5-T during its manufacture from 1950 to 1971. Length of employment in job assignments within the 2,4,5-T process area ranged from less than one year to a maximum of approximately ten years. Efforts to minimize 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) contamination of the product resulted in nondetectable concentrations using a method of detection developed in 1966 that was sensitive to 1 part per million. Within the scope of this mortality survey, no adverse effects were observed with respect to occupational exposure to 2,4,5-T or its feedstock, 2,4,5-trichlorophenol.

In 1976 Muranyi-Kovacs et al[1] published results of a bioassay of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) for carcinogenicity. The 2,4,5-T, which contained less than 0.05 parts per million (ppm) of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), was found to produce a significant increase in non-incidental tumors (diagnosed during life or causing the death of the animal) in C3HF mice, but not in XVII/G mice. Both groups of mice had been fed 80 ppm 2,4,5-T on a daily basis until death. Previously, considerable variation between species had been demonstrated in the kinetics of excretion of 2,4,5-T.[2] An earlier screening bioassay study by Innes et al[3] was not positive for tumorigenicity in two hybrid strains of mice fed 60 ppm 2,4,5-T in their diets. The authors of the 1976 bioassay article, aware of the kinetic studies and paper by Innes, suggested that additional testing of 2,4,5-T was needed. A two-year feeding study in rats was conducted in Midland, Michigan (Kociba et al[4]). Concentrations of up to 30 mg of 2,4,5-T per kilogram per day did not induce any treatment-related tumors.

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From the Medical Department, Dow Chemical U.S.A., Midland, MI 48640.

Only limited epidemiological investigations of employees exposed to 2,4,5-T have been conducted.[5,6] In 1971, Poland et al[6] reported results of a health survey of 73 male employees in a 2,4,5-T and 2,4-dichlorophenoxyacetic acid (2,4-D) manufacturing plant. This survey was a follow-up of studies published by Bleiberg et al[7] in 1964 on 29 employees in the same plant. An important finding in the follow-up was evidence of varying degrees of acne in 48 of the 73 employees. The term "chloracne" was employed to describe the moderate to severe lesions observed for 13 (18%) of the individuals. No evidence of abnormal excretion of uroporphyrins was found in the follow-up study, in contrast to the findings of the original study. Also, in their summary the authors stated that markedly less evidence of toxicity was found in other organ systems, such as the liver, than was reported in previous studies. Although not judged to be explanatory of differences in toxicity seen from the earlier work, TCDD contamination of the process-starting material, 2,4,5-trichlorophenol (TCP), had been reduced from 10-25 ppm to 1 ppm six months before the second survey. No detailed industrial hygiene measurements of 2,4,5-T or TCDD levels in the work environment were provided.

The present study examines the mortality experience of a cohort of 204 employees engaged in the manufacture of 2,4,5-T. A review of health examination findings of phenoxy herbicide workers in this plant was discussed in a paper by Johnson.[8] The current survey compares mortality due to specific causes with that of the corresponding U.S. white male population, and with results of other mortality studies conducted at this company location.

History of Process and Industrial Hygiene Measurements

The commercial production of 2,4,5-T in the company began in March 1950, with the original process being operated continuously until it was permanently shut down in May 1971. In 1967, a second operation was developed which employed different personnel and which has continued in production. Personnel from the

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second process were not included in the present study because of the shorter latency period, and because this more recent process is for the manufacture of esters of 2,4,5-T without isolation of the acid. The departmental unit under which the original process was first organized also was responsible for manufacturing a variety of other [redacted] ranging from styrene-butadiene latex to herbicides such as 2,4,5-trichlorophenoxypropionic acid and 2-methyl-4-chlorophenoxyacetic acid. Thus, many of the individuals included in the present study were potentially exposed to numerous other substances during their employment with this unit.

The 2,4,5-T was manufactured by reacting sodium monochloracetate with the sodium salt of TCP, the salt being prepared by adding caustic to TCP. This was followed by conversion to the acid. An additional step, not considered part of the process but taking place in the same building, was esterification of 2,4,5-T with propylene glycol butyl ether or with isooctyl alcohol. Continuing efforts were made to minimize TCDD contamination in the 2,4,5-T plant by proper control of a separate plant which produced the TCP later used in the 2,4,5-T process. In 1970 wipe testing, using a combined gas chromatography and mass spectrometry method sensitive to approximately 1 μg/sample, depending upon interferences, failed to detect TCDD in the 2,4,5-T work area. The 2,4,5-T process was specifically run by a crew of four operators: a reactor operator, a salt wheel operator, an acid wheel operator, and a dryer operator.

The reaction portion of the process in which the sodium salt of 2,4,5-T was produced was nearly a closed system. During the subsequent wheeling operations, the sodium salt was converted to the acid. The 2,4,5-T dust levels found in the plant were believed to have resulted primarily from finishing operations where the end product was dried and fed through a hammer mill.

An industrial hygiene survey of the process was conducted in 1969, at which time 50 area and breathing zone samples were collected, using a midget impinger containing isooctane, at a flow rate of 2.2 liters per minute. The samples were subsequently analyzed by gas chromatography for TCP, 2,4,5-T, and 2,4-D. Concentrations of 2,4,5-T or its sodium salt ranged from < 0.1 mg/m³ to 6.2 mg/m³. Estimated time-weighted average (TWA) concentrations for the three compounds by job classification are shown in Table 1. Concentrations of these substances were relatively similar for three of the job classifications: reactor operator, dryer operator, and salt wheel operator. The acid wheel operator was exposed to lower 2,4,5-T levels and higher TCP concentrations. The 2,4-D measurements are maximum levels. This product was dried occasionally in the building where 2,4,5-T was made.

Dust levels in the finishing area often were high enough to be noticeably irritating. Unacclimated industrial hygienists reported sensory responses such as nasal irritation, sneezing, and a bitter taste from exposure levels of approximately 0.1 mg/m³ of 2,4,5-T or less than 4 mg/m³ of TCP, or both. A review of medical visits from 1954 to 1970 among the 204 men in this study revealed 19 episodes associated with acute exposure to 2,4,5-T or its esters. All exposure reported involved eye or skin contact, with the mild to moderate responses apparently resulting from the irritating effects of the materials. Six of the exposure episodes occurred while the men were working as ester operators rather than directly on the 2,4,5-T process. The esters of 2,4,5-T are believed to exert toxicological effects similar to those of the acid, after adjustments for the molecular weight of the ester itself.

Table 1. — Time-Weighted Average Exposure Estimates for 2,4,5-T Process Based on 50 Samples of Up to Five Minutes Duration and Time Studies for Each Job, 1969.

Job	TCP (mg/m³)	2,4,5-T* (mg/m³)	2,4-D (mg/m³)†
Reactor operator	2.1	0.8‡	<0.4
Salt wheel operator	2.1	0.5‡	<0.4
Acid wheel operator	9.7	0.2	<0.4
Dryer operator	1.6	0.5	<0.4

* Product specifications for 2,4,5-T in 1966 called for a maximum of 1 ppm TCDD, the sensitivity of the method of detection. In 1972, the maximum was lowered to 0.1 ppm TCDD

† Highest possible values using levels of detection as real values

‡ Present in work environment as sodium salt

Method of Analysis

The employees included in the study were determined by a two-stage procedure. The first step was the identification, from annual census lists covering the period January 1951 through January 1971, of all persons who had worked in the department under which the process was organized. The second step was a review of the complete work history for each individual to determine those who had had experience on any of the four jobs of interest. These employees constituted the population of concern. This method of selecting the exposed population insured that all employees who worked continuously for at least one year in the 2,4,5-T work area were included, but could have missed some personnel who worked in the exposure area for shorter periods of time.

A crew of eight to 12 men operated the 2,4,5-T process on a daily basis. The flow of employees in and out of the department over the 21-year period resulted in 204 men having worked for one or more months on at least one of the four jobs involved. The mortality experience of these men was compared, by the indirect method, with that of the U.S. white male population (five-year age intervals) for the years 1952, 1957, 1962, 1967 and 1971. The vital status of former employees was traced initially through the Social Security Administration. Subsequently, verification of vital status has been obtained through contact with the individual or with relatives who could account for the former employee's vital status.

Table 2. — Vital and Employment Status of 204 Workers Exposed to 2,4,5-T as of December 31, 1976.

Vital and Employment Status	No. of Workers
Total group	204
Still employed	121
Retired	18
Deceased (company records)	9
Left employment other than through retirement	56
Deceased	2
Known alive	51
Follow-up through 1976 incomplete	3

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Table 3. — Duration of Exposure by Date First Exposed Among 204 Employees Exposed to 2,4,5-T.

Date Exposure Began	Total	Duration of Exposure* <1 Year	1-2 Years	3-4 Years	5+ Years
Total	204	157	30	9	8
1950-54	58	30	17	5	6
1955-59	45	36	6	2	1
1960-64	51	44	4	2	1
1965-69	35	32	3	0	0
1970+	15	15	0	0	0

* Fifty-nine of the 204 employees worked as ester operators for from <1 up to 77 months (11 of these employees had worked for at least one year as ester operators). The exposure durations as ester operators, or while employed in other capacities within the production department, were not included in the table since exposure intensities had not been estimated

In this analysis, exposure is expressed only in terms of length of employment on the four jobs of primary concern. Exposure durations do not take into account the unmeasured exposures to 2,4,5-T or to esters of 2,4,5-T encountered on other jobs within the production department. One job did involve exposure to esters of 2,4,5-T, and several other jobs may have required filling in on a day-to-day basis for the operators in the four classifications of interest, as well as other duties with minimal exposure. Since many of the employees in the 2,4,5-T study worked on a number of jobs within the department, the durations of exposure are conservatively estimated. Sixty of these employees are also known to have worked in a styrene-butadiene latex plant organized within the production department. Thus, the persons included in the present study have been exposed to a variety of chemical compounds during their employment.

Results

The vital and employment status of the 204 workers exposed to 2,4,5-T and its sodium salts are shown in Table 2. Fifty-three of the 56 former employees have been traced through personal contact with the individual or with someone who currently knows him. For three persons vital status was verified at least through 1973, but not through 1976, by personal contact or by social security checks. Two former employees had died as of the end of 1976 and nine deaths were observed among individuals followed through employment and retiree records.

The distribution of employees by duration of exposure and by date first exposed is shown in Table 3. More than 75% of the men had worked for less than 12 months in jobs involving defined exposure. None of the men were exposed to 2,4,5-T over a working lifetime.

Medical records of employees were reviewed for evidence of chloracne or of porphyria cutanea tarda, which might indicate exposure to TCDD. No case of chloracne or of porphyria cutanea tarda was found.

Tables 4 and 5 summarize mortality by duration of exposure and by interval since first exposure. In Table 4, observed deaths were increased over expected only for the cause of death category "external causes" (6 observed vs. 3.7 expected). Three deaths in this category were due to separate automobile accidents, none of which took place while the individuals were employed on jobs involving 2,4,5-T exposure. One death was the result of a non-industrial fire, and the remaining two deaths were suicides of former employees which occurred more than ten years after exposure had ceased. The single observed malignancy death in the cohort to date was due to a respiratory malignancy which was discovered in a 63-year-old retiree who had been exposed to 2,4,5-T for eight years and who had a past history of smoking up to two packs of cigarettes per day.

The trend of deaths with respect to interval since first exposure follows a pattern which we have observed in other studies at this company location.[9] The most favorable mortality experience occurs in the early years after first exposure, followed by a relative increase compared to general population mortality. We have interpreted these findings to indicate a preselection effect due to initial employment or transfer of individuals in a state of good health, which becomes less important both as the interval since employment increases and as the employees become older.

Comment

At the exposure concentrations of TCP and of 2,4,5-T (1966 product specification called for <1 ppm TCDD in the final product) experienced by the workmen in this study, no adverse mortality effects have been observed in association with the work environment. Within the scope of this limited survey, mortality has been favorable compared to that of U.S. white males, and also compares well with the background mortality experience at this manufacturing location.[9] The mortality comparisons

Table 4. — Observed and Expected* Deaths Among 204 Employees Exposed to 2,4,5-T, by Cause and Duration of Exposure, 1950-1976.

Cause of Death Category	Duration of Exposure: Total Exposed Group Observed	Total Exposed Group Expected	<1 Year Total Exposure Observed	<1 Year Total Exposure Expected	1+ Years Total Exposure Observed	1+ Years Total Exposure Expected
All causes	11	20.3	6	13.3	5	7.0
Total malignant neoplasms	1	3.6	0	2.3	1	1.3
Diseases of cardiovascular system	4	9.1	1	5.6	3	3.5
External causes (accidents and suicides)	6	3.7	5	2.8	1	0.9
All other causes	0	3.9	0	2.6	0	1.3

* Expected numbers of deaths based on U.S. white male mortality rates

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UUW 10794027 [illegible]

Table 5. — Observed and Expected* Deaths Among 204 Employees Exposed to 2,4,5-T, by Cause and Interval Since First Exposure, 1950-1976.

Cause of Death Category	Interval Since First Exposure							
	<10 Years		10-14 Years		15-19 Years		20+ Years	
	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
All causes	3	6.6	0	4.7	4	4.6	4	4.4
Total malignant neoplasms	0	1.0	0	0.9	0	0.8	1	0.9
Diseases of cardiovascular system	0	2.3	0	2.2	3	2.3	1	2.3
External causes (accidents and suicides)	3	2.0	0	0.8	1	0.5	2	0.4
All other causes	0	1.3	0	0.8	0	1.0	0	0.8

*Expected numbers of deaths based on U.S. white male mortality rates

presented in Tables 4 and 5 are point estimates and, as such, do not directly reflect imprecision in the estimates due to small sample size. Confidence interval and power calculations may be carried out using the data provided in the tables and tabulations of the Poisson distribution. Alternately, the largest SMR or relative risk that is consistent with the observations may be stated. For example, the probability of observing less than two deaths due to malignant neoplasms 15 or more years after first exposure (one actually observed), when, in fact, the true relative risk is two, is about 15%. If the true relative risk were four, the probability of observing less than two deaths would be 0.01. Because of questions raised by recent animal toxicological studies, mortality surveillance of this limited employee population will be continued. The mortality surveillance of other populations which have had past exposure to 2,4,5-T is recommended.

DOW 1079408

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Skills Productive Capital

The 1979 recipients of the Nobel Prizes for economics are W. Arthur Lewis, of Princeton University, and Theodore W. Schultz of the University of Chicago.

Schultz revived interest in human capital. He emphasized the extent to which the welfare of nations and individuals is determined by the amount of capital they have in the form of the productive skills of human beings, which has been acquired by investment in education, training, research and experience.

The second main idea associated with Schultz is the insistence, based on observation, that the behavior of people of all kinds, not only graduates of the Harvard Business School but also Indian villagers, can be explained on the assumption that they make rational and efficient use of the resources and information they have.

— From "Nobel Winner Dealt With People, Not Theory" by Herbert Stein, in *The Pittsburgh Press*, October 28, 1979.

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Science 176, p. 262, April 21, 1972. 2425

Dow Redefines Word It Doesn't Like

Teratogenicity is an unpopular word at the Dow Chemical Company. Ever since the thalidomide tragedy, the public has reserved a particular horror for any chemical suspected of causing congenital malformations. Recently Dow has had the misfortune to have one of its best selling herbicides, 2,4,5-T, found teratogenic by scientists working under contract to the federal government. The discovery eventually led to the cancellation of certain uses of 2,4,5-T by the Environmental Protection Agency.

Suspicion of teratogenicity was also cast on a related herbicide, 2,4-D. The original study indicated that 2,4-D is teratogenic in mice and a more recent experiment, by K. S. Khera and W. P. McKinley, indicates that it also causes fetal abnormalities in rats. Dow scientists decided to repeat the Khera-McKinley experiment, but, unfortunately for Dow and 2,4-D, got similar results. So they published a paper saying that 2,4-D is not teratogenic. How can a teratogenic substance not be teratogenic? Easy—you redefine teratogenesis.

Teratogenic means the property of causing any kind of congenital malformation in the fetus. Naturally there are differences of opinion as to what constitutes an abnormality and what is within the limits of normal variation. But that apart, there is broad general agreement as to what the word means.

The Dow chemists—B. A. Schwetz, G. L. Sparschu, and P. J. Gehring—have redefined teratogenicity as "that degree of embryotoxicity which seriously interferes with normal development or survival of the offspring" [*Food and Cosmetics Toxicology* 9, 801 (1971)]. This means that none of the minor deformities caused by 2,4-D in rat fetuses—such as underweight, subcutaneous swelling, delayed formation of bone, and the growth of ribs in the lumbar region—count as terata, and therefore Dow's fast selling weed-killer is not teratogenic, according to Dow's definition. Even a chemical that caused a highly disfiguring deformity would not be considered teratogenic by the Dow chemists unless it "seriously interfered with" development or survival.

Although there might be a scientific case to be made for tightening up the definition of teratogenesis, this is not the reason for the Dow scientists' attempt to refashion the English language. Public relations is the motive. B. A. Schwetz, leader of the Dow team, explained to *Science*, "If you tell congressmen or laymen or housewives that a compound is teratogenic they would think that here is something very serious that we should not be exposed to. Every compound labeled teratogenic, they assume, must be as bad as thalidomide." The Dow redefinition, Schwetz said, is intended to remedy this unfortunate reaction or, as he put it, "Out of this will come an attempt to inform the general public that teratogenicity is not teratogenicity, if you see what I mean. There are degrees of teratogenicity."

In fairness to the Dow chemists, several of the specific deformities caused by their herbicide might not be considered evidence of teratogenesis, even under the usual definition. Delayed ossification, for example, is not abnormal if it is only delayed. But lumbar ribs, also caused by 2,4-D, is a teratogenic effect. Two leading authorities consulted by *Science*, J. Warkany of the Cincinnati Children's Hospital and Clarke Fraser of the McGill Department of Genetics, Montreal, said they disagreed with the proposed new definition. "There's no need to redefine the word—why mess around?" said Fraser.

Redefining words to suit the convenience of a special interest group can have untoward consequences—indeed George Orwell wrote a book about them. But perhaps there is something to what the Dow chemists propose. If teratogenesis is to be sanitized and put out of common use by reserving the word only for thalidomide-type disasters, then perhaps the same might be done for Dow, a word which, in many people's minds, is associated with the manufacture of napalm.—N.W.

As it turns out, "government contact work" is not entirely new to the ACS. During the past year or so, several society officials have been quietly plugging for federal support of internships in government and private laboratories as a stop-gap means of alleviating scientific unemployment. In March 1971, last year's ACS president, Nobelist Melvin Calvin, suggested two such programs to the President's science adviser, Edward E. David, Jr. In September, the White House announced the initiation of a $3 million internship project to provide jobs in federal labs for 400 to 500 unemployed scientists and engineers.

This year, the ACS is asking the Labor Department, the National Science Foundation, and science adviser David to establish a special intern program for up to 1500 jobless chemists and chemical engineers. The ACS plan would have the government paying part of the salaries of the interns, who would work in industrial labs. According to a proposal it made last month, the ACS would administer this program.

A similar concept is embodied in a bill called the Scientific Manpower Act of 1972 (H.R. 14298), introduced on 11 April by Representative Ronald V. Dellums (D–Calif.). Modeled after a bill introduced in the California Assembly last year at the behest of American Chemical Society's California sections, the Dellums measure would set up an Office of Scientific Manpower in the Labor Department to administer stipends of up to $700 a month for unemployed scientists, who would work in excess federal laboratory space. By no coincidence, Dellums comes from Alan Nixon's hometown of Berkeley.

One might reasonably ask at this point why an organization with a $30.3 million annual operating budget finds it necessary to buttonhole its members for an extra few hundred thousand dollars to pay for an emergency job program. The answer seems to be that the ACS has already trimmed away all the budgetary fat it could find, and even then it rang up a $707,000 deficit last year. (Reserves from a recent dues hike apparently more than offset the loss.)

Insofar as its finances are concerned, the ACS is first and foremost a publishing house. It produces 17 journals, plus *Chemical Abstracts*, a series of monographs, three series of books, educational aids, films, and a radio program. Like the rest of the publishing industry, the ACS is caught in a tight squeeze

16994

November 9, 1977

MIDLAND, MICHIGAN 48640
P.O. Box 1706

Mr. R. F. Mountfort (PM-23)
Registration Division (WH-567)
Office of Pesticide Programs
Environmental Protection Agency
Waterside Mall, East Tower
Washington, D.C. 20460

bcc: M. L. Leng
Action File (Silvex)

Dear Mr. Mountfort:

SUBJECT: IR-4 Petition 4E1476 Regarding the Use of Silvex on Citrus

Enclosed are copies of two toxicological reports on TCDD in rats:

1) An Ultrastructural Evaluation of Liver Cells From Female Rats Maintained for Two Years on Diets Containing 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD).

2) Results of a Two Year Chronic Toxicity and Oncogenicity Study of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) in Rats.

marked confidential by Jan E

These I trust will enable you to now procede with your evaluation of the above petition. These have previously been submitted to Mr. H. L. Warnick but for your convenience copies are included for your files.

Sincerely,

W. R. Mullison
Registration Specialist
Government Registration
Health and Environmental Research

Enclosures

jan

cc: G. M. Markle
Cook College
Office of IR-4
P.O. Box 231
New Brunswick, N.J. 08903

no attachment or enclosure

cc G. H. Davidson
N. D. Heim
T. G. Lindeman
D. O. McCollister
M. J. Traynor
L. L. Smith
C. S. Williams

LIFE IS FRAGILE HANDLE WITH CARE

CANADIAN LITIGATION AGAINST
DOW MOYER V DOW

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NAME
NOM RICHARD SCHULER

NO.

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1. W. B. Fox
~~2. F. B. Jones - FBJ.~~
3. D. L. Ego
4. Safety of Pesticides

17th March, 1970.

Dr. J. Antognini, Manager,
Field Research and Development,
Stauffer Chemical Company,
P. O. Box 760,
MOUNTAIN VIEW, California,
94040, U.S.A.

Dear Joe: 2,4-D and 2,4,5-T

In view of the present controversy opposite the continued use safety of 2,4-D and 2,4,5-T, one of our large industrial accounts has asked us for all possible up-to-date data which we can forward to them on toxicology, longevity and the possible effect on ecology of the hormone herbicides, particularly 2,4-D and 2,4,5-T.

This is quite an assignment and since this customer is particularly valuable to Chipman, we are trying to gather together all information we can on this rather timely subject.

We, of course, have a great deal of data which dates back some ten or twelve years, but this information does not seem to be too valid in consideration of the present controversy.

When we met with you in Montreal, Joe, you mentioned you had read some very interesting data recently accumulated on both 2,4-D and 2,4,5-T, and that some of the evidence against 2,4-D was even worse than the original information opposite 2,4,5-T.

I should more than appreciate it if you could send me photocopies of any authentic reports, documents, etc., in connection with the toxicology, longevity, effects on the ecology, etc. of 2,4-D and 2,4,5-T, as has been developed within the past year or so.

Your co-operation in this will be more than appreciated.

Very sincerely yours,

CHIPMAN CHEMICALS LIMITED

L. M. Godfrey,
Technical Manager.

~~15792~~

c.c. C. G. Halliday

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NAME
NOM BOERRINGER

NO.

CORRESPONDENCE

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RECHTSANWALT

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Sprechzeiten:
nach Vereinbarung

Tag: 22. Februar 1990

Sehr geehrter Herr Kollege Richards,

bitte entschuldigen Sie die verspätete Antwort auf Ihr Schreiben vom 26. Januar 1990. Ihre Frage darf ich kurz wie folgt beantworten:

Es ist mir bisher einmal gelungen, ein Gericht davon zu überzeugen, daß der Magenkrebstod eines Arbeiters auf eine berufliche Dioxinintoxikation zurückgeführt werden muß. Das Urteil des Sozialgerichts Hamburg ist allerdings noch nicht rechtskräftig. Die Berufsgenossenschaft der chemischen Industrie, bei der die Arbeiter der Firma Boehringer/Ingelheim versichert sind, hat es mit dem Rechtsmittel der Berufung angefochten.

Ebenfalls einmal ist es mir gelungen, die Berufsgenossenschaft der chemischen Industrie davon zu überzeugen, daß die akute myeloische Leukämie eines Arbeiters der Firma BASF AG, die schließlich zu seinem Tod führte, auf eine einmalige, hohe Dioxineinwirkung zurückzuführen ist. Die Berufsgenossenschaft hat diesen Zusammenhang außergerichtlich durch einen entsprechenden Bescheid anerkannt.

Mir sind ferner zwei Fälle aus früherer Zeit bekannt, in dem die für die chemische Industrie nach deutschem Recht zuständige Berufsgenossenschaft einen solchen Zusammenhang bejaht hatte. Der eine Fall liegt schon sehr weit zurück. Damals ist aufgrund eines Gutachtens des früheren Toxikologen der Firma BASF AG, Prof. Dr. Heinz Oettel, der Lungenkrebstod eines Arbeiters der Firma Boehringer Ingelheim als durch "Trichlorphenol-Zersetzungsprodukte" anerkannt worden. In jüngerer Zeit ist mir ein Fall bekannt, in dem die Berufsgenossenschaft der chemischen Industrie sich mit einem weiteren Arbeiter der Firma Boehringer, der chronisch dioxinexponiert gewesen ist, ihm Entschädigungsleistungen zu gewähren. [illegible]

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17000

Ich vertrete weitere fünf ehemals dioxinexponierte Arbeiter anwaltlich, die an Krebs erkrankt sind, bei denen bisher jedoch noch keine Entscheidung über die Entschädigung, sei es außergerichtlich oder gerichtlich, gefallen ist. Möglicherweise können Ihnen auch die diesem Schreiben beigefügten Fotokopien weiterhelfen, aus denen hervorgeht, daß die Firma Boehringer bereits 1957 verschiedene amerikanische Firmen vor dem unerwünschten Nebenprodukt Dioxin gewarnt hat.

Mit freundlichen Grüßen

(Dohmeier), Rechtsanwalt

Anl. B2

An die
Dow Chemical Company
1714 Eastman Rd.
Midland, Mich. / USA

Dr. Wey/B 11. 2. 1957

Chlorakne. Darstellung von Trichlorphenol

Sehr geehrte Herren !

Wir beziehen uns auf den Schriftwechsel in der oben angeführten Angelegenheit, den wir mit Ihnen im Jahre 1955 führten. Sie waren damals so freundlich, uns Ihre Erfahrungen mitzuteilen.

Da unsere eigenen Arbeiten über die Vermeidung der Bildung des Chlorakne-Erregers zu einem gewissen Abschluss gekommen sind, möchten wir Ihnen diese Erfahrungen zugängig machen und tun das durch Beifügung der kleinen Abhandlung als Anlage

Wir hoffen, Ihnen mit unseren Ausführungen einen Beitrag zur Sicherung der Synthese der Trichlorphenoxyessigsäure gegeben zu haben und nehmen an, daß der Beitrag auch für Sie von Interesse ist.

Wir grüßen

mit vorzüglicher Hochachtung
C.H. BOEHRINGER SOHN
ppa. Fritz Weyland

Anlage

... 506 459 6720;# 8/ 8

... Boehringer Sohn
Ingelheim am Rhein

Darstellung von Trichlorphenoxyessigsäure unter Vermeidung der Bildung von Chlorakne - Erregern .

Unsere Synthese der 2,4,5 Trichlorphenoxyessigsäure läuft in folgenden Stufen :

1) Trichlorbenzol $\xrightarrow{Cl_2}$ Tetrachlorbenzol
2) Tetrachlorbenzol $\xrightarrow{NaOH}$ Trichlorphenolnatrium
   a) Autoklaven-Reaktion
   b) Abdampfen des CH_3OH
   c) Wasserdampfdestillation des Anisols
   d) Isolierung des Trichlorphenols durch Ansäuern und anschliessende Destillation
3) Trichlorphenol $\xrightarrow{NaOH,\ CH_2ClCOONa}$ 2,4,5-Trichlorphenoxyessigsaures Natrium
4) Weiterverarbeitung zu reiner krist. 2,4,5 T-Säure

Nach unseren Erfahrungen ist die chlorakne-auslösende Wirkung auf Verunreinigungen durch Nebenprodukte zurückzuführen, die bei dem konventionellen Prozeß nur dann entstehen können, wenn Trichlorphenolnatrium bzw. andere Alkalisalze von Trichlorphenol hergestellt, gereinigt und weiterverarbeitet werden und sich dabei Reaktionsbedingungen ergeben, die denen einer Salzschmelze nahe- oder gleichkommen.

Unter diesem Gesichtspunkt ergibt sich mit Bezug auf die Entstehung des Chlorakne-Erregers für die einzelnen Verfahrensstufen folgendes :

Zu 1 und 4) Diese Stufen sind völlig ungefährlich

Zu 2) Bei dieser Stufe kann der Chlorakne-Erreger entstehen.

Zu 2 a) Um dies bei der Autoklaven-Reaktion zu verhindern, ist eine Überhitzung des Autoklaven-Inhalts zu vermeiden (Höchsttemperatur 150° C) und weiter darauf zu achten, daß in möglichst grosser Verdünnung mit Methanol gearbeitet wird

Hans-Joachim Dohmeier
Lawyer

To
Clark, Drummie & Company
attn. William B. Richards
P.O. Box 6850
Station "A"
Saint John, N.B.
Canada E2L 4S3

Day: 22.February 1990

Dear colleague Mr. Richards,

please excuse the delayed response to your letter of January 26,1990. I would like to answer your question briefly in the following:

I have managed once to convince the court that the death of a worker who died of stomach cancer was caused by a work related dioxin intoxication. The verdict of the court in Hamburg (social tribunal) has however not yet been finalized. The trade association (workman compensation board) of the chemical industry, through which the workers of the company Boehringer Ingelheim are insured, has appealed the verdict.
Also once have I managed to convince the trade association of the chemical industry that the acute myeloic leukaemia of a worker of the company BASF AG that finally led to his death was caused by a one time high influence of dioxin. The trade association has acknowledged this correlation by excepting an out of court settlement.
Further I know of two cases some time ago, in which the trade association which according to german law is responsible for the chemical industry, has affirmed such a connection. The one case is from quite a while ago. Back then, on the basis of a report of the former toxicologist, Dr.Heinz Oettel, from the company BASF AG the lung cancer death of a worker of the company Boehringer Ingelheim was accepted as caused by trichlorpherol - disintegration product. Lately I know of one case in which the trade association agreed to pay compensation to another worker of the company Boehringer, who was chronically exposed to dioxin.

I legally represent five more workers who were exposed to dioxin, and who suffer from cancer, whose cases however have not yet been settled, be it in court or out of court. The photocopies attached to this letter may possibly help you out further, as they go to show, that the company Boehringer has warned different american companies of the undesired by-product dioxin as early as 1957.

Best regards,
(Dohmeier) Lawyer

To the
Dow Chemical Company
1714 Eastman Rd.

Midland, Mich. / USA

Dr. Wey/B 11.2.1957

Re: Chlorine acne. Illustration of Trichlorphenol

Dear Sirs!

We are writing in regard to the correspondence we had with you in 1955 concerning the above mentioned matter. Back then you were kind enough to share your experiences with us.

Because our own research about discouraging the forming of the chlorine acne causing agent has come to a certain end, we would like to share our findings in turn with you, and would like to do so by means of the little report attached.

We hope to have helped you secure the synthesis of the trichlorphenoxy acetic acid, with this report, and assume that you would find this of interest.

Yours truly
C.H. Boehringer Sohn

attachments

Illustration of trichlorphenoxy acetic acid avoiding the forming of chlorine acne causing agents.

Our synthesis of the 2,4,5 trichlorphenoxy acetic acid takes the following steps:

1) Trichlorobenzene -Cl2- Tetrachlorobenzene
2) Tetrachlorobenzene -NaOH- Trichlorphenolsodium
   a) autoclave reaction
   b) evaporation of OH3 Oh
   c) water vapour distillation of the anisole
   d) isolation of the trichlorphenols through acidification and following distillation

3) Trichlorphenol -NaOH CH2 ClCOONa- 2,4,5-Trichlorphenox acetic acidic sodium
4) further processing to pure crist. 2,4,5 T-acid

According to our experience the chlorine acne causing effects are stemming from pollution through by-products, which during the conventional process can only occur, if trichlorphenolsodium or other alkaline salts from trichlorphenol are produced, cleaned and processed and throughout this reaction conditions are given, that are similar or the same to that of a salt-melt.

From this perspective then the following picture for the individual processing steps emerges in regard to the development of the chlorine acne causing agent:

concerning 1) and 4) : these steps are completely safe

concerning 2) : at this step the chlorine acne causing agent may be developing

concerning 2 a) : to avoid this during the autoclave reaction, an overheating of the autoclave contend is to be avoided (max temp. 150*C) and further attention should be given, that the methanol is worked with as diluted as possible.

concerning 2 b) : during the methanol distillation the yellow water in the distillation bubble should be held back, so that the dangerous dry heating of trichlorphanolsodium is avoided. The mud temperature should not be higher than 100*C.

concerning 2 c) : the water vapour distillation ..... of the trichloranisols must be done in such a way, that no change should occur in the concentration of the trichlorphenolsodium-solution. .....water added.

concerning 2 d) : during the distillation of the unprocessed phenol it has to be watched, that no trichlorphenolsodium and no table salt is brought into the distillation bubble and heated together with the phenol.

concerning 3) : at this step chlorine acne causing agents may also develop. To avoid this the condensation of trichlorphenolsodium with chlore acidic sodium may not be done in a water free medium. A concentration of more than 40% is to be avoided in any case.

About the qualities of the chlorine acne causing agent can in short be said the following: As a neutral body it is water vapour volatile, so that it can accumulate in step 2 c) in the distilling trichloranisole. It is therefore practical to forget about using trichloranisole and to destroy it through burning.

Since the chlorine acne causing agent shows signs of sublimation already at temperatures of 100*C (even though it has a high melting point), the reaction-product of step 2) and 3) should be processed in completely closed apparatuses and the lab should be well aired.

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Dick

Your copies

Documents in Henry Case

NAME
NOM

Dick's

NO.

17011

DOW 0366855

SYMPTOM	SILVEX			TCDD		
	causes	may cause	cannot cause	causes	may cause	can not
45. BUTTOCK PAIN			X			X
46. CALCIUM DEPOSITS: IN ARM			X			X
KELOID			X			X
LUNGS			X			X
47. CENTRAL NERVOUS SYSTEM DAMAGE	X					X
48. CERVICAL GLANDS ENLARGED			X			X
49. CHEMICAL SENSITIVITY			X			X
50. CHEST PAIN			X			X
51. CHEST "RATTLE"			X			X
52. CHOKING SENSATION			X			X
53. CHOLESTEROL HIGH			X			X
54. CHOLESTEROLOSIS (GALLBLADDER)			X			X
55. CIRCULATION IN HEART POOR			X			X
56. CIRCULATORY PROBLEMS			X			X
57. CLAMMY COLDNESS			X			X
58. COLD SORES			X			X
59. CONCENTRATION IMPAIRED			X			X
60. CONJUNCTIVITIS			X			X
61. CONSTIPATION			X			X
62. CONVULSIONS	X					X
63. COUGHING (with breathing difficulty, congestion, burning in nasal passages and lungs)			X			X
64. CRAMPS			X			X
65. "CRIPPLED-UP" (unable to move due to general pain)			X			X
66. CROUP			X			X

COMMENTS ON SILVEX AND TCDD SYMPTOMS

The category cannot cause has been interpreted as usually will not cause, since it is impossible to say that something will never happen. Scientifically one cannot prove the negative. Some of the general terms such as energy loss and anxiety are so non specific as to be associated with almost any illness. Unless these are characteristic of Silvex, they have been listed under cannot cause. TCDD has been treated in a similar manner.

Only symptoms known to occur in humans have been listed under causes. Under may cause, most of the symptoms are those seen in animals or might be expected to occur based on our knowledge of the toxicity of the compound in humans. Naturally symptoms must be interpreted in relation to the time of alleged exposure and amount of exposure. For example, a dermatits that occurs months after exposure could hardly be caused by the chemical (contact dermatitis). On ther other hand, chloracne has been known to occur several months after exposure.

SYMPTOM	SILVEX			TCDD		
	causes	may cause	cannot cause	causes	may cause	cannot cause
1. ABDOMINAL ADHESIONS			X			
2. ABDOMINAL CRAMP			X			
3. ABDOMINAL PAIN			X			
4. ABDOMINAL SWELLING			X	X		
5. ACERUMENOSIS			X			
6. ACNE			X	X		
7. ACNEIFORM LESIONS			X	X		
8. ALCOHOL INTOLERANCE			X			
9. ALLERGIC REACTION (pain killers/tranquilizers)			X			
10. ALLERGY (new)			X			
1 ALLERGY (reemergence)			X			
12. ANAL PRURITUS			X			
13. ANCHLORHYDRIA			X			
14. ANEMIA			X			
15. ANGINA			X			
16. ANGIO-EDEMA			X		X	
17. ANOREXIA		X			X	
18. ANXIETY			X			
19. APPETITE LOSS		X			X	
20. APPETITE ERRATIC			X			
21. ARM PAINFUL			X			
22. ARM STIFF			X			
23 ARTHRITIS; LOWER BACK (new)			X			
24. ARTHRITIS; RHEUMATOID (aggravated)			X			

17014

	SYMPTOM	SILVEX			TCDD		
		causes	may cause	cannot cause	causes	may cause	cannot cause
25.	"ATTACKS" (simultaneous chest pain, breathing difficulty, numbness in arms/hands, dizziness, paralysis arms/legs, difficulty sleeping)			X			
26.	AUDITIVE DISCRIMINATION (decreased)			X			
27.	BACKACHE/PAIN			X	X		
28.	BED WETTING			X			
29.	BLADDER INFECTION			X			
30.	BLADDER ULCERS			X			
31.	BLEEDING NOSE/EARS			X		X	
32.	BLISTERS: FACE FEET CHEST LEGS			XXXX			
33.	BLOOD SPOTS IN EYES			X			
34.	BLOOD SUGAR LOW			X			
35.	BLOODY PATCHES: FACE HAIR MOUTH			XXX		XXX	
36.	BLURRY VISION			X			
37.	BLURRY VISION WITH LOSS OF COLOR PERCEPTION			X			
38.	BOWEL MOVEMENT DIFFICULT			X			
39.	BREAST CYSTS			X			
40.	BREAST DISCHARGE ("milky")			X			
41.	BREAST TENDERNESS			X			
42.	BREATHING DIFFICULTY			X			
43.	BRONCHITIS			X			
44.	BURNING SENSATION: LEGS			X			

SYMPTOM	SILVEX			TCDD		
	causes	may cause	cannot cause	causes	may cause	cannot cause
180. MEMORY LOSS			X			X
181. MEMORY SLOWED			X			X
182. MENSTRUAL DISTURBANCES:			X			X
HEAVY FLOW			X			X
HEMORRHAGING			X			X
IRREGULARITY			X			X
SKIPPING			X			X
183. MENTAL EXHAUSTION			X			X
184. MENTAL SYSTEMS DETERIORATING			X			X
185. MUMPS			X			X
186. MUSCLE CRAMPS			X			X
187. MUSCLE PAIN: ARMS			X			X
BACK			X			X
CHEST			X			X
NECK			X			X
LEGS			X			X
188. MUSCLE SPASM: ARMS			X			X
BACK			X			X
CHEST			X			X
EYES			X			X
NECK			X			X
LEGS			X			X
189. MUSCLE SPASM CAUSING BACK DISLOCATION			X			X
190. MUSCLE WEAKNESS	X					X
191. NAUSEA		X		X		
192. NEARSIGHTEDNESS			X			X
193. NECK PAIN (with pain left side of body)			X			X
194. NECK AND SHOULDER PAIN			X			X
195. NERVE DAMAGE:						
AREA OF SCAPULA			X			X
CENTRAL NERVOUS SYSTEM	X					
RIGHT LEG			X			X

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SYMPTOM	SILVEX			TCDD		
	causes	may cause	cannot cause	causes	may cause	cannot cause
67. CYSTS: ARM, BREAST, EYELIDS, KNEE			X			X
68. DENTAL CONDITION POOR			X			X
69. DEPRESSION		X			X	
70. DIAPHRAGM AREA PAIN			X			X
71. DIARRHEA			X			X
72. DIFFICULTY FOCUSING EYES			X			X
73. DIZZINESS WITH LIGHTHEADEDNESS			X		X	
74. DIZZINESS WITH LOSS OF EQUILIBRIUM			X		X	
75. EARACHE			X			X
76. EAR BLEEDING			X			X
77. EAR CONGESTION			X			X
78. EAR INFECTION			X			X
79. EAR PAIN			X			X
80. EAR SHEDDING SKIN			X			X
81. ECZEMATOID			X			X
82. EMOTIONAL DISTRESS			X			X
83. ENDOMETRIOSIS			X			X
84. ENERGY LOSS			X			X
85. ENZYME SYSTEM DAMAGE		X			X	
86. EYE A-V NICKING			X			X
87. EYE IRRITATION (burning, swelling, durulent itching)		X		X		

SYMPTOM	SILVEX			TCDD		
	causes	may cause	cannot cause	causes	may cause	ca... ca...
88. EYE SCARRING			X			
89. EYE SORENESS (with congenstion burning)			X		X	
90. EYE SPASM			X			
91. EYELID ITCHING			X			
92. EYELID SHAKING		X				
93. EYES TURN IN SOCKET (when in pain, shows white only)			X			
94. FACIAL BLEMISHES			X		X	
95. FACIAL GROWTHS			X			
96. FACIAL SCALES			X		X	
FATIGUE						
98. FATIGUE (with loss of strength in limbs)			X			
99. FEVER			X			
100. FINGERNAIL COLORATION (darker under nails)			X			
101. FINGERNAIL SPLITTING			X			
102. FOOT CRAMPS			X			
103. FOOT ITCHING			X			
104. FOOT PAIN			X			
105. FLAKING SKIN; HANDS/EARS			X		X	
106. FLU & COLDS			X			
107. FOOD SENSITIVITY			X			
10 GALLBLADDER DISEASE			X			
109. GAMMA (GLOBULIN) LOW			X			
110. GASTROENTERITIS			X			

SYMPTOM	SILVEX			TCDD		
	causes	may cause	cannot cause	causes	may cause	can cau
158. JOINT PAIN			X			X
159. KIDNEY, BLADDER, URINARY TRACT INFECTION			X			X
160. LACK OF MOTIVATION			X			X
161. LEAKY VEINS WITH SUFFUSION			X			X
162. LEG PAIN			X			X
163. LEG SWELLING			X			X
164. LEG WEAKNESS		X				X
165. LIBIDO INCREASED			X			X
166. LIGHT SENSITIVITY			X			X
167. LIPS SWOLLEN			X		X	
168. LOSS OF AMBITION			X			X
169. LOW BLOOD SUGAR			X			X
170. LUMP IN THROAT			X			X
171. LUMPS: ANKLES			X			X
ARMS			X			X
HANDS			X			X
KNEES			X			X
172. LYMPH NODE SWOLLEN			X			X
173. LYMPHOCYTOSIN ?			—			—
174. MALAISE			X		X	
175. MANUAL DEXTERITY DECREASE (due to numbness in hands)			X			X
176. MASCULAR LESIONS ?			—			—
177. MASS, LEFT BREAST			X			X
178. MEASLES			X			X
179. MEMORY LAPSES			X			X

SYMPTOM	SILVEX			TCDD		
	causes	may cause	cannot cause	causes	may cause	ca ca
111. GINGIVITIS			X			
112. GROWTHS			X			
113. HAIR ABNORMALITY			X		X	
114. HAIR LOSS			X		X	
115. HAIR WON'T GROW			X			
116. HALLUCINATIONS ("feels that one is being eaten from inside out, by worms")			X			
117. HAND COLDNESS			X			
118. HAND CRAMPS			X			
119. HANDS CRACK			X			
12 HANDS SHAKE		X				
121. HAY FEVER			X			
122. HEADACHE (severe, some last for weeks)			X	X		
123. HEARING DIFFICULTY/LOSS			X			
124. HEART FLUTTER	X					
125. HEART PAIN			X			
126. HEART SOUND (3d)			X			
127. HEAT SENSITIVITY			X			
128. HEELS CRACK			X			
129. HIATAL HERNIA			X			
130. HIPS PAINFUL			X			
131. HOARSENESS			X			
132. HYPERACTIVE			X			
133. HYPERINSULINISM			X			

SYMPTOM	SILVEX			TCDD		
	causes	may cause	cannot cause	causes	may cause	cannot cause
134. HYPERTENSION			X			X
135. HYPOCHROMIA			X			X
136. HYPOGAMMAGLOBULINEMA			X			X
137. HYPOGLYCEMIA			X			X
138. HYPOTHESIA			X			X
139. HYPOVITAMINOSIS			X			X
140. ILEITIS			X			X
141. ILEOCOLITIS			X			X
142. ILLNESSES EXACERBATED			X			X
143. INABILITY TO FOCUS EYES			X			X
144. INCOORDINATION/EQUILIBRIUM LOSS		X		X		X
145. INABILITY TO ACHIEVE ERECTION		X				X
146. INABILITY TO CONCENTRATE			X			X
147. INFERTILITY		X				X
148. INFLUENZA			X			X
149. INSOMNIA			X			X
150. INTESTINAL KINK			X			X
151. INTESTINAL SPASM			X			X
152. INTERTRIGO			X			X
153. IRRITABILITY			X			X
154. ITCHING			X			X
155. JAW INFECTION			X			X
156 JAW PAIN			X			X
157. JOINT DIFFICULTIES			X			X

	SYMPTOM	SILVEX			TCDD		
		causes	may cause	cannot cause	causes	may cause	cannot cause
196.	NERVOUSNESS			X			X
197.	NEURITIC PAIN			X			X
198.	NOSEBLEEDS			X		X	
199.	NUMBNESS: ARMS			X			X
	ARMS & HANDS			X			X
	FEET			X			X
	FINGERS & WRISTS			X			X
	LIPS & TONGUE (with wheezing and epigastric distress)			X			X
200.	NUMBNESS & PARALYSIS: HANDS & LEGS			X			
201.	OTITIS MEDIA			X			X
202.	OVARIAN CYSTS			X			X
203.	OVARY IRRITATION			X			X
204.	OVARY PAIN			X			X
205.	PAIN, BACK OF HEAD & AROUND EYES			X			X
206.	PALPITATION	X					X
207.	PANCREAS AREA PAIN			X			X
208.	PARAPHIMOSIS			X			X
209.	PARALYSIS OF HANDS (partial)		X				X
210.	PARALYSIS OF LEGS (partial)		X				X
211.	PARESTHESIA			X			X
212.	PELVIC INFLAMMATORY DISEASE			X			X
213.	PELVIC TENDERNESS/PAIN			X			X
214.	PERIDONTOCLASIA ?			—			—
215.	PHYSICAL EXHAUSTION			X			X

17022

VOW 036693

SYMPTOM	SILVEX			TODD		
	causes	may cause	cannot cause	causes	may cause	cannot cause
216. PHYSICAL SYSTEMS DETERIORATING			X			X
217. PNEUMONIA			X			X
218. POLYPS			X			X
219. PROSTATE ENLARGEMENT/PAIN			X			X
220. PURPURA			X			X
221. RAPID HEART BEAT						
222. RASH: ARMS		X			X	
FEET		X			X	
HANDS		X			X	
LEGS		X			X	
223. RHINITIS			X			X
224 SCALING IN EARS WITH BLOODY PATCHES			X			X
225. SCALP BLOODY			X			X
226. SENSITIVITY TO LIGHT			X			X
227. SENSITIVITY TO NOISE			X			X
228. SHORTENING OF LIFE EXPENTANCY			X			X
229. SHORTNESS OF BREATH			X			X
30. SHOULDER PAIN			X			X
31. SHRUNK ONE INCH SINCE SPRAY			X			X
32. SIDEACHES			X			X
33. SINUSITIS			X			X
34. SKIN IRRITATION (burning, itching)		X		X		
35. SKIN LESIONS: HANDS		X			X	
36. SLEEP COMPLAINTS			X			X

SYMPTOM	SILVEX: causes	SILVEX: may cause	SILVEX: cannot cause	TCDD: causes	TCDD: may cause	TCDD: cannot cause
237. SNEEZING			X			
238. SORE THROAT			X			
239. SPINAL MUSCLE SPASMS			X			
240. SPINAL PAIN			X			
241. STOMACH CRAMPS			X			
242. STOMACH PAIN			X			
243. STREP THROAT			X			
244. SUBSTERNAL PAIN			X			
245. SUSCEPTIBILITY TO INFECTION & DISEASE INCREASED			X			
246. SWALLOWING DIFFICULTY			X			
247. SWAY BACK			X			
248. SWELLING:			X	X		
ABDOMEN BLOATING			X		X	
ANKLES			X		X	
FEET			X		X	
HANDS			X		X	
LEGS			X	X		
LIPS			X			
249. TACHYCARDIA			X			
250. TANTRUMS			X			
251. TEMPORAL PAIN			X		X	
252. TENSION			X			
253. THIGH PAIN			X			
254. THROAT INFECTION			X			
255. THROAT RAW			X			
256. THYROID PROBLEMS			X			

DOW 036695

	SYMPTOM	CIGARETTES: causes	CIGARETTES: may cause	CIGARETTES: cannot cause	CIGAR: causes	CIGAR: may cause	CIGAR: cannot cause
257.	TINGLING SENSATION:			X			X
	FEET & HANDS			X			X
	FINGERS & TOES						
258.	TIRES EASILY			X			X
259.	TONSILITIS			X			X
260.	TUBALIC INFECTION			X			X
261.	TUMORS & GROWTHS			X			X
262.	ULCERS:			X			X
	BLADDER			X			X
	BLEEDING			X			X
	DUODENAL						
263.	UPPER RESPIRATORY INFECTION			X			X
264	UPSET EASILY			X			X
265.	UPSET STOMACH			X			X
266.	URINATION FREQUENT			X			X
267.	URINARY TRACT INFECTION			X			X
268.	VAGINAL DISCHARGE			X			X
269.	VAGINAL IRRITATION (may be followed by bladder infection)			X			X
270.	VAGINAL ITCHING			X			X
271.	VAGINAL LUMPS			X			X
272.	VOMITING		X		X		
273.	WARTS			X			X
274.	WEAKNESS	X				X	
275.	WEIGHT GAIN			X			X
276.	WEIGHT LOSS		X			X	
277.	WHITE BLOOD CELL LOSS			X			X

DOW 03669696

SYMPTOM	SILVEX			TCDD		
	causes	may cause	cannot cause	causes	may cause	ca
278. WITHDRAWN EMOTIONALLY			X			
279. WORD TRANSPOSITION:			X			
SPOKEN			X			
TYPED			X			
WRITTEN						
280. WORKING CAPACITY IMPAIRED			X			
281. WOUNDS HEAL SLOWLY			X			
282. WRITING DIFFICULTY:						
HANDS NUMB			X			
LACKS CONCENTRATION			X			
WORD TRANSPOSITION			X			
283. WRIST ACHE			X			

Route: ~~JC~~ 2/16/81
~~REW~~ 004150
~~HEF~~
Rtn to NGO

DOW 1714154
MN012332

12182

(LIMEAD) (1962)
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LILLE MEDICAL. LILLE.
V.7(10)104 Ser.3 (1962)
Polyneuritis after using a weed killer: containing acid 2,4-D.
AUTHOR: Foissac-Gesoux, Phil

TRANSLATOR: Farinas
DATE: November 1980

REQUESTED BY: W. Mullison, 9001
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DOW 1 7141555

Clinical Facts

Lille Medical

V. 7(10) 1049-51 (1962)

POLYNEURITIS AFTER USING A WEED KILLER: CONTAINING ACID 2-4-D.

By Philippe Foissac - Gegoux, Annie Lelievre, Bernard Basin and Pierre Warot.

By 1958, one of us (*) had already drawn attention on the risks involved with the more and the more frequent use of chemical products in agriculture: two observations were considered at the beginning of this work which concerned the dangers derived from handling organics derived from phosphorus, powerful insecticides; one of these observations concerned an agricultural worker who handled, many months before the installation of a polyradiculorephritis syndrome weed killers, sodium and

potassium salts of 2- methyl -4- chlorophenoxyacetic acid; for several reasons, we had eliminated in this case the toxic origin of the neurological troubles..., but we ignored at that time that these products could have a toxic effect.

In truth, the cases of intoxication due to weed killers are rare and are especially known by toxicologists and doctors; but it is feared that they may multiply: for almost all the substances destined to stop the development of weeds are dangerous to man. Mineral compounds were being used such as chlorates and sulphuric acid: these were three times more inconvenient with an action often little selective, hence a global destruction of grasses and cereals, of a delicate use (risks of explosion and fire) and of a sure toxicity (burns-methemoglobinemy). The "vegetable hormones", the last commers, make up an undisputed progress. This name is given to chemical bodies whose action is comparable to that of phytohormones elaborated by the plant itself. In small doses, they in fact stimulate the growth, of young vegetable cells; but in the large doses that they are used they cause "a crazy exaltation of the manifestations of growth, a disorderly activity which drives the most deverse monstruosities, the intense consumption of reserves and finally the death of the grass".

These "hormones" are oxyacetic derivations of the benzine nucleus and of the naphtalene nucleus of the phenyl, naphtyl and indolacetic, propionic and butylic acids as well as some of their derivatives. One of the most widely used is 2-4-dichlorophenoxyacetic acid (Ac. 2-4-D.) whose action powerful and

DOW 1 714156

selective, is not, however, without inconvenience as the following observation proves.

Observation:

G... Gerard, 52 years old, farmer, was referred to the Neurology Clinic on July 30, 1962 by Doctor Chuffart for sensory and motor problems of the lower limbs. This man, without any previous pathological problem, who is not an alcoholic, dates the beginning of his troubles precisely on June 2, 1962. On that date he felt, suddenly, an acute pain throughout the entire right orbital and periorbital region becoming weaker the next day making room for (burning sensation) paresthesra and numbness in the same area. Also on June 3rd, he noticed a (decreased sensitivity) hypoesthesia in the right leg.

On June 16, two weeks later, the right leg recovered a normal sensitivity but the numbness was now felt on the left leg; besides, the lower left limb is now "weaker" and cannot move except with the aid of a cane.

The problems remained about the same untill July 30 when he entered the service. He now felt a persistant hypoesthesia in the right eye area, with hypoethesia of the cornea, the patient now felt some pain in the same area.

The subject is uncertain of his lower left limb where a slight reduction -global- of the segmentary force is noticed. There is no other trophic vaso-motor trouble.

The knee reflexes are rather sharp while the ankle reflexes are suppressed. The lower left limb suffers from a global

DOW 1 714157

hypoethesia only deep sensitivity was maintained.

The neurological examination of the upper limbs is strictly negative. Besides the general condition is excellent. There is no albuminuria. The blood formula reveals an eosinophilia (8% on Aug 2 and 9% Aug 30). Two electrophoretic blood tests, several weeks apart show a slight decrease in albumina (43 then 46 grams) and an increase of alpha -2- globulines (13 then 15 grams per liter).

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The renal biological exam, the galactosuria provoked, the reactions of floculation do not show any abnormalities.

The electrocardiogram is normal. So is the backside of the eye and the E.E.G. The electrodiagnosis shows the following results: ——— proof of stimulation of Aug 2, 1962: integrity of the upper limbs; in the lower limbs there is no evident weakness but slight problems of excitability (galvanic hyperexcitability - galvanic and faradic hypoexcitability of the extensor of the left big toe ——— high chronaxies of the extensors of the left big toe) witness however a slight neurogenic seizure (Doctor Spy); ——— electromyography of the two frontal tibia on August 4, 1962 (Doctor Ramez): trace of neurogenic seizure of the two muscles examined.

The patient leaves the clinic on September 8, 1962: during hospitalization he was submitted to a daily injection of 200mg of vitamin B1 and 250mg. of vitamin B6; besides 5,000 gammes of hydrocobalamine were administered every three days. The facial aches practically disappeared; the deficiency of sensitivity in

the face and the lower left limb was notably improved; the motor deficiency disappeared and the patient was able to walk normally; the areflexia achilleine persists, there is no visible atrophy.

There are still electromyographic signs of neurogenic seizure of the right frontal tibia (the left side was not examined). On the contrary the electrodiagnostic of stimulation of August 28 are absolutely normal.

The aetiology of this polyneuritis of the lower limbs with irritative and deficient right trigeminus was suggested to us by the patient himself who was able to relate the beginning of his trouble while killing grass. Made June 1st and the last days of May 1962. This operation consisted of a spraying of two different solutions but both having a base of acid 2-4-D, containing 235 and 410 grams per liters. It was carried out with a tractor which tows the spraying device and which is in a cabin, open in the back; it was very windy when the operations took place and the wind beat the toxic substance in the cabin.

These exceptional circumstances, the long exposure to the toxic substance, we had to admit that it was a polyneuritis due to 2-4-D acid.

Besides, this observation is not alone in the litterature that includes a certain number of facts of intoxication by these substances, notably in the case of farmers: some hours after inhalation of the toxic substance there is generally vomiting,

DOW 1714159

then subjective sensitive troubles of the type of paresthesis or even pain, then motor troubles, the paralysis of the four limbs or the lower limbs. This sensitive - motor polyneuritis —— inconstantly associated with an albuminuria and an intercolite board picture chart description —— is usually irreversible or very slowly and very partially reversible.

The toxicity of these substances is equally proven in the case of intoxication of workers at a vegetable hormone factory: The penetration of the toxic substance through inhalation, but also through the skin; the workers often complained of somnolence, of the lower limbs feeling heavy, gastralgia, loss of appetite, hypersialosis, as well as hypersensitivity of hearing: all of these troubles are, generally, transient. Finally, experimentally, 2-4-D acid administered intravenously or even orally can be fatal: this happens suddenly, either in a neurological stage in the form of a coma with hypertonic of the limbs, or ventricular fibrillation with relatively large doses, but varying according to the animal tested (about 300mg to one gram). To our knowledge, there was no acute intoxication.

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(*) P. Nayrac, M. Fontan, P. Warot, J. Lescut and J. Delahousse: Lille Medical, 1958, 3, 3, 161-164.

DOW 1 714161

80-11-34

FAITS CLINIQUES

LILLE MEDICAL
V.7(10)1049-51 (1962)

POLYNEVRITE APRES USAGE D'UN DESHERBANT : L'ACIDE 2-4-D.

par Philippe Foissac-Gerbaux, Annie Lelièvre, Bernard Basin et Pierre Warot.

DOW 1 714162

Déjà en 1958, l'un d'entre nous (*) avait attiré l'attention sur les risques que comportait l'utilisation de plus en plus fréquente en agriculture de produits chimiques : deux observations étaient à l'origine de ce travail dans lequel l'accent avait été mis sur les dangers de la manipulation des dérivés organiques du phosphore, insecticides puissants ; l'une de ces observations concernait un ouvrier agricole ayant manipulé, plusieurs mois avant l'installation d'un syndrome de polyradiculonévrite, des désherbants, sels sodique et potassique de l'acide 2-méthyl-4-chlorophénoxyacétique ; pour plusieurs raisons, nous avions éliminé dans ce cas l'origine toxique des troubles neurologiques..., mais nous ignorions à l'époque que ces produits pouvaient avoir une action toxique.

A vrai dire, les cas d'intoxication par des désherbants sont rares et sont surtout connus des toxicologues et des médecins du travail ; mais il est à craindre qu'ils ne se multiplient : car presque toutes les substances destinées à entraver le développement des mauvaises herbes sont dangereuses pour l'homme. On utilisait naguère des composés minéraux parmi lesquels les chlorates et l'acide sulfurique : ceux-ci avaient le triple inconvénient d'une action souvent peu sélective, d'où une destruction globale des herbes et des céréales, d'un emploi délicat (risques d'explosion et d'incendie) et d'une toxicité certaine (brûlures - méthémoglobinémie). Les « hormones végétales », dernières venues, constituent un progrès indiscutable. On donne ce nom à des corps chimiques dont l'action est comparable à celle des phytohormones élaborées par la plante elle-même. A doses faibles, elles stimulent en effet la croissance des cellules végétales jeunes ; mais aux doses fortes auxquelles on les emploie, elles provoquent « une exaltation folle des manifestations de croissance, une activité désordonnée qui entraine l'apparition de monstruosités les plus diverses, la consommation intense des réserves et finalement la mort au stade herbacé ».

Ces « hormones » sont des dérivés oxyacétiques du noyau benzène et du noyau naphtalène des acides phényl, naphtyl et indolacétique, propionique et butylique, ainsi que de certains de leurs dérivés. L'un des plus employés est l'acide 2-4-dichlorophénoxyacétique (Ac. 2-4-D.) dont l'action, puissante et sélective, n'est cependant pas dénuée de tout inconvénient ainsi que le prouve l'observation suivante.

OBSERVATION :

G... Gérard, 52 ans, agriculteur, est adressé à la Clinique Neurologique le 30 juillet 1962, par le Docteur Chifflet pour des troubles sensitifs et moteurs des membres inférieurs. Cet homme, sans antécédents pathologiques notables, qui n'est pas éthylique, situe très précisément le début de ses troubles au 2 juin 1962. Il ressentit ce jour-là, brusquement, une douleur vive dans toute la région orbitaire et périorbitaire droite, s'atténuant dès le lendemain pour faire place à des paresthésies et à une anesthésie occupant le même territoire. Le 3 juin également, il note l'apparition d'une hypoesthésie de la jambe droite.

Le 16 juin, soit deux semaines après le début, la jambe droite a récupéré une sensibilité normale mais l'anesthésie, qui persiste à la face, a gagné la jambe gauche ; d'autre part, le membre inférieur gauche est « plus faible » et la marche n'est possible qu'avec l'aide d'une canne.

Les troubles restent sensiblement identiques jusqu'au 30 juillet, date de l'entrée dans le service. On constate alors la persistance d'une hypoesthésie dans le territoire de l'ophtalmique droit, avec hypoesthésie cornéenne ; le malade accuse encore dans ce même territoire quelques épisodes douloureux très passagers et d'intensité modérée.

Le sujet se dit incertain de son membre inférieur gauche au niveau duquel on constate une légère diminution — globale — de la force segmentaire. Il n'existe aucun trouble trophique, aucun trouble vaso-moteur.

Les réflexes rotuliens sont plutôt vifs tandis que les achilléens sont abolis. Le membre inférieur gauche est le siège d'une hypoesthésie globale, seule la sensibilité profonde étant conservée.

(*) P. Nayrac, M. Fontan, P. Warot, J. Lescut et J. Delahousse : *Lille Médical*, 1958, 3, 3, 161-164.

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L'examen neurologique des membres supérieurs se révèle strictement négatif. D'autre part, l'état général est excellent. Il n'y a pas d'albuminurie. La formule sanguine révèle une éosinophilie (8 % le 2 août et 9 % le 30 août). Deux examens électrophorétiques sanguins, à plusieurs semaines d'intervalle, montrent une baisse légère de l'albumine (43 puis 46 grammes) et une augmentation des alpha-2-globulines (13 puis 15 grammes par litre).

Le bilan biologique rénal, la galactosurie provoquée, les réactions de floculation ne montrent pas d'anomalies.

L'électrocardiogramme est normal. Il en est de même du fond d'œil et de l'E.E.G. L'électrodiagnostic donne les renseignements suivants :

— épreuve de stimulation du 2 août 1962 : intégrité des membres supérieurs ; aux membres inférieurs, il n'y a pas de réaction de ralentissement évidente mais les légers troubles de l'excitabilité (hyperexcitabilité galvanique - hypoexcitabilité galvanique et faradique de l'extenseur propre du gros orteil gauche - chronaxies élevées des extenseurs du gros orteil gauche) témoignent cependant d'une légère atteinte neurogène (Docteur Sfx) :

— électromyographie des deux jambiers antérieurs du 4 août 1962 (Docteur Ramuz) : tracé d'atteinte neurogène des deux muscles explorés.

Le malade quitte la clinique le 8 septembre 1962 : durant l'hospitalisation il a été soumis à une injection quotidienne de 200 mg. de vitamine B 1 et 250 mg. de vitamine B 6 ; en outre, l'hydrocobalamine lui a été administrée à la dose de 5.000 gammas tous les trois jours. Les algies faciales ont pratiquement disparu ; les troubles sensitifs déficitaires de la face et du membre inférieur gauche se sont notablement atténués ; le déficit moteur a disparu et la marche est redevenue normale ; l'aréflexie achilléenne persiste ; aucune atrophie ne s'est dessinée.

Il persiste des signes électromyographiques d'atteinte neurogène du jambier antérieur droit (l'examen n'a pas été pratiqué du côté gauche). Par contre, les réponses à l'électrodiagnostic de stimulation, en date du 28 août, sont absolument normales.

L'étiologie de cette polynévrite des membres inférieurs avec atteinte irritative et déficitaire trigéménaire droite nous a été suggérée par le malade lui-même qui n'a pas manqué de faire le rapprochement entre le début de ses troubles et une opération de désherbage effectuée le 1er juin et les derniers jours de mai 1962. Celle-ci a consisté en une pulvérisation de deux solutions différentes mais toutes deux à base d'acide 2-4-D. et en contenant 235 et 410 grammes par litre. Elle s'est effectuée grâce à un tracteur qui remorque le pulvérisateur et qui est surmonté d'une cabine, ouverte à l'arrière ; or, les opérations se sont déroulées par vent violent et celui-ci rabattait dans la cabine le nuage de substance toxique.

Ces circonstances exceptionnelles, la longue durée d'exposition au toxique, nous ont fait admettre qu'il s'agissait vraisemblablement d'une polynévrite due à l'acide 2-4-D.

Au reste, cette observation n'est pas isolée dans la littérature qui comporte un certain nombre de faits d'intoxication par ces substances, notamment chez des agriculteurs : quelques heures après l'inhalation du toxique surviennent habituellement des vomissements, puis des troubles sensitifs subjectifs à type de paresthésies ou même de douleurs, puis des troubles moteurs, l'atteinte paralytique pouvant intéresser les quatre membres ou les membres inférieurs. Cette polynévrite sensitivo-motrice — inconstamment associée à une albuminurie et à un tableau d'entérocolite — se révèle habituellement irréversible ou très lentement et très partiellement réversible.

La toxicité de ces substances est également prouvée par les cas d'intoxication chez les ouvriers travaillant à la fabrication des hormones végétales : la pénétration du toxique se ferait par inhalation, mais aussi par voie cutanée ; les ouvriers se plaignent souvent de somnolence, de sensations de lourdeur des membres inférieurs, de gastralgies, d'anorexie et d'hypersialorrhée, ainsi que d'une hypersensibilité de l'ouïe : tous ces troubles sont, dans la règle, fugaces. Enfin, expérimentalement, l'acide 2-4-D., administré par voie intraveineuse ou même par voie orale, peut entraîner la mort ; celle-ci survient, soit dans un tableau neurologique sous forme de coma avec hypertonie des extrémités, soit par fibrillation ventriculaire, et ce pour des doses relativement élevées, mais évidemment variables suivant l'animal en expérience (de l'ordre de 300 mg. à un gramme en une prise). A notre connaissance, il n'a pas été effectué d'intoxication subaiguë.

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DOW 1 714164

MENINGITE A LISTERIA MONOCYTOGENES DE L'ADULTE. UN CAS DE GUERISON

Pierre Warot, Jacques Desax, René Lesage et Michel Dorchies.

Longtemps considérée comme l'apanage presque exclusif de l'animal, l'infection listérienne semble se manifester chez l'homme avec une fréquence accrue : d'après Besançt et Soulier, 70 cas seulement de listériose humaine avaient été rapportés avant 1950, tandis que 300 nouveaux cas l'étaient de 1950 à 1957.

Sans doute le diagnostic bactériologique est-il fait plus souvent qu'autrefois : « on passe souvent à côté du diagnostic bactériologique parce que l'on écarte trop vite, sous l'appellation de facilité de « contaminants diphtérimorphes » des bacilles Gram sitif isolés d'hémocultures, de liquide céphalo-achidien ou de tout autre produit et qui sont d'authentiques listéria » (Lapeyssonnie). Mais il est très vraisemblable aussi que la diffusion, reconnue, de l'infection dans le règne animal entraîne la multiplication des transmissions accidentelles à l'homme.

Il est rare que le clinicien fasse le diagnostic de listériose et en demande confirmation au biologiste : rien d'étonnant à cela si l'on considère qu'il s'agit d'une infection de connaissance récente et dont la fréquence est d'ailleurs toute relative : la littérature française ne comportait en effet, en 1959, que 23 observations. D'autre part, les listérioses se présentent sous des aspects cliniques extrêmement divers : l'importante statistique de Seeliger, portant sur les 344 cas publiés dans le monde en 1956, relève 160 états septicopyohémiques du nouveau-né, 100 méningites purulentes avec ou sans encéphalite, 41 formes sanguines à type de mononucléose infectieuse, 13 conjonctivites granulomateuses, les autres cas concernant des localisations viscérales diverses : endocardites, myocardites, métrites, etc...

Tout au plus peut-on parfois soupçonner l'origine listérienne d'un état septicopyohémique du nouveau-né, ou d'une méningite purulente de l'enfant ou de l'adulte, parce qu'il s'agit là des manifestations les plus fréquentes de l'infection. Mais, le plus souvent, le mérite du diagnostic revient au seul bactériologiste... et ce n'est qu'a posteriori, lorsque le germe est identifié, que le clinicien mettra l'accent sur quelques nuances séméiologiques qui auraient dû faire évoquer la listériose, mais dont la signification lui avait échappé.

C'est ainsi que les choses se sont passées dans l'observation que nous rapportons d'une méningite purulente de l'adulte, inquiétante d'emblée de par l'intensité des troubles de la conscience et du déréglement neuro-végétatif : ce fut une surprise d'apprendre que le germe responsable en était listéria monocytogène.

OBSERVATION.

M. Léon, 60 ans, mécanicien, sans antécédent pathologique notable, présente, le 17-3-1962, très brutalement, vers 12 heures, un état infectieux d'allure grippale, avec fièvre à 39°, courbures, malaise général, qui l'oblige à s'aliter. Ces troubles s'intensifient les jours suivants tandis qu'apparaissent céphalées de plus en plus intenses et vomissements.

Le 22 mars est constatée une raideur méningée et le malade est adressé à la Clinique Neurologique. Il est admis au début de l'après-midi. L'un d'entre nous constate alors un syndrome méningé franc, un état d'obnubilation intellectuelle avec légère agitation psychomotrice ; la température est à 39°5 ; le malade a un hoquet permanent ; l'examen neurologique ne révèle aucun signe particulier. Le liquide rachidien se révèle

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October 29, 1980

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Attn: Ms. Patricia Cohn

Re: Formation of 2,4-D Task Force Research Data

Dear Ms. Cohn:

This letter is to advise you of the formation of the "Task Force on 2,4-D Research Data." The purpose of the Task Force is to develop jointly, pursuant to the provisions of § 3(c)(2)(B) of FIFRA, the additional data identified by EPA in its Order and Notice of August 29, 1980 to registrants of products containing 2,4-D.

The Chairman of the Task Force, John E. Davies, notified all registrants with manufacturing-use products of the Task Force's formation (as identified in Appendix E to EPA's Order and Notice of August 29, 1980) and invited such registrants to participate in the Task Force and attend the Task Force's organizational meeting held on October 21, 1980. Participation on the Task Force is open to all registrants with manufacturing-use products.

At the Task Force's organizational meeting the following companies indicated their desire to participate on the Task Force:

17038

COM061558S

BASF Wyandotte Corporation
Diamond Shamrock Corporation
The Dow Chemical Company
PBI-Gordon Corporation
Rhone-Poulenc, Inc.
Vertac Chemical Corporation

The Task Force would appreciate EPA advising it of any companies that should be advised of the formation of and invited to participate on the Task Force, in addition to those companies listed on Appendix E to the Agency's Order and Notice of August 29, 1980.

The Task Force looks forward to working with EPA in responding to its Order and Notice of August 29, 1980. Should you have any questions or comments, please feel free to contact me or John Conner, Jr. Thank you for assistance in this matter.

Very truly yours,

John D. Conner
Counsel for Task Force

/das

cc: John E. Davies
Rhone-Poulenc Chemical Co.

00447 I 23 12-11-80

cc: L. L. Coulter
P. M. Ritty
K. C. Barrow
V. K. Rowe, Director, Research
A. S. Wells, Region
Bill Daily

Feb[illegible], 1960

Carlyn O. Hoffman
Extension Service
Extension Range Specialist
College Station, Texas

Dear Carlyn:

I have your memorandum requesting full and complete information on the toxicology, hazards and legal aspects involving our various herbicides. I note you want precise as well as complete answers to your questions as they invove our herbicides. It will take some time for our toxicologists to fully and completely answer the questions (if the information is available).

Attached is another copy of the toxicological information which I have available at this time on 2,4-D, 2,4,5-T and silvex. Also, attached is a copy of a recent release from the National Agricultural Chemicals Association in event you have not seen a copy. In the meantime, be assured that if our herbicides are recommended or applied in accordance with general and specific recommendations as stated on the label that they would be legal to use.

As you know, before a "use" can be registered and listed on the label, it has undergone extensive field testing and the "use" has been evaluated by many people and agencies, and if a hazard exists, it would be recognized and set forth on the label.

I am sure this letter is a reduction of the information which I have given you in the past. I hope that in the near future, we will be able to provide you with satisfactory answers to your questions.

Shortly, I will send you a new set of labels which will cover the current registered and, therefore, legal uses for the product involved.

Yours very truly,

G. W. Gibson
Agricultural Chemical Development

Enc. Toxicological Information on Herbicides

JJC:mm

POOR QUALITY ORIGINAL

RECEIVED
[illegible] 1960
Dicham, Reg. Lab

POOR QUALITY
ORIGINAL

004473

National Clearinghouse
for
Poison Control Centers

Bulletin

... - April 1968

U.S. DEPARTMENT OF
HEALTH EDUCATION AND WELFARE
Public Health Service
Washington D.C. 20201

DOW 1754503
MN073280

DEATHS FROM CHLORINATED PHENOXYACETIC ACIDS
(2,4-D; 2,4,5-T; MCPA)

"The most widely used herbicides are 2,4-D, 2,4,5-T; and related compounds. Whether or not these are actually toxic is a matter of controversy."--Rachel Carson.

There may not be controversy when these chemicals are used as directed around the household or in agriculture, but the Michigan farmer who developed peripheral neuropathy four days after he reportedly used his bare hands to unplug a tractor-towed automatic sprayer might dispute this. 2,4,5-T was implicated jointly with poisoning in the illness of two sisters who played for several hours in a yard which had been sprayed heavily a short time before. The next day both girls had a generalized erythema of the skin, mild periorbital swelling of the oral and vaginal mucous membranes, slight swelling of lips and eyelids, inflammation of the mouth, albuminuria and oliguria.

Upon receipt of a fatal case history due to suicide in a 46-year-old Connecticut man, a review of the Clearinghouse's reports was made. In the past three years, the Clearinghouse has received several reports of peripheral neuritis and skin rash following exposure to these products, in addition to those already cited.

Other symptoms that were associated with the chlorinated phenoxyacetic acid derivatives were: weakness of [illegible] associated with pneumonia; bacteruria; lethargy with poor reflexes; two brothers with ataxia, [illegible] irritability, lethargy, increase or decrease [illegible]. Most [illegible] had vomited. The [illegible] 2,4,5-T

[illegible]

17041

2,4-D and its derivatives serve as a base material from which soluble esters and salts are produced. The LD50 of these products range from 300 to 700 milligrams per kilogram orally.

When the chlorophenoxy herbicides are ingested in single large doses they may produce death. Four cases have been described in the literature and a 5th case has been reported to the Clearinghouse. A Connecticut truck driver in a suicide attempt ingested a cupful of weed killer which was approximately 20% 2,4-D and 40% 2,4,5-T. Within an hour, he became nauseated and began to vomit. Approximately one hour after the ingestion he was found in a chair conscious but in a dazed condition. He was admitted to the hospital an hour and a half later, still conscious, but disoriented.

On his second hospital day he was on the hospital critical list because his general condition was getting worse. His temperature was 104° F., his blood pressure 70/50, and although his urinary output was described as good, his BUN had risen from 16 milligrams percent to 48. He was hyperventilating and had basalar rales.

Late in the second day of hospitalization the patient's blood pressure was very low despite large doses of Aramine and a trial on Levophed. He had sinus tachycardia (150), a central venous pressure of minus 3, temperature of 104° F, hyperventilation, blood PH of 7.43, and anuria. He also had a generalized erythema.

The patient developed scattered crepitant rales in the right lung and died of cardiac standstill (no ventricular arrhythmias were noticed) early in the morning of his third hospital day, approximately 46 hours after the ingestion.

This case had several similarities to the case report of poisoning by MCPA (2 methyl-4-chloro-phenoxyacetic acid). Vomiting occurring shortly after ingestion and unconsciousness appearing in a few hours. Both had lowered blood pressure but in the MCPA case it could be maintained with metaraminal. However, none of the neurological symptoms (facial twitching, constricted pupils, decreased tendon reflexes, clonic spasm of limbs) were mentioned in the present case.

Early deaths in animals by large doses of chlorinated phenoxyacetic acid derivatives were attributed to ventricular fibrillation. In delayed deaths, there was a disinclination to move, progressing to rigidity of skeletal muscles (myotonia) and ataxia. The severe cases had progressive apathy, muscular weakness of the hind limbs, paralysis, clonic spasms and finally coma.

POOR QUALITY
ORIGINAL

Ingestions of these herbicide[illegible] careful gastric lavage and symptomatic and supportive t[illegible]apy. Cl[illegible]icology of Commercial Products recommends Quinia[illegible] Sulfa[illegible] 0.2 grams orally every two hours for the first [illegible] myotonia, if present, and to suppress ventricular ec[illegible] cases may require cardiac monitoring with defibri[illegible] d to the chest. Fever should be treated using phy[illegible]cks and alcohol sponges) since antipyretics may be i[illegible] indicated.

UUM 754505

Parke - Davis PARCODE

Parke-Davis has recently initiated a numerical product [illegible]tion system known as PARCODE. The special number desig[illegible]ntifies each capsule, Kapseal, tablet and Emplet. The initials P-D identifies the product as a Parke-Davis preparation and the imprinted number identifies the particular product. Although the company's manufactured products will henceforth carry a PARCODE identification symbol, there may be considerable time required for utilization of the non-coded products currently in stock.

Coding or identification, have already been established by Eli Lilly and Company and the Norwich Pharmacal Company. The poison control centers have been sent a copy of the Parke-Davis recognition code and will be informed if any other pharmaceutical companies adopt similar systems.

ACUTE OVERDOSAGE OF DORIDEN

The CIBA Pharmaceutical Company has recently published a booklet on acute overdosage of Doriden (Glutethimide). It includes the recommended supportive care, the indications for dialysis, collection of specimens for laboratory examination, a commentary on acute overdosage as well as bibliographies. A copy of this booklet may be obtained by writing to the Medical Communications Section, CIBA Pharmaceutical Company, Summit, New Jersey 07901.

POOR QUALITY ORIGINAL

DEFEROXAMINE

DOW 1754506

For several years the Ciba Corporation has been conducting research on the use of deferoxamine (Desferal), older name desferrioxamine, in the treatment of iron poisoning. Because there have been several articles published in the medical literature on its effectiveness, there has been a series of requests for this medication when poisonings have occurred. Since this drug was under investigation, it was only available to the authorized investigators. The list of investigators, willing to accept referrals of iron intoxications, could not be published. Therefore, the National Clearinghouse initiated a service to the Poison Control Centers to provide the nearest investigator's name and telephone number when an inquiry was made for the immediate treatment of an individual case. We felt this might be of benefit to a seriously ill patient, as well as to the investigator, by providing him a larger number of observations from which to judge the usefulness of this medication. This drug has been released for general medical use, and until the Manufacturer can complete its distribution this service will be continued.

Deferoxamine, a chelating agent, complexes with iron to form ferrioxamine which prevents the iron from entering into further chemical reactions. The chelate is soluble in water, is excreted by the kidney, and produces a characteristic reddish color to the urine. Theoretically, deferoxamine will bind 8.5% of its weight of ferric iron. Thus, the initial recommended dose of 1 gram would bind 85 milligrams of ferric iron and the maximal 24 - hour dosage of 6 grams would bind over one-half gram of iron, the equivalent of 2 1/2 grams of $FeSO_4 \cdot 7H_2O$.

The manufacturer has offered to supply for distribution package inserts on its use and cautions to all of the poison control centers.

Henry L. Vernolst, Director

John J. Crotty, M.D., Associate Director

POOR QUALITY ORIGINAL

THE DOW CHEMICAL COMPANY 004495

MIDLAND
March 20, 1959

RECEIVED
MAR 23 1959
Biochem, Res. Lab.

DOW 1551627
MN0073280

Mark Wolf
Biochem Research Lab
634 Building

Dear Mark:

By review of our conversation this morning (March 18) regarding the relative toxicity of 1 1/2 to 2 gallons of Forron 245 in 100 gallons of water or Forron Brushkiller at the same concentration in water, as compared with Esteron Brushkiller O.S. in an oil-water emulsion, we would like to outline the field situation and our needs as we see it.

It is a common practice on the utility right-of-ways to use 1 gallon of Esteron Brushkiller O.S. or Esteron 245 O.S. plus 10 gallons of oil, this oil could be either No. 1 or 2 fuel oil or kerosene in 89 gallons of water for a total of 100 gallons of mix. This mixture is used because it gives quick, uniform knockdown, does a little better job on conifers and actually has been promoted by some companies because it is dramatic enough that it is easy to sell. Nonetheless it is being used very commonly and our products are used in this manner when the customers decide they want to use oil. The use of this oil has a number of problems; in the first place it costs money, it is difficult to mix with Esteron O.S. and water, it is messy to handle, it is hard to obtain, and it requires additional trucking facilities to handle the large volume of raw material to be imported. We have been shooting at a formulation which would essentially give the early uniform brown-out and kill of the oil-Esteron Brushkiller mix without having all of the disadvantages and handling problems of oil. These formulations which Chem Engineering Lab has come up with are Forron Brushkiller and Forron 245.

You have indicated to us that Forron formulations used in this manner are somewhat more toxic to the handler than the Esteron 245 or Esteron Brushkiller formulations and the question naturally comes up as to what is the relative hazard of the Forron formulations with the oil-water

17045

DOW 1 551628

combinations. Specifically, we would like to know what the relative handling hazards are of 1 1/2 or 2 gallons of Forron 245 or Forron Brushkiller per 100 gallons of water or as compared with 1 gallon Esteron Brushkiller O.S. or Esteron 245 O.S. plus 10 gallons of one of the above oils, plus 89 gallons of water. This should, of course, include skin irritation, eye irritation, possibly inhalation and any other tests which you think might be pertinent.

This information can be important to us in furthering our Forron program and in counseling our customers properly in the use of oil-water mixtures with our present brushkiller formulations. We would appreciate your checking this out for us.

Yours very truly,

L. L. Coulter

L. L. Coulter
Agricultural Chemicals Development

wb

17046

H. L. Clack/Mobile
D. B. McCaskey
W.R.M. File

004480

DOW CHEMICAL INTER-AMERICAN LIMITED

CABLE: DOWPANAM

1714 EASTMAN ROAD
MIDLAND, MICHIGAN U.S.A.

MN0733280 DOW 1 551487

April 21, 1953
(Dict. 4-16-53)

Companhia Swift Do Brasil S.A.
Rua Formosa 367
Sao Paulo, Brasil

Attention: Mr. M. W. Irwin

Gentlemen:

Your letter of April 10, 1953 about our Esteron Brush Killer causing nausea among the men applying it when it was used as a spray was very interesting to us. Our Esteron Brush Killer has been used widely in this country for the past few years, and this is the first instance of this sort that has come to my attention. It has been used widely as a spray as you are using it, and with no adverse results reported in this connection until now.

I am at a complete loss to explain this, particularly so since the product used in the DuPont formulation is chemically identical with that used in our own. This makes me wonder if this may not be one of those cases when some other factor has brought this about, and by chance it concured with the men's useage of this product.

I would therefore, suggest that this material be used again as a spray since since it's so much more economical and that a close check be maintained for other factors that might bring about this result.

Very truly yours,

W. R. Mullison
Assistant Technical Director

17047

WRM/mmc

cc: Blemco, S.A.

004497

THE DOW CHEMICAL COMPANY

30 ROCKEFELLER PLAZA
NEW YORK 20 NEW YORK

DOW 1 551482

MN073280

December 30, 1952
Dict. 12/23/52.

Dr. D. Irish
Biochemical Research Department
Midland, Michigan

cc: John A. Gird, Ilion, New York.

GERALD H. STERLING, VETERAN'S ADMINISTRATIVE HOSPITAL, HOLLAND AVENUE, NEW YORK.

Subject person was employed by John A. Gird, custom sprayer, R. D. #2, Ilion, New York, who sprayed brush this past summer with Dow Esteron brush killer. I understand that Dr. M. C. Hutchins in Albany, N.Y. has tried to determine the cause of Mr. Sterling's illness and thinks perhaps that part of it may have been caused by the chemicals in the brush killer.

Please keep this letter on file in case either Mr. Gird or Mr. Sterling or Dr. Hutchins write to you concerning the matter since we have informed them that any inquiries regarding the nature of the toxicity of Dow Esteron Brush Killer should be directed to your attention.

Very truly yours,

W. L. Corbin
Agricultural Chemical Sale

WLC:apr

17048

004483

DOW 1 551478

JUN 25 4 23PM '52

V.K. Rowe
Please handle

369 LD SL

HILLARD SMITH AG CHEM SALES

RECVD A LETTER FROM HY BRYAN, WESTERN MERCANTILE, ADVISING ONE OF THE TELEPHONE COMPANIES HAS A SUIT PENDING FOR THE DEATH OF TWO COWS. PLAINTIFF CHANGES THAT THE DOWS DIED FROM CONSUMING OUR ESTERON BRUSH KILLER. THE DEFENSE ATTORNEY HAS ASKED THAT HY FURNISH HIM WITH THE CHEMICAL FORMULATION SHOWING ALL THE INGREDIENTS OF ESTERON BRUSH KILLER. PLS FORWARD THIS INFO DIRECT TO HY IMMEDIATELY. THANKS.

R A CRANDALL

AMS

H.L.
Hy Bryan, Western Merc. Co.
Weed Control Dept.
Box 1660
Midland, Texas

17049

THE DOW CHEMICAL COMPANY
MIDLAND · MICHIGAN

BRANCH SALES OFFICES
NEW YORK CITY
SAN FRANCISCO
PHILADELPHIA
LOS ANGELES
WASHINGTON
SAINT LOUIS
CLEVELAND
HOUSTON
CHICAGO
ATLANTA
SEATTLE
DETROIT
BOSTON

004101
DOW
DOW 1 551453
MN0732280

July 27, 1951

A. E. Weil
Agricultural Chemical Division
St. Louis Office
cc: W. W. Allen
H. L. Smith
G. J. Williams
Ben Branch
Larry Southwick

SUBJECT: Esteron Brush Killer: Sprayed Area Reported to have Caused Poisoning of Cattle near Carthage, Illinois

1. I wish to compliment you on your letter of July 9 in which you give a detailed account of your investigation of the subject case. It is one of the best reports from the field I have ever seen.

2. After looking this report over, I could come only to the conclusion that the brush killer was not responsible for the death of these cattle. It does not seem likely to me that spraying on June 6 would have any effect on cattle in open pasture on June 26. We have evidence, as you know, that the sprays themselves are not poisonous and insofar as we know, the vegetation which you list in your letter as being found on the sprayed right-of-way are not known to have caused poisoning in cattle. Needless to say, we wish we had an explanation for this incident, but at the present time I am afraid we have no explanation for the death of these cattle.

3. I received the sample of Moorman's Hog Minerals and have sent it in to the Main Lab. for analyses. A check for fluoride did not reveal any. Analysis for metals did not reveal anything suspicious.

Sincerely yours,

17050

V. K. Rowe
Biochemical Research Department

bc

T2.30-13-20

004189

THE DOW CHEMICAL COMPANY

MIDLAND MICHIGAN

June 25, 1952

POOR QUALITY
ORIGINAL

DOW 1 551476

MN0732280

Mr. Dan Sanford
Agricultural Chemical Sales
1-47 Bldg.

CC: G. J. Williams, F. C. Peterson, J. W. Britton

Subject: Death of Sheep and Cattle Allegedly Due to Brush Killer

The afternoon of Tuesday, June 24, 1952, Mr. Dan Sanford called and asked me to call a Mr. Brandon, Carolina Tree Service, Shelby, North Carolina, with regard to an alleged case of livestock poisoning as a result of the spraying of an AT and T Right of Way near Frankfurt, Kentucky.

I called Mr. Brandon and he informed me that he had sprayed the Right of Way. One farmer along the Right of Way had three sheep die and another farmer along the Right of Way had one 500-lb. bull die and they were claiming that these deaths were due to the spraying. Mr. Brandon wanted to know what we could do about such a situation. I informed him that there was no question in our mind that the sheep and the bull did not die as a result of ingestion of Dow Esteron Brush Killer. He queried me with regard to the effects that might occur from the consumption of sprayed foliage, which might not otherwise be eaten and which might be poisonous. I told him I did not have an answer to that question; that it was a problem which was being investigated.

17051

DOW 1 551477

I talked to him the case which Mr. Southwick reported this morning in which cattle were found to have been killed from the ingestion of white lead from partially empty paint pails rather than Brush Killer as was alleged. I suggested that he might call Dr. Furtig at Cornell University Experiment Station for his comments, and also Dr. Grigsby at Michigan State. He inquired as to what he should do in case of future accidents in which autopsies can be performed (the animals were taken away this time before any autopsy could be made). I suggested that he get a record of their symptoms, examine for hardware, study the contents of their stomach for presence of poisonous vegetation or other foreign material, get samples for chemical analysis, and survey the pasture area for poisonous weeds. He seemed quite satisfied with the answer and agreed to keep us informed as to the outcome of this case.

Sincerely yours,

V. K. Rowe

V. K. Rowe
Biochemical Research Department
2-280 Bldg.

jc

POOR QUALITY ORIGINAL

17052

4943 72.30-13-1

DOW THE DOW CHEMICAL COMPANY

MIDLAND MICHIGAN

POOR QUALITY ORIGINAL

DOW 00766299

May 20, 1953

W. K. Rowe
4-566 Bldg.

cc:
J. E. Johnson
J. W. Britton
J. C. Van Horn
L. Southwick
H. L. Smith
D. D. Irish

DOW 752110

ACUTE ORAL TOXICITY OF DOW ESTERON BRUSH KILLER FOR CATTLE.

Esteron Brush Killer (acid equivalent of 2,4-D acid - 21.5% and 2,4,5-T acid - 21.5%) was given to cattle via a stomach tube. A steer weighing 295 kilograms was given 0.5 grams per kilogram for two consecutive days and, on the third day, rumen motility had ceased. The steer was off feed for approximately 24 hours. Thereafter, this individual consumed feed normally and, as far as could be determined, had no other after or ill effects from the previous dosage.

When 0.5 gram per kilogram was given to a second steer weighing 336 kilograms for three consecutive days, no perceptible toxic symptoms were noted and the steer remained on full feed.

A single dose of one gram per kilogram in a steer weighing 291 kilograms failed to produce any perceptible symptoms of toxicity. When one gram per kilogram was given for three successive days to a steer weighing 295 kilograms, the steer succumbed to the toxicity of the material late on the third day following the last dose.

Symptoms of Steer that Succumbed to Esteron Brush Killer:

This steer was dosed with one gram per kilogram of Esteron Brush Killer for three successive days. On the third day a slight depression was noticed in the animal, rumen motility seemed to be slowed somewhat, and the animal gave the

POOR QUALITY ORIGINAL

general appearance of some depression. The day following the third dose the animal was notably off-feed, general lassitude was noted and rumination had ceased. Temperature was still normal. The second day following the last dose incoordination was noted in the hind quarters, body temperature was slightly lower than normal, there was marked depression and general lassitude of the animal. The heart beat seemed to be a little slowed and somewhat weakened. Respiration was somewhat labored. Rumination had ceased. The third day following the last dose of Esteron the steer succumbed in a very quiet, gentle manner. There was never a sign of pain or struggling; the animal just seemed to get progressively more depressed, respiration was noticeably slower, heart rate was considerably slowed and weak. Temperature continued to decline from the second day following the final dose until death ensued.

DOW 752111

Autopsy:

The entire carcass appeared normal with the exception of the following in the viscera. The rumen showed signs of general stasis, ingesta was very dry and coarse. There was still a strong odor of Esteron present. The abomasum was impacted, the intestinal contents were completely fluid, and there was no fecal material in their entire length. All mesenteric vessels in the abdominal viscera were markedly congested. The spleen seemed somewhat shrunken and excessively dark and pulpy. All other organs appeared normal grossly. Sections were taken from the liver, kidney and spleen and sent to Biochem. for sectioning.

T. A. Kymas
Agricultural Chemical Research
Extension 8321

TAK:ljl

17054

T2.30-13-1

DOW THE DOW CHEMICAL COMPANY

MIDLAND MICHIGAN

POOR QUALITY ORIGINAL

December 9, 1953

RECEIVED
DEC 10 1953
Biochem. Res. Dept.

DOW 752106

W. K. Rowe
Biochemical Research Dept.
280 Building

cc: J. E. Johnson
G. E. Lynn - 2
T. C. Barrons

Subject: Esteron Brush Killer Toxicity to Cattle

Prolonged feeding experiments with Esteron Brush Killer, the following formulation, have been conducted:

2,4-dichlorophenoxy acetic acid, propylene glycol butyl ether esters	34.8%
2,4,5-trichlorophenoxy acetic acid, propylene glycol butyl ether esters	33.0%
Inert ingredients	32.2%

A steer of mixed breeding weighing 250 kilograms was dosed via a stomach tube with 100 milligrams per kilogram of body weight per day for 17 consecutive days. There was no indication of toxicity exhibited by this animal any time during the entire experimental procedures and the animal continued to gain weight at a normal rate. This critter was autopsied 48 hours following the last dose of Esteron Brush Killer. Autopsy revealed some petechial hemorrhage in the duodenum and a mild diffuse irritation was noted in the entire abomasum. Otherwise grossly, all organs and viscera of this critter appeared to be normal. Tissue specimens were submitted to Biochemical Laboratory for histological examination.

T. A. Hymas
Agricultural Chemical Research
Phone 8321

dr

17055

MN0697799 DOW 7521071

To: V. K. Rowe, BRD

Subject: HISTOPATHOLOGIC IMPRESSIONS OF STEER FED DOW ESTERON BRUSH KILLER

Lung:	Normal
Heart:	Normal
Liver:	Moderate pathology characterized by areas of focal hemorrhagic necrosis surrounded by areas of moderate fatty degeneration.
Kidney:	Very slight interstitial edema and congestion in the medulla and cortical medullary region.
Spleen:	Normal
Adrenals:	Normal
Pancreas:	Normal
Testes:	Degenerated and non-spermatogenic.
Thyroid:	Normal
Lymph Node:	Normal
Thymus Gland:	Normal
Bladder:	Normal
Rumen, Reticulum, Omasum, and Abomasum:	Mucosa, submucosa, and muscle layers appeared normal with no evidence of congestion, hyperemia, nor edema.
Conclusions:	The lesions in the liver are characteristic of toxic necrosis.

F. Oyen
2-18-54

jcw

17056

CAGE:
MARK:
BIRTH DATE:
AGE IN DAYS:
STARVED: Steer

SLIDES FILED 20C+21C
BLOOD COUNTS ( )
BONE MARROW COUNTS ( )

BIOCHEMICAL RESEARCH DEPARTMENT

TISSUE EXAMINATION

ANIMAL NO.: ~~Cage~~ 4
MATERIAL: Estrus swab Killer - 100 mg/kg

FILE NO. T 2.30 - 13
EXPT. NO.
RUN NO.
DAYS 20
DIED ( )
KILLED (✓)

GROSS EXAMINATION

DATE: 11-27-53
CONDITION:
BODY WT.: _____ GRAMS
KILLED BY DECAPITATION (✓)
OR
EXAMINATION OF ORGANS:
APPEARANCE OF VISCERA:

MICROSCOPIC EXAMINATION

FORMALIN (✓) OR _____
DATE REMOVED FROM FIXATIVE 12-3-53
EMBEDDED: PARAFFIN (✓) OR _____
SECTIONED BY J. Coppen
STAINS: HEMATOXYLIN AND EOSIN (✓)
OR _____
EXAMINATION OF SECTIONS:

752108

WT. (g)	TISSUE SAVED	DEGREE OF DEG.		SLIDE PREP.	DEGREE OF DEG.	
			LUNG:			LUNG: Normal
			HEART:			HEART: Normal
			LIVER:		++	LIVER: Areas of focal hemorrhage with slight fat degen.
			KIDNEYS:		±	KIDNEYS: Vac. slight interstitial edema or congestion
			SPLEEN:			SPLEEN: - Normal
			ADRENALS:			ADRENALS: - Normal
			PANCREAS:			PANCREAS: - Normal
			TESTES:		+++	TESTES: - Pigmented + some hemorrhage
			BONE MARROW:			thyroid - Normal
			STOMACH:			lymph nds - normal
						Reticulum - Mucosa, submucosa & muscularis normal.
						Rumen - " " " "
						Duodenum - Normal
						Bladder - Normal
						Thymus gland - "
						Omasum - Normal
						Abomasum - "



DATED _____ SIGNED _____ DATED 2-17-54 SIGNED T. Ogata

1219-8 PRINTED IN U.S.A.

FEB 1964

4947 -(1)

Biochemical Research Department

The Dow Chemical Company

RESULTS OF RANGE FINDING TOXICOLOGICAL TESTS ON M-697 (ESTERON BRUSH KILLER-TYPE FORMULATION)

File T2.30-66-/
Sample No. 1
Chg. 1219-2
Rept. By T. R. Torkelson

BC T2.30-66

Signed T R Torkelson Checked D. D. McCollister

Date May 2, 1956 Date May 3, 1956

THIS REPORT IS THE PROPERTY OF THE DOW CHEMICAL COMPANY

MN 0697999 DOW

PROBLEM

This material is a proposed formulation for use as a brush killer. What is its toxicity and what handling precautions will be necessary? How does it compare with Esteron 245T and 24D brush killer?

CONCLUSIONS

This material has a low acute oral toxicity. There is no problem from ingestion incidental to the handling and use of this substance. The undiluted material and a 5% solution of kerosene may be expected to cause a moderate response on the skin. Precautions should be taken to avoid prolonged or repeated skin contact. Protective clothing may be required. A 10 and 1% emulsion in water caused only a slight response upon the skin. Precautions should be taken to avoid repeated and prolonged contact with such dilutions.

The material, its emulsion (10% and 1%) in water and a 5% solution in kerosene cause only a slight transitory effect

(Continued)

(CONCLUSIONS CONTINUED)

DOW 752078

upon the eye. Safety glasses should probably be worn to avoid the pain and discomfort that results from contact.

M-697 is very similar in toxicity to the brush killer formulation reported in T25.14-86-1. They both have a low acute oral toxicity and cause slight skin and eye irritation. For practical purposes the two materials should be handled the same.

These conclusions are based upon range finding toxicological tests and are limited to precautions for industrial handling of the material and its use as a brush killer. Development of this or other uses may require consideration of the health problems presented and of the need for further toxicological studies.

HAZARDS, PRECAUTIONS FOR SAFE HANDLING, AND FIRST AID MEASURES

Ingestion

The material has a low acute oral toxicity. There is no problem from ingestion incidental to the handling and use of this substance. If large quantities are swallowed, accidentally or willfully, some injury may result; the likelihood of serious injury is remote. Containers of the material should be labeled so that accidental swallowing due to mistaken identity cannot occur.

DOW 7520719

Eye Contact

The undiluted material causes a slight effect upon the eye. Pain and conjunctival irritation persists for several days. Precautions should be taken to prevent contact with the eyes. Safety glasses should provide satisfactory protection. If the eyes are contaminated, they should be flushed immediately with copious amounts of flowing water for at least 15 minutes. Medical attention should then be obtained.

Emulsions (10% and 1% in water) and a 5% solution in kerosene have a very slight effect upon the eye. Contact is but very slightly painful and irritating and may cause transient irritation to the conjunctival membranes. It seems advisable to prevent contamination of the eyes simply to avoid the discomfort which may result. Minimal eye protection should be satisfactory. If the eyes are contaminated, they should be flushed with copious amounts of flowing water.

Skin Contact - Irritation

The undiluted material has a slight effect upon intact skin. Several exposures are needed before definite response occurs. The undiluted material is not likely to cause appreciable irritation unless exposures are quite severe. Good care and cleanliness should be exercised. Protective clothing may be helpful in preventing contact. Any injuries or irritations which may develop should receive medical attention. A 10 and 1%

DOW 752080

emulsion in water cause even less irritation upon the skin than does the 100% material. Reasonable care and cleanliness should avert irritation. Any injuries or irritations which may develop should receive medical attention.

The 5% solution in kerosene, however, causes a moderate response upon skin. A single exposure for 24 hours to a 5% solution in kerosene is capable of causing slight irritation. Repeated prolonged contact over a period of several days may result in blistering and a superficial burn. The material also causes a slight folliculitis. Precautions should be taken to prevent skin contact. Protective clothing, impermeable to the material, should be worn as required by circumstance. Contaminated skin should be washed with soap and plenty of water. Contaminated clothing and shoes should be removed and not re-used until thoroughly cleaned.

SAMPLE INFORMATION

C.R.I. Name: M-697

Common Name: M-697 (Esteron type formulation brush killer)

Source: George Scoles

Ref.: WS B6P53

M.P.: Below 0°F.

Sample No.: 1

Date Request Received: 11-29-55

Date Sample Received: 11-29-55

Physical State: Light amber solution

Sol.: Kerosene, xylene, Emulsifiable with water

Composition:

35.1% Dowanol 97B ester of 2,4,-D
32.5% Dowanol 97B ester of 2,4,5-T
2.5% Dow Polyglycol 59-1
2.5% Caryly base 137B
27.4% Penola heavy aromatic naphol

DOW
7520081

DOW
752082

SUMMARY OF RANGE FINDING TOXICOLOGICAL DATA

Acute Oral Toxicity

Animal	Preparation Fed	Dose (g./kg.)	No. Died No. Fed.	Response-Remarks
Male Rat	20% emulsion in water	3.0	2/2	--
Male Rat	20% emulsion in water	2.0	1/2	Slight cloudy swelling in the kidneys.
Male Rat	20% emulsion in water	1.0	0/2	Slight cloudy swelling in the kidneys.
Male Rat	20% emulsion in water	0.5	0/2	Essentially no effect.
Male Rat	20% solution in kerosene	2.0	2/2	--
Male Rat	20% solution in kerosene	1.0	0/2	Pathology essentially negative.

Eye Contact - Rabbit

Material	Treatment	Response-Remarks
100%	Unwashed and washed with water.	Slight pain, moderate conjunctival irritation, very slight iritis which healed in 2 days.
10% emulsion in water.	Unwashed and washed with water.	Very slight pain, slight conjunctival irritation which healed within 2 days.
1% emulsion in water.	Unwashed and washed with water	Very slight pain, slight conjunctival irritation which healed within 2 days.
5% solution in kerosene	Unwashed and washed in water.	Very slight pain, slight conjunctival irritation which healed within 2 days.

DOW

Skin Contact - Rabbit

Material	Condition of Skin	No. of Appl.	Site	Response - Remarks
100%	Intact	10	Ear	Slight hyperemia, slight necrosis and slight exfoliation. Slight folliculitis after 10 applications.
100%	Intact	10	Belly	Slight hperemia, slight edema, very slight necrosis, and moderate exfoliation.
100%	Abraded	3	Belly	Moderate hyperemia, slight edema, very slight necrosis.
10% emulsion in water.	Intact	10	Ear	No response.
10% emulsion in water.	Intact	10	Belly	Very slight hyperemia, slight exfoliation.
10% emulsion in water.	Abraded	3	Belly	Slight hyperemia, very slight edema and necrosis.
1% emulsion in water.	Intact	10	Ear	No response.
1% emulsion in water	Intact	10	Belly	Very slight hyperemia, slight exfoliation after 5 exposures.
1% emulsion in water	Abraded	3	Belly	Slight hyperemia and slight exfoliation.
5% solution in kerosene	Intact	10	Ear	Slight exfoliation and slight hardening and folliculitis of the ear.
5% solution in kerosene	Intact	3	Belly	Moderate hyperemia, slight edema and moderate necrosis, moderate exfoliation with scab and scar formation.

DOW 7520084 -

Skin Absorption

There is no indication from the skin irritation tests conducted, that this material is absorbed through the skin in toxic amounts.

DOW 752085

UNIT INDEX

Effects resulting from ingestion, eye contact and skin contact are given. Hazards precautions for safe handling, and first aid measures are discussed.

INDEX HEADINGS

C.R.I. Name: M-697 (Esteron type formulation brush killer)
Esteron 245T
Esteron 24D
Brush Killer

DISTRIBUTION

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mo

September 18, 1957

J. Burton - Newark
Pentachlorophenol
Chloracne

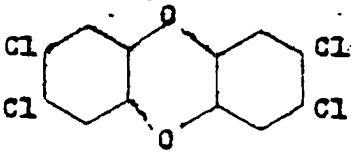
cc: J. J. Lukes
R. C. Sutter-Cleveland

D. J. Porter - Painesville

Dr. Kudszus of Boehringer was here last week to discuss the acquisition from Diamond of our know-how for the production of pentachlorophenol. He asked specifically if we had observed any indications of chloracnegene in our product. I told him that in the work that Al Hirsch and Irving Rosen had done several years ago and the more recent work done by Jack Jennsy in the laboratory and by Al Lewis in the pilot plant we had not been scrupulously careful to avoid contact, but at the same time had had no indications of chloracne trouble.

He then asked if we had received his report on the solution to the chloracne problem which at one time had forced the shutdown of the Boehringer trichlorophenol plant. I told him I didn't think we had seen it. He promised to send over a copy.

In the meantime he pointed out that a compound



identified as an extremely toxic material and probably the cause of some of the chloracne difficulties. This material is not formed if the trichlorophenol autoclave temperature is kept below 155°C and if the dried TCP-caustic crude mixture is not allowed to exceed 120° C. In view of our problems with chloracne in our trichlorophenol plant, it would certainly seem in order to check these observations, if possible, in trial plant runs.

It is quite likely that by dropping our reaction temperature 15° or more from what I understand is our current level of operation of about 170° C, we may suffer a significant decrease in reaction rate and prolongation of our reaction cycle time. I believe Ray Guidi has had a good bit of experience in continuous caustic chlorobenzene reactions and I would guess that we might be able to convert our existing autoclave to a continuous unit by providing a slurry charge pump, a reflux condenser, and a blow-off control valve. Since complete conversion would not be essential, it should be possible to operate such a unit at the point on the autoclave curve at which the rate of reaction should be fairly great and we might be able to affect an actual increase in our production capacity and at the same time eliminate chloracne problems.

D. J. Porter

DJP:sjm

DS 00017415

17067

September 18, 1957

J. Burton - Newark
Pentachlorophenol
Chloracne

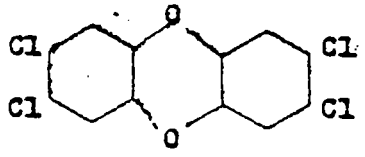
D. J. Porter - Painesville

cc: ~~J. J. Lukes~~
R. C. Sutter-Cleveland

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D. J. Porter

DJP:sjm

17068

DS 00017415

AUG 13 19

L.P.S.
D.C.K.
H.S.W.
H.F.W.
✓ J.A.B.
FILE
DESTROY

C. H. BOEHRINGER SOHN

CHEMISCHE FABRIK

Postanschrift: C.H. Boehringer Sohn, (20) Ingelheim am Rhein

Ingelheim 2020
Boehringer Ingelheimbein
Fernschreiber 0417 855
Alle Codes in Gebrauch
Landeszentralbank Mainz 48/81
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Mr. J.A. Borroy
c/o DIAMOND ALKALI COMPANY
Union Commerce Building
Cleveland 14, Ohio / USA

Ihre Zeichen	Ihre Nachricht vom	Unsere Nachricht vom	Unsere Zeichen	(20) Ingelheim am Rhein
			Dr.Mz/Fk GC/Sg	den August 10, 1960

Betrifft

Dear Mr. Borroy:

Recently we received a letter from Mr. J. Burton, dated June 23, 1960, addressed to Mr. Doll, Managing Director of CELA G.m.b.H. Mr. Burton requested to have the answer addressed to you. Unfortunately his letter was sent by surface mail which meant a several weeks' delay. We therefore hasten to let you have an answer and the desired information.

We thank you, also in the name of CELA, for the information regarding your process for the production of 2,4,5-Trichlorophenol from 1,2,4,5-Tetrachlorobenzene, as well as for the description of the explosion which occurred in your Factory. It was very interesting for us to read that in your laboratories you are presently working on a modified method according to which the autoclave is at first loaded with the full quantity of Tetrachlorobenzene adding slowly the solution of caustic soda. We have had good experiences over long years with a principally equal process which in our opinion offers a great operating safety if working below certain temperatures. Here below we are outlining our standard process:

We are loading the autoclave of 7400 Litres with 1400 Kg (= 6,5 Kg Mol) cold symmetrical Tetrachlorobenzene, suspended in 1000 Litres Methanol, and dilute therein with another 2500 Litres Methanol. This amount of Methanol is regenerated from former batches and has a content of 95%.

DS 00022020 17069

H. Boehringer Sohn
Ingelheim am Rhein

Mr. J.A. Borroy, Diamond Alkali Co. USA 10-8-1960

The autoclave is then locked and heated to an internal temperature of 130 - 135°, the pressure thus reaching 9 atü. The steam is shut off and over a period of 5 hours 730 Kg of aqueous caustic soda solution minimum 49% are injected (= 18,24 Kg Mol 100%). The heat thus developped brings the contents of the autoclave to a temperature of 150-153° within one hour. Generally a further increase in temperature in the course of reaction of 12 hours will not take place. By the end of reaction it is necessary to add some heat in order to maintain temperature at 150°. 8 hours after having finished the injectionof caustic soda solution a pressure of 20 atü is reached, which rests constant until the end of reaction.

Now the contents of the autoclave is cooled down to 105° and filled in a distilling apparatus of 7000 Litres in order to distill off the Methanol. Following the evaporation of the Methanol during which the temperature must not exceed 115°, and after adding 300 Litres of water by blowing in steam (3,5 atü), the formed Trichloroanisol is distilled off. It remains a solution of about 36% 2,4,5-Trichlorophenol in surplus caustic soda solution for onward processing into Phenol.

We consider it especially important that whilst evaporating methanolic or aqueous solutions of Trichlorophenolate solutions a concentration of 40% is not exceeded because otherwise there exists the danger of a sudden exothermic formation of chloride acne-active substances which, as you know, has led to a severe damage to the staff of an important European Factory. In a letter dated September 20, 1957, addressed to your Research-Center, Painesville, Ohio, we described our own experiences in this connection.

RFL

We should be pleased if you - in supplement of your letter dated June 26, 1960 - would tell us how you elaborate the reaction product of the autoclave to Trichlorophenolate. The information regarding your process will, of course, be treated strictly confidential and we sincerely ask you to act accordingly with regard to our indications.

Yours very truly,
C.H. BOEHRINGER SOHN
ppa. ppa.

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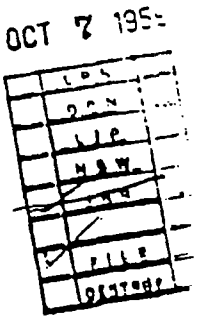
MEMORANDUM

Frankfurt, Germany
September 30, 1959

TO: J. Burton

SUBJECT: Boehringer - Chloracne Problem

cc: ~~C. S. Brumbaugh~~
J. A. Borror
H. E. Everson
D. J. Porter
L. P. Seyb
H. S. Weiner



The acne cure announced by Boehringer in Chem. Week for June 20, 1959 is confirmed as inactive for chloracne.

Boehringer has had no new cases of chloracne in 3-5 years. They did this by discovering the compound which is the bad actor and eliminating it as a by-product. After they accomplished this processwise, they then cleaned up their factory in a major fashion before reopening - it was closed a year.

Dave Porter's memo of September 18, 1957 to you and yours to me of July 28, 1959 set forth substantially the requirements. As Dave points out, the bad actor is a tetrachlorobenzodioxime. As you pointed out, certain conditions of temperature in the process can cause the trouble.

In addition, even though Boehringer is sure it has no more dioxime in its process, it ventilates its plant with great care, issues clean work clothes every day and continuously checks its trichlorophenol on rabbit ears per the test described in the Dermatologica paper (Derm. 115, 540, 1957) copy of which you sent me.

Kudszus has reneged on sending out the report he promised Dave - says the dioxime is so active as to be a chemical warfare chemical. But we have all dope orally.

Do you distill TCP? This is said to be a most dangerous step. In distillation, if any alkali or salts are present, oxime forms very rapidly. Recommend that alkali and salt be washed from crude TCP before distillation.

Referring to your points 1, 2 and 3 in your memo to me of July 28, 1957 (H. S. Weiner has a copy):

1. After dilution with methanol, the reaction mass is only dangerous over 170° C.

2. Distill out major portion of methanol under 110°, then strip out remainder of methanol with steam preferably at 100° (120° C., cited by you said to be dangerous).

Boehringer offers to review your process conditions and advise of further danger points - if these ideas don't do the job.

Finally, after Boehringer did all the above, they tore out plaster walls, floors and similar parts of buildings until no remaining structure gave positive rabbit ear test. This done by carefully protected workmen. Once clean and following above process steps, they have enjoyed good experience. Better try a few rabbit ears on your joint if you are still having trouble. Oh, yes, Boehringer liver damage cases are still on compensation after more than five years!

Thornton F. Holder

TFH:sjm
10/5/59

THE DOW CHEMICAL COMPANY

MIDLAND, Michigan
March 29, 1965

Copy to Bill Haber on 1-27-69 - OKR

V. K. Rowe
Biochemical Research Laboratory
1701 Building

cc: F. H. Riley
R. N. Smiley
L. B. Grant
C. O. Hutchenreuther
F. C. Amstutz
W. P. Falsey
G. E. Lynn
W. M. Gill
M. G. Wiltse
D. E. Pletcher
W. L. Corbin
D. D. Irish
J. E. Peterson
J. C. Tucker
J. W. Harris
H. W. Feinauer
E. C. Staehling
C. E. Otis
K. Y. Hansen
R. C. Hoff
W. J. McCoy
J. D. Doedens
K. C. Barrons
H. R. Hoyle
B. B. Holder, M.D.
S. E. Sadek

REPORT ON THE CHLORACNE PROBLEM MEETING ON 3/24/65

Present: Dr. J. Wilkenfeld and
Mr. Raymond Verhoeze, Hooker Chemical Corporation

Mr. Francis Kennedy and
Dr. Ed Chandler, Diamond Alkali Company

Mr. C. L. Dunn and
Dr. John P. Frawley, Hercules Powder Company

V. K. recapped the Dow situation in terms of the problem and the initial studies by Toxicology and Environmental Research Laboratory regarding the in-plant situation. He expanded this in general terms to the study of end products, ours and other peoples. He made reference to symmetrical tetrachloro-p-dibenzodioxin. He referred to the evidence for unknown acnegens. There were some questions from the group about the unknowns. We (Dow) were not able to answer these questions except to review the evidence for their existence in the process samples and end products.

CONFIDENTIAL - SUBJECT TO INJUNCTION
D.C. E.D. MI. 4-4-73; DOW/EPA AGREEMENT 9-79

Dr. Holder reviewed the medical side of the Dow experience; he said that we now have approximately 60 to 70 cases of individuals with chloracne ranging from two severe cases to some very mild cases that were difficult to diagnose. He showed slides of the more dramatic cases. The slides were exclusively views of the faces of the individuals afflicted. He described in fair detail the appearance of the individuals mentioning the blackheads specifically. He then reviewed the clinical studies that are being made on these people with emphasis on the liver function tests. He mentioned the single liver biopsy that has been taken and studied in which the liver was normal although the man had a rather pronounced case of chloracne. Dr. Holder also mentioned the incidence of fatigue among the afflicted people as being the only other significant finding in these folks. He touched briefly on treatment indicating that various topical treatments were not particularly effective. He described the cycling of this disorder in individuals who had been completely removed from exposure. He mentioned that some fellows are approaching the end of their trouble two or two and one-half years after onset of the skin disorder. He also described "acute chloracne" which is an acute inflammatory condition that appears considerably sooner than the normal chloracne in individuals and appears after pronounced single exposure. The acute chloracne shows up within a few days of exposure. Dr. Holder mentioned five to eight days specifically. There was considerable discussion by the group on the skin disorder itself. The Hooker representatives related experience of skin condition thirty years after exposure. Their cases were more similar to the Dowicide bumps which Dow has experienced in that there were large boils or large bumps rather than the multitude of small blackheads and eruptions which Dow is seeing in the current cases.

Dr. Sadek showed slides of ears and livers of rabbits that had been exposed to the symmetrical tetrachloro-p-dibenzodioxi He discussed the pathology in detail which I will not attempt to summarize.

V. K. mentioned the studies in which the rabbit ears have been treated with TCBD in benzene or corn oil and then washed with soap and water at various time intervals later. If exposure occurs for very long, washing does little good. He also briefly mentioned the oral studies but without detail. Silverstein described the plant study on washing of contamination from tools and surfaces. This study indicated that benzene, acetone and Chlorothene NU were effective in removing the contaminant from tools and also that detergent and water with scrubbing action could clean up tools and equipment. Some discussion ensued on the use

of detergent and water and the point was made again that strong scrubbing action was necessary for this approach to be successful.

Harold Gill then discussed the analysis for tetrachloro-p-dibenzodioxin by vapor phase chromatography. He listed the limit of sensitivity on various process materials. He mentioned the oil which he defined as a non-saponifiable mixture of chloro anisoles, tetrachlorobenzene and trichlorobenzene; the limit of sensitivity for TCBD in this material is 10 ppm. The limit is 1 ppm for 2,4,5-trichlorophenol, and for 2,4,5-T Acid, either acetic or propionic. Gill then defined 1 ppm as a very discernible peak. He mentioned that he might estimate 0.5 ppm in some instances but to be conservative the analyst reports <1 ppm if the peak does not measure up to the quite identifiable level of 1 ppm. The analytical problem has not yet been solved for the T-Acid esters. The general procedure used for the T-Acids is to extract the sample (arbitrarily about 20 grams) with chloroform (about 40 milliliters), filter the chloroform to remove solids and wash with an equal volume of N/10 caustic to remove any acidic materials. The chloroform extract then is concentrated by evaporation to one-tenth the original volume; thus, the concentration of the dioxin in the chloroform will be ten times higher than in the original sample. When the analysis is conducted on trichlorophenol, the material is dissolved in N/1 caustic to the extent of 10%, and this solution is then extracted with the chloroform and handled as indicated above.

A question was asked about the utilization of detectors other than the flame ionization which is specified in the Analytical Laboratory write-up for this analysis. Gill has not tried the micro coulometric detector because he is not set up to do so, but he has experimented with electron capture. He stated that theoretically this unit should not provide any greater increase in sensitivity. In actuality he found a slight increase in sensitivity but there are usually too many chlorinated species present which may saturate the electron capture cell whose recovery is too slow to be of practical use. He summarized by saying that the slight increase in sensitivity is not worth the effort to switch from flame ionization to electron capture. A question was asked about how the extraction is performed. Gill stated that it is performed in a wide mouth bottle on a shaker for one hour. (It was not mentioned, but it is the case that this is done at room temperature.) He mentioned that spiked samples have been

run this way and the recovery ranged from 90 to 100 per cent. The ratio of solvent to the material being extracted on this step is not critical according to Gill. Their standard procedure is 20 grams of sample and 40 milliliters of chloroform. On trichlorophenol samples specifically, 20 grams of phenol is converted to phenate — about 10 per cent concentration in water. The phenate solution is extracted with 20 milliliters of chloroform in a single extraction. The chloroform is then concentrated so that the concentration of the dioxin will be ten times that in the original sample.

The question of volatility of dioxin came up and Harold Gill stated that he found he can distill o-dichlorobenzene away from tetrachlorobenzodioxin. He said that in his opinion the secret was to avoid distilling to dryness.

A member of the group asked if samples of standard TCBD were available. The answer was yes and 100 mg samples were provided to one of the representatives from each company. (A sample had previously been given to Dr. Kelly of Monsanto.) A question of laboratory safety in the analytical work came up and the basic precaution of wearing vinyl gloves was mentioned. Information relative to the gloves we used was provided to the group.

Disposal of contaminated laboratory materials and plant materials was discussed. We mentioned that Dow burns some small amounts of waste. Harold Gill stated that his laboratory study of combustion showed that 99.96 per cent of the dioxin sample was burned at 800°C. We described why we felt that our practice of burning small amounts of dioxin was a safe one.

V. K. then outlined the project in which plant samples and products (not mentioned by name) were spiked with known amounts of the TCBD. The spiked samples were split for the purpose of checking our analytical procedures for recovery and correlating these results with the bio-assay method.

The question of specification, quality control specification that is, was raised and we were asked if we could give levels of dioxin contamination which were permissible limits. V. K. mentioned that at present we are using zero with a confidence of 1 ppm in process samples. There was some discussion on the problem of customers using finished products under far less desirable conditions of health control than we can provide our workmen in our own plant. There seemed to be agreement among the group that we could not afford to sell contaminated products.

Jack Peterson then discussed the data from animal experiments using pure symmetrical tetrachlorobenzodioxin. Doses ranging from 2 parts per billion to 1000 parts per million of tetrachlorobenzodioxin in benzene had been administered to the rabbit ear. Dosage in most cases was 0.1 ml per day. Both single and multiple exposures have been studied and multiple exposures administered on a five days per week basis. The significant factors in the study are dose, the number of applications and the days on exposure of the animals. The response which is reported in the gross observation of the condition of the rabbit's ear by the toxicologists. This does not include pathological findings -- there is not enough data in this area to discuss. The level of response ranges from none through very slight, slight, slight to moderate, moderate, moderate to severe, severe, and extremely severe. Jack indicated to the group that there is not a sharp definition between these categories of response and indicated also that there is some difficulty in graphing this type of response. He described the response from single applications to the rabbit ear first: at 100 parts per million there was a severe response in eight days; at 40 parts per million there was a slight response in eleven days; at 20, 10, 7 and 4 parts per million there was no response. These tests were run on single rabbits and without washing the material off. Jack then discussed the multiple application data which he took from his major graph of this data. The important points that he made from this data were first that at the limit of VPC sensitivity a severe response may be produced. In other words, even if the VPC does not detect TCBD, an animal response may still occur. His second important point was that the induction period for response averaged about ten days on the animals in the studies.

There was a brief discussion then about the air samples that were taken in the plant. Silverstein mentioned that some air samples have shown activity on the animals. The degree of response is slight and the number of samples that show activity is small out of the total number taken and the amount of air that must be sampled is very much larger than the amount a man normally breathes in an eight hour day.

The meeting was adjourned. 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.

L. G. Silverstein
Biochemical Research Laboratory
1701 Building

LGS:sjl
17077

Postscript

All participants seemed to appreciate well the problem and al indicated that they would return home and attempt to convince their management to institute safety specifications (really quality control) for their various products in this area. Al agreed that the industry should meet its own responsibility. All were very appreciative of Dow's effort to steer them away from a danger area. Time will tell whether we accomplished our mission, but as of now I feel satisfied with our effort and the reception it received.

VKR

THE DOW CHEMICAL COMPANY

MIDLAND, MICHIGAN 48640

July 30, 1964

102

Mr. H. R. Hoyle
Environmental Research
1701 Bldg.

Subject: MANUFACTURE OF TRICHLORPHENOL AT 199 BLDG.

We started making 2,4,5-Trichlorphenol in 199 Bldg. in mid 1946. We dissolved flake (anhydrous) caustic in [methanol] and used enough of this solution to supply: of caustic per mole of tetrachlorbenzene. This reaction was run in batch (tumbler) reactors until late 1952.

In late 1952 we started to run this same reaction in a continuous co reactor. We used the same chemicals and the same mole ratios. Reaction time and temperatures were similar to those of the batch reactor

In April of 1962 we started adding water to the caustic solution. We added enough Huron water to be equivalent to 73% caustic which we hoped to eventually substitute for the flake caustic We used the same amount of [redacted] and tetrachlorbenzene as with the aqueous caustic and made a long term plant run to study the effect of water on this reaction. The temperature was adjusted upward to give the same conversion. Yield and quality were as good or better than when we used anhydrous caustic, but we still had all of the mechanical operating troubles caused by the insoluble sodium chloride formed in the reaction. We operated this way until July 1, 1963, except for a short pilot plant run made in September 1962.

In September 1962 we made a two week pilot plant run using pipe line caustic (app. 32% NaOH) diluted with Huron water to app. 24% caustic. The same amount of [redacted] and tetrachlorbenzene were again used. The temperature was raised to give app. the same conversion, the yield and quality were good. In fact there was a slight drop in the impurities which the Infrared Lab had long referred to as A and B. The caustic insoluble oil made during this run was studied by the Biochem Lab, Report No. T2-113-1 dated 12-20-62. The sodium chloride formed in the hydrolysis was soluble in this reaction mixture so the coil plugging from salt has been eliminated. With the old process, most of the time we had been able to wash the coils before they plugged, but often they did plug and this unplugging operation was always a serious safety hazard.

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Between late September 1962 and July 1, 1963 we designed and built equipment to increase our capacity to hydrolyze tetrachlorbenzene re Russian Thousand% caustic method. During this time we ran the plant again rt Orch. Flake caustic diluted to 73% caustic equivalent. The plant was " Prochlorination 7-1-63 for installation of the new equipment.

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on, MDL No. 381

The plant was started up in late July 1963. We had some start-up difficulties but not serious, and because of a tetrachlorbenzene shortage we were not pushed. Most of our trouble was caused by a small amount of paradichlorbenzene in the tetrachlorbenzene receiv from 466 Bldg.— 466 Bldg. started making all of their tetrachlorbe zene from paradichlorbenzene app. July 1, 1963, before this time t used monochlorbenzene or orthodichlorbenzene. Part of this paradi distilled over with our recovered | and we could not keep i back. This paradichlor then separated out in the caustic- solution and caused plugging of lines because of freezing. We got extra exposure because of this plugging. Eventually we got all li traced and covered but this had never been a problem before.

In November and December 1963 and January and February 1964 we wer running at the limit of our hydrolyzing capacity. The caustic ins uble oils were running higher than normal and because our decanter small we were drawing off oil (which goes to the burner) every day we have done for years. Because we were pushing the equipment and having trouble with the presence of paradichlorbenzene we had more exposure than normal.

About February 1, 1964 we noticed the first trouble with chloracne Two supervisors, three trichlorphenol operators and one laboratory employee started to have a rash on their faces. We called the Environmental Research group almost immediately. Also we installe capacitance probe (app. 2-10-64) in the oil draw-off line so that operators do not have to be exposed to vapors while they watch the separation. The operators started wearing an air hood when they lowered the oil drain pipe into the dempster box, or took measureme etc. We thought the most exposure came from around this oil draw-o and we knew this oil has always been bad.

Starting in the middle of February 1964 Phoenix contractors moved i 199 Bldg. to install a 10" steam line, an additional reactor coil, larger oil decanter and revised water lines to the | . column condensers. Their work was all in the area of the trichlorphenol p from the roof level to the floor. They did not make any tie-in to caustic insoluble oil lines. We started to use the reactor coil an new oil decanter in early April and the contractors were finished b 4-15-64 when they left this area.

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The reaction product from our reactor goes directly to the recovery column. (See attached flow sheet and equipment layout). | comes off the top of the recovery column and the phenate and caustic insoluble oils off the bottom. The bottoms go through an oil decanter and then to the top of the steam stripper t the last traces of caustic insoluble material. The steam an volatile materials have always gone to the air. We never had any trouble with this vent until about November 1, 1964, then, at incre caustic mist started falling out around the phenol treating etc. A demister installed in December 1963 stopped the caus but then paradichlorbenzene started falling out as wet sno which collected on roof and on above roof structure. This demister

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probably a bad source of contamination.

The Phoenix crew worked in this area part time for a few days. On 5-12-64 we installed a line taking the tops (vent) from the strippi column and put it in the bottom of the [redacted] column. This volat material should now join the stream of oil removed by the oil decan which goes to the burner. Since early April 1963 we have had the larger oil decanter and have only drawn off oil twice a week instea of daily as we had done for several years.

Summary

1. Started making trichlorphenol in 199 Bldg. in 1946, using anhyd caustic and batch reactors.
2. Started using a continuous coil reactor in 1952, with same chem and rates.
3. Used 73% caustic April 1962 to July 1, 1963.
4. Pilot plant run, of two weeks duration, in September 1962, using pipe line caustic diluted to 22% NaOH.
5. Plant started on 22% caustic 8-1-63.
6. November 1963 pushing existing plant to limit.
7. December 1963 demister installed.
8. February 1, 1964, six cases of chloracne trouble recognized.
9. February 10, 1964, installed oil draw-off probe.
10. Early April 1964, new coil and large decanter installed.
11. May 12, 1964, vent from top of stripping column to bottom of [redacted] column.

Ray Holmes
199 Bldg.

wpg

A&G000087

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April 6, 1966

Mr. J. O. King

Dow Chemical Co.

Mr. J. C. Kelly

SC

COPY

On March 21, we directed a sample of our Technical 2,4,5-T Acid to subject account. In talking with Ken Hanson on April 4, he advised that they would not be in a market for our material. Apparently, they feel that our material could conceivably re-create a chlor-acne problem at Midland and, as such, would not entertain the purchase of our present production.

J. C. KELLY

JCK/im

cc. Mr. F. R. Kennedy - Newark
Mr. R. A. Guidi

17082

DS 00012690

Diamond Shamrock Chemical Company
Fine Chemicals Division / 60 Park Place / Newark, New Jersey 07102 / Telephone (201) 484-8400

September 24, 1973

Chemicaland Corporation
c/o Cloray, N. J. Corp.
80 Lister Avenue
Newark, New Jersey 07105

Att.: Mr. William Mitchell

Dear Mr. Mitchell:

It was a pleasure to meet you on my visit to your place on September 11, 1973. As I said at that time I will do what I can in the time available to assist you and your personnel in the start-up of 2, 4 - D operations.

Per John Brennan's request I delivered two copies each of the following on my visit:

MCA operating instructions, W. Tobin 7/15/63
DCP operating instructions, W. Tobin 7/15/63
MCA process flowsheet, drawing no. NF-200-3
DCP process flowsheet, drawing no. NF-200-4

Enclosed are two copies each of the following items that you requested:

1. Product specifications for
   2, 4 - D acid
   Muriatic acid
   2, 4 - DCP
   4# Dimethylamine - D
   6# Dimethylamine - D

2. 2, 4 - D operating instructions
   2, 4 - D Condensation Reaction, W.A.Goodloe/J.Matits, Jr. 12/19/69
   New "D" Melt Unit, F.G.Steward 10/27/67
   Prep of DCP Sol'n for D Reactor
   Revised 2, 4 - D Acidification Procedure, W.A.Goodloe 1/16/69

3. Monthly Operating Data August 1968 - July 1969

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4. Chloracne Information
   2 memos reporting a meeting with representatives of Dow, Hooker, Hercules and Diamond regarding chloracne.

The requested data on lab tests run on the products and necessary lab equipment is not yet available. It will be forwarded as soon as I can get it together.

Very truly yours,

DIAMOND SHAMROCK CHEMICAL COMPANY

F. Gordon Steward

F. Gordon Steward,
Production Manager
Nopco Chemical Division

FGS:bk

cc: Mr. F. R. Kennedy
Mr. M. C. Heisele

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3/25/65

JOHN CORT, JR. S. L. CHANDLER

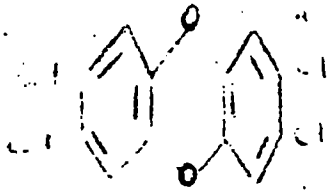
CHLOROACNE - DOW MEETING

cc: F. R. Kennedy - Mgr., Newark plant
J. O. King
M. F. Wilkerson

COPY

On March 24, Mike Kennedy and I met with two people from Hooker Chemical Co., two from Hercules, and with the Dow group to discuss the toxicological impurities associated with 2,4,5 trichlorophenol and related materials.

Dr. Rose of Dow Chemical opened the meeting by stating that they had operated for 25 years without trouble; but, in the last year, they had 60 to 70 cases of chloroacne. Ten of these were moderate, and five to ten were extremely severe. Their approach was a qualitative one at first. They wanted to find the causative material, learn how to identify it, and try to avoid continual trouble with the unknown. They tested various materials from tar fractions and from, as they put it, "gunk", etc. They found that there are a number of suspect materials, probably 26 or 27; but the major "bad actor" that they identified and which seemed to consistently cause the problem was 2,3,7,8-Tetrachlorodibenzo p-Dioxin (symmetrical).



→ 2,3,7,8-TETRACHLORODIBENZO p-DIOXIN (SYMMETRICAL)

This incidentally was previously listed as a suspect material by Cy Perkins of our company. A similar material is the unsymmetrical 1,3,7,8-TCDD, also sometimes listed as 2,3,7,9-TCDD.

The Dow people used the white glove approach and found this contaminant on tool handles, benches, instruments, and other fomites. In test animals, they could consistently cause the symptoms to appear. Dr. Holder of Dow, one of their medical doctors, had excellent color slides of the various patients. The difficulty starts with multiple blackheads resulting in closed cystic structures which make the patient look like he needs to wash his face. The disease develops slowly, not appearing until six weeks to two months after mild exposure but appearing in five to seven days with very heavy exposure.

One bench chemist has been under treatment for two years and his face is starting to show signs of clearing. Dr. Holder says that he believes this man's problems will be solved in another six months. Dr. Sadek, who does their microscopic work in connection with their animal laboratory, showed photomicrographs of the cysts as they formed in the ears of rabbits. The cysts correlated with those found on the faces of the men.

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Basically, there is a carotinoid deposit in the hair follicles and oil ducts in the face. These eventually go from the blackhead stage to form a closed, heavy core deposit. The chemical cannot be found in the facial tissues or in the cores, but the problem still persists after exposure. The best description of the acute stage is that the facial tissues resemble the exaggerated surface texture of an orange, rather glazed and warbly with the enclosed hard core deposits.

A secondary symptom, which does not correlate directly with the amount of facial dermatitis, is a fatigue reaction where the employee is completely listless, tired out, and nearly incapacitated. A complete biopsy of liver, kidney, etc., showed no degeneration of major organs. A complete clinical examination of the patients showed no measurable affect on heart, blood pressure, respiration rate, blood sugar, etc. The fatigued patients seemed to be helped by heavy doses of vitamins, perhaps related in some way to the carotene metabolism of the body (involving vitamin A, etc.)

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An oral dose of 17 micrograms immediately killed the test animals. The Dow people did not lower this dosage to obtain an LD_{50} but decided that, when they can detect this compound, it should not be in the product. They found that, after exposure to the material, washing within 15 minutes did not help a great deal, but did slow down the speed at which the symptoms appeared. Washing after one hour was of absolutely no help whatsoever in reducing total dermatitis or speed of appearance of the reaction. Moderate scrubbing with detergent does not remove this material. Extremely hard scrubbing can accomplish the task or the use of solvents, such as 1,1,1-trichloroethane.

Dow has developed a new analytical method in which they have confidence in their sensitivity to 1 ppm. They can only state in levels below this that some may be present below the 1 ppm. They stated that they have not used micro-colorimetric methods, and the electron capture tests that they ran made only a very slight improvement in sensitivity with this compound. Their analytical chemist stated that the electron cell saturates because of the presence of other materials in high concentration compared to the dioxin.

This material has some strange properties. It has a fairly high vapor pressure but nevertheless is quite persistent as a contaminant. It can be separated from benzene by boiling if it is not carried down to dryness. The Dow people are extremely careful in all of their work with this compound. They use PVC throw-away gloves, and all samples are burned in a special furnace which operates at 800°F. These samples are sealed before going to the burner. They use bioassay methods on rabbits for qualitative checking only.

The Dow people state that they intend to set a limit of zero with sensitivity of plus or minus 1 ppm on this material. They have analyzed materials from other companies, including our company, and have found amounts as high as 10 ppm in 2,4,5-T acid and 20 to 30 ppm in phenates.

They have made a single application to the ears of test rabbits and found that 20 ppm will not give folliculitis. Forty ppm does give a slight effect, and 100 ppm is severe. They have made repeat applications of from 10 to 100 ppb, and 25 of these treatments do not cause a response; however, 1000 ppb (1 ppm) gives a slight response with nine applications and a severe reaction with 11 applications.

They conclude, therefore, that 1 ppm with repeat exposure can create a real problem.

Dow's people outlined a method for extracting and running samples on 2,4,5-T; 2,4,5-TP; and phenols. It involves a chloroform extraction, followed by

MEETING HELD ON WEDNESDAY MORNING, MARCH 24, 1965
AT DOW'S BIO-CHEMICAL RESEARCH LABORATORIES, MIDLAND, MICHIGAN

Other visitors to the meeting included Mr. Dodds, who accompanied Dr. Priestley from Hercules Powder. Dr. Kelly from Monsanto did not attend, but had visited with Dow the previous week. The Dow people at the meeting were as follows: V. K. Rowe, Assistant Director - Bio-Chemical Research Lab; Dr. Holder, M.D., Physician responsible for treatment of patients; Dr. Sedek, Pathologist; K. Silverstein, Chemist; J. Peterson, Chemical Engineer handling statistics, and Howard (?), Chemist responsible for the development of the gas chromatograph method of analysis.

Dr. Holder opened the meeting with colored slides of Dow patients being treated as a result of exposure in 1963. The pictures showed a typical blackhead formation around the eyes and forehead. The eruptions pictured were much more intense than anything I personally have seen at our Plant.

V. K. Rowe had said they had 5 to 10 cases, but this statement was quickly corrected by Dr. Holder, to 70 to75 cases. During a question and answer period, Dr. Holder described the presence of comedones and carbuncles across the shoulder blades, back and buttocks areas. Up until this point, I wondered if there were two separate types of chloracne we were discussing. He claims that 2-1/2 years out of the contact area is sufficient to clear a patient of symptoms. This does not seem possible, since 2-1/2 years have not elapsed. He claims to have noted fatigue as a symptom also.

Five of their more severe cases were submitted to extensive testing, which included eyes (?) liver biopsy; porphyrins; standard metabolic tests; kidney, thyroid, lung and heart functions. In all cases, all of these tests showed normal functioning of the organs involved. Skin biopsies taken did not show any abnormalities other than the characteristic increase in keratins. They

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have not as yet ascertained whether exposure is through fumes or is systemic. They are reasonably positive that it is not caused by direct contact, as every case is bi-lateral.

Contrary to some of our feelings, they put little stock in natural immunity and experience no difference in skin types. Dr. Holder seems to be paralleling the treatment work done by Dr. Bleiberg, that of treating the symptoms by blackhead and comedone removal and the administration of vitamins, particularly Vitamin A.

The entire Dow group are completely convinced that the chloracnegen 2,3,6,8-dichloro-dibenzo-p-dioxin. This is the compound suggested by Cy Perkins in a report to Jack Berror on June 27, 1960. There is an unsymmetrical isomer - 1,3,7,8 - this has some activity, but does not approach that of the symmetrical. In their studies, they looked for the dibenzene-furan, a known acnegen in naphthalene production. They did not find this compound, but had not eliminated its possibility. The dioxin solubility is less than 10 ppm in ethanol and about 400 ppm in benzene. Benzene was used to extract wipe samples in the Plant and as a carrier for their rabbit tests. One interesting note - the significantly short time of contact necessary that will cause chloracne. In one case, they washed off with dioxin 15 minutes after application. The rabbit's ear became affected in spite of continuous washings every one-half, up to 4 hours.

Dr. Sodek showed slides of cell structure which is in the skin of rabbit ears, with mild and severe cases of chloracne. Most of his presentation was beyond my comprehension. The rabbit sustained liver damage in almost all cases. This damage (necrosis?) occurred very close to the bile duct. Dr. Sodek stated that in cattle, [illegible] correlated very closely with

Vitamin A deficiency. The buildup of Vitamin A in the blood stream is a very slow process. The amount of work done by the Bio-Chemical Section was thorough and extensive. Tests of a small dose of 20 ppm showed no response. 40 ppm developed a slight folliculitis in 11 days. A single dose of 100 ppm caused a severe reaction in 8 days. Dow uses a word scale of 8 terms, varying from "No Response" to "Very Severe", so that interpretation of results is confusing. On a multiple application of 1 ppm, a moderate response was detected after 9 applications, and a severe response after 11 applications. 25 applications each of 10, 20 and 100 ppb showed no effect.

As part of their program, they tested samples from all competitors and were kind enough to send the results of their findings personally to me at the Plant. Three of our T-acid samples produced in September of 1961 showed slight response after 13 days on the rabbits, and 2 of the samples showed 5 and 16 ppm analytically. Of two samples of trichlorophenate, one showed a slight to moderate response in 14 days, while the other showed no response in 26 days. Neither of these samples were analyzed by chromatograph. At this time, the origin of the phenate samples has not been determined.

White rats are not used for this type of skin test because they do not respond properly (?); do not develope coloreens (?).

V. K. Rowe stated that phenates as high as 20 ppm were found and T-acid as high as ppm. This latter [illegible] not agree with the analytical results of 16 sent to me. When Dow was experiencing their problems in the Plant, they detected 20 ppm in their phenate. K. Silverstein spoke of cleaning up their plant area, tools, etc., with various solvents. Although benzene and [illegible] were used, [illegible] the material, they were impractical for plant use. He further stated that 1,1,1-trichloroethane worked

as well. Strong detergents are not effective without intense scrubbing and hard work. From his comments, I imagine a decontamination process was performed in their unit. From their tests, it was determined that the dioxin decomposes at 800°C. Even though Dow has a very large industrial waste burner with furnace temperatures of over 1200°C, they continue to bury their wastes. They were hesitant to continue discussions along these lines.

Laboratory wastes, including gloves required in handling this material, are incinerated. Howard (?) stated that the chromatographic method of analysis can detect 10 ppm in an anisole sample and 1 ppm in TCP and T-acid. As of yet, they have no method for esters or formulations. TCP sample preparation for analysis is as follows: 20 grams of TCP were converted to the sodium salt and extracted with 20 cc of chloroform. The chloroform extract is concentrated 10 to 1 and injected into the machine. Phenate solutions are reduced to a 10% phenate concentration extracted with chloroform and handled as above. T-acid samples are prepared by extracting 20 grams of the T-acid with 40 cc of chloroform. The chloroform is filtered and caustic-washed with one-tenth normal caustic and the chloroform concentrated as above.

Plant wipe samples were extracted with 2 cc of chloroform and used as such. We will have to develop our own method of determining chromatograph response in terms of ppm. Throughout the entire meeting, one theme seemed to be presented. For everyone's protection, everyone should clean up his final product and certainly on the local level, this is very necessary. Mr. Rowe stated many times that each organization could handle the problem in their own way.

From his presentation, I gathered that detection was the primary problem and that steps to eliminate its carry-over into the final product was well within the capabilities of all people involved. A small sample of the dioxin was given to each company attending the meeting.

DS00014662

[1 April 1991]

Long-Term Chemical Carcinogenesis Experiments For Identifying Potential Human Cancer Hazards.

Collective Data Base
of the
National Cancer Institute & National Toxicology Program
(1976 - 1991)

by
James Huff & Joseph Haseman

National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina USA

[Presented at the Conference on Data Bases of Genotoxicity and Carcinogenicity and Their Usefulness for Hazard Evaluations. Castello Simon Boccanegra in Genova, Italy, 16 - 18 January 1991]

Note: Parts of this overview paper come from our previously reported and published analyses and interpretations. Thus for those wishing more details and perhaps larger bibliographies please consult the references given at the end of this paper. Most of the papers authored by us or the individual printed Technical Reports on the chemical carcinogenesis studies are available upon written request.

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Abstract

The carcinogenicity data base used for this paper originated in the late 1960s by the National Cancer Institute (NCI) and since 1978 has been continued and made more comprehensive by the National Toxicology Program (NTP). The extensive files contain among other sets of information detailed pathology data on more than 400 long-term (most often 24 month) chemical carcinogenesis studies, comprised of nearly 1600 individual experiments having at least ten million tissue sections that have been evaluated for toxicity and carcinogenicity. Using this data set we have 1) determined the concordance in carcinogenic responses between rats and mice to be 74%, and between sexes to be 85% (rats) to 87% (mice); 2) discovered that using male rats and female mice would have identified correctly 96% of the positive or no evidence chemical carcinogenicity results obtained using the more extensive protocol; 3) established an historical control file of tumor incidence data; 4) evaluated the false positive rate in the interpretation of carcinogenesis studies, concluding that this rate is probably no more than 7-8%; 5) compiled listings of chemicals having like carcinogenic target sites for each of the 37 organs or systems for which histopathology diagnoses have been recorded routinely; 6) demonstrated that evaluation of site-specific carcinogenic effects are preferable to doing analyses based on overall (all sites combined) tumor rates; 7) learned that few chemicals cause only benign tumors or only liver tumors, the most common target site for chemically induced cancers; 8) identified key sources of variability in tumor rates in long-term carcinogenesis studies; 9) ascertained that corn oil gavage or gavage per se exhibits little if any adverse impact on long-term studies; 10) showed that the Salmonella multi-strain assay was as good as a battery of four short-term in vitro tests for predicting in vivo carcinogenicity, yet was only 66% concordant with an 89% positive predictivity and a 55% negative predictivity. 11) investigated the relationship between chemically induced toxicity and chemically associated carcinogenicity, finding that very few chemicals cause tumors only at the highest exposure concentration (EMTD). These (and other) derived compilations are most useful for maintaining an historic and objective perspective when evaluating the carcinogenicity of contemporary experiments.

17093

Introduction

Since the introduction of exposing animals to chemicals in 1918 by Yamagiwa & Ichikawa for detecting chemical carcinogens (1, 2), much has been learned about the relevance of these findings for possible effects in humans. Likewise an enormous amount of knowledge has been gained over the years on how to design, conduct, monitor, evaluate, and interpret the data collected from these carcinogenesis studies (3-7). Evaluating chemicals in laboratory rodents as surrogates for potential human health hazards remains as the cornerstone for identifying those chemicals most likely to cause cancer in humans (8-14).

Besides human experience and epidemiological investigations, long-term studies in laboratory animals are the only validated and universally accepted means to determine carcinogenic hazards to the public health and to the environment (as examples 5, 6, 8-21). The major public health attribute of these long-term chemical carcinogenesis experiments is to allow better risk assessment (22) and risk management decisions (23, 24) to be made for reducing, preventing, or eliminating exposures to those chemicals identified as constituting real risks to humans (25-27). The findings from these long-term studies assume a major role in the key first step in the risk assessment-risk management process, and a contributory part in the second step of the process (Table 1).

As illustrative and important examples of preventative medicine, the International Agency for Research on Cancer (25, 28, 29) periodically re-evaluates all those chemicals or agents having available human data,

and these consensus findings and rationale are published in Supplements that contain groupings of chemicals and agents considered to be carcinogenic, probably carcinogenic, or possibly carcinogenic to humans; and those not classifiable or probably not carcinogenic to humans (25). Similarly, and as mandated by the U.S. Congress, the Department of Health and Human Services via the U.S. National Toxicology Program (NTP) evaluates the available data and places chemicals into one of two categories: known human carcinogens and those reasonably anticipated to be human carcinogens (27). Once these are identified by either of these organizations, other state, national, and international agencies as well as public and private interest groups assess the possible adverse health impact these agents may have on their particular constituents. Various actions may be taken to reduce or eliminate exposures to the identified hazard, to locate and study relevant human cohorts for possible carcinogenicity, and to attempt further studies to better characterize the identified potential risk to humans (8, 10, 12, 13).

In the middle 1960s and early 1970s, the National Cancer Institute (NCI) initiated an extensive carcinogenesis bioassay screening program, and published in 1976 the first of 200 Technical Reports (30, 31). The National Toxicology Program (NTP) continues these efforts, and about 200 more Technical Reports have been issued or are in press (11, 32). These data and various sub-combinations form the bases for this overview paper. The overriding aim for doing these individual and collective analyses comes from the never-ending need to more completely understand the fundamental biological principle that extrapolation of experimental and epidemiological findings among the mammalian kingdom is sound science.

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The ultimate value of these data and resultant interpretations will continue to allow more knowledgeable public, occupational, and environmental health decisions.

Materials & Methods

The chemical carcinogenesis data given in this paper come from the NCI & NTP Technical Reports series which describe the results of long-term studies in rodents (11, 32). Compared to others who compile information about carcinogenicity of chemicals, our Program is unique in that we design, conduct, and evaluate our own experiments, whereas others typically record the results and conclusions made by the various investigators reporting their data in the literature. Further, and most importantly, our data and interpretations are peer reviewed in public sessions before the Technical Reports are finalized and made ready for printing and distribution. In total, the data base used for this paper comprises 379 long-term chemical carcinogenesis studies involving 1394 individual experiments: male rats, female rats, male mice, & female mice (10).

These toxicology studies are typically carried out using both sexes of two species of rodents divided randomly into sets of 50 - 60 animals per group; a control group and two or three exposure concentrations are graduated down from a carefully selected top level (3, 5, 6, 11, 19, 33-35). The species most often used by the NTP are the inbred Fischer 344 rat and the hybrid B6C3F1 (C3H x C57B16) mouse. Duration of exposure is generally two years (or about 2/3 the life span of these rodent species).

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The data, results, evaluations, and interpretations are peer-reviewed in public meetings, and this chemical-specific information is made available in the NTP Technical Report Series (11).

Results and Interpretative Observations

Long-term chemical carcinogenesis studies. A continuing evaluation of the NCI/NTP database of long-term chemical carcinogenesis studies has resulted in a number of useful scientific findings, several of which are summarized in this section. Nearly 400 chemical-specific studies have been reported, most often involving groups of male and female rats and mice exposed to a chemical for two years (11, 30-32, 36, 37). The collated findings are evaluated, interpreted, and presented in public meetings to a non-government peer review panel of experts in chemical carcinogenesis.

Each sex-species experimental grouping is given an overall level of evidence of carcinogenicity selected from 5 categories: two positive levels (clear evidence and some evidence), one uncertain (equivocal evidence), one for no observed response (no evidence), and one for seriously flawed experi-ments (inadequate experiment) (38-41).

Roughly one-half of the chemicals induced a positive carcinogenic response in at least one of the several experiments (Table 2). Only 43 of the 313 chemicals (13.7%) studied adequately in male & female rats and in male & female mice caused cancer in all four experimental groups; and 25 (8.0%) produced cancer in one or more sites in three of the four experiments (Table 3). These findings will generally cause a chemical to

be placed into the *sufficient evidence of carcinogenicity* category (25, 26) and into the group of *substances reasonably anticipated to be carcinogens* (27). A prime value of these results permits identification of those chemicals considered most likely to be potentially carcinogenic to humans, and thus epidemiological investigations having adequate cohorts could be initiated. As an example, the carcinogenicity of 1,3-butadiene was first determined in animals, and a subsequent epidemiological investigation revealed a positive association between exposure and cancers (8).

Species correlations. In these studies similar results are observed in both species 74% of the time, and the concordance between sexes within a specie ranges from 85% (rats) to 87% (mice) (Table 4) (42). To maintain the important contribution of hormonal influence on the carcinogenesis process, we conducted a retrospective evaluation on this question: for how many of the outcomes would we have found the same (a simple qualitative 'yes' [+] or 'no' [-]) result if we had used a reduced protocol of only one-half the experimental groups? Using male rats and female mice, the answer was that 96% of the chemicals would have been correctly matched to the + or - result of the more extended experimental protocol (10). Importantly however, 12 chemicals causing single sex-species positives in either female rats (four) or in male mice (eight) would have been missed as would 2 chemicals causing carcinogenic effects in both female rats and in male mice (Table 3). For all 14 chemically associated responses there were only single target organs per sex-species (not considering here equivocal responses), and for only one chemical was the target site sex-specific (uterus).

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The major questions that arise from this retrospective evaluation centers on whether using this modified protocol in the future on the next group of 400 equally diverse chemicals would 1) permit the same percentage of 'correct' responses and 2) allow us not to miss any potential carcinogenic hazards to humans? While we contemplate answers to these questions, perhaps one could consider using a modified protocol for certain structural certainties: that is if an organization had to study a certain nitrosamine, a benzidine or anthraquinone dye, or an aniline compound, as example, then a modified protocol could be possible. For 'unknown' chemicals one would be wise to remain with the historically and currently acceptable paradigm of both sexes of two rodent species.

Historical control tumor data. Although when evaluating long-term chemical carcinogenesis experiments the most appropriate control group for comparative and interpretative purposes is always the concurrent control, there are instances in which the use of historical control information can aid an investigator in the overall evaluation of tumor incidence data. One example is for rare (or uncommonly occurring) tumors; another is for a tumor type that shows a marginally significant chemically related increase relative to concurrent controls.

The NTP historical control tumor data file is a "moving window" of studies conducted within approximately a 4-5 year time period, and is updated approximately twice a year. Thus as new data are entered, the oldest data are removed (but of course not discarded). Periodically, control tumor rates are published for informational purposes (43-45).

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The extensive NTP database is an important and frequently used source of information on historical control tumors, and in some respects differs from others in that 1) typically the tumor diagnoses and therefore incidence data have been verified by comprehensive quality assurance and pathology review procedures, 2) tumor diagnostic nomenclature and criteria across experiments and laboratories are consistent, and 3) these data come from one source (albeit several laboratories conduct the studies & record the initial tumor diagnoses) whereas other available tumor data bases often come from myriad locations. In each NTP Technical Report the relevant historical control tumor incidence data are given for all tumors showing possible chemically related effects. Most important are relatively recent studies carried out at the particular study laboratory. Investigators from industry and other governmental agencies also frequently request use of the historical control database so that they can better interpret and compare the background tumor data of their own studies.

False positive and false negative rates. In long-term chemical carcinogenesis studies approximately 30-40 different tissue or organs are examined for possible carcinogenic effects in male and female rats and mice. Under these conditions it is not unusual to find "statistically significant" changes in tumor incidence that merely reflect random variability. Our data base provides a unique opportunity to examine the pattern and frequency of site-specific tumor incidences, and to estimate the likelihood of finding statistical differences by chance alone.

For example, Haseman (46) examined the false positive rate in NTP studies by deriving a statistical decision rule that closely approximated the

complex scientific judgement process used in the evaluation of these studies. This "rule" (useful as a guideline, but should not be applied rigidly) is to declare an increase in the incidence in a commonly-occurring tumor to be biologically significant if the uppermost exposure level incidence compared to controls is significantly different at the $p<0.01$ level. For an uncommonly occurring tumor (background rate less than 1 or 2%), a $p<0.05$ increase is typically required. From this evaluation, the false positive rate associated with this decision rule was demonstrated to be no more than 7-8%, implying that the false positive rate in NTP studies is reasonably well controlled. Coupled with biological significance, possible mechanistic relevance, an overall historical perspective, and public peer review, we believe that false positives results have been minimized in our program. A more difficult public health issue that has rarely been considered is the false negative rate within these relatively insensitive assays. Perhaps this will receive more attention in the future.

The NTP database is also quite valuable for the study of statistical decision rules, particularly those that require knowledge of the incidence and variability of historical control data. Although such rules should not be rigidly applied, as noted above, these statistical methods may be useful in that they employ a formal multiple comparisons adjustment to limit the overall false positive rate. For a discussion of statistical decision rules that might be used in the evaluation of laboratory animal carcinogenicity studies, see Haseman (47).

While attention is often focused primarily on controlling false positive rates, one must remember that rodent carcinogenicity studies

with only 50-60 animals per group are relatively insensitive for detecting weak to moderate carcinogenic responses. Thus, this insensitivity must also be considered when deciding upon how to guard against false positive outcomes. For example, as mentioned below, we demonstrated that analyses based on overall (all-sites combined) rather than site-specific tumor rates would have resulted in a marked increase in the false negative rate. That is, several chemicals showing positive results evaluated using site-specific comparisons would not have been identified using total numbers of tumor-bearing animals (48). Thus, the interpretative emphasis should continue to be on site-specific effects.

Site - specific neoplasia. Using this data set we have compiled listings of chemicals having like carcinogenic target sites for each of the 34 organs or systems for which histopathology diagnoses have been recorded routinely (49). The most common tumor site is the liver (15% of all experiments; 50), followed in rank order by lung; hematopoietic system & kidneys; mammary glands; forestomach; thyroid glands; Zymbal glands; urinary bladder; and skin & uterus (Table 5)(49). These compilations are most useful for maintaining an historic perspective when evaluating the carcinogenicity of contemporary experiments. Equally important, the chemical-tumor-organ connection permits an evaluation of how well chemically induced cancers in a particular organ in one sex or species will predict or correlate with the other sex or species. Using liver cancers as an example, the overall inter-species concordance is 80%. Likewise target site predictions can be made for chemicals selected for study that may be similar to those already evaluated, thereby experimental protocols could be adjusted to allow for example more extensive pathology on preselected

target organs (i.e., serial sections of the kidney). Further from these observations, one could decide to use two strains of mice to evaluate a short-chain chlorinated aliphatic compound or to study a human carcinogen in a sex-species known to develop chemically induced tumors in the same site observed in humans. Structural classes of chemicals having a propensity for certain organs can be easily identified from these data. Sex-species responders to particular chemically induced cancers, such as the kidney in male rats, can be recognized at a glance.

Like humans, the top ten sites of cancer are somewhat different between the sexes of rodents. Yet when compared among the mammalian species in general (including humans) the sites and rankings are remarkably similar (10, 12, 20, 49).

Site specific versus total tumors. Using a sub-set of 81 carcinogenicity studies, we evaluated the issue of interpreting the tumor incidence results based on the proportion of animals with primary tumors (all sites) or the proportion of animals with malignant neoplasms (all sites) compared to analyses of site-specific carcinogenic effects (48). Less than half of the 45 chemicals considered to have induced a carcinogenic response in at least one site in one sex-species experiment showed a significant increase in the incidence of primary tumors combined (22 chemicals) or malignant tumors combined (21 chemicals). Among the 29 chemicals interpreted as not carcinogenic based on site-specific effects, two showed significant increases in overall tumor incidence. Thus, consideration of overall tumors rates seemingly masked several important site-specific effects, while identifying only two additional chemicals apparently "missed" by

using site-specific analyses. These latter two "carcinogenic responses" were not considered to be biological relevant (48).

In our opinion, at least two major problems are associated with an evaluation based on overall (all sites) tumor rates: 1) combining tumor types of varying morphologies and topographies is biologically unsound and scientifically questionable, and 2) pooling various tumor types reduces study sensitivity for detecting chemically related increases in site-specific tumor incidences. Further most national and international guidelines for studying chemicals for carcinogenicity in rodents (or in humans) emphasize site-specific effects (6). Thus, despite purported advantages of analyses based on overall tumor rates (e.g., simplicity; reducing occurrence of false positive and perhaps false negative results), primary emphasis should continue to be placed on site-specific analyses.

Benign tumors. The importance and relevance of benign neoplasia in evaluating the carcinogenic potential of a particular chemical remains a area of active discussion, even though few if any chemicals only cause benign neoplasia. To explore this issue we evaluated the long-term carcinogenesis results for the 143 chemicals reported by the NTP: 81 of these showed neoplastic responses in one or more of the 524 species-gender experiments (51). Of these 81 positive studies, 60 (74%) were considered positive based on malignant neoplasia; 16 (20%) were positive due primarily to benign neoplasia, but had supporting evidence of malignant neoplasia in the same organ/tissue; and 5 (6%) were positive based on benign neoplasia alone.

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Thus, only 5 of the 143 chemicals evaluated induced benign neoplasia alone (3.5%), and those observed benign neoplasms are known to progress to malignancy (51, 52). Accordingly. we consider chemically induced benign neoplasia to be an important indicator of a chemical's carcinogenic potential in rodents, and believe these should continue to be made an integral part of the overall weight-of-the-evidence evaluation process for identifying potential human health hazards.

Sources of variability. A major advantage of an extensive historical control database is that it allows an examination of trends in tumor incidence (and other potentially changeable biological parameters) over time and within & between laboratories, thereby permitting the identification of important sources of variability. This information is useful in the design of long-term chemical carcinogenesis studies, and may allow the investigator to address what would otherwise be confounding factors in the evaluation and interpretation of the data. Potential sources of variability include the animal room environment, longevity and survival patterns of animals, dietary factors, and differences related to pathology (4, 53).

For example, we learned that the Fischer 344 rats used in our program have shown a steady increase in the background rate of certain commonly occurring neoplasms (e.g., leukemia, and for certain glandular organs such as pituitary, mammary, thyroid, and adrenal glands), together with a decreased survival and an increased body weight (54). A review of slides from early and relatively recent studies identified possible reasons for these shifts. [note: every slide from every study is kept in a

security archives that allows these historical comparisons, and also permits others to view slides to verify our diagnoses; further for at least ten years after a study is reported, the tissues and remaining organs from each animal are retained in case new slides are needed]. The possibilities include 1) changes in histopathology diagnostic criteria over time, (2) changes in the amount of tissue examined, (3) intra- and inter-laboratory variability, and (4) dietary factors; i.e., the incidence of certain neoplasms (particularly endocrine system and mammary gland tumors) are known to be positively correlated with body weight; differences in protein content influence kidney lesions in the rat.

A similar investigation in B6C3F1 mice (55) did not reveal the same striking time-related changes as seen in rats. The only notable change was an increased incidence of pituitary gland neoplasms in female mice in the more recent studies, which may have been associated with increases in the amount of pituitary gland tissue examined. Additional investigation revealed that liver tumor incidence in mice (particularly in females) was highly correlated with body weight (53). Another factor that might have influenced body weight (thereby perhaps indirectly affecting liver tumor incidence) was a program change in protocol made in 1984 that resulted in mice being housed individually rather than in groups (56).

Our investigation of sources of variability will likely lead to certain other suggested changes in experimental protocol or design. For example, an alternative diet containing (among other modifications) less protein and more fiber is being studied and will probably be adopted in the near future. This should improve survival and reduce tumor rates by limiting

the weight gain of the animals, as well as reducing the amount and severity of protein-associated lesions in the rodent kidney. We have also gained a better understanding of the value and limitations of historical control data in the overall assessment of tumor incidence (mentioned earlier).

Routes of exposure. The optimum route of exposure for chemical carcinogenicity experiments should be one that most closely mimics the major human exposure route; this is not always possible, but the attempt should be made. Historically, chemicals have been administered by a single route of exposure: usually in the feed (60 % of the time for the data base of the nearly 400 studies we evaluated), but also by oral intubation (27 %), by inhalation (5 %), by application to the skin (3 %), by intraperitoneal injection (3 %), or in drinking water (2 %) (10). Intubation is generally used for administering unstable, volatile, or reactive chemicals. Microencapsulation is a newly developed technique for administering these agents in feed, and will generally be used to replace the gavage technique (57, 58). This data base permits an evaluation of the possible effects of route of administration on carcinogenic response.

Since oral gavage frequently employs corn oil as the vehicle, a question of particular interest was whether or not corn oil affects tumor incidence. To answer the question, a comparison was made of tumor rates in untreated (or basal diet) controls and corn oil gavage controls, taking into account any inter-laboratory variability and time-related trends. Haseman et al., (44) found that corn oil has no apparent effect on tumor incidence in male and female B6C3F1 mice or in female F344 rats. In male

F344 rats, however, corn oil was associated with a decreased incidence of mononuclear cell leukemia from approximately 27% to 14% and an increased incidence of acinar cell tumors of the pancreas from approximately 0.2% to 4.4%. These changes appeared related to corn oil rather than to the gavage technique itself, since controls from gavage studies using water as the vehicle showed a tumor response for leukemia and pancreatic acinar cell tumors similar to that observed for untreated basal diet controls. Interestingly, acinar call tumors of the pancreas were not affected uniformly, since contemporary controls administered corn oil from the identical batch did not show similar increases. Further, if the two control groups with the largest average body weights are removed from the analysis the difference for pancreatic tumors between basal and corn oil controls is no longer statistically significant.

A long-term study was designed to evaluate the influence of various levels of corn oil and of select other oils (sesame seed, sunflower seed, and tricaprylin) on the carcinogenic potential in F344 rats. Preliminary results strongly confirm both of the effects noted above. Our increased understanding of the impact (or in most cases, the lack of impact) of corn oil gavage on tumor incidence increases our confidence in the interpretation of studies using corn oil as the vehicle (and gavage as the route of administration). These results may also have implications concerning possible dietary changes to increase the survival of F344 rats (leukemia is the leading cause of death in these animals).

Predicting carcinogenicity with genetic toxicity assays. Four widely used in vitro genetic toxicity assays were evaluated to determine their

individual & collective concordance with the carcinogenicity of a number of chemicals. The end-points and short term assays were mutagenesis in Salmonella *typhimurium* and in mouse lymphoma cells and chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells. The original investigation with 73 chemicals (59) has been followed up with an additional 41 chemicals (60-63).

Results from both studies were similar, and are summarized in Table 6 for the combined 114 chemicals. Salmonella performed best among the four short term tests, achieving a 66% (75/114) concordance, an 89% (32/36) positive predictivity, and a 55% (43/78) negative predictivity of carcinogenicity. Chromosome aberrations also showed a significant association with rodent carcinogenicity, but none was observed for the sister chromatid exchange or mouse lymphoma assays.

Although the performance of individual short term tests was of interest, the primary focus of the investigation was whether the performance of individual short term tests for predicting carcinogenicity could be improved by utilizing a battery of two or more tests. Importantly, these data demonstrate, at least for these assays and for this particular 114 chemical data set, that there was no evidence of complementarity among the four short-term tests, and no combination constructed from these assays improved substantially the performance over the Salmonella multi-strain assay alone.

These results led our program to adopt Salmonella as the primary in vitro short term assay now used to identify mutagens. Use of the three

other short term tests noted above has been curtailed. The NTP is now evaluating in vivo tests for chromosome aberrations and micronuclei as a possible means of predicting or confirming in vitro mutagenicity and in vivo carcinogenicity.

Chemical toxicity and carcinogenicity. The possible interrelationships between toxicity (histopathological observations), genotoxicity (i.e., Salmonella), and chemical carcinogenicity in laboratory rodents was investigated using information obtained and reported from two-year studies involving 99 chemicals (64). Although target organ toxicity and carcinogenicity occurred together in some studies (particularly for the nasal cavity and kidney), many chemicals produced carcinogenic effects in organs showing no evidence of toxicity, and conversely, toxicity was frequently observed in organs showing no chemically related carcinogenic effects. The data suggested that only seven of the 53 chemicals causing cancer in at least one organ of one sex of one species exhibited the types of target organ toxicity that might have been the cause of the observed carcinogenic effect.

Of the 127 positive sex-species experiments that utilized multiple doses, 54 (43%) produced statistically significant ($p<0.05$) increases in tumor incidence only at the top dose. However, in 78% (42/54) of these experiments the incidences of site-specific tumors in the lower-dose groups were also numerically elevated relative to controls, and were considered to be biologically relevant. Thus, only 9% (12/127) of the carcinogenic effects appeared to reflect a "high dose only" response. Moreover, no apparent difference in mutagenicity as measured by the

Salmonella assay was observed between "high dose only" carcinogens and the entire set of chemical carcinogens. In a subsequent correlational analyses of an additional 31 chemicals, the results substantiate those summarized above (65).

Although cell proliferation and its possible impact on carcinogenic response were not assessed directly, these results nevertheless suggest that only a relatively small percentage of chemical carcinogens can be identified as possibly acting through an indirect or secondary mechanism. Thus, any attempt to develop generic regulatory policy for chemical carcinogens based solely on the use of two-year rodent studies to differentiate between "primary" and "secondary" carcinogens will likely be ineffective and/or inaccurate unless specifically backed by relevant mechanistic studies (64).

Melnick (66) evaluated the available information on the influence of cell proliferation (or mitogenesis) on the carcinogenic process in rodents. Although cell proliferation has long been known to have a role in chemically induced tumor development, Melnick (66) concluded that a correspondence between sustained cellular proliferation and carcinogenic response has not been demonstrated adequately to support the hypothesis that chemically induced cell proliferation causes liver cancer. Further, the proliferative response resulting from exposure to many "non-genotoxic" carcinogens is not at all well sustained, yet the elicitation of a carcinogenic response by these chemicals often requires a prolonged exposure duration. Thus, much more research needs to be accomplished before any basic axioms about this important issue can be established (67).

Deductive Conclusions

Long-term chemical carcinogenesis studies must be properly designed, adequately conducted and monitored, subjected to multi-tier pathology diagnoses review, and objectively evaluated and interpreted. In addition to having these essential scientific characteristics, NTP studies undergo a unique peer review process that is conducted in open and public sessions. In our view, this makes the findings and results from these long-term chemical carcinogenesis experiments even more useful and valuable for identifying potential carcinogenic hazards to public health. In addition to alerting us to possibly new chemical concerns and substantiating epidemiological observations, the collective data are valuable and useful for a myriad of other scientific purposes. Some have been given in this paper. Others used or developed by us have been published or are at various stages of being published . In one manner or another most if not all allow us to bring further knowledge to and support for increasing confidence in extrapolating results from animals to humans. The knowledge extends from the clear awareness that all of the chemicals known to induce cancer in humans also cause cancer in adequate long-term animal studies (8, 10, 12) to the increasing awareness that oncogene activation patterns in human and animal tumors are strikingly similar and represent evolutionary conservation (e.g., 68-70).

In our opinion, the data from these studies together with our experience over the years permit us to make the following conclusions (not given in any particular rank order):

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1. Carcinogenicity findings from experiments in laboratory animals are logical and scientifically reasonable for identifying and predicting potential carcinogenic effects to humans.

2. Most chemicals are not carcinogenic.

3. Chemicals considered to be carcinogens may differ significantly with regard to the strength of the induced carcinogenic response, and for practical purposes can be divided into qualitative groups based on these empirical indicators of "potency": i.e., exposure concentrations, number of positive experiments, multiplicity of tumor sites, numbers of tumors per site, common versus uncommon tumors, site correspondence across sexes and species, magnitude of incidence rates, dose response patterns, latency, metastases, preneoplastic lesions (see Table 3 for example).

4. Malignant and benign tumors of the same site and/or type should be combined for interpretation. However, combining biologically unrelated tumors for statistical evaluation should be avoided.

5. Benign tumors induced by chemicals are relevant for judging carcinogenicity; few chemicals produce only benign tumors.

6. Site-specific tumor analyses should be used for determining carcinogenic effects.

7. Liver tumors are appropriate and valid for identifying chemical carcinogens and for determining potential cancer hazards to humans.

8. Cellular toxicity and resultant sequelae are not uniformly associated with chemically induced carcinogenicity. Many chemicals produce carcinogenic responses in organs showing no evidence of toxicity, and conversely toxicity frequently occurs in organs exhibiting no chemically related carcinogenic effects.

9. Most chemical carcinogens do not cause cancer only at the highest exposure used.

10. Mechanisms of action are not yet considered to be understood well enough to become significant factors in the evaluations of chemically induced carcinogenesis, but certainly all relevant biologic information (oncogene activation and tumor suppressor genes, pharmacology and pharmacokinetics, hormonal influences, DNA damage and repair, among others) should be considered when deciding a single level of evidence of carcinogenicity.

11. Cell replication (proliferation, mitogenesis) is an important factor in chemical carcinogenesis, yet scientific data do not sustain the hypothesis that enhanced cellular proliferation in a particular organ associates consistently with an increased induction of neoplasia.

12. The route of exposure has little or no effect on the inherent carcinogenicity of a chemical, although the specific sites of carcinogenicity may vary with the route of administration used.

13. Corn oil has little or no influence on whether or not a chemical is or is not a carcinogen.

14. Inter-species concordance in carcinogenic response is good, yet at least two species should in most cases continue to be used for identifying chemical carcinogens.

15. Salmonella mutagenicity has a relatively low concordance with rodent carcinogenicity.

16. Cage location and related factors have no important impact on chemical carcinogenicity.

17. Chemical structure in general does not allow for cancer prediction in rodents or humans.

18. False positive rates associated with evaluating chemically induced carcinogenic effects in rodents are quite low. Unfortunately, little is known about the more public health important false negative rate.

In conclusion, much has been learned from these largely 'observational' studies that permits us to make the above statements, all of which are based on the data and facts garnered from the extensive chemical carcinogenesis data base developed in sequence by the National Cancer Institute and by the National Toxicology Program. This data base is unique in the sense that not only is it the single largest available collection of program-generated chemical carcinogenesis facts and figures, but it is perhaps the only system containing carcinogenesis (and other) data obtained from experiments that have been conducted and evaluated using a reasonably consistent core of design protocols, histopathological diagnostic criteria, and interpretational guidelines (all of which have been established and honed by us over the years to keep reasonable pace with new and relevant scientific advancements).

Another unique character of our data collection and complementary pathology archives of tissue specimens and histopathology slides is that we make the original data & slides available to others to use in any way they wish. Not only that but we invite individuals and organizations to study and scrutinize the 'raw' data and tissue specimens & sections that represent the actual experimentally generated information sources of the data base.

Staff consistency and balanced scientific standards together with a public peer review process and a keen awareness of the public health ethos must also be considered unique, desirable, and supportive of the value of this particular data collection.

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Table 1
RISK ASSESSMENT -- Comparative Definitions

National Research Council National Academy of Sciences 1983	Task Force on Health Risk Assessment 1985
1) **Hazard identification:** The determination of whether a particular chemical is or is not causally linked to particular [adverse] health effects.	1) **Hazard identification:** The qualitative indication that a substance/condition may adversely affect human health.
2) **Dose-response assessment:** The determination of the relation between the magnitude of exposure and the probability of occurrence of the [adverse] health effects in question.	2) **Hazard characterization:** The qualitative and quantitative evaluation of the nature of the adverse effects, including their expression as functions of the amount of exposure (dose).
3) **Exposure assessment:** The determination of the extent of human exposure before or after application of regulatory controls.	3) **Exposure characterization:** The qualitative and quantitative evaluation of the degree of human exposure likely to occur.
4) **Risk characterization.** The description of the nature and often the magnitude of human risk, including attendant uncertainty	4) **Risk determination:** The integration of these steps into a scientific determination of the level of risk as a basis for policy consideration

Table 2

Summary results from 379 carcinogenicity studies in rodents

Study Result	By Experiment					By Chemical		
	Male Rats	Female Rats	Male Mice	Female Mice	Total	Rats	Mice	Overall
Positive	127	107	102	123	459	146	137	198
Equivocal	41	36	35	20	132	48	35	53
No evidence	183	211	204	205	803	162	178	128
Totals	351	354	341	348	1394	356	350	379

Taken from reference 49.

Table 3

Carcinogenicity results for 313 chemical studies in rodents•

Proportion of Positive Studies	Male Rats	Female Rats	Male Mice	Female Mice	Number of Studies With These Results		%
4/4	+	+	+	+	43		
					Subtotals	43	13.7
3/4	+	+	+	-	1		
	+	+	-	+	11		
	+	-	+	+	7		
	-	+	+	+	6		
					Subtotals	25	8.0
2/4	+	+	-	-	19		
	+	-	+	-	2		
	+	-	-	+	7		
	-	+	+	-	2		
	-	+	-	+	3		
	-	-	+	+	23		
					Subtotals	56	17.9
1/4	+	-	-	-	17		
	-	+	-	-	4		
	-	-	+	-	9		
	-	-	-	+	8		
					Subtotals	38	12.1
0/4	-	-	-	-	151		
					Subtotals	151	48.2
Totals						313	100

• Includes only those long-term studies considered adequate in all four sex-species experiments. Note: Equivocal evidence (or marginal) results are considered to be between a positive response and no evidence of a response; these results were placed into the no evidence category. Taken from reference 49.

Table 4

Intra- and inter-species concordance in carcinogenic responses in 379 chemical carcinogenicity studies in rodents

Comparison	Observed Response ++	+-	-+	--	% Concordant (++ or --) Responses
Male rats vs female rats	88	38	16	207	84.5 (295/349)
Male rats vs male mice	54	54	40	169	70.3 (223/317)
Male rats vs female mice	70	41	41	169	74.5 (239/321)
Female rats vs male mice	53	38	42	185	74.8 (239/318)
Female rats vs female mice	65	28	47	183	76.8 (248/323)
Male mice vs female mice	88	14	31	206	86.7 (294/339)
Rats vs. mice	82	40	40	151	74.4 (233/313)

Note: Equivocal evidence (or marginal) results are considered to be between a positive response and no evidence of a response; these results were placed into the no evidence category.
Taken from reference 49.

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Table 5. Organs/systems most frequently observed in RATS & MICE with chemically induced site-specific carcinogenic effects from 379 long-term chemical carcinogenesis studies.

Rats		Mice		Rats and Mice	
Site	No. Positive Studies	Site	No. Positive Studies	Site	No. Positive Studies
1. Liver	44	Liver	86	Liver	104
2. Kidney	28	Lung	23	Lung	30
3. Mammary Glands	22	Forestomach	17	Hematopoietic System	29
4. Zymbal Glands	18	Hematopoietic System	15	Kidney	29
5. Thyroid Glands	17	Circulatory System	11	Mammary Glands	27
6. Hematopoietic System	17	Thyroid Glands	9	Forestomach	23
7. Forestomach	15	Mammary Glands	9	Thyroid Glands	19
8. Skin	15	Ovary	8	Zymbal Glands	18
9. Urinary Bladder	14	Harderian Glands	7	Urinary Bladder	16
10. Clitoral glands	10	Uterus	7	Uterus & Skin (@)	15

note: Table taken & updated from reference 10.

Table 6. Pattern of short term in vitro test results and long-term in vivo carcinogenesis results for 114 chemicals

	Short term in vitro test and results				Rodent carcinogenicity results			
	SAL	ABS	SCE	MLA	Pos		Neg	
4/4	+	+	+	+	22		3	
					Subtotals	22		3
3/4	+	+	+	-	0		0	
	+	+	-	+	2		0	
	+	-	+	+	4		1	
	-	+	+	+	8		6	
					Subtotals	14		7
2/4	+	+	-	-	0		0	
	+	-	+	-	0		0	
	+	-	-	+	2		0	
	-	+	+	-	2		3	
	-	+	-	+	0		0	
	-	-	+	+	7		12	
					Subtotals	11		15
1/4	+	-	-	-	2		0	
	-	+	-	-	1		1	
	-	-	+	-	3		1	
	-	-	-	+	3		6	
					Subtotals	9		8
0/4	-	-	-	-	11		14	
					Subtotals	11		14
				Totals		67		47

SAL: Salmonella typhimurium; ABS: Chromosome aberrations (CHO cells); SCE: Sister chromatid exchanges (CHO cells); MLA: Mouse lymphoma

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17134

2225 18.269

File T23.14-25-1
Chg. 1219A
Rec'd 3-15-45
Fin'd 8-8-45
Work By C. Geisel

Subject TOXICITY OF 2,4,5-TRICHLOROPHENOXY ACETIC ACID.

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

To Tech. Service & Develop Check C. W. Adams 8-28-45
W. W. Allen
W. R. Veazey

Rept. By T. K. Rowe 8-25-45

Problem -

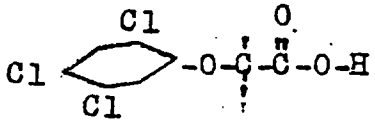
What are the handling hazards to be associated with 2,4,5-trichlorophenoxy acetic acid?

Material -

Name - 2,4,5-trichlorophenoxy acetic acid - K4568-2

Formula -

Structural -



Empirical - $C_8H_5O_3Cl_3$

Source - Organic Research Lab. - L. Begin

Ref. - #410-5-258

Experimental Results -

Acute Oral - Weighed doses of the acid were emulsified in 5-10% gum arabic solution and fed to cavies in single oral doses by means of a stomach tube. The material as the sodium salt, adjusted to pH = 10, was also fed. The results are given in Table I

Table I

The Acute Oral Toxicity of 2,4,5-Trichlorophenoxy Acetic acid and its Sodium Salt for Cavies.

Material	100% Survival Dose g./kg.	100% Lethal Dose g./kg.
Acid	0.3	1.0
Salt - pH = 10	0.3	0.5

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MOW 032715

These figures indicate that the subject material is moderately toxic when given in single oral doses. No information upon the effect of repeated administrations was obtained.

It was noted in this acute oral work that the animals did not exhibit the nervous symptoms caused by 2,4-dichlorophenoxy acetic acid, sodium salt. The animals fed large doses of this latter material exhibited paralysis of the posterior portion of their bodies.

Skin Irritation - The acid as a 10% solution in butyl carbitol acetate was applied 10 times in 11 days to the ear and shaven belly of a rabbit. A very slight irritation developed on the ear and a slight to moderate irritation appeared on the belly.

A 1% aqueous solution of the sodium salt failed to produce any significant irritation on the ear even after 20 exposures in 27 days; similar exposure on the belly resulted in a very slight simple irritation.

Conclusions -

2,4,5-Trichlorophenoxy acetic acid has a moderate acute oral toxicity and is slightly irritating to the skin of rabbits.

We conclude that excessive exposure to the dust of either the free acid or the salt would be likely to cause skin irritation as would exposure to concentrated solutions for prolonged periods of time. Exposure to dilute solutions such as those used in practical application would not be expected to cause trouble except among those who persist in spraying themselves or who do not take the necessary precautions to prevent prolonged contact with the material.

Reasonable handling precautions which will prevent ingestion and prolonged skin contact with the material will suffice to prevent serious trouble.

jf-5 copies.

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Test on K4568-2 (Trichlorophenoxyacetic acid)

Acute oral toxicity. ~~Rats~~ Cavy Prob. T 23.14-23-1

Date	Animal #	Weight kg.	Dose gm/kg	Dose gm.	Dose cc.	Wt. 3/23	Wt. 3/27	Wt. 3/30	Remarks
3-21-45	26307	570	0.1	.057		595	627	647	
	26607	467	0.1	.047		491	538	560	Killed 3-30-45
	16707	534	0.3	.160		558	596	618	
	18707	.670	0.3	.201		631	667	685	
	16807	.504	1.0	.504		Dead 3-22-45			
	18307	.520	1.0	.520		Dead 3-22-45			
	18507	.555	3.0	1.665		Dead 3-21-45			
Cage 82	30107	.637	3.0	1.911		Dead 3-21-45			
	17707	.667	10.0	6.67		Died within 1 hour 3-21-45			
	40507	.577	10.0	5.77		Died within 1 hour 3-21-45			
	X signed & finished 3-30-45 CL								

1219-43-5C-10-43

17137

Feed on Na Salt
pH adjusted to 10

BIOCHEMICAL RESEARCH LABORATORY

DOW 032717

Test on K4564-2 (Trichlorophenoxyacetic Acid) (Salt in K45S

Acute oral toxicity. ~~Rat.~~ Cavy 07 Prob. T 23.14-23-1

(1 c c = 0.01 gm) in H_2O.

Date	Animal #	Weight kg.	Dose gm/kg	Dose gm.	Dose cc	Remarks	4/3	4/6	4/
3-30-45	224	510	0.1	.0510	5.10		528	550	56
	218	520	0.1	.0520	5.20	Fed in single feeding 9:30 AM. 10:45	580	595	60
	225	521	0.2	.1042	10.42	— 6 c.c.	442	590	599 61
						Fed in two feedings 7 c.c.			
	214	558	0.2	.1116	11.16	—	416	590	604 62
72	205	590	0.3	.1770	17.70	10 c.c.	7.70	592	627 6
	204	614	0.3	.1842	18.42	Fed in two feedings 10 c.c.	842	645	652 69
	203	535	0.5	.2675	2675	Fed in two feedings 10 c.c.	10. cc	6.75	Dead 3-3
	207	516	0.5	.2580	25.80	Fed in two feedings 10 c.c.	10 c.c.	5.80	Dead 3-3
	222	568	1.0	.568	568	Fed in two feedings 10 c.c.			Dead 3-30-45
	215	571	1.0	.571	57.1	Fed in two feedings 10 c.c.	10 c.c.	10	10 10 Dead 3-30-45

Animals here did not seem to respond as did those fed the dichloro compound. No rigidity in the hind quarters was apparent although the rectal temperatures were about 1° low. — up

X signed + finished 4-20-45 CS

1219-43-5C-642

17138

Feed as Na Salt
pH adjusted to 10

UCW32718

BIOCHEMICAL RESEARCH LABORATORY

Test on 1145-68-2 (Trichlorophenoxy Acetic Acid)

Acute oral toxicity. ~~Rats~~ Cavy ♂ Prob. T 23.14-23-1

(1 cc = 0.01 gm in H_2O)

Date	Animal #	Weight kg.	Dose gm/kg	Dose gm.	Dose cc	Remarks	wt. 4/13	4/17	4/20
4-11-45	207	406	0.3	.1218	12.18	5.00 7.18 1:00 PM	404	430	433
	60	357	0.3	.1071	10.71	5.00 5.71	368	382	391
	212	330	0.3	.099	9.90	9.90 — 11:30 AM	347	380	384
	225	362	0.5	.181	18.1	10.00 8.10	318	Dead 4-16-45	
	267	350	0.5	.175	17.5	10.00 7.50	Dead 4-13-45		
	67	399	0.5	.1995	19.95	10.00 9.95	344	Dead 4-16-45	
	X	signed & finished 4-20-45 CH							

1219-43-5C-642

17139

10% in N.C.Q.

BIOCHEMICAL RESEARCH LABORATORY

Test on K4568-2 (Dichlorophenoxy Acetic Acid).

Skin Irritation — No. of Applications up to 10

~~Quantitative~~ — Rt. Ear — ~~Abdomen~~

Apply 5 times a week.

Rabbit # 9-17207 Cage # 9 Prob. T23.14-23-1

Date	Day #	Exp. #	Reaction
3-19-45	0	1	1.99 Kg. .76 mm
3-20-45	1	2	Nothing
3-21-45	2	3	"
3-22-45	3	4	"
3-23-45	4	5	"
3-26-45	7	6	Follicles v. slightly enlarged. 96 mm.
3-27-45	8	7	Rt. epilation
3-28-45	9	8	Same and sl. hyperemia
3-29-45	10	9	Same. "
3-30-45	11	10	Loss of hair, hyperemia, follicles sl. enlarged.
4-2-45	14	X	1.02 mm Same.
4-4-45	16		Sl hyperemia + sl. enlarged follicles
4-6-45	18		Same + sl loss of hair
4-9-45	21		1.02 Rt. hyperemia, enlarged follicles and loss of hair
	X signed & Finished 4-9-45 CQ		

1219-20-1M-145

17140

10% in D.C.a

BIOCHEMICAL RESEARCH LABORATORY

Test on K4568-2

Skin Irritation — No. of Applications 4 to 10

~~Quantitative~~ — ~~Eye~~ — Abdomen

Bandage on 5 times a week.

Rabbit # 9-17207 Cage # 9 Prob. T 23.14-23-1

Date	Day #	Exp. #	Reaction
3-19-45	0	1	1.99 Kg. .78 mm (2X)
3-20-45	1	2	Slight hyperemia and edema
3-21-45	2	3	Moderate hyperemia + el edema.
3-22-45	3	4	Severe hyperemia, moderate slicting and edema
3-23-45	4	5	Same.
3-26-45	7	6	1.94 Kg. 140 mm (2X)
3-27-45	8	7	Sl edema, hyperemia. Eschar scab
3-28-45	9	8	1.92 Sl edema and sl hyperemia exfoliation
3-29-45	10	9	Marked exfoliation, v. sl edema, v. sl. hyperemia.
3-30-45	11	10	Same
4-2-45	14	X	1.97 Kg. 220 mm (2X) Same + scaliness
4-4-45	16		Sl. hyperemia
4-6-45	18		Sl scar remains
	X signed & finished 4-6-45 CH		

1219-20-1M-145

17141

1% in H_2O as Na. Salt

BIOCHEMICAL RESEARCH LABORATORY

Test on K4568-2 (Trichloroethoxy Acetic Acid)

Skin Irritation — No. of Applications up to 20

~~Quantitative~~ — Ear — ~~Abdomen~~

Apply 5 times a week to left ear

Rabbit # 9-190 Of — Cage # 38 — Prob. T23.14-23-1

Date	Day #	Exp. #	Reaction
3-29-45	0	1	.63 mm
3-30-45	1	2	Nothing
4-2-45	4	3	" .63 mm
4-3-45	5	4	"
4-4-45	6	5	"
4-5-45	7	6	"
4-6-45	8	7	"
4-9-45	11	8	" .62 mm.
4-10-45	12	9	"
4-11-45	13	10	"
4-12-45	14	11	"
4-13-45	15	12	"
4-16-45	18	13	.62 mm Nothing
4-17-45	19	14	"
4-18-45	20	15	V. sl. exfoliation
4-19-45	21	16	Same
4-20-45	22	17	Nothing
4-23-45	25	18	Same Nothing
4-24-45	26	19	"
4-25-45	27	20	"
4-26-45	28	X	"
			+ U.K. Rowe
			4-26-45

1219-20-1M-145

BIOCHEMICAL RESEARCH LABORATORY

as Na. Salt.

Test on K9568-2 (Trichloroglycyl Acetic Acid.)

Skin Irritation — No. of Applications 4 to 20

~~Quantitative~~ — Ear — Abdomen

Bandage on 5 time a week.

Rabbit # 9-190 O+ Cage # 38 Prob. T 23.14-23-1

Date	Day #	Exp. #	Reaction
3-29-45	0	1	2.32 Kg. 1.02 mm (2X)
3-30-45	1	2	V. sl. hyperemia
4-2-45	4	3	2.33 Kg. 1.02 mm (2X) sl hyperemia
			and sl exfoliation
4-3-45	5	4	V. sl. exfoliation
4-4-45	6	5	V. sl. hyperemia
4-5-45	7	6	sl exfoliation & sl hyperemia
4-6-45	8	7	Same "
4-9-45	11	8	2.58 Kg. 1.60 mm (2X) Same.
4-10-45	12	9	sl. exfoliation & sl. hyperemia
4-11-45	13	10	Same "
4-12-45	14	11	Same
4-13-45	15	12	Same
4-16-45	18	13	2.94 Kg. sl. exfoliation
4-17-45	19	14	Same
4-18-45	20	15	Same
4-19-45	21	16	Same
4-20-45	22	17	sl hyperemia
4-23-45	25	18	2.95 Kg V. sl hyperemia
4-24-45	26	19	sl hyperemia
4-25-45	27	20	V. sl. "
4-26-45	28	X	3.04 Kg. Nothing
		&	O.T. Rem
			4-26-45.

1219-20-1M-145

1714

BIOCHEMICAL RESEARCH LABORATORY

as Na. Salt.

Test on K4568-2 (Trichloroglycolic Acetic Acid.)

Skin Irritation — No. of Applications 15 to 20

~~Quantitative~~ — Ear — Abdomen

Bandage on 5 times a week.

Rabbit # 9-1904 Cage # 38 Prob. T 23.14-23-1

Date	Day #	Exp. #	Reaction
3-29-45	0	1	2.32 Kg. 1.02 mm (2X)
3-30-45	1	2	V. sl. hyperemia
4-2-45	4	3	2.33 Kg. 1.02 mm (2X) sl hyperemia and sl exfoliation
4-3-45	5	4	V. sl. exfoliation
4-4-45	6	5	V. sl. hyperemia
4-5-45	7	6	sl. exfoliation & sl hyperemia
4-6-45	8	7	Same "
4-9-45	11	8	2.58 Kg. 1.60 mm (2X) Same
4-10-45	12	9	sl. exfoliation & sl. hyperemia
4-11-45	13	10	Same "
4-12-45	14	11	Same
4-13-45	15	12	Same
4-16-45	18	13	2.94 Kg. sl. exfoliation
4-17-45	19	14	Same
4-18-45	20	15	Same
4-19-45	21	16	Same
4-20-45	22	17	sl hyperemia
4-23-45	25	18	2.95 Kg V. sl. hyperemia
4-24-45	26	19	sl hyperemia
4-25-45	27	20	V sl. " "
4-26-45	28	X	3.04 Kg. Natural
		&	D.T. Rem
			4-26-45.

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Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols

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Epidemiological studies have revealed an increased risk of cancer, notably soft-tissue sarcomas and non-Hodgkin's lymphomas, in people occupationally exposed to chlorophenoxy herbicides, including those contaminated by 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD). We report here a historical cohort study of mortality in an international register of 18 910 production workers or sprayers from ten countries.

Exposure was reconstructed through questionnaires, factory or spraying records, and job histories. Cause-specific national death rates were used as reference. No excess was observed in all-cause mortality, for all neoplasms, for the most common epithelial cancers, or for lymphomas. A statistically non-significant two-fold excess risk, based on 4 observed deaths, was noted for soft-tissue sarcoma with a standardised mortality ratio (SMR) of 196 and 95% confidence interval (CI) 53–502; this was concentrated as a six-fold statistically significant excess, occurring 10–19 years from first exposure in the cohort as a whole (SMR=606 [165–1552]) and, for the same time period, as a nine-fold excess among sprayers (SMR=882 [182–2579]). Risks appeared to be increased for cancers of the testicle, thyroid, other endocrine glands, and nose and nasal cavity, based on small numbers of deaths.

The excess of soft-tissue sarcomas among sprayers is compatible with a causal role of chlorophenoxy herbicides but the excess does not seem to be specifically associated with those herbicides probably contaminated by TCDD.

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Introduction

Chlorophenoxy herbicides have been used extensively since the mid-1950s for control of weeds and for removing unwanted brush on non-crop land.[1] In the 1960s an equal mixture of 2,4-dichloro and 2,4,5-trichloro phenoxyacetic acids (agent orange) was heavily used in South Vietnam and Cambodia for defoliation by the US armed forces. Since 1969 in several industrialised countries, production and use of some compounds, and especially of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its derivatives have been reduced or banned. Chlorinated phenols are

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intermediates in the production of these chlorophenoxy herbicides and are also used directly for wood preservation. Both groups of compounds may be contaminated during the production process with polychlorinated dioxins and furans, including tetrachlorodibenzo-*p*-dioxin (dioxin, TCDD), which is a widespread contaminant of the general environment.[1]

Studies of cancer risks have revealed excesses for soft-tissue sarcoma and non-Hodgkin's lymphoma in populations exposed to chlorophenoxy herbicides, chlorinated phenols, dioxins, and furans during manufacture and spraying or after accidents.[2-26] In 1987 an International Agency for Research on Cancer (IARC) working group concluded that there was "limited" evidence of human carcinogenicity for chlorophenoxy herbicides and chlorinated phenols.[27] A recent paper,[16] focusing on exposure in chemical plants to "dioxin", reported excesses for cancer of the respiratory tract and soft-tissue sarcoma, but could not exclude the contribution of smoking and other exposures in the workplace. We present here the first detailed mortality analysis of a large international cohort of workers (the International Register of Workers Exposed to Phenoxy Herbicides and their Contaminants) set up by the IARC in association with the US National Institute of Environmental Health Sciences (NIEHS). Results for some cohorts in the register have been reported earlier[4,8,9,13] but for different follow-up periods.

Material and methods

Study population

The register incorporates information on 17 372 male workers, 1537 female workers, and 1 of unknown sex, distributed among twenty cohorts from ten countries (table I). Since publication of the register population[28] minor corrections have led to the exclusion of 62 workers found to be ineligible. Workers from one British company which both produced and sprayed herbicides have been separated here into two cohorts (14 and 20).

The register includes workers ever employed in production or spraying, except in the cohorts from Australia, Canada, and New Zealand, in which minimum employment periods of 1 year, 6 months, and 1 month, respectively, were specified. Eligibility of cohorts depended on the completeness at company level of records identifying workers and on the ability to ensure tracing rates of 95% or more. Follow-up for mortality was based either on computerised national record systems or on active follow-up procedures. Additional information on cases of soft-tissue sarcoma and non-Hodgkin's lymphoma cases was sought from medical records and cancer registries. Denmark, New Zealand, Finland, and Sweden provided incidence data from population-based cancer registries. Person-years at risk were calculated from 1955 onwards since only from that year were cancer-specific mortality rates available for all participating countries. Excluded from the analysis were 220 workers who either died or were lost to follow-up before 1955, 105 workers with unknown year of first exposure, 131 with unknown year of birth, 1 with unknown sex, and 63 with other missing information. The 18 390 workers included comprise 16 863 males and 1527 females, and 307 488 person-years at risk were accumulated, with an average follow-up of 17 years. Workers lost to follow-up constituted 5% of the total cohort, and in no individual cohort did this proportion exceed 10%.

Exposure assessment

Questionnaires were constructed for factories producing chlorophenoxy herbicides or chlorinated phenols and for spraying cohorts. These were completed with the assistance of industrial hygienists, workers, and/or factory personnel. Industry and other production records were also used. Job histories were examined when available. Workers were classified as exposed, probably exposed, exposure unknown, or non-exposed:

TABLE I—DESCRIPTION OF COHORTS IN INTERNATIONAL REGISTER

Cohort	No of subjects	Type of cohort	Sex	Period at risk	Main chemicals sprayed or produced
1, Australia	2177	S	M	1955–83	2,4,5-T/2,4-D
2, Austria	159	PC	B	1971–88	2,4,5-T/2,4-D MCPA/2,4,5-TCP 2,4-DCP
3, Canada	1222	S	M	1955–82	2,4,5-T/2,4-D
4, Denmark*	3843	P	B	1955–82	MCPA/MCPP 2,4-DP
5, Denmark	616	P	B	1955–82	2,4-DP/MCPA
6, Finland	62	P	B	1955–85	2,3,4,6-TeCP
7, Italy	325	P	B	1970–86	2,4,5-TCP
8, Italy	81	P	B	1967–86	2,4-D/MCPA
9, Netherlands	1167	P	B	1955–85	2,4,5-T/2,4,5-TCP
10, Netherlands	1143	P	B	1965–86	MCPA/MCPP/2,4-D
11, New Zealand	1038	P	B	1969–87	2,4,5-T/2,4-D MCPA/MCPB/ 2,4,5-TCP
12, New Zealand	780	S	B	1973–87	2,4,5-T/MCPA/2,4-D
13, Sweden	270	P	B	1965–86	2,4-D/MCPA/MCPP 2,4,6-TCP
14, UK*	1531	P	M	1955–87	MCPA
15, UK	145	P	M	1960–85	PCP
16, UK	1147	P	M	1975–87	2,4-DB/MCPA MCPP/2,4-D/2,4-DP 2,4,5-T
17, UK	353	P	M	..†–87	MCPB/PBA
18, UK	275	P	M	1969–87	2,4-DP/2,4-DB MCPA/MCPP
19, UK	528	P	M	1969–87	MCPA/MCPP/2,4-D 2,4-DP
20, UK	2013	S	M	1955–87	MCPA

s = sprayers; p = production; PC = chloracne cases in production.
M = males; B = both sexes.
2,4-D = 2,4-dichlorophenoxyacetic acid; 2,4-DP = 2-(2,4-dichlorophenoxy)-propanoic acid; 2,4-DB = 4-(2,4-dichlorophenoxy)butanoic acid; 2,4,5-T = (2,4,5-trichlorophenoxy)-acetic acid; 2,4,5-TP = 2-(2,4,5-trichlorophenoxy)-propanoic acid; MCPA = (4-chloro-2-methyl-phenoxy)-acetic acid; MCPP = 2-(4-chloro-2-methyl-phenoxy)propanoic acid; MCPB = 4-(4-chloro-2-methyl-phenoxy) butanoic acid; 2,4-DCP = 2,4-dichlorophenol; 2,4,5-TCP = 2,4,5-trichlorophenol; 2,4,6-TCP = 2,4,6-trichlorophenol; 2,3,4,6-TeCP = 2,3,4,6-tetrachlorophenol; PCP = pentachlorophenol; PBA = phenoxybutyric acid.
*35 additional subjects from Denmark and the United Kingdom were exposed during both production and spraying.
†Formulators and packers = 1982–87; handymen = 1967–87; process workers = 1963–87.

Exposed workers (n = 13 482) comprise all known to have sprayed chlorophenoxy herbicides and all who had worked in any of the following departments at factories producing chlorophenoxy herbicides or chlorinated phenols: *synthesis, finishing*, formulation, packing, maintenance/repair, laboratory, chemical effluent/waste, cleaning, shipping/transportation/stores/warehouse, plant supervision, cleaning during accident, and other and unclassified exposure.

Probably exposed workers (n = 416) comprise all workers in cohorts 15 and 18; no job titles were available but it was judged that most workers would have been exposed. (Exposed and probably exposed are aggregated for some analyses, as indicated in the text.)

Workers with unknown exposure (n = 541) had no information on exposure status.

Non-exposed workers (n = 3951) were those never employed in the parts of factories which produced chlorophenoxy herbicides or chlorinated phenols and who never sprayed chlorophenoxy herbicides came mainly from Australia, Denmark, Netherlands, New Zealand, and UK (224, 1966, 1283, 214, and 180, respectively). Although not exposed to chlorophenoxy herbicides they were exposed to other chemicals, such as dyes and rodenticides.

Workers were also categorised as producers (12 492) and sprayers (5898).

Exposed and probably exposed workers were also classified by groups of chemicals produced or sprayed (9377 chlorophenoxy herbicides, 408 chlorinated phenols, and 4113 both) and within the manufacturing cohorts by department (3034 main production, 1522

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TABLE II—MORTALITY BY DETAILED CAUSE AND EXPOSURE TO CHLOROPHENOXY HERBICIDES AND/OR CHLOROPHENOLS. BOTH SEXES

Cause of death (ICD 8)	SMR (95% CI) (no of observed deaths)			
	Exposed	Probably exposed	Non-exposed	Unknown
All causes	92* (88–96) *(1870)*	122 (93–158) *(58)*	103 (93–114) *(392)*	157* (119–203) *(57)*
Malignant neoplasms (140–207)	101 (92–110) *(499)*	129 (74–210) *(16)*	99 (81–120) *(100)*	135 (72–231) *(13)*
Buccal cavity and pharynx (140–149)	116 (58–207) *(11)*	0 (0–1942) *(0)*	59 (2–330) *(1)*	667 (17–3714) *(1)*
Oesophagus (150)	60 (26–119) *(8)*	0 (0–971) *(0)*	255 (83–595) *(5)*	0 (0–2170) *(0)*
Stomach (151)	89 (64–121) *(40)*	0 (0–305) *(0)*	85 (34–175) *(7)*	0 (0–492) *(0)*
Intestine, except rectum (152–153)	113 (81–154) *(41)*	0 (0–479) *(0)*	67 (22–156) *(5)*	164 (4–913) *(1)*
Rectum (154)	110 (70–163) *(24)*	179 (5–995) *(1)*	43 (5–156) *(2)*	238 (6–1327) *(1)*
Liver, gallbladder and bileduct (155–156)	44 (12–113) *(4)*	0 (0–2170) *(0)*	83 (10–300) *(2)*	435 (11–2423) *(1)*
Pancreas (157)	112 (73–164) *(26)*	185 (5–1032) *(1)*	61 (13–177) *(3)*	0 (0–820) *(0)*
Peritoneum (158)	156 (19–564) *(2)*	0 (0–12 296) *(0)*	0 (0–1085) *(0)*	3333 (84–18 572) *(1)*
Unspecified digestive organs (159)	331 (90–846) *(4)*	0 (0–12 296) *(0)*	870* (105–3141) *(2)*	0 (0–18 444) *(0)*
Nose & nasal cavities (160)	291 (60–851) *(3)*	0 (0–12 296) *(0)*	0 (0–2170) *(0)*	0 (0–36 889) *(0)*
Larynx (161)	145 (63–285) *(8)*	0 (0–3074) *(0)*	90 (2–502) *(1)*	0 (0–3074) *(0)*
Trachea, bronchus and lung (162)	102 (87–118) *(173)*	221* (110–395) *(11)*	140 (100–190) *(40)*	110 (23–320) *(3)*
Connective and other soft tissue (171)	201 (55–515) *(4)*	0 (0–7378) *(0)*	0 (0–878) *(0)*	0 (0–12296) *(0)*
Skin (172–173)	32* (7–94) *(3)*	0 (0–2838) *(0)*	144 (30–422) *(3)*	0 (0–2049) *(0)*
Male breast (174)	345 (42–1246) *(2)*	0 (0–36 889) *(0)*	0 (0–3689) *(0)*	0 (0–36 889) *(0)*
Female breast (174)	30 (1–166) *(1)*	— —	114 (31–293) *(4)*	0 (0–1537) *(0)*
Female genital organs (180–184)	94 (19–274) *(3)*	— —	89 (18–260) *(3)*	0 (0–753) *(0)*
Prostate (185)	111 (75–158) *(30)*	0 (0–671) *(0)*	40 (5–143) *(2)*	217 (6–1211) *(1)*
Testis (186)	225 (90–464) *(7)*	0 (0–5270) *(0)*	0 (0–444) *(0)*	0 (0–3074) *(0)*
Bladder (188)	80 (42–136) *(13)*	227 (6–1266) *(1)*	56 (7–202) *(2)*	0 (0–1085) *(0)*
Kidney (189)	97 (48–173) *(11)*	0 (0–1537) *(0)*	35 (1–197) *(1)*	0 (0–1366) *(0)*
Brain (191–192)	38* (14–82) *(6)*	0 (0–1025) *(0)*	86 (18–250) *(3)*	556 (67–2007) *(2)*
Thyroid gland (193)	367 (100–940) *(4)*	0 (0–12 296) *(0)*	0 (0–1230) *(0)*	0 (0–18 444) *(0)*
Other endocrine gland (194)	462 (95–1349) *(3)*	0 (0–36 889) *(0)*	0 (0–1942) *(0)*	0 (0–36 889) *(0)*
Ill-defined sites (195, 199)	131 (83–197) *(23)*	0 (0–802) *(0)*	153 (50–357) *(5)*	323 (8–1797) *(1)*
Lymphosarcoma (200, 202)	97 (48–173) *(11)*	0 (0–1476) *(0)*	178 (48–455) *(4)*	0 (0–1757) *(0)*
Hodgkins disease (201)	39 (5–141) *(2)*	769 (19–4286) *(1)*	0 (0–332) *(0)*	0 (0–3353) *(0)*
Multiple myeloma (203)	69 (19–178) *(4)*	0 (0–2838) *(0)*	160 (19–578) *(2)*	0 (0–3074) *(0)*
Leukaemia and aleukaemia (204–207)	117 (70–186) *(18)*	0 (0–1118) *(0)*	88 (18–256) *(3)*	0 (0–1025) *(0)*
Benign and unspecified neoplasms (210–239)	199* (103–348) *(12)*	0 (0–2459) *(0)*	317* (103–739) *(5)*	0 (0–2306) *(0)*
Circulatory system (390–458)	90* (84–97) *(857)*	111 (72–165) *(25)*	99 (84–116) *(162)*	113 (64–183) *(16)*
Respiratory system (460–519)	72* (60–86) *(125)*	95 (31–221) *(5)*	106 (69–156) *(25)*	191 (52–490) *(4)*
Accidents, poisonings, violence (E800–E999)	100 (86–116) *(174)*	169 (55–394) *(5)*	108 (77–146) *(41)*	319* (182–518) *(16)*
Unknown causes	— *(50)*	— *(0)*	— *(11)*	— *(1)*

*p < 0·05.

maintenance and cleaning, 1665 other, 1907 unclassifiable). A substantial number of workers producing chlorophenoxy herbicides may also have exposed to chlorophenols (eg, *p*-chloro-*o*-cresol) which are used as raw materials in the synthesis of chlorophenoxy acids. Exposure to the most toxic dioxin congener (2,3,7,8,-TCDD) may occur during production of 2,4,5-TCP and 2,4,5-T, and during spraying of herbicides containing 2,4,5-T or its derivatives.[1] Factories 4,5,6,8,10,14,15,17,18, and 20 (n = 6845) had either not produced 2,4,5-T or had produced very little of it (around 10 tonnes per year during the study period). Workers in these factories were exposed to various chlorophenoxy herbicides, chlorinated phenols, polychlorinated dibenzodioxins, and furans but were probably not exposed to TCDD. Thus within the register population it was possible to differentiate workers probably exposed to TCDD and workers probably not exposed to TCDD.

Production accidents were known to have occurred in two cohorts (factories 7 and 9), 319 workers being exposed. There were 181 chloracne cases among workers in the cohort, 128 of whom came from cohort 2, which incorporated only workers diagnosed with chloracne. 9 production workers with a history of chloracne from exposure to polychlorinated dioxins in 1971–73 had a median level of 340 pg TCDD per g blood lipids (range 98–659), higher than 4 unexposed workers from the same plant (median 18, range 8–28 pg/g) and 17 external controls (median 16, range <5 to 23 pg/g) (M. Neuberger et al, to be published elsewhere.)

Statistical analysis

The person-years method was used to derive standardised mortality ratios (SMR) with 95% confidence intervals (CI) based on the Poisson distribution.[29] An excess or deficit of an SMR is regarded as statistically significant at $p < 0.05$ (two-tail) when the CI does not include 100. The WHO Mortality Data Bank was used to compute national mortality reference rates for sex, age (in 5-year age groups), and calendar period (in 5-year periods, except when such a period coincides with an ICD revision). Duration of exposure was treated as a time-dependent variable in the allocation of person-years at risk. Poisson regression analysis was applied for selected sites.[30]

Coding

Coding of underlying cause of death was done nationally. A conversion table has been prepared in IARC to allow the pooling of results over different ICD revisions.[31–33] About 40% of soft-tissue sarcomas (one of the a priori neoplasms of interest) develop in parenchymal organs[34] and are not coded under ICD 171 (8th and 9th revision, "malignant neoplasms of connective and other soft tissue"). Histological diagnoses were not generally available and reference mortality rates are not available for sarcomas not coded as ICD 171. SMRs for soft-tissue sarcoma therefore relate only to sarcomas coded as ICD 171. Information on other sarcomas, identified from medical records and cancer registration, is presented but no statistical analysis was done.

Results

All-cause mortality was lower than expected from national rates (SMR = 95 [95% CI 91–99]). Among exposed workers, this was mainly because of low mortality for circulatory and respiratory diseases (SMR = 90 [84–97], SMR = 72 [60–86], respectively). Workers with unknown

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TABLE III—MORTALITY FOR ALL MALIGNANT NEOPLASMS AND FOR SOFT-TISSUE SARCOMA AND NON-HODGKIN'S LYMPHOMA SEPARATELY, BOTH SEXES

	All malignant neoplasms			Soft-tissue sarcomas			Non-Hodgkin's lymphomas		
—	Obs	Exp	SMR (95% CI)	Obs	Exp	SMR (95% CI)	Obs	Exp	SMR (95% CI)
Exposure									
Exposed and probably exposed	515	508·85	101 (93–110)	4	2·04	196 (53–502)	11	11·64	95 (47–169)
Non-exposed	100	101·08	99 (81–120)	0	0·42	0 (0–878)	4	2·25	178 (48–455)
*Type of cohort**									
Production	253	258·91	98 (86–111)	1	1·03	97 (3–541)	8	5·36	149 (64–294)
Sprayers	262	249·94	105 (93–118)	3	1·01	297 (61–868)	3	6·28	49 (10–140)
*Chemicals produced or sprayed**									
Both	112	106·70	105 (86–126)	1	0·48	208 (5–1161)	4	2·37	169 (46–432)
Phenoxy	384	385·28	100 (90–110)	3	1·50	200 (41–585)	7	8·96	78 (32–161)
Chlorophenols	19	16·82	113 (68–176)	0	0·06	0 (0–6148)	0	0·31	0 (0–1190)
*TCDD exposure**									
Probable	236	215·12	110 (96–125)	2	1·00	200 (24–723)	5	5·76	87 (28–203)
Unlikely	279	293·76	95 (84–107)	2	1·04	193 (23–695)	6	5·88	102 (37–222)
*Years since first exposure**									
30+	74	88·60	84 (66–105)	0	0·24	0 (0–1537)	2	1·68	119 (14–430)
20–29	171	159·19	107 (92–125)	0	0·52	0 (0–709)	3	3·38	89 (18–259)
10–19	170	166·49	102 (87–119)	4	0·66	606 (165–1552)	5	3·94	127 (41–296)
0–9	100	94·53	106 (86–129)	0	0·50	0 (0–738)	1	2·67	38 (1–209)
Duration of exposure (yr)*									
20+	36	42·17	85 (60–118)	0	0·15	0 (0–2459)	1	1·02	98 (3–546)
10–19	74	76·16	97 (76–122)	2	0·29	690 (84–2491)	1	1·81	55 (1–308)
1–9	234	230·54	102 (89–115)	0	0·89	0 (0–415)	3	5·36	56 (12–164)
<1	168	155·68	108 (92–126)	2	0·59	339 (41–1125)	6	3·35	179 (66–390)
*Department**									
Production	62	60·38	103 (79–132)	0	0·29	0 (0–1272)	2	1·40	143 (17–516)
Maintenance	40	42·02	95 (68–130)	0	0·15	0 (0–2459)	1	0·91	110 (3–612)
Other exposure	42	39·65	106 (76–143)	1	0·16	625 (16–3482)	3	0·90	333 (69–974)
Unclassified	107	114·10	94 (77–113)	0	0·35	0 (0–1054)	2	2·08	96 (12–347)

*Exposed and probably exposed workers are grouped together.

exposure status had high all-cause mortality (table II), especially for accidents, poisoning, and violence including suicide (SMR = 319 [182–518]).

Table II gives SMRs (and 95% CIs) and observed deaths for major causes of death and for malignant neoplasms by site and exposure for both sexes combined since only 10 deaths from cancer were available for analysis among exposed females. Significant excesses were observed among males for malignant thyroid and benign and unspecified neoplasms in the exposed category, malignant neoplasms of trachea, bronchus and lung in the probably exposed category, and malignant neoplasms of unspecified digestive organs and benign and unspecified neoplasms in the non-exposed category; significant deficits were observed for malignant neoplasms of skin and of brain.

Exposed workers had SMRs above 200 for neoplasms of unspecified digestive organs, neoplasms of the nose and nasal cavity, soft-tissue sarcoma, breast cancer (in males) and for neoplasms of the testis, other endocrine glands and thyroid.

Table III gives combined SMRs for exposed and probably exposed workers of both sexes, for all neoplasms, soft-tissue sarcomas and non-Hodgkin's lymphomas. The pattern of risk for all neoplasms by time first exposure did not indicate a strong healthy worker effect, and mortality did not vary substantially between the groups examined.

Soft-tissue sarcoma

4 deaths were observed, all among exposed male workers (table III). No increased risk was observed among production workers (1 death), whereas mortality appeared to be increased among sprayers (3 deaths, SMR = 297 [61–868]). All deaths occurred 10–19 years after first exposure, giving rise, for this time interval, to a six-fold excess risk in the cohort as a whole (table III) and an even greater excess among exposed sprayers (3 deaths, SMR = 882 [182–2579]). No differentiation in risk was observed in relation to duration of exposure or probable TCDD exposure. 5 additional cases of soft-tissue sarcoma were recorded in cohort members who were alive at the end of follow-up or who had died with a certified cause of death other than ICD 171. These included 1 non-fatal case in the non-exposed group. Details of all 9 cases are given in table IV.

Malignant lymphoma

14 deaths from non-Hodgkin's lymphoma (ICD 200, 202, 8th and 9th revision) were observed among men and 1 among women; 11 deaths were in exposed workers, all men. Mortality for exposed/probably exposed workers was close to expected (SMR = 95) with production workers having a small statistically insignificant increase in mortality (8 deaths, SMR = 149) (table III). 10 out of 11 deaths occurred more than 10 years after first exposure. 6 deaths occurred among workers exposed for than a year, and no difference in risk could be seen in relation to exposure to TCDD or type of chemical produced. The highest SMR among production workers was for those in "other jobs" (transport/storage, laboratory workers, plant supervisors). 4 deaths from non-Hodgkin's lymphoma were observed among non-exposed workers in one Danish factory (cohort 4). Mortality for non-exposed workers was higher than that of all exposed

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to TCDD. Of the 5 additional registered cases of soft-tissue sarcoma, identified from other morbidity or mortality records (3 production workers, 1 sprayer, 1 non-exposed) 1 was in a worker probably exposed to TCDD.

A small, non-significant increase in mortality from non-Hodgkin's lymphoma was observed among production workers, most deaths occurring more than 10 years after first exposure. 6 out of the 11 deaths were in workers exposed for less than one year. Other studies[1,4,21] have, however, shown risks associated with exposure to chlorophenoxy herbicides higher for non-Hodgkin's lymphomas than for soft-tissue sarcomas. There was no increase in mortality from Hodgkin's disease, and the evidence for an association of with exposure to chlorophenoxy herbicides has been weaker than that for non-Hodgkin's lymphoma.

We found increased risks for some uncommon neoplasms but these results are difficult to interpret because of the small numbers. Neoplasms of the thyroid and other endocrine glands have not been previously linked with chlorophenoxy herbicides in man but exposure to TCDD and chlorophenols have been associated with neoplasms of the thyroid and the adrenals in mice and rats.[35]

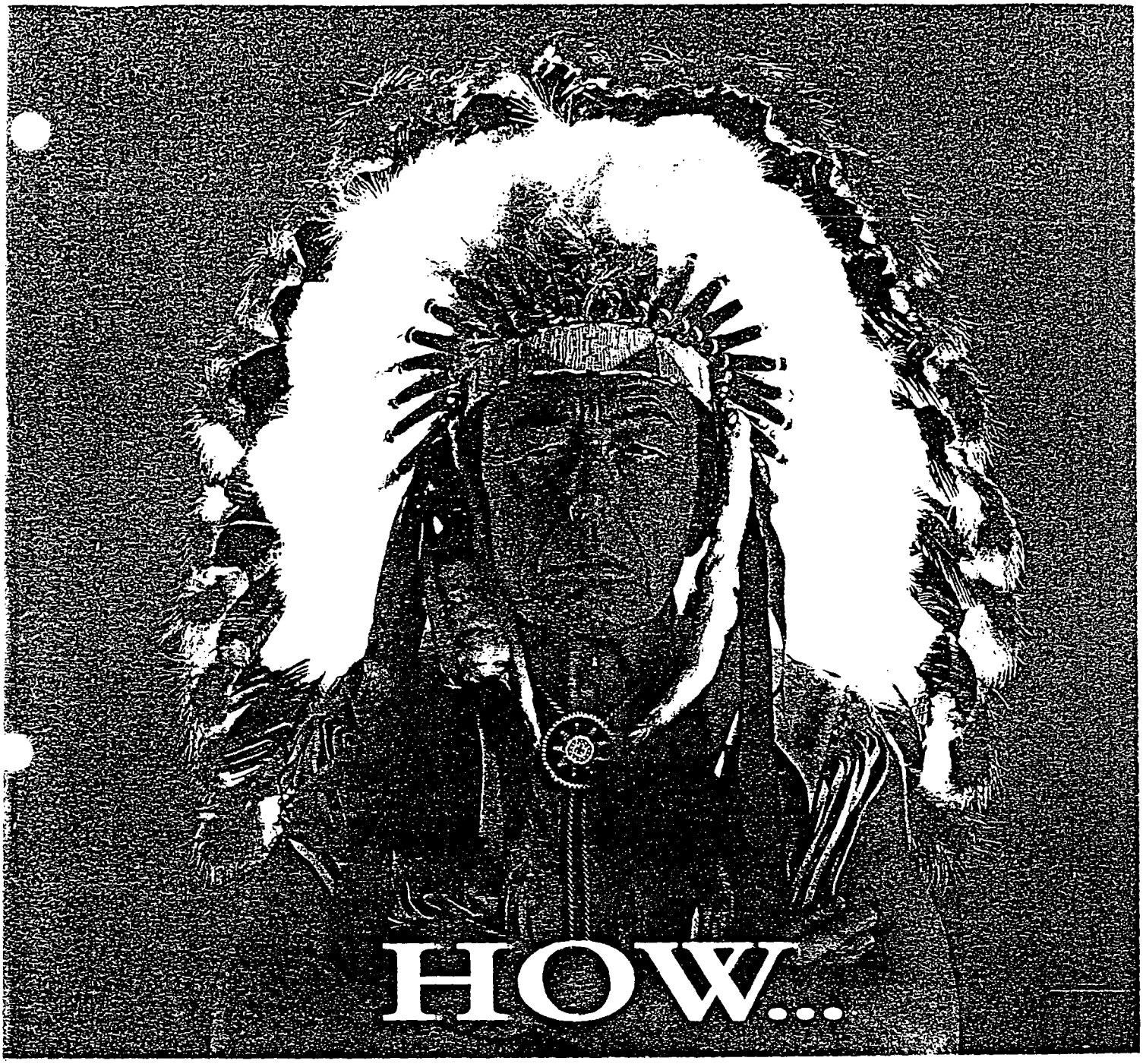
Interpretation of our findings will be easier when follow-up of this large cohort is longer—ie, when the number of recorded deaths is greater. The pattern so far indicates no increased mortality for neoplasms in general for the most common epithelial cancers, and no clearly detectable excess for non-Hodgkin's or for Hodgkin's lymphoma. The significant six-fold excess of soft-tissue sarcomas occurring in the period 10–19 years since first exposure in the whole cohort, rising to a nine-fold excess in sprayers, is compatible with a causal role for chlorophenoxy herbicides, though not specifically for those probably contaminated with TCDD.

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TABLE IV—DESCRIPTION OF 9 CASES OF SOFT TISSUE SARCOMAS

Case*	Sex, age	Year of death†	Cause of death	Histology‡	Longest held job	Years since first exposure	Years of exposure
1, Australia	M, 46	<1980	Connective tissue lower limb (ICD 171)	Fibrosarcoma of the hip	Sprayer	16	16
2, Denmark	M, 32	<1980	Connective tissue lower limb (ICD 171)	Neurofibrosarcoma, lower limb	Production, transportation/storage	10	<1
3, Denmark	M, 34	Alive, Jan, 1984	..	Mesenchymal sarcoma (possible liposarcoma, retroperitoneum)	Production unspecified	14	<1
4, Denmark	M, 47	<1980	Ill-defined cancer	Haemangiopericytoma, back	Production transportation/storage	21	8
5, Denmark	M, 64	<1980	Prostate cancer	Leiomyosarcoma, prostate	Production, transportation/storage	17	2
6, New Zealand	M, 35	Alive, Jan, 1988	..	Fibrous histiocytoma, lower limb	Sprayer	12	12
7, New Zealand	M, 55	1980+	Connective tissue upper limb (ICD 171)	Neurilemmoma	Sprayer	14	12
8, UK	M, 43	<1980	Connective tissue unspecified (ICD 171)	Spindle cell neurilemmomal sarcoma	Sprayer	18	<1
9, Denmark	M, 56	Alive, Jan, 1984	..	Leiomyosarcoma, larynx	Non-exposed	26	<1

1 additional incident case occurred after the end of follow-up in New Zealand.
*Cases 2, 3, 4, 5, 8, and 9 previously reported.[2,4,7]
†Precise year of death not provided for reasons of confidentiality.
‡Histology from cancer registration or medical records. Histology record not retrieved for case 1.

workers, and similar to that of production workers (table III). The cases arose in seven countries. (Not included in table III are 3 cases in cohort members who were alive at the end of follow-up or whose certified underlying cause of death was not ICD 200 or 202.)

Mortality from Hodgkin's disease was below expectation.

Other neoplasms

More than two-fold increases in risk were noted among exposed workers for several less common neoplasms, most of which have not been previously associated with exposure to chlorophenoxy herbicides. 7 deaths from testicular cancer were recorded, with at least a two-fold increase in mortality for the combined group of exposed workers (SMR = 220 [89–454] and for the production workers (5 deaths, SMR = 278 [90–648]). 5 deaths occurred 5 or more years after first exposure, and risk was higher in workers probably exposed to TCDD (SMR = 296) compared to those probably not exposed (SMR = 164). Thyroid cancer mortality was increased for the combined group of exposed workers (4 deaths, SMR = 357 [97–914]), the excess applying both to sprayers and production workers, with deaths registered in three countries. 3 deaths from thyroid cancer occurred 10 or more years after first exposure, and risk was higher for workers probably exposed to TCDD (SMR = 426) compared to those probably no exposed (SMR = 308). 3 deaths from neoplasms of other endocrine glands occurred in the UK with increased mortality for the combined group of exposed workers (SMR = 454 [94–1328]), and separately in sprayers and production workers. Increased mortality from neoplasms of nose and nasal cavity (3 deaths, SMR = 283 [58–827]) was similarly observed only in the UK, with the highest risk in sprayers.

The mortality of cases exposed through accidents was not increased either for all causes (33 deaths, SMR = 98 [67–137]) or for all neoplasms (13 deaths, SMR = 120 [64–205]). Similarly, no increased risk was seen for chloracne cases for all cause mortality (13 deaths, SMR = 66 [35–113]) or for al neoplasms (5 deaths, SMR = 98 [32–228]). No deaths from soft-tissue sarcoma or non-Hodgkin's lymphoma were observed in these groups, but the expected numbers were very low.

Results were virtually unchanged when analyses were repeated with exclusion of all workers with less than one year exposure. Analyses by time since first exposure and duration of exposure for workers probably exposed to TCDD did not show any trends. Analysis using Poisson regression for all cause mortality, all neoplasms, soft-tissue sarcoma, and non-Hodgkin's lymphoma, did not reveal different pattern of risk than that shown in the SMR analysis.

Discussion

The IARC register provides an opportunity to study, with a common protocol, the mortality experience of workers producing and spraying chlorophenoxy herbicides and/or chlorinated phenols in ten countries. This cohort study is the largest to have been done on these categories of workers. Nonetheless the attempt to associate risks with specific agents was only partly successful because there was often simultaneous exposure to several different chlorophenoxy herbicides or chlorophenols (table I) and to other pesticides, raw materials, intermediates, and processing chemicals. The risk specifically related to chlorophenoxy herbicides is best evaluated by looking at sprayers, who are exposed mainly to these compounds and, in smaller amounts, to other herbicides, and only to negligible amounts of chlorophenol impurities. Workers producing chlorophenoxy herbicides may also have been exposed to chlorophenols during the production process. It was not possible to identify a large group of workers exposed solely to chlorophenols. The most toxic dioxin (TCDD) can be formed during production of 2,4,5-T or 2,4,5-TCP so the identification of factories which did not produce 2,4,5-T or produced only very small amounts and of sprayers not using 2,4,5-T allowed a population to be distinguished in which exposure to TCDD was unlikely (with the caveat that even occasional exposures to high concentrations of TCDD may lead to accumulation of high tissue burdens[18]).

A non-significant increased risk was observed for soft tissue sarcoma, the excess being significant for sprayers in an analysis by time since first exposure. All 4 cases (in four countries) occurred 10–19 years after first exposure, a time shorter than that observed in Sweden[10] or the USA.[16] The increased risk was not confined to workers probably exposed

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OCCUPATIONAL CHLORACNE CAUSED BY AROMATIC CYCLIC ETHERS

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by

[illegible] and W. H. Schulz

University Clinic of Dermatology, Hamburg-Eppendorf

Dermatologica, 115 (1957) 540 - 546

Thirty-one cases of chloracne were found among workers engaged in the production of 2,4,5-trichlorophenol and in the conversion of the latter into 2,4,5-trichlorophenoxyacetic acid and its esters. Animal experiments, carried out by painting rabbits' ears, have shown the cause of chloracne to be not trichlorophenol itself, but toxic by-products formed in the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene into 2,4,5-trichlorophenol. Compounds that may arise in this process were synthesized, and tri- and tetrachlorodibenzofuran and tetrachlorodibenzodioxin were found to be highly active. Furthermore, 2,3,6,7-tetrachlorodibenzodioxin was isolated as a by-product formed in the manufacture of trichlorophenol, and the possibility of its formation from sodium trichlorophenoxide was established.

Chlorinated compounds, used as industrial materials or formed as by-products, occupy an important position among the chemical and physical intoxicants capable of producing acne and folliculitis.

The first cases caused by these compounds were observed at the beginning of the century with the introduction of the electrolytic chlorine process. The view put forward, and later corrected, by Herxheimer, according to which the disease is caused by free chlorine, has led to the confusing but common designation "chloracne".

Since the introduction of chlorinated naphthalenes, used in various branches of industry on account of their useful properties (resistance to acids, non-inflammability, waterproofness, good insulation), contact with these compounds has often resulted in chloracne[2,3,8]. Both Bauer[3] and Teleky[8] have suggested the term "Perna-krankheit" ("perchloronaphthalene disease"), which again is unsatisfactory in many respects.

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Chloracne has recently been observed in the manufacture of pentachlorophenol. It will later be discussed shortly whether pentachlorophenol itself is to be regarded as the intoxicant proper in these cases.

The cases whose etiology is now discussed were found among workers in a chemical plant in Hamburg, who were engaged in the manufacture of 2,4,5-trichlorophenol and in its conversion into the herbicidal 2,4,5-trichlorophenoxyacetic acid and its esters. Out of a total of 31 patients, 9 showed severe, 14 moderate, and 8 slight symptoms.

The symptoms developed in the summer and fall of 1954. In the case of more highly exposed workers, facial dermatitis accompanied by erythema and swelling appeared first, but withdrew later to give way to acneiform symptoms on the face, then on other parts of the body as well. In most cases, however, the history started not with acute dermatitis but with comedones and then pustules, affecting the zygomatic-temporal region.

The dermatological symptoms found on first examination consisted of numerous comedones, retention cysts, ranging from the size of a pinhead to that of a lentil, follicles filled with hyperkeratotic material, inflamed papules, pustules, and larger furuncles. The face, external ear, neck, and the nape were invariably affected, severe cases also exhibiting symptoms on the chest, back, abdomen, extensor sides of arms and thighs, and on the genitals.

The efflorescence was generally so dense that practically no follicle remained unaffected. Whereas facial symptoms were mainly characterized by comedones and retention cysts, secondary infected efflorescence (furuncles and pustules) was frequent on the nape and the trunk (see Figs. 1 and 2). In addition to dermatological symptoms, several patients developed chronic blepharitis and conjunctivitis. Most patients complained of loss of appetite, debility, and weakness in the legs, in other words, of symptoms indicating general intoxication.

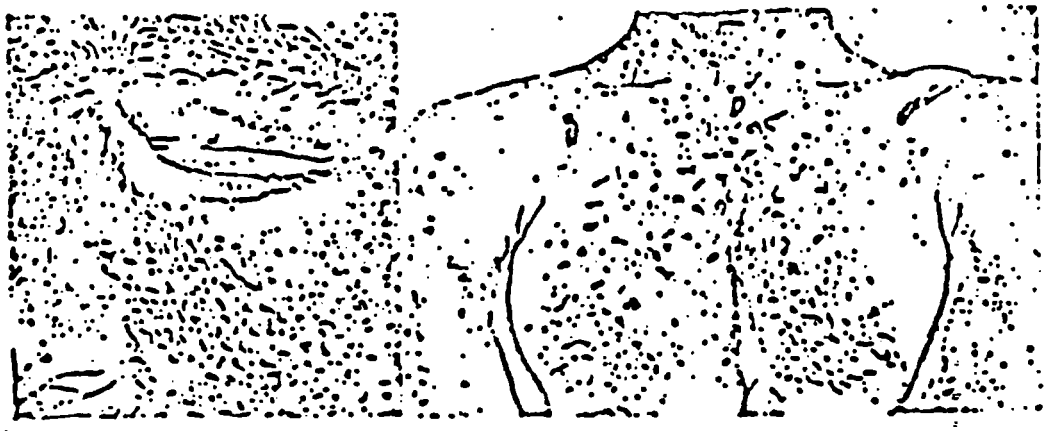


Fig. 1

Fig. 2

No change in the liver, kidneys, central nervous system, and in the hemopoietic system was first found on thorough clinical examination. Some patients had an anacidity of the gastric juice. Owing to persistent complaints, new internistic and neurological examinations were carried out on several patients a few weeks later, revealing affected liver in three cases. Detailed clinical diagnoses will not however be discussed here.

The course of the disease was exceedingly long and persistent. Although contact with the intoxicants had been discontinued, relapsed dermatological symptoms appeared even 15 - 20 months later, despite intensive internal and external therapy.

Etiology

Animal experiments were carried out with a view to clarifying the etiology of chloracne by the use of rabbits' ears, on which Hofmann and Neumann[5], Braun[2], Landes[6], and others had succeeded in inducing symptoms by using chlorinated naphthalenes, the symptoms resembling those of chloracne in man. In each case the inside of one ear was painted daily with a polyglycol solution of the substance to be tested for its chloracne-inducing activity, whilst the other ear, serving as a control, was treated with the solvent alone.

In cases of positive test, flat surface inflammation first developed in 2 to 4 weeks, followed a few days later by the appearance of follicular swelling, hyperkeratosis, and small cysts (see Fig. 3).

Histological examination showed acanthotic extension of the epidermis, edema, and loose, inflamed cell infiltration in the cutis. The follicles were distended and filled with keratotic material. Larger cysts were formed in later stages (see Fig. 4).

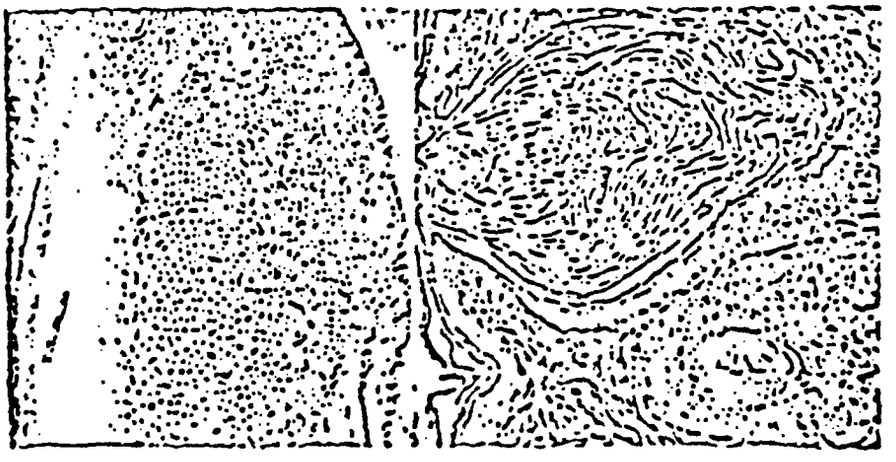


Fig. 3

Rabbit's ear treated with a 0.1% solution of tetrachlorodibenzodioxin

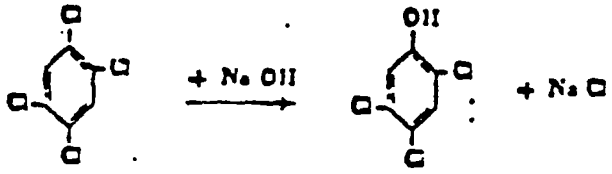
Fig. 4

Histological picture of the rabbit's ear shown in Fig. 3

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having been used with more than 100 substances in the past two years, the rabbit-ear test enables the chloracne-inducing activity of a substance to be ascertained with high probability.

The first results were reported by one of us[7] at the 23rd Congress of German Dermatologists in Vienna. It was first shown that, contrary to previous assumptions, 2,4,5-trichlorophenol was not to be considered as the chloracne-inducing factor. This emerged from the observation that the expected symptoms were not produced on the rabbits' ears with a 5% solution of pure 2,4,5-trichlorophenol in polyglycol, but they were produced by the technical product. Since the starting material, 1,2,4,5-tetrachlorobenzene, was inactive on the rabbits' ears, it was to be assumed that the intoxicant was among the by-products formed in the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene into 2,4,5-trichlorophenol.



1,2,4,5-tetrachlorobenzene — 2,4,5-trichlorophenol

Since the distillation residue could not at first be separated, a number of such synthetic compounds were selected for testing, which were likely to be formed in the hydrolysis of tetrachlorobenzene at 180°C, these compounds being the chlorine derivatives of diphenyl ether and of dibenzofuran (diphenylene oxide).

Whilst the chlorine derivatives of diphenyl ether and unsubstituted and monochlorinated dibenzofuran were inactive in the animal experiments, trichloro- and tetrachlorodibenzofuran resulted in the expected symptoms, even when they were applied in 0.05% solutions.

In addition to the above symptoms, both compounds exhibited strong hepatotoxic properties. The oral administration of a single dose of 0.5 to 1 mg/kg led to severe hepatic conditions in rabbits. However, chlorinated dibenzofurans could not be detected as a by-product in the production.

The clinical examination of a laboratory assistant who developed a severe case of chloracne after contact with tetrachlorodibenzodioxin indicated the possible causative function of chlorinated dibenzodioxins (diphenylene dioxides). Further experiments with rabbits' ears showed tetrachlorodibenzodioxins, especially 2,3,6,7-tetrachlorodibenzodioxin, to be very highly active. Three or four painting with 0.01 - 0.005% solutions, applied at intervals of 3 to 4 days, were found to be sufficient to produce severe inflammation and follicular hyperkeratosis. A single dose of 0.05 - 0.1 mg/kg (per os) resulted in severe hepatic conditions, and, in most cases, in death within 8 to 20 days. Autopsy revealed distended necrotic tissues and engorgement of the liver.

It was shown that 2,3,6,7-tetrachlorodibenzodioxin can be formed from two molecules of sodium trichlorophenoxide with the elimination of two molecules of NaCl. Moreover, 2,3,6,7-tetrachlorodibenzodioxin was isolated as a by-product formed in the alkaline hydrolysis of tetrachlorobenzene into trichlorophenol. This observation leads to the conclusion that tetrachlorodibenzodioxin is responsible for the observed cases of chloracne if not entirely, certainly to a considerable extent.

It should be added that neither pure 2,4,5-trichlorophenol nor pure pentachlorophenol could induce the expected symptoms on rabbits' ears. It is therefore probable that the reported[7] cases of chloracne, ostensibly arising after contact with pentachlorophenol, were caused not by this compound, but likewise by toxic by-products, related to those examined in the present work, especially since pentachlorophenol is prepared from hexachlorobenzene by alkaline hydrolysis, analogously to the preparation of trichlorophenol.

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7. Schulz, K.H., Lecture delivered at the 23rd Congress of German Dermatologists, Vienna, May 23 - 27, 1956

IP-0018

OCCUPATIONAL ACNE
(Chloracne, so-called)
By Kimmig & Schulz
Dermatologica 115, 540, 1957

Translated from German
by J. Barandy
3/59

Among the different chemical and physical toxicants whi cause skin acne and follicultis to a pathogenic extent, chlorinated products and byproducts have been playing an important role.

The first such cases of illnesses, induced by chlorinated materials, were observed around the end of the century in connection with the newly-introduced process of obtaining chlorine through electrolysis. The opinion which Herxheimer expressed, but later changed, was that free chlorine was the cause of illnesses, and led to the widespread misuse of the word "chloracne" in German literature.

Since the introduction of chlorinated naphthalene, which, due to its advantageous technical properties (like acid resistance, fire-water repellency, good isolation capacity, etc.) appeared in different industrial applications, the occurrence of chloracne also has increased. (Teleki, Braun, Grimmer, etal). Wauer & Teleki identified these illnesses with the quite inappropriate word "Dernadiseas

More contemporary are the observations of intoxications from pentachlorophenol production, where pentachlorophenol in contact with the skin, caused chloracne. Although for these cases, the pentachloropehnol itself can be responsible, we will have to carry on further investigations.

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The actual observations to which we by experiments could achieve were performed on workers of one of the chemical factories in Hamburg, engaged in the production of 2,4,5-TCP and its endproduct, the herbicide 2,4,5-trichlorophenoxyacetic acid and its esters. A total of 31 persons became sick, from which 9 showed widespread, heavy deformations; 14 persons' general conditions deteriorated, and 8 persons showed only minor changes.

The clinical appearances developed in summer and autumn of 1954. On one worker, obviously heavily exposed, symptoms appeared first as a dermatitis on the face, accompanied by erythema (redness) and swelling of the face, after which conditions on the face acne (like deformations) developed. Still later, other types of pustules formed.

In most cases, the symptoms appeared as blackheads in the beginning, while in the latter stage, boils developed on the cheekbone region, without acute dermatitis.

As far as the first observations of these skin deformations are concerned, they could be composed of innumerable blackheads, and/or retention systems with size varying from pinheads to lentil, of follicular bond hyperkeratosis, of inflamed boils, or of furuncles. In all cases, the infected parts were the face, earlobes, necks, while in heavier cases, the symptoms spread on the chest, back, abdomen, sides, upper leg and on genitals.

In general, the allocations of these eruptions were unusually thick, to such an extent that hardly a

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a follicle remained undeformed. While most blackheads and retention systems have been observed on the face, types of secondarily infected eruptions (furuncles) were quite frequent on the neck and on the trunk of the body. Several patients -- besides these skin deformations -- developed chronic eyelid conjunctivitis. Generally, the other complaints of the patients were loss of appetite, weakness in the legs, and other symptoms which indicated an overall intoxication.

The further clinical examinations reported damage of the liver, damage of central nervous system and damage of the blood-recovery system, also. Several patients suffered hypoacidity (less acid) in their stomach juice. A week or so later, due to aggravated cases, internal and neurological examinations were resumed on several patients. This time, indications proved liver damage, in three cases. We will not describe here the details of this clinical report.

The duration of the illness proved to be long and enduri Although there was not any contact with the toxic substances, despite intensive internal and external therapy, even 15-20 months after the beginning, marks of skin deformations kept appearing.

INVESTIGATIONS OF THE CAUSE (ETHIOLOGY)

Animal experiments have been conducted in order to find the toxic agent causing the illness. As test objects,

the rabbit's ear was found the most suitable, on which Hoffman, Neumann, Braun, Landes, etal., had already worked with chlorinated naphthalene, having induced appearances similar to that of human chloracne. The internal surface of one ear was daily treated by the substance suspected as the cause of chloracne. The substance was dissolved in polyglycol. The other ear as control was treated only with the solvent (polyglycol).

In positive cases, the tests resulted first (within 2-4 weeks) in flat spread inflammation and days later, swollen follicles, hyperkeratosis and small cysts.

Histological findings have been: Acanthus, like widening of the epidermis, ademata and closely developed cell infiltrations in the cuticle, the enlarged follicles were filled with keratoid material; in later phases these developed themselves into even larger cysts.

As the almost two years long research, carried on with more than 100 substances with the rabbit ear test indicated, one can safely make statements about the chloracne-causing effect of certain materials.

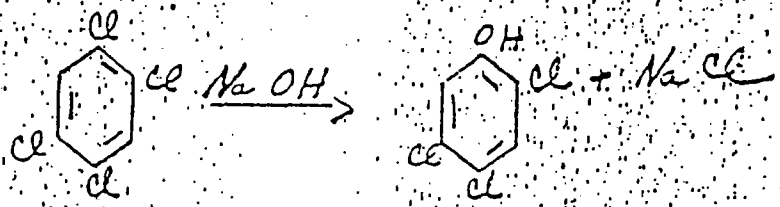
The first results presented by us, had been reported at the 23rd German Dermatological Congress in Wien (Schulz). The report first pointed out that it is not the 2,4,5-trichlorophenol which is the cause as was originally believed, because treatment with pure 2,4,5-trichlorophenol

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(5% polyglycol solution) did not show any observable appearances on rabbit's ear, but treatment with technical product did cause chloracne. Because the starting product, 1,2,4,5-tetrachlorobenzene spread on the rabbit's ear has been without effect, we had to assume that the toxicant we are searching for must be one of th byproducts generated by alkaline hydrolysis from 1,2,4,5-tetrachlorobenzene to form 2,4,5-trichlorophenol.



Because it wasn't possible to isolate the byproducts from the residue, we looked for compounds, within reason, that could form from the saponification of tetrachlorobenzene at 180°C. At first, there was made available to us some chlorinated products of diphenyl ether and dibenzefuran.

While the chlorinated derivations of diphenyl ether, nonsubstituted and monochlorinated dibenzofuran in the animal test proved ineffective, the trichloro and tetrachlorodibenzofuran in a concentrate of 0.05% already induced described deformations. Both of these ompounds have strong liver poisoning capacity. One dose of 0.5 to 1.0 mg per kg body weight taken orally by the rabbitd resulted in serious liver injuries. But so far,

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no one could detect chlorinated dibenzofurane in the byproducts.

The clinical observation of one worker, who after the exposure to tetrachlorodibenzodioxine became seriously ill of chloracne, pointed to chlorinated dibenzodioxine (diphenylenedioxide) as an important causing agent. As further studies indicated, tetrachlorinated dibenzodioxine, especially 2,3,6,7-tetrachlorodibenzodioxine, infected the rabbit's ear with an unusually strong vigor. Three to four times brushings with 0.01 - 0.005% solution within 3-4 days were sufficient to cause serious swellings, also abnormalities of follicles, accompanied by hyperkerotitic deformations. One orally administered dose of 0.05 - 0.1 mg/kg body weight resulted in heavy liver injuries. Most of the animals treated as above expired within 8-20 days after treatment. Autopsy found extensive necrosis and fatness of the liver.

Meanwhile, it was chemically proven that 2,3,6,7-tetrachlorodibenzodioxine itself forms from two molecules Na-trichlorophenate, splitting off two molecules NaCl. Furthermore, we succeeded in isolating 2,3,6,7-tetrachlorodibenzodioxine from the byproducts, produced by the technical saponification of tetrachlorobenzene to trichlorophenol. On the ground of this finding, we are able to conclude that this tetrachlorodibenzodioxine is

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responsible, if not entirely, at least essentially, for the observed illnesses due to chloracne.

In conclusion, be reminded that application of pure 2,4,5-trichlorophenol and pentachlorophenol on rabbit's ears did not induce any described symptoms whatsoever. Therefore, it is highly probable that the published chloracne cases caused by pentachlorophenol (Baader & Baber) actually were not caused by the compound itself, but likewise by toxic byproducts. These byproducts were in the submitted substance (penta) because the manufacturing process of pentachlorophenol is similar to the process of trichlorophenol, an alkaline hydrolysis of hexachlorobenzene.

SUMMARY

Amongst workers who are employed in the preparation of 2,4,5-trichlorophenol and its transformation to 2,4,5-trichlorophenoxyacetic acid or its esters, 31 cases of so-called chloracne were seen. It could be shown experimentally by brushing into a rabbit's ear, that it is not trichlorophenol itself but a toxic product formed by the alkaline hydrolysis of 1,2,4,5,-tetrachlorobenzene to 2,4,5-trichlorophenol which is the cause of the chloracne. From the synthesised combinations, which might come in questior 3 and 4 times chlorinated dibenzofuran and also tetrachlorobenzodioxine proved very active. 2,3,6,7-tetrachlorodibenzodioxine was isolated out of the byproducts and the possibility of its formation from Na-trichlorophenate is proved.

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TO M. E. Getzendaner
Technical Subcommittee
NACA Herbicide
Committee

THE DOW CHEMICAL COMPANY
MIDLAND MICHIGAN

MAIN LABORATORY

REPORT SHEET

DATE 5 March 1956 CHARGE

MAIN LAB. NUMBER

YOUR NUMBER

DESCRIPTION Investigation of methods for the determination of 2,4-D in the presence of chlorophenols and/or other impurities

ANALYSES OR TEST

The problem, as presented to this laboratory, was to develop a method or methods of analyses for commercial 2,4-D and 2,4,5-T formulations that will determine the 2,4-D and/or 2,4,5-T content. It was desired to have a method or methods, preferably one which requires skill and equipment that are not too involved, that will determine only the respective phenoxyacetic acid in the event of possible adulteration, contamination, the use of a chlorinated solvent as part of the formulation or possibly the presence of other acids.

The following report is based on the work done by this laboratory, at your request. It is our hope it will help towards solving some of the problems mentioned above. Through co-operative action with other members of the committee perhaps a set of methods can be worked out that will meet the needs of the industry. This report is not an exhaustive study of the problem but it is our ideas and approach based on the analytical experience we have had with 2,4-D and 2,4,5-T formulations.

One problem, as we see it at present, is the determination of the 2,4-D or 2,4,5-T, especially 2,4-D in the presence of unreacted chlorophenols. Our analytical work with competitors' formulations has turned up a few that contain an excessive quantity of chlorophenols that have apparently been calculated as part of the total 2,4-D content.

The AOAC methods, 5:133 and 5:134 (JAOAC, Vol VIII, 1955) now being used, will determine the total organic acid content in the case of amine formulations or the total chlorine content in the case of ester formulations. These totals will be calculated as 2,4-D or 2,4,5-T respectively. The AOAC methods are entirely suitable when a good grade of 2,4-D or 2,4,5-T acids are used to make the formulations. However, when a crude grade of acid is used AOAC method 5:133 falls down in that it shows a higher value for

BY

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the 2,4-D or 2,4,5-T content than is actually present. The re for this is, that in a crude acid some unreacted phenol, 2,4-c chlorophenol in the case of 2,4-D, has not been removed and th compound is acidic enough to titrate with a base and contains high chlorine content.

I Amine Salt Formulations

The AOAC method for 2,4-D and its salts is given below fc information purposes.

5.133 2,4-DICHLOROPHENOXYACETIC ACID (2,4-D) (44)--OFFICIAL

(a) 'In preparations of free acid with no insoluble carrier.--Weigh 1 g sample into 250 ml erlenmeyer, dissol in 75 ml neutral alcohol, and titr. with 0.1 N NaOH, usin 1 ml phenolphthalein, 2.12(d).' (1 ml 1% alc. thymol-phthalein soln may be substituted, provided this indicator has been used to stdze the alkali.). 1 ml 0.1 N NaOH = 0.0221 g 2,4-dichlorophenoxyacetic acid.

(b) 'In herbicides containing free acid and insolubl carrier.---Weigh sample equiv. to 1 g of the acid into 250 ml beaker, add 25 ml normal Na_2OH and 50 ml H_2O, warm and stir 15 min. to dissolve acid, and adjust to room temp. Filter thru paper into 250 ml separator and wash any insol. matter, collecting washings in separator. Neutralize contents of separator with 10% H_2SO_4, and 10 ml excess, and ext. with two 75 ml portions ether. Combine 2 ether exts in separator, wash free from H_2SO_4 with three 10 ml portions H_2O, and filter thru cotton pledget (previously satd with ether) into 400 ml beaker. Rinse separator with ether, and filter rinsings thru the cotton into beaker. To contents of beaker add 25 ml H_2O and few boiling chips, evap. on steam bath until ca 25 ml ether remains, and then remove balance of ether at room temp. in air current. To residual aq. soln add 100 ml neutral alcohol and titr. with 0.1 N NaOH as in (a).

(c) 'In herbicides containing salts of 2,4-dichloro-phenoxyacetic acid.--Weigh sample equiv. to ca 1 g of the free acid and dissolve in 50 ml H_2O. If insol. carrier is present, filter thru paper and wash residue. Transfer clear soln to 250 ml separator, and proceed as in (b), beginning 'Neutralize contents of separator.'

Proposed Method for Amine Salt Formulations

Perhaps the simplest method of analyzing for 2,4-D acid in the presence of 2,4-dichlorophenol is to use the above AOAC method and determine the end point with a different indicator, or preferably by the use of an electrometric titration. The

accompaning curves (chart) show the effect of the presence of 2,4-dichlorophenol when titrating 2,4-D containing 2,4-dichloroph

It can be seen the 2,4-D gives a sharp break from about pH 7 to pH 10 with a mid-point at pH 8.5. The indicators now used phenolphthalein (about pH 9) or thymolphthalein (about pH 10), catch this break very nicely. As the 2,4-dichlorophenol content is increased the break becomes less sharp. With 10% of 2,4-dichlorophenol added there is one break for the 2,4-D at pH 6 to pH 7 and the 2,4-dichlorophenol continues to titrate and then gives another break at about pH 10.5.

What is proposed, is to titrate to an end point of pH 7 potentiometrically, or use a suitable indicator, such as methyl red and calculate the per cent 2,4-D from this titration. This end point may give slightly lower values for 2,4-D on acids containing no dichlorophenol and slightly higher values for acids containing dichlorophenol.

If the titration were continued from pH 7 to pH 10 one could tell whether there was any 2,4-dichlorophenol present by the nature of the break. If the break was sharp chlorophenols could be assumed to be absent and the regular end point could be used for the calculation of per cent 2,4-D. In the case of a large difference in titration between pH 7 and pH 10, the pH 7 end point could be used with the realization that some accuracy is forfeited for the benefit of screening out the chlorophenols.

An inspection of the table given below and the accompanying curve will illustrate the above points.

Table I

Sample		% 2,4-D (Theory)	pH at Theoretical end point	% 2,4-D at pH 7	% 2,4-D at pH 1
I	Dow Technical 2,4-D	99.4	8.5	99.0	99.7
II	2.5% 2,4-Dichlorophenol added	96.9	7.5	96.5	100.4
III	5.2% 2,4-Dichlorophenol added	94.2	6.7	94.5	101.9
IV	10.2% 2,4-Dichlorophenol added	89.3	7.0	89.3	103.4

II Ester Formulations

A question arises. Does the unreacted 2,4-D or 2,4,5-T which is often present in ester formulations count towards the acid equivalent of the ester? We at Dow have been making a separate free acid analyses, when necessary, and correcting the total acid

equivalent for the free acid found. It appears that some companie are calculating all the 2,4-D or 2,4,5-T present in their figures for pounds of acid equivalent per gallon as indicated by the analyses of their formulations. The present AOAC method for ester formulations apparently justifies this. However, the determination of free acid is a simple matter with most formulations.

Proposed Method for Free Acid Content

1. Principle

The free acid present in ester formulations is determined by adding a sample of the formulation to alcohol and titrating the acidity with standard sodium hydroxide to pH 7.

2. Reagents

(a) Sodium hydroxide, 0.1 N standard solution.

(b) Alcohol, 95%. Formula 30 or Formula 2B.

3. Apparatus

(a) pH meter. Beckman Laboratory Model G, or its equivalent, with a glass electrode and calomel reference electrode.

4. Procedure

Weigh a 10.0 gram sample of the ester formulation into a 250-ml. beaker and add 100 ml. of alcohol. Titrate the free acid potentiometrically with 0.1 N sodium hydroxide to pH 7.

5. Calculations

(a) $\frac{\text{ml. 0.1 N NaOH} \times 0.0221 \times 100}{\text{g}} = \%$ free 2,4-D

or

(b) $\frac{\text{ml. 0.1 N NaOH} \times 0.0255 \times 100}{\text{g}} = \%$ free 2,4,5-T

Discussion

Chlorophenols have also been found by this laboratory in some ester formulations now on the market. These formulations analyzed in the order of 2 to 3% chlorophenols on an extracted acid basis by both chemical and infra red methods. This would raise the acid equivalent analysis of the formulations about 1 to 1.5% on the usual 3.34 or 4.0 lbs. acid eq. per gallon formulation.

An extraction method is presented which could be used to supplement the AOAC method when the presence of chlorophenols is suspecte

This procedure is based on the extraction and isolation of the acid after the ester has been saponified followed by the acid-base titration. The same comments apply to this titration as to the titration in part I.

It is recommended to the committee that the following method should be investigated further as it appears to work fairly well on many formulations but one cannot be sure that it would work equally well on all formulations. The main difficulty arises in trying to break the emulsions formed by wetting agents whose compositions are unknown to the analyst. Perhaps through co-operative effort this problem can be overcome.

Proposed Extraction Method for 2,4-D in Ester Formulations

1. Principle

The 2,4-D ester present is saponified with alcoholic KOH solution. After evaporating off the alcohol the solution is acidified and the 2,4-D is extracted with methylene chloride which is evaporated off and the acid is titrated with 0.1 N NaOH.

2. Reagents

(a) Sodium hydroxide. Standard 0.1 N solution.

(b) Methylene chloride, preferably redistilled.

(c) Sulfuric acid, reagent grade, 1-4 dilution.

(d) Methyl orange indicator.

(e) Methanol, ACS grade or other suitable alcohol.

(f) Methanol - KOH solution. Dissolve 12-14 grams of KOH in water and after the solution has cooled to room temperature dilute to 100 ml. with methanol. This solution is standardized against 0.1 N HCl using phenolphthalein indicator.

3. Procedure

(a) Weigh accurately into a 125-ml. soxhlet extraction flask approximately 2.5 grams of sample. Add a sufficient amount of methanol - KOH solution to completely saponify the sample.

(b) Add 25 ml. of methanol and 20 ml. of water and a few boiling chips to the solution. Connect the flask to a water cooled condenser and reflux on a hot plate for 1.5 hours.

(c) Remove the flask from the condenser after washing down with water and then cool.

(d) Transfer the solution to a 400-ml. beaker, washing out the extraction flask with methanol. Place the beaker on a steam bath and evaporate off the methanol.

(e) Cool the beaker and wash the water solution into a 300 ml. pear-shaped separatory funnel. Make acid to methyl orange with 1: H_2SO_4. Add 50 ml. of redistilled methylene chloride and shake thoroughly. Allow the layers to separate. Draw off the methylene chloride layer, and wash it with 25 ml. portions of distilled H_2O to remove the mineral acid. Extract the water layer twice more with 50 ml. portions of methylene chloride as above. Combine the washed methylene chloride layers in a 400-ml. beaker. Add 25 ml. of water and a few boiling chips and evaporate off the methylene chloride on a steam bath.

(f) Cool the water mixture and add 100 ml. methanol to dissolve the extracted acid.

(g) Titrate with 0.1 N NaOH taking readings at pH 7 and pH 10.

$$\frac{0.1\text{ N NaOH} \times 0.0221 \times 100}{\text{sample weight}} = \%\ 2,4\text{-D}$$

The following table shows the results obtained by this method.

Table II

Sample	% 2,4-D to pH 7	% 2,4-D to pH 10
1. Dow formulation. 2,4-D = 25.2% by specification analysis. (saponification).	24.5 24.4	25.0 25.3
2. Dow formulation with 5% 2 4-dichlorophenol added. 2,4-D = 25.9% (calculated)	24.1 24.1	30.8 30.8

After the acid has been extracted and dried the impurities present can also be determined by an infra-red spectrographic analysis if the equipment is available.

III The Determination of 2,4-Dichlorophenol in Formulation of 2,4-D

The method presented below works very well with amine salt formulations. With ester formulations some 2,4-dichlorophenol is indicated even on samples that are known to contain none. Thus a value of up to 0.5 - 0.6% does not appear to be significant in the case of esters. The reason for the high values is not known as yet. Each constituent of an ester formulation was determined separately without showing the presence of 2,4-dichlorophenol but the formulation made from these materials showed an apparent value of 0.5%.

Proposed Method

1. Scope

This method is applicable to the determination of 2,4-dichlorophenol in the presence of the oils, amines, esters, and wetting agents used in the various formulations of 2,4-D acid.

2. Principle

The 2,4-dichlorophenol is steam-distilled from an aqueous acid mixture and the distillate is collected in a receiver containing an aqueous base. The amount of iodine that will react with the 2,4-dichlorophenol, producing 2,4-dichloro-6-iodophenol, is determined.

3. Apparatus

(a) A standard steam-distillation apparatus filled with a 500 ml. distillation flask.

(b) Erlenmeyer flask, 500 ml.

4. Reagents

(a) Sulfuric acid, approximately 2 N solution. Pour 56 ml. of concentrated H_2SO_4 (97%) into about 800 ml. of water and dilute the solution to 1 liter.

(b) Sodium carbonate, approximately 1 N solution. Dissolve 58 grams of anhydrous sodium carbonate in about 400 ml. of water and dilute the solution to 500 ml.

(c) Iodine, 0.1 N solution. Dissolve 12.7 grams of iodine and 27.9 grams of potassium iodide in about 100 ml. of water and dilute the solution to 1 liter.

(d) Sodium thiosulfate, 0.1 N standard solution.

(e) Starch indicator solution. Make a paste with 3 grams of soluble starch in about 15 ml. of water and pour the paste into a liter of boiling water. Stir the water until the starch has dissolved.

5. Procedure

(a) Place 1 to 3 grams of sample weighed to the nearest milligram in the 500-ml. distillation flask. Add 100 ml. of 2 N sulfuric acid and attach the flask to the distillation apparatus.

(b) Place 5.0 ml. of 1 N sodium carbonate in the 500-ml. Erlenmeyer flask and use the flask as the receiver on the distillation apparatus.

(c) Steam-distill until 150-175 ml. of distillate has collected in the receiver.

(d) Pipette 25.0 ml. of 0.1 N iodine into the receiver containing the distillate and let the solution stand for 5 minutes, then acidify the solution with 10 ml. of 2 N sulfuric acid.

(e) Titrate the excess iodine with 0.1 N sodium thiosulfate, using starch indicator solution.

(f) Perform a blank titration as follows: Place 5.0 ml. of 0.1 N sodium carbonate and 150 ml. of water in the Erlenmeyer flask. Pipette 25.0 ml. of 0.1 N iodine into the flask and let the solution stand for 5 minutes. Then acidify the solution with 10 ml. of 2 N sulfuric acid and titrate the iodine with 0.1 N sodium thiosulfate, using starch indicator solution.

6. Calculation

(a) ml. 0.1 N sodium thiosulfate (blank titration) - ml. 0.1 N sodium thiosulfate (sample titration) = ml. 0.1 N iodine used to react with the 2,4-dichlorophenol.

(b) $\frac{\text{ml. 0.1 N iodine} \times 0.00815 \times 100}{\text{sample weight}} = \%$ 2,4-dichlorophenol

7. Notes

(a) The reaction between 2,4-dichlorophenol and iodine is as follows:



One mole of iodine is equivalent to 1 mole of 2,4-dichlorophenol

(b) The analytical procedure is not specific for 2,4-dichlorophenol. Many other phenols will react similarly.

(c) The sample used for the determination should not contain over 0.15 grams of 2,4-dichlorophenol.

8. Literature Reference

Kohn, Sussmann, Monatsh. 46, 594 (1925).

IV Conclusions

From the preceding work it can be seen that the presence of dichlorophenols in amine type formulations can be readily detected or

analyzed to eliminate any contribution it would make towards the 2,4-D content.

However, in the case of ester formulations, a small quantity of dichlorophenols, possibly up to 1% in the initial acid, might go undetected or give results whose validity could be questioned. It appears that any gross contamination would be readily detected.

The above methods are entirely chemical and should be able to b performed by any laboratory now checking weed killers by the AOAC methods. Those laboratories to which an infra red spectrometer would be available (such as state labs with access to university facilities) have another method of analysis. Using methods I or II, the 2,4-D acid and accompanying impurities could be isolated, and an infra red spectrum of the acid would show the amount and identity of the impurities present. An infra red spectrum could also be made on the formulation and compared with a standard to detect any deviation. Some users are already doing this.

V Suggestions for Further Work

1. It is felt that the method for esters presented in part II should be tried in the laboratories of the other members of the technical subcommittee. Special attention should be given to any modifications necessary in order to make the method applicable to formulations containing the various wetting agents used.

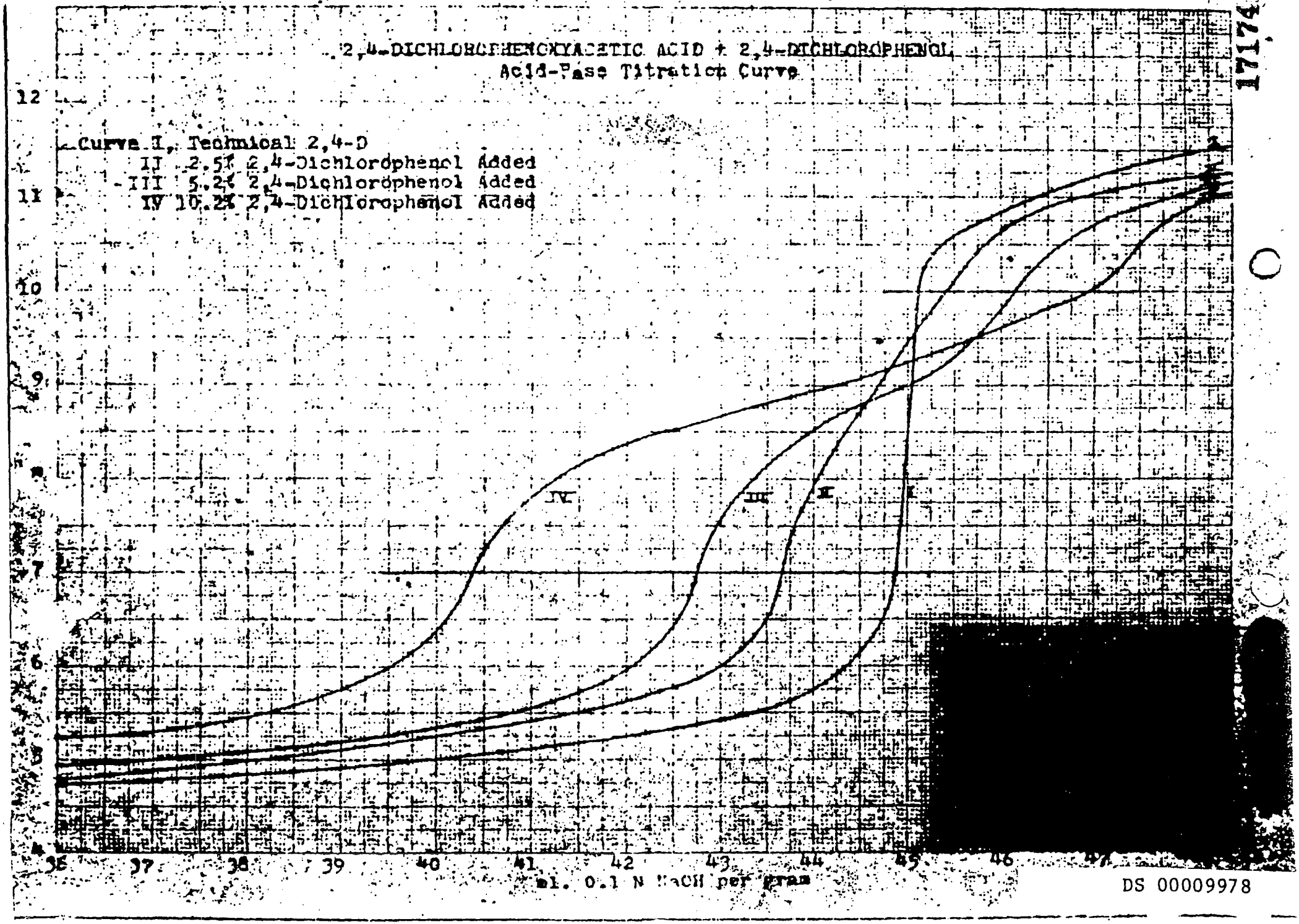
2. The method presented for phenols in part III is apparently not the approach the subcommittee wishes to take but it is presented here for information purposes and for the consideration of the subcommittee. Some work would have to be done to refine the procedure to give better results with ester formulations.

3. It is also suggested that the methods presented be tried on 2,4,5-T formulations with the hopes that they may be applied with little or no modification.

4. Some work is being done with the infra red spectrophotometer in analyzing ester formulations directly both qualitatively and quantitatively. A recent article on the subject appeared in the Ontario Research News, Vol. VII No. 2, April-June 1955 published by the Research Division, Hydro-Electric Power Commission of Ontario, Toronto, Ontario, Canada. It was "Infra Red Analysis of Herbicides" by D. C. Cordingley.

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The Dow Chemical Company cannot assume any liability in connection with the use of these methods.


2,4-DICHLOROPHENOXYACETIC ACID + 2,4-DICHLOROPHENOL
Acid-Base Titration Curve
Curve I, Technical 2,4-D
II 2.5% 2,4-Dichlorophenol Added
III 5.2% 2,4-Dichlorophenol Added
IV 10.2% 2,4-Dichlorophenol Added
12
11
10
9
7
6
5
4
IV
III
II
I
36
37
38
39
40
41
42
43
44
45
46
ml. 0.1 N NaOH per gram

DS 00009978

October 29, 1962

Mr. F. W. Jarvis

Mr. M. F. Wilkerson

Dow Patent

RE: Mixed Alkyl Esters of 2,4-D and 2,4,5-T

COPY

We are attaching copies of H. S. Weiner's letter of October 5th and D. M. Warburton's letter of September 4th on subject. Oversimplified, The Dow Chemical Company contends Diamond Alkali Company is infringing their patents which claim mixtures of various lower alkyl esters of 2,4-D and 2,4,5-T, in limited amounts, alone and in combination with a hydrocarbon oil, permit lower freezing point compositions. This subject has been under running discussion between our Patent Department and Dow's Patent Department for almost a year now. At this point, Messrs. Warburton and Weiner have recommended that we take out a license under subject patent. I personally cannot agree with their recommendations and counter-suggest we advise Dow our chemical know-how and, indeed, practice in this area predate the issuance of their patent and hence we are exempted. I feel Dow should also be advised, in view of this and to preserve present good relationship, we are willing to accept a royalty-free license position under this patent and by so doing acknowledge to outsiders we were operating under their license.

My conclusions are based on the following observations:

1. Dow first called this patent to our attention the latter part of 1961, immediately following the sale of Butyl-T Ester to the U. S. Army Chemical Procurement District. The Chemical Procurement bid invitation and specification clearly fell within the realm of the Dow patent. At this time a rather complete examination of this situation with Newark personnel indicated we not only practiced this chemistry prior to the date of Dow's patent, but Ray Guidi and others at that plant were willing to give dispositions to this effect. In addition, one of our lab notebooks confirmed this, unfortunately not specifically by date. A complete examination of old Kolker records was impossible due to the loss of most of these records during the 1960 Newark explosion. Further an examination of Cleveland contract and purchase records did not turn up conclusive evidence which could be used to definitely establish our predating Dow's patent. Despite all of this, the key people involved express confidence of the validity of our position regardless of the absence of evidence to make an air tight case in court.

2. Dow's actions are not those of a corporation who is completely confident of their own position. They initially asked for 5% royalties and they later modified this to 1-1/2% royalties with a forgiveness clause prior to November 1, 1961.

Cont'd —

Dow Patent

3. There is no uniformity of opinion as to how much of our present, as well as historical production at Newark, falls within the scope of this patent. I am fearful acceptance of Dow's current 1-1/2% royalty offering would literally leave us liable for this same royalty payment on the bulk of our total production at Newark.

I will be happy to discuss this subject further at your indication, and I believe it is safe to say both Messrs. Warburton and Weiner will be happy to further expound their views.

M. F. Wilkerson

MFW:vk
enc.
cc: Mr. D. M. Warburton - Concord
Mr. H. S. Weiner
Mr. R. A. Guidi - Newark
Dr. H. E. Everson - Concord
Mr. R. G. Richards

COPY

DS 00011465 17176

Diamond Alkali Company

OFFICE CORRESPONDENCE

October 5, 1962

TO

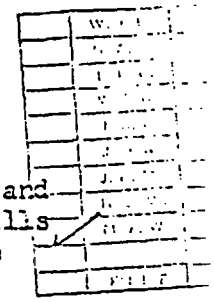
FROM

Mr. M. F. Wilkerson

Mr. H. S. Weiner

SUBJECT: Mixed Alkyl Esters of 2,4-D and 2,4,5-T

OCT 5 1962



This is in reply to your request for comments on the subject memo of September 14th from Dick Warburton.

There is no question but that the production of mixed esters of 2,4-D and 2,4,5-T made against government order #DA 30-070-CML-1635, NY 2-612 falls within Dow patents. The subsequent negotiations with Dow were for the purpose of reducing any payments to them down to an absolute minimum (preferably zero) because of selling material that fell within their patent claims. The two arguments which were used in the discussions with Dow were:

a. Dow had used a questionable technique in their enthusiasm for having the government specify material which fell within Dow's patents.

b. Validity of Dow's patents may be voided if litigation is pursued by Dow.

Dow originally was pressing for a royalty of 5% of sales together with an annual minimum. At the end of the discussions, Dow became willing to accept a license fee of 1.5% with no annual minimum. This is a very reasonable fee for a specialty license.

Although we have questioned the validity of Dow's patents, Dick Warburton has stated that we do not have adequate data to assure ourselves that we could break the patents. It would be fairly expensive to search out additional information for use in trying to break the Dow patent, assuming that this information exists.

For many years our Newark plant has been producing some materials which might be questionably interpreted as falling within Dow's patents. If Dow vigorously pursued analysis of some of our field materials, they could make the situation uncomfortable for us; and they might use this approach if we antagonize them further in the particular area in question.

Based on the information we now have on hand, I would recommend that we accept the 1.5% royalty fee on the complete block of Dow patents and assume that the only products which we have produced and are producing that fall within these patents has been the one specific government order in question.

The agreement that Dow offers is cancelable at anytime at our desire; thus, at anytime we feel we have enough information to break the Dow patents we can cancel our agreement. Furthermore, the agreement which Dow offers, essentially overlooks any activity in the patent area prior to November 1, 1961. This means that even if Dow should decide at any future time that our normal production over the past many years infringes their patent, they still would not request royalty payments on any material produced prior to

17177

November 1, 1961. However, if we did not accept their present proposal, Dow would not be subject to this time limitation.

I am assuming that Dick Warburton will comment if he disagrees with the presentation in this memo.

H. S. Weiner

HSW:nk

cc: Mr. D. M. Warburton

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DOW THE DOW CHEMICAL COMPANY

August 31, 1962

ABBOTT ROAD BUILDINGS
MIDLAND, MICHIGAN

Mr. J. O. King
Diamond Alkali Company
Union Commerce Building
Cleveland 14, Ohio

Dear Mr. King:

Russ Ashworth has requested us to furnish you with a "complete" analysis of 2,4-Dichlorophenoxyacetic Acid.

Our current sales specification has the following requirements:

2,4-Dichlorophenoxyacetic acid minimum	99.0%
Bromine absorption (calculated as 2,4-dichlorophenol), maximum	0.5%
Freezing point, minimum	135° C

We are enclosing our analytical method number 21310 covering the determination of the above items. The Assay method shown is that recommended by the Association of Official Agricultural Chemists. The bromine absorption determines unsaturates which are reported as 2,4-Dichlorophenol. The freezing point determination of course is just another method of establishing a minimum purity. While not a part of the specification, the following impurities might be present in the amounts shown. Inorganic chlorides, calculated as NaCL, could be present up to 0.15%. The sodium salt of 2,4-D could be present up to 0.1%. Water could be a maximum of 0.1%. Diphenoxy compounds and trichlorophenoxyacetic acid if present will be found as traces. The items covered in this paragraph are not routinely determined on each lot and are not a part of the specification.

We hope the above information will answer the questions which you have had.

Very truly yours,

W. J. McCoy

W. J. McCoy
Resale Products Section
Agricultural Chemicals Sales

eb

DS 00025788

Enc.

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THE DOW CHEMICAL COMPANY

MIDLAND MICHIGAN

ANALYTICAL METHOD

March 26, 1958 Method No. 21310

2, 4-DICHLOROPHENOXYACETIC ACID

A. Scope

This method is applicable to the quality testing of 2, 4-Dichlorophenoxyacetic Acid (2, 4-D). Procedures are given for determining the assay, bromine absorption, and freezing point.

B. Assay

1. Principle

The total acidity is determined by titration with standard sodium hydroxide solution and is reported as 2, 4-dichlorophenoxyacetic acid.

2. Reagents

(a) Alcohol, 95% ethyl alcohol (2B), neutralized to the phenolphthalein indicator end-point.

(b) Phenolphthalein indicator, 1% solution in 95% ethyl alcohol.

(c) Sodium hydroxide 0.1 N standard solution. Dilute 8.00 grams of 50% sodium hydroxide solution with recently boiled distilled water to one liter, and standardize against benzoic acid of known purity.

3. Procedure

(a) Weigh a one-gram sample into a 250-ml. Erlenmeyer flask. Dissolve in 75 ml. of neutral alcohol and titrate with 0.1 N standard sodium hydroxide, using one ml. of phenolphthalein indicator.

(b) Optionally, the titration may be followed with a standard pH meter such as the Beckman Model H-2. A pH reading of 9 is used as the end-point.

4. Calculation

$$\frac{(\text{ml. of } 0.1 \text{ N NaOH}) \times 0.0221}{\text{grams of sample}} \times 100 = \%\ 2, 4\text{-dichlorophenoxyacetic acid.}$$

C. Bromine Absorption

5. Principle

The sample is treated with an excess of bromine from a standard bromate-bromide solution. The amount of bromine absorbed is calculated to dichlorophenol.

6. Reagents

(a) Bromate-bromide, 0.1 N solution. Dissolve 2.8 grams of reagent grade potassium bromate and 12 grams of potassium bromide in water and dilute to one liter.

(b) Sodium thiosulfate standard 0.1 N solution. Dissolve 25 grams of sodium thiosulfate, $Na_2S_2O_3 \cdot 5H_2O$, and 0.5 gram of sodium carbonate in one liter of water. Standardize against 0.1 N potassium iodate, according to the procedure given in Kolthoff and Sandell (see 12).

(c) Sulfuric acid, 1: 4 solution in water.

(d) Potassium iodide, 5% solution in water.

(e) Starch indicator solution. Mix one gram of soluble starch and five mg. of mercuric iodide with a little cold water. Add more water to make a fluid suspension, and pour this into 500 ml. of boiling, distilled water. Boil for several minutes and then cool to room temperature. Keep in a glass-stoppered bottle.

7. Procedure

(a) Weigh a five-gram sample and transfer it to a 500-ml. glass-stoppered flask containing 200 ml. of water. Add exactly ten ml. of 0.1 N standard bromate-bromide solution, 35 ml. of 1: 4 sulfuric acid and stopper immediately. Shake vigorously for 15 seconds and allow to stand for ten minutes. Add 15 ml. of 5% potassium iodide solution and mix well. Titrate the liberated iodine with standard 0.1 N sodium thiosulfate solution, adding a few ml. of starch indicator solution near the end-point.

(b) Run a blank in the same way (without any sample). Subtract the sample titration volume from the blank titration volume to obtain the measure of bromine consumed by the sample.

8. Calculation

$$\frac{(\text{net ml. of 0.1 N reagent}) \times 0.00815}{\text{grams of sample}} \times 100 = \%\ 2,4\text{-dichlorophenol.}$$

D. Freezing Point

9. Principle

During the crystallization of a material from its liquid state, a maximum temperature is reached which is maintained for a period of time. This temperature is considered the freexing point and is an indication of the purity of the material.

10. Apparatus

(a) Thermometer, partial immersion, calibrated in 0.2°C, range including 135°C.

(b) Agitator, nichrome wire with a 10-mm. diameter coil at the lower end to encompass the thermometer.

(c) Test tubes, 20 x 150-mm. and 38 x 200-mm., Pyrex. Support the smaller tube concentrically in the larger which serves as an air bath. Pass the thermometer into the inner tube through a one-hole cork stopper which is slotted to permit movement of the wire agitator.

11. Procedure

(a) Into the 20 x 150-mm. test tube, place sufficient sample that the melt will cover the thermometer up to the immersion mark.

(b) After melting the sample, place the tube in the air bath. Agitate continuously. After crystallization starts, record the maximum temperature as the freezing point of the sample.

E. Reference

12. Literature References

Kolthoff, I. M., and Sandell, E. B., "Textbook of Quantitative Inorganic Analysis," Third Edition, Chapter 39, The Macmillan Company (1952).

* * * * * * *

The analytical procedures given herein have been adapted from literature sources or developed upon the basis of experimental data which are believed to be reliable. In the hands of a qualified analyst they are expected to yield results of sufficient accuracy for their intended purposes. However, The Dow Chemical Company makes no representation or warranty whatsoever concerning the procedures or results to be obtained and assumes no liability in connection with their use. Users are cautioned to confirm the suitability of the methods by appropriate tests. Anyone wishing to reproduce or publish the material in whole or in part should request written permission from The Dow Chemical Company.

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NACA 24D COMMITTEE

Esters of 2,4-D and 2,4,5-T

1. Butyl Ester
2. Isopropyl Ester
3. 2-Ethylhexyl Ester
4. Iso-Octyl Ester
5. Polyethyleneglycol Ester
6. Butyoxyethoxypropyl Ester

Amine Salts of 2,4-D and 2,4,5-T

1. Dimethylamine salt of 2,4-D
2. Dimethylamine and Triethylamine mixed salts of 2,4-D and of 2,4,5-T
3. Triethylamine salt of 2,4-D and 2,4,5-T
4. N-Oleyl-1,3-Propylenediamine salts of 2,4-D and 2,4,5-T
5. Isopropylamine salt of 2,4-D and 2,4,5-T
6. Diisopropylamine salt of 2,4-D and 2,4,5-T
7. Triisopropylamine salt of 2,4-D and 2,4,5-T

Miscellaneous hormone formulations

1. Dimethylamine salt of MCP
2. Dimethylamine and Triethylamine mixed salts of MCP
3. Sodium salt of 2,4-D and 2,4,5-T
4. Wettable powders of 2,4-D and 2,4,5-T
5. Isooctyl ester of 2,4,5-TP (Silvex)
6. Dissolved 2,4-D and 2,4,5-T acids in solvents and emulsifiers

DS 00025792

Diamond Alkali Company

INTER-OFFICE CORRESPONDENCE

DACO 118-1A

DATE: August 23, 1960

TO: Mr. J. O. King-Cleveland

FROM: Mr. C. L. Troph-Chicago

SUBJECT:

REPLY REQUESTED BY (DATE)

SWIFT & COMPANY
CHICAGO, ILLINOIS

CC: Mr. H. S. Weiner
Mr. R. Guidi

Subject have individual customer presently hospitalized, who has written them stating that while using a knapsack sprayer charged with Gold Bear 40 he experienced spillage which saturated the shoulder strap of the sprayer. He admitts that he did not wash this material off and now is afflicted with a "poison ivy" like skin eruption characterized by pustular inflammation, itching etc.

I briefly discussed hyperkeratosis and other forms of dermatitis sometimes caused by chlorinated hydrocarbons. Apparantly this man is seeking only advice in dealing with his problem and does not anticipate legal action. In any event, I told Swift that since the inquiry was addressed to them, we would be disinclined to contact this person directly; however, we would be happy to contact Swift and offer any appropriate advice. I also pointed out that we naturally could not recommend medical treatment but perhaps could suggest a qualified specialist familiar with this disease.

Will you please forthwith see that D. J. Campbell of the subject is contacted relative to this problem.

C. L. TROPH

CLT/sb

DS 00022474

17184

THE DOW CHEMICAL COMPANY

POST OFFICE BOX 512
MIDLAND, MICHIGAN 48641

November 22, 1966

Mr. C. L. Dunn
Synthetics Department
Hercules Incorporated
910 Market Street
Wilmington, Delaware 19899

Dear Chuck:

Enclosed is the draft of the proposed comments on behalf of the NAC ITFPHT, which we discussed by telephone November 22.

Although we have until December 8 to submit comments I would like ours to be mailed by Friday, December 2, to avoid any slip-up. Therefore, I will need your suggestions and those of the others receiving this letter early in the week of November 28.

As discussed, we will not hold up the letter for any discussions with FDA and hope that our comments will provide the opening for a conference with the proper parties in FDA if we sense the need for one.

I would suggest the telephone for comments, and for your convenience my telephone number is (area code 517) 636-5014.

Sincerely,

G. E. Lynn, Chairman
ITF on Phenoxy Herbicide Tolerances

cc: Members ITFPHT
Dr. L. L. Danielson
Dr. W. L. Popham
J. A. Noone

abc

Enclosure

DS 00025741

17135

- DRAFT -

Hearing Clerk
Room 5440
Department of Health, Education and Welfare
330 Independence Avenue
Washington, D. C. 20201

Dear Sir:

The National Agricultural Chemicals Association Industry Task Force on Phenoxy Herbicide Tolerances representing the basic manufacturers (Chipman Chemical Co., Inc., Diamond Alkali Co., The Dow Chemical Co., Hercules Inc., Monsanto Co., Thompson Chemicals Corp., and the Thompson-Hayward Chemical Co.) of 2,4-D (2,4-dichlorophenoxyacetic acid) herbicides; submits the following comments concerning the proposal published in the Federal Register of November 8, 1966, pages 14359-14360, to establish tolerances of 2,4-D in or on certain grains by amending 21 CFR 121.142 and adding new sections under part 121.____.

1. The industry manufacturers and markets 2,4-D products registered by the USDA for uses on the grains listed which are not covered by the salt or ester forms given in the proposal.

2. In §121.142 as proposed there are certain items which we do not understand, or believe to be typographical errors:

   In paragraph (b)(2) We are not familiar with the usage of "n" in the nomenclature: n-oleyl-1,3-propylene diamine. The "normal" configuration of oleyl is usually considered inherent.

   In paragraph (b)(3) the proposed list includes "isopropyl methyl octyl (isooctyl)," which would appear to lack necessary punctuation. We presume it should read "isopropyl, methyl, octyl (isooctyl),".

In paragraph (b)(d) we do not recognize the name "polyethylene glycol butyl ether" as an ester moiety of 2,4-D now being marketed. However, propylene glycol butyl ether esters are registered and marketed. Clarification of this apparent discrepancy is needed.

In paragraph (b)(3) "tetrahydropropyl" as an ester moiety is unknown to us. However, the tetrahydrofurfuryl ester is one which has been registered and marketed. Clarification of this apparent discrepancy is needed.

3. Many of the salt and ester forms of 2,4-D now manufactured, registered, and marketed for use on grain are not covered by the salt and ester forms given in the proposal. Furthermore, it is likely that future availability and manufacturing economics will dictate the desirability of using ester and salt moieties other than those listed in the proposal.

In order to overcome these two deficiencies in the present proposal, and to avoid a hardship on the industry with respect to their particular needs for latitude in the selection of economic 2,4-D forms for manufacture, and the hardship which could be worked on the farmer due to the lack of suitable and economic 2,4-D forms, we propose that the salt and ester forms permitted by the order follow a more generic description as follows:

§ 121.142 ------

(b) ------

(1) The inorganic salts, such as calcium, lithium, magnesium, potassium, and sodium.

(2) Organic amine salts, such as alkyl, alkylene, or alkanol amine salts.

(3) Organic esters, such as alkyl or alkoxyalkyl esters, or other esters as tetrahydrofurfuryl.

The other, but much less preferred, alternative would be to amend the list of salts and ester forms according to comments received from individual companies for inclusion of the 2,4-D forms they manufacture and market.

In view of the wide differences in the specific salts and esters listed in the proposal as published we can only assume that it was the intent of the proposal to provide for equal treatment of all of the 2,4-D forms now being used. We favor such an objective, but as pointed out the list falls short of including all of the 2,4-D forms now marketed and those that may be marketed in the future.

We respectfully request that our proposals as set forth above be considered as means to accomplish the objective as we have interpreted it.

Sincerely,

G. E. Lynn, Chairman

Diamond Alkali Company

OFFICE CORRESPONDENCE

DATE 3/25/65

TO JOHN CORT, JR. ✓

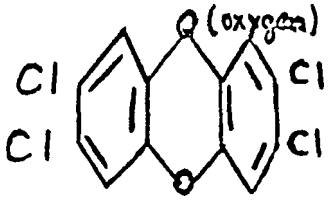
FROM E. L. CHANDLER

SUBJECT CHLOROACNE - DOW MEETING

cc: F. R. Kennedy - Mgr., Newark plant
J. O. King
M. F. Wilkerson

On March 24, Mike Kennedy and I met with two people from Hooker Chemical Co., two from Hercules, and with the Dow group to discuss the toxicological impurities associated with 2,4,5 trichlorophenol and related materials.

Dr. Rowe of Dow Chemical opened the meeting by stating that they had operated for 25 years without trouble; but, in the last year, they had 60 to 70 cases of chloroacne. Ten of these were moderate, and five to ten were extremely severe. Their approach was a qualitative one at first. They wanted to find the causative material, learn how to identify it, and try to avoid continual trouble with the unknown. They tested various materials from tar fractions and from, as they put it, "gunk", etc. They found that there are a number of suspect materials, probably 26 or 27; but the major "bad actor" that they identified and which seemed to consistently cause the problem was 2,3,7,8-Tetrachlorodibenzo p-Dioxin (symmetrical).



→ 2,3,7,8-TETRACHLORODIBEN
p-Dioxin
(Symmetrical)

This incidentally was previously listed as a suspect material by Cy Perkins of our company. A similar material is the unsymmetrical 1,3,7,8-TCDBD, also sometimes listed as 2,3,7,9-TCDBD.

The Dow people used the white glove approach and found this contaminant on tool handles, benches, instruments, and other fomites. In test animals, they could consistently cause the symptoms to appear. Dr. Holder of Dow, one of their medical doctors, had excellent color slides of the various patients. The difficulty starts with multiple blackheads resulting in closed cystic structures which make the patient look like he needs to wash his face. The disease develops slowly, not appearing until six weeks to two months after mild exposure but appearing in five to seven days with very heavy exposure.

One bench chemist has been under treatment for two years and his face is starting to show signs of clearing. Dr. Holder says that he believes this man's problems will be solved in another six months. Dr. Sadek, who does their microscopic work in connection with their animal laboratory, showed photo micrographs of the cysts as they formed in the ears of rabbits. The cysts correlated with those found on the faces of the men.

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Basically, there is a carotinoid deposit in the hair follicles and oil ducts in the face. These eventually go from the blackhead stage to form a closed, heavy core deposit. The chemical cannot be found in the facial tissues or in the cores, but the problem still persists after exposure. The best description of the acute stage is that the facial tissues resemble the exaggerated surface texture of an orange, rather glazed and marbly with the enclosed hard core deposits.

A secondary symptom, which does not correlate directly with the amount of facial dermatitis, is a fatigue reaction where the employee is completely listless, tired out, and nearly incapacitated. A complete biopsy of liver, kidney, etc., shows no degeneration of major organs. A complete clinical examination of the patients showed no measurable affect on heart, blood pressure, respiration rate, blood sugar, etc. The fatigued patients seemed to be helped by heavy doses of vitamins, perhaps related in some way to the carotene metabolism of the body (involving vitamin A, etc.)

An oral dose of 17 micrograms immediately killed the test animals. The Dow people did not lower this dosage to obtain an LD_{50} but decided that, when they can detect this compound, it should not be in the product. They found that, after exposure to the material, washing within 15 minutes did not help a great deal, but did slow down the speed at which the symptoms appeared. Washing after one hour was of absolutely no help whatsoever in reducing total dermatitis or speed of appearance of the reaction. Moderate scrubbing with detergent does not remove this material. Extremely hard scrubbing can accomplish the task or the use of solvents, such as 1,1,1-trichloroethene.

Dow has developed a new analytical method in which they have confidence in their sensitivity to 1 ppm. They can only state in levels below this that some may be present below the 1 ppm. They stated that they have not used micro-colorimetric methods, and the electron capture tests that they ran made only a very slight improvement in sensitivity with this compound. Their analytical chemist stated that the electron cell saturates because of the presence of other materials in high concentration compared to the dioxin.

This material has some strange properties. It has a fairly high vapor pressure but nevertheless is quite persistent as a contaminant. It can be separated from benzene by boiling if it is not carried down to dryness. The Dow people are extremely careful in all of their work with this compound. They use PVC throw-away gloves, and all samples are burned in a special furnace which operates at 800°F. These samples are sealed before going to the burner. They use bioassay methods on rabbits for qualitative checking only.

The Dow people state that they intend to set a limit of zero with sensitivity of plus or minus 1 ppm on this material. They have analyzed materials from other companies. including our company, and have found amounts as high as 10 ppm in 2,4,5-T acid and 20 to 30 ppm in phenates.

They have made a single application to the ears of test rabbits and found that 20 ppm will not give folliculitis. Forty ppm does give a slight effect, and 100 ppm is severe. They have made repeat applications of from 10 to 100 ppb, and 25 of these treatments do not cause a response; however, 1000 ppb (1 ppm) gives a slight response with nine applications and a severe reaction with 11 applications.

They conclude, therefore, that 1 ppm with repeat exposure can create a real problem.

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Dow's people outlined a method for extracting and running samples on 2,4,5-T; 2,4,5-TP; and phenols. It involves a chloroform extraction, followed by

a caustic wash, and a reduction by boiling to one-tenth the volume before putting it in the chromatograph. They have given the gas-liquid chromatography method to us, along with analytical-grade dioxin material. Mike Kennedy has these materials and intends to pursue the laboratory work necessary to ascertain where and how much, if any, of this dioxin appears in our 2,4,5-T process.

The purpose of this meeting was obviously designed to help us solve this problem before outsiders confuse the issue and cause us no end of grief. Dow is sending the test results on our material to us, incidentally; and this will further check our technique, etc.

Sincerely,

E. L. Chandler

ELC:een

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— AGNEW V DOW
MOYER V DOW

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07

T23.14-23-Y

CABLE ADDRESS DOWCHEMCO
BRANCH SALES OFFICES
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SAN FRANCISCO
PHILADELPHIA
LOS ANGELES
WASHINGTON
SAINT LOUIS
CLEVELAND
HOUSTON
CHICAGO
SEATTLE
DETROIT
BOSTON

THE DOW CHEMICAL COMPANY

MIDLAND • MICHIGAN

TRADE DOW REG. U. S. PAT. OFF.

December 15, 1949

DOW 7511294
MD069799

Dr. V. A. Drill
Department of Pharmacology and Therapeutics
Wayne University College of Medicine
1512 St. Antoine Street
Detroit 26, Michigan

Dear Dr. Drill:

We are sending to you under separate cover, samples of 2,4-D (2,4-dichlorophenoxyacetic acid) and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) for use in the toxicological studies on dogs.

The sample of 2,4-D being sent is regular production material assaying 98.5% and having a freezing point of 132.8°C.

The sample of 2,4,5-T being sent is also regular production material assaying 100% and having a freezing point of 148.8°C.

Both of these materials are being supplied to you in the acid form. Both are fairly soluble in olive oil and both can easily be put in aqueous solution with caustic. I believe you will find that a slight excess of caustic is required to put these materials in solution and that once in solution, a large part of the excess alkali can be neutralized. Hence, for a 5.0% aqueous solution of the sodium salt of 2,4-D, the pH after solution is effected, can be adjusted down to 7.2 with HCl; with 2,4,5-T the final pH of a 1.0% aqueous solution can probably be in the neighborhood of 10.

When 2,4-D or 2,4,5-T is used as an herbicide, the concentration usually ranges from 0.1% to 0.2%. The active material may be applied in any one of a number of forms depending upon the particular requirements of the job. The most common forms are the sodium salt, alkanol amine salts, and esters.

Almost all the toxicological work so far reported deals with 2,4-D administered either as the free acid in oil or as the sodium salt in aqueous solution at a pH of 7.2. We have conducted a fair amount of toxicological work on the other forms of 2,4-D and also on 2,4,5-T in its various forms. We have observed that the form of the material makes little difference to warm blooded animals and that, acutely, there is not much difference between 2,4-D and 2,4,5-T.

The toxicity picture as we have it is given in the following tabulations:

Toxicity of 2,4-D when administered in Single Doses.

Animal	Route	Source	Approx. LD_{50} (g./kg.)
Rat	Oral	Lit. Na Salt	0.666
Rat	Oral	Dow-Incomplete	
		Na Salt	0.70
		Acid	0.5 - 0.6
		Isopropyl esters	0.5 - 0.7
Mouse	Oral	Lit. Na Salt	0.375
		Dow - Incomplete	
		Acid	0.3 - 0.5
Mouse	Sub-Cut.	Lit. Na Salt	0.280
Guinea Pig	Oral	Lit. Na Salt	1.000
		Dow - Incomplete	
		Na Salt	0.5 - 0.7
		Acid	0.5 - 0.7
Chicks	Oral	Lit. Na Salt	0.38 - 0.76
		Dow - Just started	

Toxicity of 2,4-D when administered in Repeated Doses.

Animal	Route	Source	Notes
Dogs	Sub Cut or I.V.	Lit.	Na Salt 0.200 g./kg./day-death in 2 da 0.100 g./kg./day death in 2-4 days 0.050 g./kg./day death in 3 days 0.025 g./kg./day marked affects
Guinea Pigs	Orally (?)	Lit.	Na Salt 0.100 g./kg./day 10 times in 12 day was tolerated
Rats	Orally in diet	Lit. Dow	0.1% tolerated 0.1% -caused very slight effects 0.03% clear
Mice	I.P.	Lit.	No marked histopathological findings No neoplastic growths Reproduction O.K.

DOW 751295

17194

Toxicity of 2,4-D when administered in Repeated Doses. - Cont'd.

Animal	Route	Source	Notes
Chicks	Orally	Lit.	0.028 g./kg. 3 times/week for 4 weeks - O.K. 0.280 g./kg. 3 times/week for 4 weeks - growth depression
	Orally in Diet	Dow	0.1% for 1 week - O.K. 0.3% for 1 week - O.K. except for slightly depressed growth rate.

Toxicity of 2,4,5-T When Administered in Single Doses Orally

(This information is from our data and is not complete - We are finishing it.)

Animal	Notes
Rat	LD_{50} for the acid lies between 0.5-1.0 g./kg LD_{50} for the isopropyl ester lies between 0.3 - 1.0 g./kg.
Mouse	LD_{50} for the acid lies between 0.3-0.7 g./kg
Guinea Pig	LD_{50} for the acid lies between 0.3-1.0 g./kg For both the acid and Na salt
Chick	Work just begun

Neither 2,4-D nor 2,4,5-T are more than very mild skin irritants even in concentrated form. In diluted form ready for use, they present no health hazard.

Studies conducted upon guinea pigs by Hill and Carlisle on the inhalation of 2,4-dichlorophenoxy acetic acid dust, either wet or dry, but of unknown particle size, indicate that the dust is not likely to cause systemic intoxication. This has been born out by our own experience with men handling the dust. The dust, however, is capable of causing irritation of the nose if the concentration in the breathing zone becomes sufficiently high.

The following references may be helpful if you wish to consult the literature for a more detailed description of procedures, etc.:

DOW 751296

17195

1. Toxicity of 2,4-Dichlorophenoxy Acetic Acid for Experimental Animals.
Edwin V. Hill and Harold Carlisle (Camp Detrick, Frederick, MD.)
J. Ind. Hyg. Toxicol. 29, 85-95 (1947)
C.A. 41: 3217_2 (May 20, 1947)

2. Tolerance of Farm Animals to Feed Containing 2,4-Dichlorophenoxy acetic acid.
J. W. Mitchell, R. E. Hodgson and C. F. Gaetjens (U.S. Dept. of Agr., Washington, D. C.)
J. Animal Sci. 5, 226-32 (1946)
C.A. 40 (17); 5198_2 (Sept. 10, 1946)

3. 2,4-D Toxicity. I. Toxicity Towards Certain Species of Fish.
Jos. W. E. Harrisson and Edward W. Rees (La Wall and Harrisson, Research Consultants, Philadelphia, Pa.)
Am. J. Pharm. 118, 422-5 (1946)
C.A. 41 (2529) (1947)

4. Effects of 2,4-Dichlorophenoxy Acetic Acid on Experimental Animals.
Nancy L. R. Bucher (Harvard University)
Proc. Soc. Exptl. Biol. Med. 63, 204-5(1946)
C.A. 41: 808 (1947)

Data on the acute oral toxicity of both 2,4-D and 2,4,5-T for dogs is lacking. Therefore, it is suggested that the acute oral studies be started at your earliest opportunity so that information will be available for choosing appropriate dosage levels for the 90 day feeding tests.

In the single dose experiments we suggest that a notation be made regarding any symptoms exhibited at the various dosage levels, body weights for each day during 3 or 4 days immediately following administration and on alternate days during the rest of the 2-week observation period. We do not feel that it is necessary to do any elaborate tissue studies on acutely dosed animals. We would, however, like to see animals that die and those that survive autopsied and the gross condition of the G.I. tract, liver, and kidneys noted. A few sections at critical dosage levels might also be desirable - at your discretion.

DOW 751297

In the 90 day feeding tests, we suggest that the material be administered with a part of the diet. Dosage levels cannot be decided upon until acute data is available. We would suggest that general observations, growth records, and periodic hematological examinations (initially, after 30 days, and after 90 days on the experiment) be conducted during the experiment. At autopsy, gross and histopathological studies on the liver, kidney, stomach, intestine, spleen, lung, heart, adrenal, testis or ovary, and possibly brain and vascular system are of importance. We believe that negative findings at upper dosage levels make similar studies at lower dosage levels unnecessary.

The requisition for this work has been approved and I will see that an appropriate check is deposited as before.

If there are any details which are not clear or if any problems arise, please contact us at once.

I regret that I did not have more time last week to spend with you. Nevertheless, I was very glad to get home early and avoid the snowstorm that settled on this area about 5:00 p.m. that evening. Please give my regards to Dr. Hays.

Sincerely yours,

THE DOW CHEMICAL COMPANY

V. K. Rowe

V. K. Rowe
Biochemical Research Department

VKR/mg

DOW 751298

9-12-66

Before attempting to question the validity of the requirement for restricting livestock from sprayed areas for seven days following application it is necessary that we make some reasonable assumption as to the amount of herbicide remaining on any edible forage in the treated area. In the special case of ... right-of-way spraying this is an extremely difficult thing to do since much of the material used is for the specific purpose of tree stump control and as such does not actually come into contact with the livestocks normal forage.

DOW510645

In a general review of the herbicidal literature the greatest application rate found was 6.0 # per acre (B). This value, as a maximum, has also been cited in correspondence from The New York State Cooperative Extension Service at Ithica (James E. Dewey to Paul C. Couldin, April 8, 1966) and as such seems to be a more than fair amount to assume is being sprayed on the actual forage-bearing portions of the right-of-way.

6#/acre comoutes to 62.5mgm/sq. ft. and based on the data of Grigsby and Farwell (19) to 890 mgm 2,4-D or 355 mgm 2,4,5-T per pound of forage. Just why the 2,4-D, sprayed at equivilant rates per acre, shows up at a greater concentration in the forage is unclear but is probably related to the grasses greater absorption rate for this chemical. Grigsby and Farwells data on this point is also somewhat variable with some tests showing only half as much (450mgm) 2,4-D remaining in the crops. Since right-of-way spraying uses a mixture of both 2,4-D and 2,4,5-T, some assumption is necessary as to how the 6 pounds of spray per acre is split between the two chemicals. For the purpose of calculation it will be assumed here that this split is 2:1 2,4-D to 2,4,5-T, since this arrangement will favor that compound (2,4-D) which shows up to the greatest extent in the forage. Actually, I believe the NYSE&G literature on the subject indicates a predominance of 2,4,5-T.

Based on the above assumption the amounts of chemical remaining in the forage are roughly 600mgm 2,4-D/# and 120mgm/# 2,4,5-T for a total concentration of 720 mgm/#. Although 2,4-D and 2,4,5-T differ somewhat in their toxicological properties it is well recognized that either may be consumed by livestock at rates of 100mgm/kgm for extended periods without inducing any ill effects in the animals (15&17). In order for an average ruminant (770 #) to acquire this doseage (which would cause him no harm) he would have to injest the rather unlikely amount of 48.5 # of sprayed forage per day.

Even were an animal actually to acquire the above doseage, and this assumes that not only does he actually consume 48.5 # of forage per day but that all of it comes from the sprayed right-of-way, there is ample evidence in the literature to suggest that he could continue to do so for time periods greater than 2 1/2 months (15) before even slight evidences of damage were noticed. Obviously, long before this time period could elapse, the normal loss of chemical through evaporation, penetration in the soil and dilution by periodic rainfall would act to reduce the concentration in the forage to the point that no danger whatever could possibly exist.

The above example should help to dispel any unfounded notions as to the toxicity of herbicides to grazing livestock and to put into proper perspective the obviously over-restrictive condition listed on 2,4-D labels. In assessing the forgoing remarks it should be borne in mind that the amount of herbicide chosen for the example (6#/acre) is undoubtedly far greater than the rate which would probably be used for forageable areas on the right-of-way. Actually the rate of application of these chemicals is proportional to the amount of brush and undergrowth in the area and as such an application rate of 6#/acre would indicate an almost completely overgrown area with little if any available forage.

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In addition to the above example, a perusal of the existing scientific literature discloses several points which argue against the necessity of restricting cattle from sprayed areas for seven days following application.

1. Because of the already mentioned dissipating affects of the elements on the concentration of herbicide remaining in the forage it is clear that the greatest danger of livestock poisoning is of short duration- perhaps, as suggested only for the first week following the spraying treatment. While the above example has cited evidence to show that even unusually high concentrations of herbicide are not harmful over extended time periods, there is also evidence to indicate that livestock have enormous resistance to very high doseages for short term exposures. Dr. V. K. Rowe (17) for instance has run experiments which show that single doseages of 500 and 1000 mgm/kgm of Esteron Brush Killer (1:1 2,4-D: 2,4,5-T) can be injested by livestock without having mortal effects. Even at the lower concentration this would mean that a grazing cow could accidentally drink over two gallons of the NYSE&G mixed spray without suffering any ill effects. Obviously, the possibility of such an occurrence is extremely remote but the example does indicate that the resistance of the livestock to short term exposures is so great that even very sloppy handling of the spray materials should present no untoward danger to foraging animals.

2. Grigsby and Farwell (19) in a well documented paper in 1950 have reported a succesful experiment which should also point out the over-restrictiveness of the directions on the 2,4-D label. In their tests cattle were fenced into small plots and forced to graze on land sprayed with 3.3 #/acre of both 2,4-D and 2,4,5-T for a period of two weeks. Despite the fact that the livestock were present when the sprays were applied and had no alternative but to graze the sprayed forage, they were completely healthy at the end of the two week test

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period. The above reference is from the Quarterly Bulletin of the Michigan Agricultural Experiment Station and can certainly be considered tobe unbiased.

3. Additional evidence for the low toxicity of herbicidal sprays even immediately following application can be gained from a paper by H.E. Goldstein and J.F. Long (16). These investigators actually sprayed 2,4-D and 2,4,5-T directly on livestock without causing any harmful effects. In another test cut forage was sprayed twice a day with the herbicides and then fed to the cattle without inducing any ill effects. The above experiment was continued for six straight weeks and still no illness was noted in the livestock. The above situation clearly represents a degree of herbicide accumulation which would be unlikely to be obtained in a field situation even immediately following a spraying treatment and argues convincingly for both the short and long term safeness of 2,4-D and 2,4,5-T.

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All available editions of Chemical Abstracts for the year 1966 were researched under the headings "Herbicides - in milk", and "Milk - Herbicides or Pesticides In". One reference was found (70841 H (a) in the Aug. 29th no.) and this was in the last issue available on Oct. 10, 1966. No reference to the Klingman (b) et al paper has as yet been indexed. Similarly no reference as yet exists in the abstracts for the related paper by Yip and Ney (c) which describes the analytical test method used by Klingman.

The paper by Klingman has been analyzed for incorporation into the literature study and also has been commented on as it relates to the case at hand. References (a) and (c) are being sought through the Mann Library at Cornell.

(a) Determination of 2,4-D Residues in Animal Products. D.G. Crosby and J.B. Bowers. Bull. Environ. Contam. Toxicol 1(1) 104-7 1966.

(b) Residues in the Forage and in Milk from Cows Grazing Forage Treated with Esters of 2,4-D. Dayton L. Klingman, Chester R. Gordon, George Yip and H.P. Burchfield. Weeds Vol. 14, p164-167 1966.

(c) Analysis of 2,4-D Residues in Milk and Forage. George Yip and Ronald E. Ney,Jr. Weeds Vol. 14 p167- 1966.

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July 9, 1965

Albert M. Kligman, M.D., Ph.D.
Department of Dermatology
Hospital of the University of Pennsylvania
36th and Spruce Streets
Philadelphia 4, Pennsylvania

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Dear Dr. Kligman:

I am sending you under separate cover a small amount of 2,3,7,8-tetrachlorodibenzo-p-dioxin. This is the material which is a potent acnegen and is highly toxic. I have checked back on our figures and find that the single dose oral LD_{50} for rabbits is in the neighborhood of 100 micrograms/kilogram, and we had one animal die which had received a single dose of 16 micrograms/kilogram. It is safe to say, however, that doses of 0.5 to 1.0 mg/kg are always fatal, although deaths may be delayed for 10 to 20 days post treatment. The typical clinical picture is severe liver and kidney injury.

In regard to the skin response on rabbits, we have attempted to quantitate this by applying 0.1 ml of test solution to one to two square inches of the surface of the inner face of the rabbit ear. We find that when the total dose does not exceed about 0.2 of a microgram of the acnegen, no follicular prominence or epithelial hyperplasia develops. When the total dose is about 0.5 of a microgram on this area, the response is marginal; 1 to 2 micrograms almost always produces a response, and 4 to 8 micrograms usually produce a severe response. We have not as yet been able to quantitate the dose required to cause 50% mortality from skin exposure, but we are sure it is well above the total dosages noted above.

In view of this information, it does not seem probable that the dosages shown in the accompanying suggested protocol for the human work would be likely to constitute any serious systemic hazard because the dose on a per kilogram basis would be far below that which produces any significant effect systemically in the rabbit. I might add that the rabbit is far more sensitive than the rat to this type of compound. Nevertheless, the seriousness of the consequences that might develop from testing with this type of compound require that we approach the matter in a highly conservative manner. It

is with this thought in mind that I have developed the attached protocol. The number of persons per experiment is your decision; I would suggest two as a starter. When applications are repeated, I would like to have them made on consecutive days, if it is convenient to do so. Although the time required to conduct these experiments will require several months, I believe it is the safe way to proceed, using a few people at a time with careful observations on each. The observations are to be made at your discretion, but I would urge routine SGOT's and alkaline phosphatases as a minimum.

There is another item upon which comment should be made. I have indicated in the suggested protocol that a two week observation period should be used prior to starting the next series of experiments. This is because our experience with both animals and man indicates that there is an induction period. In a few instances, we believe an eruption in the human has developed four to six weeks post exposure. Also, we have had a few serious flare-ups which have developed within a matter of days, post exposure. I have compromised on a two-week observation period, but of course, any treated individual should be watched for at least two months post test.

You asked about materials in which this test substance is soluble. I have indicated it is quite soluble in chloroform and benzene and slightly soluble in alcohol. I believe that a solution in 50/50 alcohol and chloroform would be quite appropriate for your work. In regard to covering the exposed area, I would suggest that when the treated area has dried that it be covered lightly with a gauze simply to keep the material from being brushed away or having a person contaminate his hands or clothing inadvertently.

I hope I have answered your questions, but if you have any others, please do not hesitate to contact me.

Sincerely yours,

V. K. Rowe
Biochemical Research Laboratory
1701 Building

VKR/jd

Attach.

cc: Medical Department:
Gordon, Holder, Kramer
J. E. Peterson
L. Silverstein
H. R. Hoyle
V. K. Rowe (2)
T06.25-66681-7

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raised a quandary around the country regarding disposal. I would be the first to admit that we do not have any easy answers for this problem.

There have been some recommendations made to me by staff as to what we might issue publicly, and I have personally turned them down because they do not answer the question properly.

We are, therefore, holding a national conference on the 30th of July in which we are having people come in from various segments of interest, including conservationists, to discuss this problem, to look at the solutions that some people are trying out in the States, and to see if we can develop some guidelines to solve this question of disposal, not only of those which we are trying to remove from the market, but also routine disposal of containers.

This is one action we are taking in order to get at this problem. We admit it is a problem.

Mr. BUCKWIT. You say that you suspended certain uses of 2,4,5-T because an imminent hazard exists, and you canceled rather than suspended use on food crops because, although a hazard existed in that case, it was not an imminent hazard. That statement brings to mind several questions.

First of all, do you believe you are required to suspend use of an economic poison whenever the use in question creates an imminent hazard? We know you cannot suspend unless an imminent hazard exists, but when an imminent hazard is present, are you required to suspend?

Dr. BAYLEY. I do not see the difference. If there is one, do you want to tell me?

Mr. BUCKWIT. An imminent hazard we know is necessary for suspension. What I am asking is whether it is also sufficient?

Senator HART. Have you got that straight?

Dr. BAYLEY. I am not sure I understand the legal difference.

Senator HART. Let me see if I can state it. We are agreed that an imminent hazard is required before you may suspend. If an imminent hazard is present, must you suspend?

Dr. BAYLEY. I have to admit I would be more comfortable if I had a lawyer sitting with me to answer that question because there may be a legal distinction that I am not aware of.

Senator HART. The only thing the question raises is whether you are required by the law in the event an imminent hazard is disclosed to suspend or whether you merely may suspend if there is an imminent hazard disclosed.

Dr. BAYLEY. I am not clear on that point. I will be honest with you. I am not clear on that point.

Mr. BUCKWIT. Another question your statement brings to mind is exactly what the difference is between an imminent hazard and just a plain hazard. We adverted to the fact that Congress did not define the difference. Can you articulate the difference as you see it and as you apply it in your practice in suspension and cancellation?

Dr. BYERLY. May I try and answer to that as nearly as I may paraphrase the one in the dictionary that I use? It seems that imminent means something threatening to happen immediately.

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Now, we have, of course, given the top priority, the high priority, in addition to the something threatening to happen immediately to any hazard to human health.

Dr. BAYLEY. That is my understanding of it also.

Mr. BICKWIT. Then, in the case of food products, if there is a hazard, it is not an imminent one? Certainly one of the hazards we are concerned about is that of birth deformities that may be occurring right now. How would you respond to that?

(The following information was subsequently received for the record:)

DEPARTMENT OF AGRICULTURE,
OFFICE OF THE SECRETARY,
Washington, D.C., July 1, 1970.

Senator PHILIP A. HART,

Chairman, Subcommittee on Energy, Natural Resources, and the Environment, Senate Commerce Committee, U. S. Senate, Washington, D.C.

DEAR SENATOR HART: In the transcript of testimony presented to you I indicated I was not clear about a question you asked. Your question related to the requirement of FIFRA to suspend if any imminent hazard were found.

Our Office of General Counsel advises me that the law is permissive and not mandatory on this point. It states, "The Secretary may, when he finds that such action is necessary to prevent an imminent hazard to the public, by order, suspend the registration of an economic poison immediately."

I recommend that this clarification be added to the record.

Respectfully submitted,

NED D. BAYLEY,
Director, Science and Education.

Dr. BYERLY. Well, let us look at this. At April 15 or May 1, if, for example, rice is planted in the spring and harvested in the fall—is something that might occur on the rice that will be eaten 6 months hence imminent; is it threatening to happen immediately now?

Senator HART. I am glad Mr. Bickwit is conducting the questioning.

Mr. BICKWIT. Six months is not imminent in your view. Is that what you are suggesting?

Dr. BYERLY. No, sir; that is not what I am saying.

Mr. BICKWIT. How about 5? Where would you draw the line?

Dr. BYERLY. Well, I guess I will not go beyond the word "now." Imminent hazard means threatening to happen immediately.

Mr. BICKWIT. In the case of food crops, will it always be the case that they will be eaten 6 months after spraying with 2,4,5-T?

Dr. BYERLY. Not always, though, as I recall, the risk of food crops for which there are registered uses, I think that taking into account the time of the issuance of cancellation order and the specific list of food crops, as far as I recall them, that is the case.

Mr. BICKWIT. Does is follow that if the evidence were absolutely clear that whenever we applied 2,4,5-T to food crops and those food crops were eaten, we stood a 75 percent chance of a birth defect or, say, a 99 percent chance of a birth defect, that the use on food crops would not constitute an imminent hazard to health and you would not be authorized to take action?

Dr. BAYLEY. I think we are getting back to where we concluded the hearings last time. We are speculating without data. I find it very difficult to develop a precise percentage standard without

having some concrete data in front of me in order to make a judgment.

Dr. BYERLY. May I give you a tangential answer and point again to a comment that Dr. Bayley made with respect to our need for authority to make a temporary cessation of movement while we determine whether or not an imminent hazard would result? And it seems to me the case that you provided would be such a case.

Mr. BUCKWIT. You would have authority to act?

Dr. BYERLY. We do not now have authority in my opinion—not clear authority—to act in such a case. Obviously, there would come a time if we were sure of the hazard when such authority could be exercised. And we would do well to warn, if we could warn, of impending action.

Dr. BAYLEY. I think what we are doing is pointing up the difficulty in making this kind of a decision.

Mr. BUCKWIT. I think it certainly does point out the difficulty. If imminent hazard is to be defined in terms of months, or less than months, and if due process may take as much as 2 or 3 years, then clearly, if imminent hazard is so defined, you do not have adequate authority now to protect the public health.

Dr. BYERLY. We believe we need additional authority. We said that earlier.

Mr. BUCKWIT. The Hays memo which Mr. Wellford referred to prescribes cancellation in the case of a reasonable doubt as to safety. Do you believe there is no reasonable doubt in the use of 2,4,5-T on pasture lands?

Dr. BAYLEY. The word "reasonable" here, of course, is subject to interpretation. And our interpretation is that there is not sufficient evidence to have reasonable doubt in regard to range and pasture-land; that is right.

Mr. BUCKWIT. Is there not a reasonable doubt about the degradability of dioxin? Can you say that it has been proved beyond a reasonable doubt that dioxin is degradable?

Dr. BYERLY. Dr. Bayley reviewed the state of our knowledge in the formal statement. You will recall that our knowledge at the present time stated that photolysis occurred rather quickly in solution exposed to sunlight. One may rationalize, but one does not know, that the leaf surface allows photolysis to take place. In the soil surface apparently dioxin is so bound that destruction does not take place. Neither does it move. And, therefore, bound to the surface, the hazard is not immediate. This is as far as our knowledge goes. And we are seeking, as you well know, to obtain knowledge as quickly and as thoroughly as we can in this very difficult area.

Mr. BUCKWIT. I am not sure I heard you correctly so let me summarize what I think you said.

In solution, when subjected to a sunlamp, dioxin will degrade rather quickly, but when bound to soil, when put on soil, even under a sunlamp it will not degrade rapidly.

Dr. BYERLY. That is our information currently; yes, sir.

Mr. BUCKWIT. And as to grass, when you put it on grass, we have no determination as yet?

Dr. BYERLY. We have no direct determination; no, sir.

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Mr. BICKWIT. In that case, can we say it has been proved beyond a reasonable doubt that dioxin will degrade when put on grass? That is a rhetorical question of course.

Dr. BAYLEY. I think we have to put this in context of the history of the use of the materials. We should recognize the wide number of materials in which dioxins may be present at relatively low levels. Certainly, there has been sufficient public exposure if dioxins were accumulating over a long period of years for something to have happened.

It is also indicative that when there have been problems with dioxins, we have been able to pinpoint them immediately and correct them and eliminate those problems even in regard to the chloracne aspects of them. I think we have to weight this evidence along with all the rest that we have.

Mr. BICKWIT. I agree with you.

Dr. BAYLEY. I think there is no basis for action at this point.

Mr. BICKWIT. But as you say we have to weight the evidence that you describe. What I am asking is whether you believe that that evidence is sufficient to sustain the burden of proof—which Dr. Hays has stated is a burden of proof beyond a reasonable doubt—that dioxin is not a hazard.

Dr. BAYLEY. Are you using Dr. Hays' words? I do not have that memorandum in front of me.

Mr. BICKWIT. He refers to five groups of actions. Group two is the group under which cancellation would be classified. And he writes:

> The cancellation should take place when a reasonable doubt exists as to the safety or effectiveness of a registered product when it is used as directed or in accordance with commonly recognized practices.

Dr. BAYLEY. Yes. That is different than the way you stated it just a few minutes ago.

Mr. BICKWIT. It is? I read "a reasonable doubt exists as to safety" as meaning when grouped with the assumption that the burden of proof is on the manufacturer, which you have stated is the case, that the manufacturer must prove beyond a reasonable doubt that there is safety. He must eliminate that doubt. If he does not eliminate it, we have a reasonable doubt, and cancellation should ensue.

Dr. BAYLEY. We have to come back to the statement that we have not found a basis for reasonable doubt that the product as it is now registered and used is unsafe.

Mr. BICKWIT. Which leads you to the conclusion that you have not found a basis for reasonable doubt that dioxin on pastureland is not degradable?

Dr. BAYLEY. Well, that conclusion is not one to which I would be led because in the process of determining whether or not dioxins exist and in what level they exist. You recall that on the 7th of April, whichever it was, when we were here, we entered into the record first confirmd examination of current levels of dioxins in 2,4,5-T which were on the whole quite low. Those are a matter of record. So we have to take into account first what are the facts. And we must, I believe, determine the facts with respect to whether or not and to what extent dioxin is present.

[illegible] productive to go into it any further, but I would like to say that if you had no reasonable doubt as to dioxin's degradability, why are you running these tests?

Dr. BAYERLY. I would not go beyond the facts. What we reported is that in 96 hours on the soil surface, we found no evidence as to the degradability in sunlight.

Mr. BUCKWIT. And you have no evidence as to the degradability of dioxin on grass?

Dr. BAYERLY. That is correct.

Mr. BUCKWIT. And you have no evidence as to the degradability of dioxin in cows, in cow tissue and in human tissue if humans should ingest products which are the produce of those cows?

Dr. BAYLEY. I would hesitate to say that we have to have reasonable doubt about a product before we make a scientific inquiry in regard to the phenomenon involved. I would hesitate to say that.

Mr. BUCKWIT. I withdraw that. But I will not withdraw my conclusion that you have not proved to me beyond a reasonable doubt that there is no hazard.

Dr. BAYLEY. That is a judgment.

Mr. BUCKWIT. Applying this same form of approach to 2,4-D, did not the Bionetics Report say that 2,4-D was potentially dangerous? And is there any difference between the terms potentially dangerous and reasonable doubt as to safety?

Dr. BAYERLY. The formal record contains, I believe, a direct quote from the report which referred to three esters of 2,4-D and also referred to 19 test litters subjected to 2,4-D, per se, in which no increase of abnormal fetuses per litter occurred.

Mr. BUCKWIT. Are these three used in products currently on the market?

Dr. BAYERLY. Oh, yes.

Dr. BAYLEY. The Department of Health, Education, and Welfare would be testifying further in regard to 2,4-D tomorrow.

Mr. BUCKWIT. That is true, but you do make the decision as to whether or not a product ought to be canceled. I know you seek advice from the Department of HEW. You are required to. But as of now, you have made the decision not to cancel 2,4-D. Therefore, I would like to cite certain evidence which, again, in my mind creates a reasonable doubt as to the safety of 2,4-D, perhaps only as to safety of the 2,4-D esters which you mentioned, but you have admitted that these esters are presently in marketed products.

I am told that Dr. Clara Williams at FDA is running an experiment on a strain of hamsters and has produced teratogenic effects. In the Whiteside article, it was stated that the incidence of birth defects was higher than in the case of comparable doses of 2,4,5-T. The Bionetics data showed a high incidence of abnormalities in the offspring of mice. Finally, Dr. Verrett's studies showed comparable abnormalities in chicks, comparable to those found in 2,4,5-T.

In light of this evidence and in light of the possibility that there may be dioxin in 2,4-D it would appear to me that the requisite reasonable doubt exists.

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Dr. BYERLY. Well, sir, I hope and I trust that you will ask those questions when the HEW witness is before you tomorrow. And in the meantime, it is obvious, sir, that we have not the basis for reasonable doubt sufficient to warrant in our opinion the cancellation of registered uses of 2,4-D.

Mr. BUCKWIT. Which means that you have not found a reasonable doubt as to the safety of 2,4-D in current uses.

Dr. BYERLY. Yes.

Mr. BUCKWIT. Does the evidence I cited create any doubt whatsoever in your mind?

Dr. BYERLY. Sir, I have reviewed the evidence most carefully. The Department has not found sufficient basis for establishment of a reasonable doubt warranting the cancellation of 2,4-D. And I concur in that position.

Mr. BUCKWIT. Our first witness this morning, Mr. Wellford, suggested that action to limit the use of 2,4,5-T would be incomplete without similar action on Silvex, which is closely related to 2,4,5-T. Mr. Wellford's reasoning was that both pesticides have 2,4,5-trichlorophenol as an intermediate product and that dioxins are formed in producing this intermediate.

I am informed that Dr. Verrett's work at FDA has shown Silvex to be highly teratogenic to chicks. How would you answer Mr. Wellford's argument?

Dr. BYERLY. Again, referring to HEW the question, the preliminary information that we have which is limited, I believe, to a single complete assay with some confirmation of that assay and verbal reports of other examinations on 2,4,5-T, that current manufacture is assumed to contain less than 1 ppm of tetrachlorodibenzo-para dioxin.

I have tried to be careful in my answer because the evidence upon which [illegible] is very small.

I am sorry, I meant Silvex to which I refer, I said 2,4,5-T. I am sorry, I meant Silvex.

Mr. BUCKWIT. But though the evidence is small, you regard it as proof beyond a reasonable doubt?

Dr. BYERLY. Beyond a reasonable doubt that what, sir?

Mr. BUCKWIT. As to the safety of Silvex.

Dr. BYERLY. I have said there is sufficient evidence in my opinion at present available to establish a reasonable doubt of the safety of the registered uses of Silvex.

Mr. BUCKWIT. I notice that Silvex is one of the 18 pesticides that you listed to be checked for dioxin content.

Dr. BYERLY. It is, indeed. It is one of the trigroup in which in my opinion most probably tetradioxin will be present. And, therefore, we are seeking to determine whether or not in fact it is present.

Mr. BUCKWIT. And when do you expect the results of the tests on this and the other 17 products?

Dr. BYERLY. I very much hope that within 3 months, we will have completed at least the first go-around on all of the 18.

Mr. BUCKWIT. Why 3 months?

Dr. BYERLY. Why?

Mr. BUCKWIT. I ask this question from ignorance.

Dr. Bayley. I understand.

It is simply a matter of the care and sophistication of the method, the time required to get the job done. We have built, Dr. Bayley has pointed out, an isolation laboratory—I say built, I change that to equipped an isolation laboratory. We have the scientists. We are, in fact, ready to proceed. The time, therefore, would be the time required to do the analyses and verify them.

Mr. Beckwit. Thank you very much.

Senator Hart. Gentlemen, thank you. It has been an interesting and informative morning. Congratulations again for the effort that you, I am sure, put into developing and then persuading departmental acceptance of the suggested amendments. I hope improvement in that basic law soon will be written.

Dr. Bayley. Thank you, Mr. Chairman.

Senator Hart. We adjourn, to resume tomorrow at 11 a.m. in the morning in the hearing room of the Cominittee on Commerce 5110.

(Whereupon, at 12:40 p.m., the hearing recessed to reconvene at 11 a.m. on Thursday, June 18, 1970.)

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EFFECTS OF 2,4,5-T AND RELATED HERBICIDES ON MAN AND THE ENVIRONMENT

THURSDAY, JUNE 18, 1970

U.S. SENATE,
COMMITTEE ON COMMERCE,
SUBCOMMITTEE ON ENERGY, NATURAL RESOURCES,
AND THE ENVIRONMENT,
Washington, D.C.

The subcommittee met, pursuant to adjournment, at 11:35 a.m. in room 5110, New Senate Office Building, Hon. Philip A. Hart (chairman of the subcommittee) presiding.

Present: Senator Hart.

Senator HART. The committee will be in order.

Let me attempt to apologize to the witnesses who have been inconvenienced by this 35 minute delay. A meeting was called yesterday of the Democratic caucus for 10 a.m. and I felt compelled to participate. I wish we could manage things a little more responsibly around here, as busy as Congress is running everybody else's business.

Our first witness today is the distinguished science advisor to the President, Dr. DuBridge.

STATEMENT OF DR. LEE A. DuBRIDGE, SCIENCE ADVISOR TO THE PRESIDENT AND DIRECTOR, OFFICE OF SCIENCE AND TECHNOLOGY; ACCOMPANIED BY DR. EDWARD J. BURGER, JR., TECHNICAL ASSISTANT

Dr. DuBRIDGE. Mr. Chairman, I have asked my associate, Dr. Burger, of my office, to accompany me. He is an M.D. who has been following the matters related to health and the other effects of pesticides.

Mr. Chairman, I have testified before this committee on April 15 on the 2,4,5-T subject, and I am not sure there is very much to add to what I said at that time, but there are a few points I would like to review and emphasize.

I reviewed then something about the history and development and value of the use of this herbicide and I used that review as a text from which to draw what I considered to be some important generalizations about pesticides, and these are some of the matters I would like to repeat.

Let me begin by pointing out that 2,4,5-T is a pesticidal chemical which has been introduced intentionally into man's surroundings because of the benefits presumed to follow. Its purpose was to serve as an adjunct to other means of weed and brush control in land and

waterway and agricultural management. Over a period of 20 years it has proved its utility so that we are now in a position of relative dependence on this material.

However, especially in recent months, we have begun to question in greater and greater depth the possible human health effects of pesticides like 2,4,5-T and this has required a greater sophistication in research and testing than was previously thought adequate.

The example, of course, was the Bionetics study for the National Cancer Institute. Previous research on 2,4,5-T had concentrated on the acute toxicity of that compound and had shown this to be of a low level.

The Bionetics study represented a departure in that it investigated the potential of the herbicide to provoke tumors, birth defects and genetic alteration in appropriately exposed experimental animals. 2,4,5-T emerged from this study as a possible teratogenic agent.

As I have said, this study was a departure in several ways. Whereas nearly all of the background toxicology on pesticides had been performed as part of the development process by the developing company or industry, this study was launched and paid for by the Government.

I hinted that this might represent a precedent. If our society demands a very high level of sophistication in this type of research, industry may not be able to afford the increased cost of development and further development of valuable new products may be discouraged or prevented. Hence I suggested that new ways of distributing the costs of this work may have to be found. Expenditures of public funds and Government participation in this research may be desirable.

I emphasized that at any point in time, we find it difficult to get complete information about the true hazards of any pesticide or any other chemical substance. That is, research in this area (as in any other) has no finite end points. It may take long experiments with all kinds of levels and all kinds of circumstances to make any such assertion and one can never be sure what new research results will turn out.

As one performs more research to investigate various hypotheses, one inevitably raises additional questions—as well as answers. It follows from this that any regulatory system for pesticides must be able to accommodate new and unexpected information.

I pointed out that our present arrangement for regulation is not sufficiently flexible to reflect new information as it emanates from research. Again, these points were clearly illustrated by the case of 2,4,5-T.

What I said in April was that there does not exist a mechanism whereby the Government may exercise prudent and unequivocally effective restraint temporarily on the receipt of new, unexpected information and possibly preliminary results and while awaiting more definitive conclusions.

In many ways the Federal Government did act with dispatch in the case of 2,4,5-T. After the October 29 announcement about restrictions imposed on 2,4,5-T additional research studies were begun in a number of agencies. These studies were initiated both by the Government and by industry. The aim in every case was to confirm

or extend the unexpected results obtained from the Bionetics-National Cancer Institute studies.

One of the new issues examined in the new set of investigations was the importance of impurities present in many samples of 2,4,5-T. It had been discovered that over a period of years commercial 2,4,5-T contained varying amounts of a highly toxic impurity which was a member of a family of polychlorinated dioxins. It was of obvious importance to ascertain the relative contributions of the 2,4,5-T and the dioxin impurity as potential teratogenic agents. The dioxin was known to be very toxic. Hence this question became part of the experimental aim.

Fortunately, teratogenesis is a relatively acute affair and experiments necessary to investigate this phenomenon are short-term experiments. Answers were expected in a fairly short period of time.

Some of these confirmatory experiments were undertaken by one of the National Institutes of Health—the National Institute of Environmental Health Sciences. The results of these experiments were reported to you as fresh out of the laboratory at the time of the last hearings.

In brief, you may recall, these results implicated both 2,4,5-T and 2,3,7,8-tetrachlorodibenzo-p-dioxin as potentially teratogenic in nature. In rats, over the same dose range, only the dioxin appeared to produce birth defects.

It was principally on the basis of these results that Secretary Hardin, Secretary Finch and Secretary Hickel jointly announced the series of restrictions on the use of 2,4,5-T. These were related to you by the Surgeon General, Dr. Steinfeld.

In brief, the philosophy behind these restrictions was hoped-for protection of women of childbearing age. Thus the Department of Agriculture suspended the registration of liquid formulations of the weedkiller for uses around the home and of all formulations for use on lakes, ponds and ditch banks.

In addition, registrations were cancelled for uses of nonliquid formulations around the home and of all formulations for use on food crops intended for public consumption.

Of the total amounts of 2,4,5-T used in this country for all purposes it was estimated that these restrictions applied to about 20 percent—the 20 percent of the cases where human exposure was possible.

I firmly believe that the issues raised by the case history which I outlined in April continue to be prominent. In a way, I suppose, we can thank the existence of the questioning about 2,4,5-T for bringing to our attention matters such as the ones I have described.

This study has served as a most useful vehicle and we may learn some lessons for future studies. However, as I warned, any attempt to answer the research questions raised will inevitably raise some additional questions.

I suggested that in some ways we were fairly lucky in our investigations of 2,4,5-T. The issues have appeared fairly straightforward and it was possible to start confirmatory experiments fairly quickly and to get confirmatory results quickly.

Yet, while this appears to have been a modest success story, some may rightly ask: Shouldn't the kinds of experiments which were

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mobilized on the spur of the moment for 2,4,5-T have been accomplished on a more systematic basis and without the spirit of a crisis necessary to urge them on?

Further, one might ask whether or not it might be desirable to support a fairly sophisticated level of investigation for a large number of pesticidal chemicals—not just 2,4,5-T.

Now, I and others have outlined the research work on 2,4,5-T and I have termed it relatively sophisticated. Yet I will have to admit that there has been almost no work done to elucidate the metabolic handling of this herbicide in the animal organism. There is little known in biochemical terms of the mechanism of its actions and there is essentially no knowledge of any possible interactions between this chemical and other materials.

In similar fashion we are poorly informed about the characteristics of the dose-response relationship for very low dose levels. This, of course, is the situation which we face in real life in the case of a variety of environmental agents—including pesticide residues. Here the problem is a statistical one. In order to derive meaningful answers with any useful level of confidence very large colonies of experimental animals must be tested, often over a long period of time.

I suggest these comments to illustrate that there are various levels of sophistication in research.

In the realm of pesticides the level of our research activities may not have kept up with the state of that art nor with a corresponding level of questioning to which policy makers and the public are now seeking answers.

The very excellent report on research needs compiled by an advisory task force to the National Institute of Environmental Health Sciences outlined these research areas very well and very explicitly. This report, I am informed, is just now being published.

All of this—more sophisticated research, more expensive research, research sponsored by the Government—will cost money. Again, I repeat, if a really serious thrust is taken in this direction we may be obligated to find new institutional avenues for accommodating this research since, as a part of the cost of development, the bill to industry may be higher than we might desire.

All of this discussion brings me once again to a point which I made in my previous testimony and which I feel is worth emphasizing. While we as a society have recently begun to ask more penetrating questions about the possible adverse health effects of environmental agents it is not clear that we know how penetrating this questioning should be or must be.

What I said before was that we had set our sights higher. What I should add is that we are not sure how high they should be set. For example, up to the present time we have been willing to live with a system under which the amount of toxicological research performed on a pesticide was to some extent related to the probability of human exposure. With a low or seemingly negligible probability of exposure, relatively little understanding was sought and little research was undertaken. In fact, one could argue that since the appearance of residues of 2,4,5-T have been rare events—it is very rare to find measurable residues of 2,4,5-T on food—therefore one

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did not have to know too much about the toxicology of the herbicide. Now we are more particular.

I feel that we should be more explicit about assumptions such as these. If they are valid they will stand on their own merit. If they are not valid we should change them. I am happy to say that my office is examining questions such as these at the present time.

Thank you, Senator Hart.

Senator HART. Thank you.

You suggest the possibility that the Government may have to assume a greater role in any testing area but specifically in the matter of pesticides.

Dr. DUBRIDGE. Yes.

Senator HART. You indicate that otherwise the bill to industry might be higher than we might desire, which I suppose is another way of saying an industry could not afford it. How should we read that?

Dr. DUBRIDGE. What I meant to say is if industry is required to carry on years of very expensive research before any new product can be manufactured, obviously industry will no longer be interested in manufacturing new products because they could not recover the loss. Thus the community, the society would be robbed of many future very valuable chemicals which society might find extremely important for health and other reasons. To impose the burden on a particular company that before it can market a product it must undertake millions and millions of dollars more worth of research than it has in the past would simply stop the development of new products. Therefore it seems to me only fair, since we want to protect society as a whole but also to encourage benefits to society, that society as a whole ought to participate in the cost of determining what the damages may be as well as what the benefits may be.

Senator HART. That then would be your basic answer to the suggestion or argument that research is just another element of the cost of production.

Dr. DUBRIDGE. Yes.

Senator HART. That the user of the product should bear that cost along with other costs.

Dr. DUBRIDGE. Yes. Exactly. I am not saying that the manufacturer should not also bear substantial costs. He should make sure that the product that he is proposing to market is not dangerously poisonous, does not have obvious adverse human health effects. Industry should be required to undertake a reasonable set of experiments, and they always do, to assure that this product has a relatively good safety factor. But it may take years to find out low level and easily hidden dangers which sometimes may become obvious only when mass use is undertaken. To help avoid these dangers I think some Federal participation in the research program would be desirable.

Senator HART. Do you know whether the administration intends to embark on broad new research programs in this area?

Dr. DUBRIDGE. There are several agencies which are developing plans, pursuing research in this area, and I believe an advisory committee of the Department of HEW headed by Dr. Emil Mrak

is making some proposals to HEW about substantially extending its research and testing activities in this field of pesticides, and about developing extensive facilities, large animal colonies and large-scale testing equipment and personnel, to carry out extended tests in this field.

These are recommendations that are being formulated and are being proposed to HEW. I do not know what the status of them is at the moment.

Senator HART. It is likely you would not have the figure with you, but let me ask the question. Perhaps it could be provided for the record and I have no idea what it will show. But would it be possible to identify those activities which are not undertaken by the Department of Defense that are comparable to the line item research and development that is done by the Department of Defense? The total figure for research by the Department of Defense is in the range of $7 billion a year. How much are we spending in other research?

Dr. DUBRIDGE. The total Federal budget for research and development in this current year is close to $17 billion.

Senator HART. Including the DOD?

Dr. DUBRIDGE. Including the DOD. If you take out somewhat over $7 billion of DOD funds, it is $9 billion to $10 billion in all other branches of the Government.

Senator HART. We will let others judge whether the allocation of the resources is or is not prudent. I think it is good to have it in the record.

Yesterday we received testimony from the Department of Agriculture. When we think about changes in the system of pesticide research and control we have to think about changes in the basic law of pesticide regulations. Included in the testimony yesterday from the Department of Agriculture were a number of suggestions and changes that they recommend be made in the basic act. Are you familiar with those suggestions?

Dr. DUBRIDGE. Dr. Burger told me about them this morning and I have a copy of them here, and we have discussed them. These are in line with some of the suggestions we have had with Agriculture and other agencies; namely, that there is not sufficient flexibility in the present statute to take a suitable action in all cases where new information becomes available.

Sometimes new information like the Bionetics study is very suggestive but cannot be said to be finally conclusive because of the small number of animals and small number of circumstances involved and the separation of an impurity may not be taken care of.

It will frequently happen that you will get preliminary suggestive results not sufficient to abolish the use of a chemical but sufficient to take some prudent action until more final results have been obtained.

I think the Agriculture suggestions do move in this direction to give, for example, what they call preliminary suspension authority. So if a danger sign is raised you take prudent temporary action and continue further research. If the further research confirms that safety is there after all you can remove the suspension. If further research proves the danger, then permanent suspension can be achieved.

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Senator HART. I did not quarrel yesterday with the Department of Agriculture's interpretation of the basic act. Overnight I have tried, as we always do, to justify what we did, namely, those of us who wrote the law. I am not convinced that that statute prohibits the Department of Agriculture, when, as you say, the signal goes up from suspending the marketing of the product—I am not sure that Congress should be held to have said that we excluded the possibility of a temporary suspension.

Just as I was not yesterday, I am not sure you are not equipped, and did not plan to debate what limits there are under the existing law.

Dr. DUBRIDGE. No, I am not an expert on the question of interpretation of the law, but it has simply been taken for granted, maybe not properly and maybe under an interpretation that should be further developed, but it has been taken for granted that preliminary or temporary suspension was not provided for, explicitly at least, in the statute.

If the law were interpreted to allow this, it would be fine.

Senator HART. I cannot imagine there would be any different criteria for a temporary suspension than a suspension. I still have the feeling that the suspension is not for a thousand years. If you suspend and then discover that your alarms were groundless, surely you can unsuspend. That would argue that you can temporarily suspend.

Dr. DUBRIDGE. If that is the case I think that is fine. It apparently needs to be made more explicit to the people who are doing the suspension because they do not feel that they have this authority.

Senator HART. Clearly they do not.

Are you yet in a position to advise whether you would support or recommend support of the suggestions for law changes made yesterday by Agriculture?

Dr. DUBRIDGE. I think it is fair to say that we would believe these are proper moves. Again, as I say, we are not experts in the regulatory field and the legal field. What we tried to do is to find the science and technology that is applicable, and we leave it to the Congress and the legal authorities to determine what specific regulations and statutes are required.

But I think this additional flexibility does in principle sound very desirable to us, simply because research results, you know, are never the final answer unless they are extremely conclusive results of extreme danger.

It is almost never possible to say that all the research has been done and it proves that the thing is forever safe.

Senator HART. Conversely, forever unsafe.

There were several other suggestions that Agriculture made. One regarded the ineffectiveness of handling pesticide regulation by labeling. They were going to recommend restructuring the law to require a grading by degree of the hazards of a pesticide and to ensure that extremely hazardous products would be permitted to be handled only by individuals or institutions licensed to do so. Do you have any comment on that one?

Dr. DUBRIDGE. I think I have no very expert comment except to note the experience within my own family that labels on packages

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are often not adequately read and that the labeling problem is a difficult one.

Senator HART. As Agriculture indicated, not a very reliable handle for protection against injury to health or environment.

Well, we would hope that you will lend your distinguished scientific support to the recommendations that Agriculture has made.

A couple of other questions, and this goes to the different actions that have been taken with respect to pesticides or herbicides by different departments of the Government.

Agriculture suspended I think you said about 20 percent of the use of 2,4,5-T.

Dr. DUBRIDGE. I did not intend to imply that was all Agriculture. I said the total suspension amounted to 20 percent of the total use.

Senator HART. It is my understanding that the Department of Defense has suspended it entirely for use in Vietnam.

Dr. DUBRIDGE. That is correct.

Senator HART. And the Department of Interior very recently suspended it for use on public lands; lands in its ownership.

Dr. DUBRIDGE. Yes.

Senator HART. How do we explain the different reactions from the several departments with respect to the same product?

Dr. DUBRIDGE. I do not know that I can fully explain it, but the situation in military operations is not necessarily the situation in normal peaceful operations in this country.

In military operations, by necessity, these chemicals are distributed by aircraft, and it is not always easy to control where they go and how far away they blow or even that the aircraft is hitting the right target. Therefore I think somewhat more prudence may be required.

When you are doing it in a normal way, in agricultural practice or land management, you can be much more careful and make sure that the material does not get on food crops or in your waters, which will contaminate the waters, or get on grazing lands on which animals will be grazing and therefore get into milk or meat.

Fortunately 2,4,5-T degrades quite rapidly. It is not like DDT. If you spray a pasture with 2,4,5-T, essentially all traces of it are gone after about three months' exposure to wind, rain, and sun. Therefore cattle can quite safely graze on grazing land treated with 2,4,5-T after this period.

Also, if it gets on food it is likely to degrade pretty rapidly, though it is desirable to have no tolerance for food. But where it is used in areas where there is no human population and where there is no danger of contaminating food or water, then a controlled use can be extremely valuable, and since no dangers would be resulting I think it is perfectly proper to have controlled use in this country.

Senator HART. What do you say, then, to Interior's prohibition for use on its lands?

Dr. DUBRIDGE. I guess I am not familiar with how extensive that use is.

Senator HART. I am told that Interior's action was taken only yesterday.

Dr. DUBRIDGE. I see. I am not familiar with the background for that action or the extent of it; or maybe they found that other ma-

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terials could be used on public lands other than 2,4,5-T which would serve the purpose. I just do not know.

Senator HART. But it contributes to the uneasiness of the public when we see these *seemingly conflicting reactions.*

Dr. DUBRIDGE. This is one of the very delicate things that the Government faces; that is, not to overreact to situations which will do damage by overreaction. But there is an opposite injury of under reaction and not taking prompt or adequate action when dangers are evident. I would like to defer to the Department of the Interior in this case, and with your permission, have that Department submit a statement for the record.

(The information follows:)

STATEMENT ON INTERIOR PESTICIDE POLICY

The Department of the Interior policy statement, issued by Secretary Hickel on June 18, does not differ markedly from the one that has been followed for several years. Nevertheless, it adds some chemicals about which we have received additional data within the last year and recognizes the concern expressed by cooperating Departments on some others.

The prohibition against most of the chlorinated hydrocarbon insecticides had been in effect for several years and that on 2,4,5-T since October 1969. The hazards of mercury have been recognized for some time but were accentuated *by monitoring results in the last six or eight months. Amitrol was included* because of the objections of the Food and Drug Administration to the use of carcinogens.

The Department of the Interior policy is not intended as a Federal pesticide policy. It has long been the policy of this Department to set a standard in its use of pesticides that is beyond reproach from the standpoint of safety. Consequently, our position may be more strict than some others will wish to set. If research demonstrates that some of the pesticides listed may be less hazardous than we suspect then they may be restored for use on Interior lands.

Senator HART. You reminded me of a question I kicked myself yesterday for not having asked the Department of Agriculture witnesses. Perhaps you can help.

You mentioned DDT. As I recall the testimony yesterday, under the FIFRA Act, a science advisory committee is established when there is a cancellation procedure aimed at a product. They explained that in the case of DDT that some six months have passed since the cancellation procedure was initiated and no committees have been formed; hence the passage of time has been extended at last by this amount during which, under the cancellation procedures, *continued marketing of the product goes on. Why the 6-month de*lay?

Dr. DUBRIDGE. I cannot explain that. I do not know why there should be a long lag between these two events. The only thing I can think of is since the Secretary's pesticide advisory commission has been continuously at work on the pesticide problem, especially with attention to DDT, they were depending on it to examine this particular problem.

Senator HART. I repeat, I should have asked them yesterday and I did not. But if they read so strictly the statute with respect to suspension, I would assume the same strict reading would tell them that they cannot substitute the Mrak Commission for the explicit statutory requirement that there be a science board established for each of these products.

Dr. DuBRIDGE. I would agree. I think maybe the law does not set a time at which the science advisory commission shall be established.

Senator HART. No; it does not. It was assumed that it would be established at least with all deliberate speed, and 6 months seems to be undue delay.

Dr. DuBRIDGE. Yes, I agree. With your permission, I would like to ask the Department of Agriculture to provide an explanation of this apparent delay.

(The information follows:)

DEPARTMENT OF AGRICULTURE,
OFFICE OF THE SECRETARY,
Washington, D. C. July 7, 1970.

Dr. LEE A. DuBRIDGE,
Executive Secretary, Council on Environmental Quality, Executive Office of the President, Washington, D.C.

DEAR DR. DuBRIDGE: In reference to the question raised at the Hart Committee hearing as to why it has taken so long to establish an advisory committee on DDT, we submit the following explanation:

(*a*) After the announcement of cancellation, the companies involved did not request an advisory committee or public hearing for the four uses of DDT to be cancelled until the latter part of the 30-day period provided for appeals by the Federal Insecticide, Fungicide, and Rodenticide Act.

(*b*) Meetings and discussions were held with representatives of the National Academy of Sciences on makeup of the committee.

(*c*) Previously we had asked for lists of names of persons to serve on advisory committees for other cancelled products, and they were already in the process of compiling them.

(*d*) Due to unfavorable publicity related to conflict-of-interest charges regarding authorities that served as consultants to the Department in the past, some experts were not willing to serve.

(*e*) Two additional requests to NAS for candidates to serve, besides the original, were necessary in order to complete the committee.

(*f*) Two of three companies requesting advisory committees withdrew, leaving only one for a tracking powder use.

(*g*) Getting written position from DHEW as to whether tracking powder was considered an essential use from a public health standpoint.

(*h*) Contacting and getting approval of proposed candidates to serve on the committee.

(*i*) Notifying committee members that they were selected to serve on the committee.

(*j*) Conflict-of-interest review and evaluation within the USDA.

Sincerely,

NED D. BAYLEY,
Director, Science and Education.

Senator HART. I would hope in connection with the cancellation proceeding on 2,4,5-T an advisory committee will be formed with less delay.

This next question bears directly on your broad background. One of the difficulties in this 2,4,5-T story was the difficulty experienced in obtaining information which might have been of public health significance.

Under what conditions do you suggest scientific information ought to be kept secret when a question is raised as to the safety of the product?

Dr. DuBRIDGE. If you are talking about scientific information, I do not think it should be kept secret. When you are talking about information having to do with the manufacture of commercial products, that is a very different situation because the costs of development, testing and getting a commercial product into production are

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very high. It is quite proper that the manufacturer or [illegible] be protected so that he will have an opportunity to recover costs. He should have a patent or a protection for his invention or his product so that he can recover the very large costs to develop it. Whereas, if he instantly published all the information about how to make this product so that others would instantly start making it without the expense of development, this would obviously be an unfair kind of competition.

Our whole system is based upon the fact that inventors of new processes and products have protection to regain their investment and recover their costs. Therefore I think the publication and the distribution of information with regard to the manufacture of products and materials is a proper trade secret.

On the other hand, when it is clear that human health is at stake I would assume there should be mechanisms by which Government agencies in proper authority could be told something about the composition of the product so that they would be able to determine whether or not there might be materials in the product which ought to be investigated for their harm.

I do not know exactly what the law is on this, but it would seem sensible.

Senator HART. Your suggestion is that when a question of health is raised with respect to a product, data and information on the product should be made available to the appropriate Government agency for its determination as to a question of health and safety?

Dr. DUBRIDGE. Yes, sir.

Senator HART. That excludes, of necessity, the judgment and the comment of perhaps very gifted men and women of science in arriving at the determination of whether public health is or is not in jeopardy. This is not to suggest that the appropriate agency lacks qualified and competent people but surely they do not have a monopoly on that.

Is there some way, notwithstanding the obligation to protect trade secrets and encourage invention and discovery, we can do a better job of permitting the outsider, whether it is the head of the chemistry department at Cal Tech or someplace else, being brought in and having an opportunity to sharpen the judgment of everybody?

Dr. DUBRIDGE. Well, I think that the various advisory mechanisms available to the various Government agencies ought in general to accomplish that objective. A science advisory group can be called in to consult on a particular problem, on the possible dangers of the particular chemicals that happen to be in a particular commercial product.

I am sure that they could tap the rest of the scientific community to find out whether chemical A or chemical B is of a nature that it would likely be harmful. They do not have to reveal the whole composition of the product in order to say this product happens to contain a certain amount of compound A, is there any evidence or any chance or any reason to believe that this compound A is harmful. I think the knowledge of the scientific community could be obtained.

Senator HART. Should be obtained?

Dr. DUBRIDGE. And should be, of course.

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TERATOLOGY STUDIES WITH CHLORODIBENZO-P-DIOXINS

K. Diane Courtney

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Please send proof to:

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Research Triangle Park, NC 27711

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ABSTRACT

Teratology studies with chlorodibenzo-p-dioxin compounds: Courtney, K.D. (1973). Toxicol. Appl. Pharmacol. 00,000-000. The oral administration of 100 or 200 µg/kg/day of a mixture of 40% 2,7 dichloro- and 60% 2,3,7 trichlorodibenzo-p-dioxin or doses of 5 or 20 mg/kg/day of octachlorodibenzo-p-dioxin to pregnant CD-1 mice from day 7-16 of gestation did not affect fetal viability or gross morphology. The oral or subcutaneous administration of 100 to 1000 µg/kg/day of 1,2,3,4 tetrachlorodibenzo-p-dioxin to pregnant CD-1 mice from day 7-16 of gestation was not teratogenic. In contrast, the oral or subcutaneous administration of 25 to 200 µg/kg/day of 2,3,7,8 tetrachlorodibenzo-p-dioxin produced a high incidence of fetal mortality, cleft palate and hydronephrosis.

and pathological effects has been presented by Kimbrough (1972). Possible mechanisms of action or actions of TCDD were suggested at a symposium on Dioxins (NIEHS Conference, 1973). To date, it is not known how many of this class of compounds share the extremely toxic and teratogenic properties of TCDD. Thus, this study was undertaken to evaluate the teratogenic potential in mice of other members of the class of chlorinated dibenzo-p-dioxin compounds.

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MATERIALS AND METHODS

Female CD-1 mice and pregnant CD-1 mice with known insemination dates were procured from Charles River Laboratories, Wilmington, Massachusetts. Detection of a vaginal plug indicated day 1 of pregnancy. The mice, from a procurement bred at the same time, were randomly selected and assigned to control or experimental groups. The various chlorinated dibenzo-p-dioxins were prepared and supplied by Dr. A. Pohland of the Food and Drug Administration (Pohland and Yang, 1972).

Compounds were administered orally or subcutaneously. Oral administration was by means of gastric intubation using a volume of 0.1 ml/mouse/day. The following solutions were used for oral administration. Dibenzo-p-dioxin was dissolved in corn oil. The octachlorodibenzo-p-dioxin was dissolved in 15% anisole in corn oil.

The remaining compounds were dissolved in 5% anisole in corn oil. Compounds administered subcutaneously were dissolved in DMSO employing 0.1/mouse/day.

In order to select dose levels for the teratology studies, the various chlorinated dioxins were administered by gastric intubation daily to female CD-1 mice for 14 days. They were observed for an additional 7 days.

For the teratology studies, compounds were administered from the 7th through the 16th day of gestation. These mice were sacrificed on day 18 except those receiving octachlorodioxin and their respective controls. They were sacrificed on day 17 of gestation. Upon sacrifice, fetuses were weighed, examined and stored in Bouin's solution until necropsied. The following conventions were observed in compiling data. If a fetus was either dead or resorbed, it was regarded as a dead fetus. Only live fetuses were examined for physical abnormalities. A fetus was classified abnormal if it was alive and had at least one type of anomaly (regardless of type). A fetus was said to have abnormal kidneys if at least one of its kidneys was affected. In calculating the ratios of liver to body weight in the mother, maternal body weight was defined as the difference between the weight of the mother on the day it was killed and the gravid uterus weight. Maternal weight gain was defined as the difference in the corrected maternal weight on the day it was

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killed and its weight on day 6 of pregnancy. Averages were calculated for each litter, then across litters. Statistical analyses were performed using the student's "t" test.

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RESULTS AND DISCUSSION

The results from treating female CD-1 mice with various doses of the different dibenzo-p-dioxins are presented in Table 1. Administration of the compounds for 14 days at the doses indicated produced no lethal dose values. The dosages for the dibenzo-p-dioxin, dichlorodibenzo-p-dioxin, and octachlorodibenzo-p-dioxin are expressed as milligrams per kilogram of body weight per day while the others are expressed as micrograms per kilogram of body weight per day. The change in body weight reflects the difference in body weight on the first day of the study to the last day which was seven days after the last dose. The only unusual value is from those mice which received 50 mg/kg of dibenzo-p-dioxin. Further study is needed to determine if this increase of almost seven grams is real or not. Limitations of the supply of these compounds precluded further exploration of dose studies at this time. In general, none of the dibenzo-p-dioxins studied were as toxic as TCDD, the 2,3,7,8 tetrachlorodibenzo-p-dioxin isomer, and some of the compounds could be considered relatively non-toxic.

Toxicologic results of administering the various dibenzo-p-dioxins to pregnant CD-1 mice are presented in Table 2. The diluent control solutions of 5% anisole in corn oil, DMSO or 15% anisole in corn oil did not adversely affect fetal mortality or fetal weight.

The mixture of the dichloro- and trichlorodibenzo-p-dioxin administered orally at doses of 100 and 200 micrograms/kg/day had no adverse effects on the fetal and maternal parameters. The fetal weights of these two groups are higher than those of their respective controls. They are also higher than values which might be anticipated for a gestational day 18 mouse fetus. It is assumed that these mice were very near term since one member of the experimental groups littered (omitted from these data), and thus, these mice might be considered almost day 19 mice instead of day 18. The maternal weight gains of the experimental groups were slightly higher than the values of the control groups, but these differences were not statistically significant. This slight increase in maternal weight gain was also seen in mice treated with the 1,2,3,4 tetrachlorodibenzo-p-dioxin isomer administered orally at doses ranging from 100 to 1000 micrograms/kg/day. Whether or not this increased weight gain is a true increase in weight or a manifestation of edema needs to be explored since studies with TCDD produced marked maternal edema. In contrast, the subcutaneous administration of the 1,2,3,4 tetrachloro- isomer produced a slight decrease in maternal weight gain compared to controls. The

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difference in these values was not statistically significant.

In marked contrast, TCDD adversely affected fetal weight and mortality, and maternal weight gain at a dose of 100 micrograms/kg/day. Dose levels of 200 and 400 µg/kg/day produced generalized edema in the mothers, and vaginal bleeding after the sixth dose with some mice aborting shortly thereafter.

The increase in the ratio of liver to body weight seen in the mice receiving the lower doses either orally or subcutaneously is primarily due to an increase in the liver weight. The dose of 50 µg/kg/day produced a decrease in maternal weight gain, and at the two highest doses the obvious edema made it difficult to interpret maternal weight changes. The subcutaneous administration of TCDD produced more fetal mortality at lower doses than oral administration. This suggests that the bioavailability of a subcutaneous dose is greater than that of an orally administered dose.

Treatment of pregnant mice with octachlorodibenzo-p-dioxin at 5 mg/kg/day had no adverse effects on fetal or maternal parameters. At a dose of 20 mg/kg/day, there was a slight reduction of fetal weight which was not statistically significant. Also, the reduction in maternal weight gain was not statistically significant due to a

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very large standard deviation. The increase in the ratio of liver to body weight was primarily due to a loss in body weight. Fetal mortality was not affected at either dose.

All of the live fetuses were examined for malformations. These results are shown in Table 3.

The mixture of dichloro- and trichlorodibenzo-p-dioxin produced a slight increase in the number of abnormal fetuses. At the lower dose this was partly due to an increase in kidney malformations which were a mild form of hydronephrosis. Since most of these fetuses (9/10) were from one litter, and kidney malformations were not observed at the higher dose, it is very doubtful that this malformation was produced by the compound under study. At both dose levels there was an increase in the incidence of clubfoot. This may reflect uterine crowding, since these fetuses weighed slightly heavier and the litters were slightly larger than the controls. However, this does not negate a possible compound effect.

The 1,2,3,4 tetrachloro- isomer did not increase the incidence of malformation at any dose level by either oral or subcutaneous administration. Since this strain of mouse has a tendency to display clubfoot, the 8% incidence of this anomaly observed at the 1000 microgram/kg/day dose level needs further substantiation before being accepted as a compound effect.

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In contrast TCDD produced many abnormal fetuses at all doses studied and by both routes of administration. The majority of the malformations were cleft palates and hydronephrotic kidneys, both unilateral and bilateral. A few other anomalies such as hydrocephalus and open eye were occasionally seen. TCDD administered subcutaneously produced a greater teratogenic response at a lower dose than administration by the oral route. Administration of the isomer by the subcutaneous route at the lowest dose produced about 87% abnormal fetuses per litter. This made it difficult to demonstrate a dose related response since this is close to being a maximum response. At the higher dose with both routes of administration many fetuses were observed with marked edema and petechiae.

The oral administration of 5 or 20 mg/kg/day of octachlorodibenzo-p-dioxin to pregnant CD-1 mice did not affect fetal development morphologically. The only malformation detected in this group of fetuses was a single cleft palate at the low dose.

CONCLUSIONS

TCDD, the 2,3,7,8 tetrachlorodibenzo-p-dioxin member of this class of compounds was the most fetotoxic and teratogenic compound studied. The related compounds were relatively non-toxic and were not teratogenic at the doses studied.

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The oral administration of 100 or 200 micrograms/kg/day of a mixture of 40% 2,7 dichloro- and 60% 2,3,7 trichlorodibenzo-p-dioxin to pregnant CD-1 mice from day 7 through 16 of gestation did not affect fetal viability or gross morphology.

The oral administration of 100 to 1000 micrograms/kg/day or the subcutaneous administration of 500 or 1000 micrograms/kg/day of 1,2,3,4 tetrachlorodibenzo-p-dioxin to pregnant CD-1 mice did not affect fetal viability or gross morphology.

The oral administration of 5 or 20 milligrams/kg/day of octachlorodibenzo-p-dioxin to pregnant CD-1 mice did not affect fetal viability or gross morphology.

The oral administration of 25 to 200 micrograms/kg/day of 2,3,7,8 tetrachlorodibenzo-p-dioxin, TCDD, to pregnant CD-1 mice produced a high incidence of fetal mortality and malformations. The malformations were almost exclusively cleft palate and hydronephrosis. Maternal toxicity was evident at the higher dose levels with marked edema, vaginal bleeding and abortion.

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Table 1. Oral Administration of Dioxins to Female CD-1 Mice for 14 Days

Compound	No. of Mice	Dose/ Day	No. Dead/ Doses	Change Body Wt. (gms)
Dibenzo-p-dioxin	6	1 mg/kg	0	+0.6
	6	10	0	-0.3
	6	50	1/14	+6.8
2,7-Dichlorodibenzo-p-dioxin	6	0.5 mg/kg	0	-0.1
	6	1.0	1/8	+1.5
Combination of:				
40% 2,7-Dichlorodibenzo-p-dioxin	6	10 µg/kg	1/9	+1.2
60% 2,3,7-Trichlorodibenzo-p-dioxin	6	50	0	+0.8
	6	100	1/13	+1.6
2,3,4-Tetrachlorodibenzo-p-dioxin	6	5 µg/kg	0	0
	6	10	0	-0.2
	6	50	0	+0.8
	6	100	0	-0.9
2,3,7,8-Tetrachlorodibenzo-p-dioxin	10	10 µg/kg	0	+0.1
Octachlorodibenzo-p-dioxin	6	0.5 mg/kg	1/11	+0.1
	6	0.75	0	+0.7
	6	1.0	0	-0.4

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Table 2. Toxicologic Evaluation of Chlorinated Dibenzo-p-dioxin Compounds in Pregnant CD-1 Mice (Compounds Administered from Day 7 to 16 of Gestation)

Dibenzo-p-dioxin Compound	Route	Dose/kg/day	No. of Litters	Av. % Fetal Mortality/ Litter	Fetal Weight (gms)		Maternal Weight Gain (g)		Maternal Liver/Body Weight x 100	
					$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
5% anisole:corn oil	oral	0.1 ml/mouse	15	6	1.02	0.16	3.5	1.93	7.8	0.59
2/3 mixture[a]	oral	100 µg	6	3	1.36	0.13***	4.6	1.10	8.0	0.84
	oral	200 µg	5	5	1.25	0.19**	4.4	1.59	7.5	0.46
1,2,3,4-tetrachloro	oral	100 µg	4	10	1.09	0.09	4.8	0.51*	7.8	0.47
	oral	250 µg	4	20	1.10	0.12	4.8	1.44	7.7	0.37
	oral	500 µg	5	5	1.08	0.08	4.5	1.56	7.8	0.43
	oral	1000 µg	5	10	1.03	0.09	3.7	1.31	8.3	0.58
	subc	500 µg	5	7	1.24	0.07	3.4	0.82	7.6	0.40
	subc	1000 µg	6	2	1.31	0.07	2.3	0.57	8.1	0.44
DMSO[b]	subc	0.1 ml/mouse	6	14	1.19	0.17	3.1	1.96	7.5	0.94
2,3,7,8-tetrachloro	oral	25 µg	7	6	1.13	0.13	3.4	2.20	8.6	0.63**
	oral	50 µg	7	13	1.01	0.13	3.4	1.07	9.4	0.44***
	oral	100 µg	6	14	0.95	0.12	2.1	3.57	7.8	1.00
	oral	200 µg	6	87	d		d		d	
	oral	400 µg	5	97	d		d		d	
	subc	25 µg	5	36	1.25	0.07	3.0	0.86	9.7	0.42***
	subc	50 µg	6	56	1.20	0.15	2.3	1.17	9.0	1.09*
	subc	100 µg	6	72	d		d		d	
	subc	200 µg	6	76	d		d		d	
15% anisole:corn oil[c]	oral	0.1 ml/mouse	5	8	0.61	0.05	0.6	1.47	6.2	0.22
octachloro[c]	oral	5 mg	6	14	0.60	0.06	0.3	1.40	6.6	0.22
	oral	20 mg	6	12	0.53	0.05	-0.1	2.31	7.2	0.60*

a mixture = 40% 2,7 dichlorodibenzo-p-dioxin and 60% 2,3,7 trichlorodibenzo-p-dioxin
b DMSO = dimethylsulfoxide
c sacrificed day 17 of gestation: all others sacrificed day 18.

* = 0.05; ** = 0.01; *** = 0.001

Table 2. Toxicologic Evaluation of Chlorinated Dibenzo-p-dioxin Compounds in Pregnant CD-1 Mice
(Compounds Administered from Day 7 to 16 of Gestation)

Dibenzo-p-dioxin Compound	Route	Dose/kg/day	No. of Litters	Av. % Fetal Mortality/ Litter	Fetal Weight (gms)		Maternal Weight Gain (g)		Maternal Liver/Body Weight x 100	
					$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
5% anisole:corn oil	oral	0.1 ml/mouse	15	6	1.02	0.16	3.5	1.93	7.8	0.59
2/3 mixture[a]	oral	100 µg	6	3	1.36	0.13***	4.6	1.10	8.0	0.84
	oral	200 µg	5	5	1.25	0.19**	4.4	1.59	7.5	0.46
1,2,3,4-tetrachloro	oral	100 µg	4	10	1.09	0.09	4.8	0.51*	7.6	0.47
	oral	250 µg	4	20	1.10	0.12	4.8	1.44	7.7	0.37
	oral	500 µg	5	5	1.08	0.08	4.5	1.56	7.8	0.43
	oral	1000 µg	5	10	1.03	0.09	3.7	1.31	8.3	0.58
	subc	500 µg	5	7	1.24	0.07	3.4	0.82	7.6	0.40
	subc	1000 µg	6	2	1.31	0.07	2.3	0.57	8.1	0.44
DMSO[b]	subc	0.1 ml/mouse	6	14	1.19	0.17	3.1	1.96	7.5	0.94
2,3,7,8-tetrachloro	oral	25 µg	7	6	1.13	0.13	3.4	2.20	8.6	0.65**
	oral	50 µg	7	13	1.01	0.13	3.4	1.07	9.4	0.44***
	oral	100 µg	6	14	0.95	0.12	2.1	3.57	7.8	1.00
	oral	200 µg	6	87	d		d		d	
	oral	400 µg	5	97	d		d		d	
	subc	25 µg	5	36	1.25	0.07	3.0	0.86	9.7	0.42***
	subc	50 µg	6	56	1.20	0.15	2.3	1.17	9.0	1.09*
	subc	100 µg	6	72	d		d		d	
	subc	200 µg	6	76	d		d		d	
15% anisole:corn oil[c]	oral	0.1 ml/mouse	5	8	0.61	0.05	0.8	1.47	6.2	0.22
octachloro[c]	oral	5 mg	6	14	0.60	0.06	0.3	1.40	6.6	0.22
	oral	20 mg	6	12	0.53	0.05	-0.1	2.31	7.2	0.60*

a mixture = 40% 2,7 dichlorodibenzo-p-dioxin and 60% 2,3,7 trichlorodibenzo-p-dioxin
b DMSO = dimethylsulfoxide
c sacrificed day 17 of gestation: all others sacrificed day 18.

* = 0.05; ** = 0.01; *** = 0.001

Table 3. Teratogenic Evaluation of Chlorinated Dibenzo-p-dioxin Compounds in CD-1 Mice

Dibenzo-p-dioxin Compound	Route	Dose/kg/day	No. of Litters	Av. No. Live Fetuses/ Litter	Av. No. Abnormal Fetuses/ Litter	% Anomalies/Total Fetuses		
						Cleft Palate	Kidney	Clubfoot
5% anisole:corn oil	oral	0.1 ml/mouse	15	11.0	0.8	0	1	4
2/3 mixture[a]	oral	100 µg	6	12.3	3.2	0	10[d]	9
	oral	200 µg	5	12.8	3.8	0	1	22
1,2,3,4 tetrachloro-	oral	100 µg	4	11.8	0.8	2	0	2
	oral	250 µg	4	11.5	0.5	0	1	3
	oral	500 µg	5	11.6	0.2	0	0	0
	oral	1000 µg	5	11.8	1.0	0	0	0
	subc	500 µg	5	11.6	5.4	0	0	2
	subc	1000 µg	6	12.2	1.0	1	4	3
DMSO[b]	subc	0.1 ml/mouse	6	11.3	0.2	0	0	1
2,3,7,8 tetrachloro-	oral	25 µg	7	10.9	4.6	3	34	3
	oral	50 µg	7	11.0	8.1	19	72	7
	oral	100 µg	6	9.7	8.3	66	71	13
	oral	200 µg	6	1.5	1.5	100	100	14
	oral	400 µg	5	0.4	0.4	100	50	50
	subc	25 µg	5	7.7	6.7	82	53	11
	subc	50 µg	6	5.3	5.0	79	58	17
	subc	100 µg	6	3.5	3.5	85	95	0
	subc	200 µg	6	3.3	3.1	100	38	18
15% anisole:corn oil[c]	oral	0.1 ml/mouse	5	11.2	0	0	0	0
octachloro-[c]	oral	5 mg	6	11.2	0.2	1	0	0
	oral	20 mg	6	11.6	0	0	0	0

a mixture = 40% 2,7 dichlorodibenzo-p-dioxin and 60% 2,3,7 trichlorodibenzo-p-dioxin
b DMSO = dimethylsulfoxide
c sacrificed day 17 of gestation: all others sacrificed day 18
d 9/10 from one litter

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U.S. EPA SUSPENSION OF 2,4,5-T, SILVEX FOR USES ON:

RIGHTS-OF-WAY
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NOT SUSPENDED FOR USE ON:

RANGELAND
RICE

SILVEX ALSO SUSPENDED FOR:

AQUATIC USES
TURF AND LAWN USE
OTHER CANCELLED 2,4,5-T FOOD CROP USES
EXCEPT RICE

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

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

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

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

Employees who worked in the area of TCP production or were involved in the clean-up began to develop symptoms immediately following exposure to the material which was discharged from the autoclave. Symptoms included eye and respiratory tract irritation, headache, dizziness and nausea, and a severe irritant reaction of the exposed skin. After these initial symptoms subsided, the chloracne and other symptoms became evident. Ashe and Suskind[3-6] examined a total of 12 more severely affected workers on three occasions during the period of 1949 to 1953. Another 26 persons with chloracne, apparently not related to the accident, were also examined in 1953. The

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clinical symptoms, in order of relative frequency,[4] included acneform lesions; severe pains in muscles of upper and lower extremities, shoulders and thorax on exertion; fatigue; nervousness and irritability; decrease in libido; dyspnea; vertigo and intolerance to cold. On examination, all of the cases had chloracne. Several were severely hyperpigmented, especially on the face. Of the six workers examined in 1949 and 1950, four had liver enlargement and one had sensory loss in one foot. Liver impairment as indicated by hepatomegaly, tenderness and soreness in the right upper quadrant and epigastrium and a delayed prothrombin time, was observed.[3,5,6]

In 1953, four of the six workers examined in 1949 and 1950 were re-examined and six additional workers involved in the accident were also examined. The findings in this later examination indicated a general regression of both the cutaneous and noncutaneous symptoms which had been present earlier. All of the workers showed a marked improvement in their skin lesions — there were residua of the acne and a few active lesions. In a few cases, workers continued to complain of aches and pains of the lower extremities and back; nervousness, excessive fatigue, and dyspnea. No clinical explanation for these complaints could be made based on the results of the physical examination.[4]

The findings of the examinations by Ashe and Suskind are consistent with those which have been reported in other industrial episodes which occurred subsequently.[1] The acute health effects of TCDD exposure are described in the literature,[7] but little is known of the chronic effects.

Several reports describe the occurrence of cancer and other deaths in workers exposed to TCDD which suggests an association between exposure and the subsequent development of a variety of neoplasms.[8-11] These reports, however, are generally of small groups of workers with relatively short periods of follow-up and are considered to be preliminary in nature. In a 25-year follow-up study, 17 deaths were observed among a cohort of 75 German workers who had been involved in a 1953 TCP process accident.[8] Of the 17 deaths observed (11-25 expected depending on the choice of a control population), six were from cancer (four or fewer expected), five from cardiovascular disease (as expected), two from suicide (fewer than one expected), one from liver cirrhosis, one from a urogenital tract disease, and two from external causes. Of the six cancer deaths, three were from stomach cancer in the age group 60-69, a number significantly higher than expected. Two other cancer deaths were from oat-cell carcinoma of the lung and one was from adenocarcinoma of the colon.

A similar accident occurred in the Netherlands in 1963 in a factory producing 2,4,5-T.[9] Eight deaths have been observed among 93 exposed workers. Five or six of these deaths were from cardiovascular disease. The proportion of deaths due to myocardial infarction was noted to be high.

Jirasek et al[9,10] and Pazderova[11] followed 55 of the 78 Czechoslovakian workers who were affected by chloracne resulting from occupational exposure to 2,4,5-T and pentachlorophenol. In this study, five deaths were observed. These included two deaths from bronchiogenic carcinoma (less than one expected), one from cardiovascular disease, one from liver cirrhosis, and one from an accidental industrial intoxication.

In 1976, a TCP process accident in Meda, Italy, resulted in the contamination of a large and densely populated area.[8] A preliminary mortality study has been conducted in two of the 11 towns affected. The overall mortality rate did not differ from that expected, but increases in deaths from liver cirrhosis and leukemia were suggested.

The chronic toxicity of TCDD exposure to animals has been more extensively studied. TCDD toxicity has been thoroughly reviewed.[7] Chronic toxicity to TCDD is manifested by liver necrosis, thymic atrophy, and depletion of the lymphoid organs. Two studies indicate that chronic administration of low levels of TCDD to rats is associated with an increased incidence of neoplasia. In one study, the oral administration of TCDD produced an increase in hepatocellular carcinomas and squamous cell carcinomas of the lung, hard palate/nasal turbinates, or tongue.[12] In another study, TCDD fed to rats produced tumors in 38% of the test animals.[13] Neoplastic nodules and cholangiocarcinomas of the liver were observed.

The study reported here will examine the mortality experience of a cohort of 121 employees involved in the 1949 trichlorophenol process accident, with special emphasis on cardiovascular disease and on neoplasms, particularly of the stomach, liver, lung, and skin.

Population and Methods

In this study, the development of chloracne, a hallmark of TCDD exposure, was used to identify employees for study. The study population consists of all persons with chloracne which could be attributed to the 1949 TCP process accident. One hundred and twenty-two employees who developed chloracne following this incident were identified from plant safety records dating to the time of the accident, and from workmen's compensation and plant medical records. One hundred and twenty-one white males were included in this study — one female who was living as of the endpoint of the study was not included in this mortality analysis. It is assumed that all of the skin disorders recorded in the plant records represent true cases of chloracne and not other types of occupational or nonoccupational dermatitis. An analysis of the chloracne cases and exposures not associated with this accident but rather with the normal TCP/2,4,5-T production processes will be the subject of a future paper.

The data were analyzed by the modified life-table method using the updated Monson program.[14] In this method of analysis, the age-, race-, time- and cause-specific mortality rates for a standard population (in this case, the population of the United States) are applied to the person-years lived classified by age, race, and time. A standardized mortality ratio was calculated as the ratio of the observed deaths to the expected deaths for 22 selected causes of death. The statistical significance of differences between observed and expected numbers was based on the Poisson distribution and statistical significance was determined at the 5% level of significance.

For the purpose of analysis, each member of the study cohort was assumed to have entered the study on March 8, 1949, the date of the accident. The vital status of each member was determined using standard follow-up techniques and ascertained as of December 31, 1978. For each person found to be deceased, a death certificate was ob-

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

Cause	ICD No. (Eighth Revision)	Observed	Expected	SMR
All causes of death		32	46.41	0.69*
All malignant neoplasms	140-209	9	9.04	1.00
Buccal cavity and pharynx	140-149	0	0.30	†
Digestive organs and peritoneum	150-159	0	2.59	†
Stomach	151	0	0.50	†
Liver	155-156	0	0.18	†
All other digestive organs	—	0	1.91	†
Respiratory system	160-163	5	3.02	1.66
Lung	162,163	5	2.85	1.75
All other respiratory organs	—	0	0.17	†
Skin	172,173	1	0.15	†
Genitourinary organs	185-189	0	1.16	†
Lymphatic and hematopoietic tissue	200-209	3	0.88	†
Other sites	—	0	0.94	†
Diseases of the nervous system and sense organs	320-389	0	0.36	†
Diseases of the circulatory system	390-458	17	25.01	0.68
Arteriosclerotic heart disease, including coronary heart disease	410-413	13	17.74	0.73
All other disease of the circulatory system	—	4	7.27	†
Diseases of the respiratory system	460-519	1	2.78	†
Diseases of the digestive system	520-577	0	2.26	†
All other diseases	—	2	3.18	†
External causes of death	800-998	3	3.78	†

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

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

Results

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

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

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

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

Discussion

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

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

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

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

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

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

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

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Future Risk

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

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

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Mortality Experience of Employees Exposed to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)

DOW0977202

Ralph R. Cook, M.D., M.P.H.; Jean C. Townsend, M.S.; M. Gerald Ott, M.S.; and Lawrence G. Silverstein, M.S.

This study describes the mortality experience of a cohort of 61 males involved in a 1964 chloracne incident. Presumably as a result of skin absorption of the process contaminant, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD or dioxin), 49 of these trichlorophenol production workers developed the skin condition. Within the limitations posed by cohort size and length of follow-up, TCDD does not appear to have adversely affected mortality experience. Overall, four deaths occurred and 7.8 were expected. Of these, one death was due to cardiovascular disease (3.8 expected) and three deaths were attributed to cancer (1.6 expected). None of the findings were statistically significant at $\alpha = 0.05$. Further follow-up is contemplated.

Chlorodioxins are found as trace contaminants of various commercial chlorinated phenols and as minute byproducts of routine combustion.[1] The most toxic of the 75 possible isomers is 2,3,7,8,-tetrachlorodibenzo-p-dioxin, known also by the less specific rubrics TCDD or dioxin.[2]

At sufficient dose, TCDD produces the dermatologic condition chloracne.[3] This was the most prominent clinical sequela of the Seveso, Italy, accident[4] and is usually considered the sine qua non of excessive dioxin exposure. Among industrial populations exhibiting chloracne, researchers have also found porphyria cutanea tarda, hepatotoxicity, and a variety of ill-defined neurological abnormalities.[5]

Investigations of human effects with long latency only recently have been initiated. Because of allegations by Vietnam veterans of delayed health problems from exposure to dioxin in Agent Orange,[6] U.S. Air Force personnel who worked with this defoliant are being studied.[7] Health, Education and Welfare (HEW) agencies are setting up a dioxin exposure registry for U.S. industrial workers,[8] and research teams from several universities are evaluating those exposed during a 1949 chemical plant explosion in Nitro, West Virginia.[7]

In this mortality study, vital status was traced for 61 employees of the Dow Chemical Company who were exposed to TCDD in 1964. The objectives were to determine whether overall mortality through 1978 was greater than expected and whether, among the deceased, unique patterns of exposure or mortality were obvious.

Methods and Materials

The possibility of exposures to TCDD was manifested in early 1964 when employees from a trichlorophenol manufacturing area began reporting to the industrial medical department with skin conditions which were subsequently diagnosed as chloracne. Intense evaluations by industrial hygiene and toxicology personnel demonstrated that the condition probably resulted from skin absorption of the process contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin. As a result of changes in both plant operations and personal hygiene, potential for exposure had decreased by June 1964.

To facilitate epidemiologic research, the industrial hygienist assigned to the process area categorized all job classifications into high and low potential exposure. This was based on conditions existing prior to control changes. The high-exposure group included (1) production employees who worked in the area of highest TCDD contamination, (2) employees engaged in sampling opera-

From Dow Chemical U.S.A., Midland, MI 48640 (Dr. Cook, Director, U.S. Area Epidemiology, Ms. Townsend, Epidemiologist, Michigan Division, Mr. Ott, Biostatistician, U.S. Area Epidemiology, and Mr. Silverstein, Research Manager, U.S. Area Industrial Hygiene). Mr. Ott is currently at the University of Michigan, School of Public Health, Dept. of Epidemiology

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Table 1. — Age Distribution of 61 Employees Potentially Exposed to TCDD During 1964 by Job Category and by Date First Employed in Process Area.

Exposure Group and Age Distribution	Total	First Employed in Process Area: Prior to June 1964	First Employed in Process Area: July to December 1964
Group 1. (High potential exposure)			
Total	39	34	5
20 - 24	3	2	1
25 - 34	13	12	1
35 - 44	10	8	2
45 - 54	8	7	1
55 - 64	5	5	0
Group 2. (Low potential exposure)			
Total	22	16	6
20 - 24	4	0	4
25 - 34	6	5	1
35 - 44	9	9	0
45 - 54	3	2	1
55 - 64	0	0	0

tions, and (3) maintenance personnel assigned to production equipment. The low-exposure group included production personnel who worked away from areas of highest contamination and maintenance employees not directly involved with production equipment. The exposure groups were further subdivided into those who worked in the process area sometime between November 1963 and June 1964, and those who first worked in the area from July through December 1964.

Sixty-one employees were identified from department monthly census lists and from a list of maintenance employees known to have worked in the building during 1964. The age distribution of these employees, by exposure group and by date first employed in the area, is shown in Table 1. Vital status of all 61 men was determined through December 31, 1978. Following methods previously described, expected numbers of deaths were computed from cause-specific and age-specific mortality rates for the U.S. white male population.[9]

Results

Acne-like lesions were observed among 49 of the total cohort of 61. The severity ranged from questionable (i.e., a few comedones on the face which the employee thought predated his work in the process area) to severe (cysts and comedones over face, scalp, ears, neck and back). Subdivision of the population by date of exposure appeared to be more important than job classification in discriminating between persons with and without chloracne. Among those employed prior to July 1964, an acnegenic response was observed in 30 of 34 persons in the high-potential-exposure group and in 14 of 16 in the low-potential-exposure group. Only five positive responses were observed among the 11 men first employed after June 1964; four of these five were in the high-potential-exposure group.

The vital and employment status of these 61 employees as of December 31, 1978, is shown in Table 2. Overall, four deaths were observed, compared with 7.8 expected. Of the observed deaths, one was due to cardiovascular disease, versus 3.8 expected; and three were due to malignant neoplasms, versus 1.6 expected. None of these findings was statistically significant at $\alpha = 0.05$. Environmental and health parameters of the deceased are described below.

Case 1. — The subject worked 35 years with the company, beginning in 1928. During his first 17 years of employment he was a loader and truck driver. After a five-year absence, 14 of his remaining 18 years with the company were spent in the trichlorophenol area. During 1964, he worked on a job involving potentially high exposure to TCDD. Although a few comedones were observed on his face and back, his recurrent acne was described in 1964 as not typical of chloracne. He had a positive smoking history: a pack per day for an unknown number of years. In 1972, three years after his retirement at age 60, he died of adenocarcinoma, primary site unknown. No autopsy was performed.

Case 2. — The subject worked in construction and maintenance for 24 years. In 1964 he was assigned to trichlorophenol production, working in an area of low potential TCDD exposure. During this period, he was seen for a rash of the right ear and face. No definitive diagnosis of chloracne was made. Records indicate he was a cigarette smoker, averaging a pack per day for 35 years. He died of a fibrosarcoma in 1975 at age 53. Autopsy was performed.

Case 3. — The subject worked 31 years with the company, beginning in 1942. During 24 of these years, he worked in the trichlorophenol process area. Although in 1964 he was in the low-exposure category, he developed chloracne. He smoked a pack of cigarettes per day for 20 years. His death, in 1976 at age 56, was attributed to a

Table 2. — Vital and Employment Status Through December 31, 1978, of 61 Employees Potentially Exposed to TCDD During 1964.

Vital and Employment Status	No. of Employees
Total	61
Still working	40
Retired	11
Deceased	4
Left company	
Deceased	0
Alive	6

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glioma with metastases. No autopsy was performed.

Case 4. — The subject began working with the company in 1946 at the age of 41. He spent 20 years in the trichlorophenol area. In 1964 he was in the high-exposure group and, during this period, he developed mild chloracne on the face. He smoked for 30 years but quantity is not recorded. He died in 1976, seven years after his retirement, of hypertensive heart disease at the age of 71. No autopsy was performed.

Discussion

This cohort was relatively small and therefore provides results of low statistical power; nevertheless, the findings are of clinical significance. Overall mortality was about 50% of that expected, below the "healthy worker effect" postulated for a population with this length of follow-up.[10] Much of the decrease was due to a deficit in cardiovascular deaths. While cancer mortality was slightly elevated (3 deaths observed versus 1.6 expected), each of the malignancies was a different type and none was apparently primary in the liver, a site of concern.[6] In the absence of a sentinel tumor such as those found in asbestos (mesothelioma) or vinyl chloride (angiosarcoma), one could postulate that 2,3,7,8-tetrachlorodibenzo-p-dioxin depresses human immunological response, thereby increasing the risk to all malignancies; however, in the animal study that would tend to support this hypothesis, the dose required also produced a variety of systemic toxic effects.[11] In the cohort studied here, only one of the cancer deaths occurred in an individual with documented chloracne, and no deaths occurred as a result of other diseases related to depressed immunologic capacity. These findings, and the lack of a dose-response based on exposures defined by an industrial hygienist, suggest that the cancer mortality experienced by this cohort was a chance occurrence.

The latency period for this cohort, at least in respect to the peak exposures experienced in 1964, exceeded 14 years. This latency period would seem sufficient to allow the identification of a potent human carcinogen, especially one producing unique tumors. In addition, many of the employees had worked in the trichlorophenol areas prior to 1964 and, thus, the effective latency for *any* potential exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin extended beyond the years of study. All of this suggests that 2,3,7,8-TCDD is not a potent human carcinogen. Further research on this and other cohorts will have to be conducted to determine whether it is a weak carcinogen in humans.

Conclusion

This analysis of the mortality experience of 61 males indicates that, within the limitations posed by cohort size and length of follow-up, 2,3,7,8-tetrachlorodibenzo-p-dioxin even at levels sufficient to produce chloracne, does not increase overall mortality (4 deaths observed vs. 7.8 expected). Further, it does not appear to increase risk of cardiovascular death. While overall cancer deaths were slightly above expected (3 observed vs. 1.6 expected), no single type of tumor was predominant and therefore dioxin cannot be considered a potent human carcinogen with organ or tissue specificity. Continued surveillance of this group's mortality experience should provide additional information pertaining to the chemical's potential as a weak carcinogen for humans.

The authors wish to thank Ms. Maxine Coin for editing the manuscript.

All correspondence regarding this report should include the reference number B-600-027-80.

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ASPLUNDH TREE EXPERT CO.

P. O. BOX 268, DANVILLE, KY 40422 • AREA CODE 502 • TELEPHONE 361-8811

GASTON ROSE
VICE PRESIDENT

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DOW 013542

September 25, 1978

Federal Register Section
Technical Service Division (WH-569)
Office of Pesticide Programs, EPA
Room 401 East Tower
401 M. Street, SW
Washington, D.C. 20460
Attn: OPP 30000/26

Gentlemen:

I represent the Asplundh Tree Expert Company in the state of Kentucky and have been Vice President for three years.

I have been using 2,4,5,-T in Kentucky for the past 26 years to control brush on right-a-ways for the various utilities in the state. I started using it as a sprayman on a crew. It has been the most effective method of controlling brush along the right-a-ways, and I have seen no ill effects to wildlife or any other livestock.

If 2,4,5-T is not to be re-registered, we will turn to hand clearing or mowing, which would cost us approximately five times as much. Neither of these methods would be nearly as effective as 2,4,5-T.

Needless to say, I am very much in favor of 2,4,5-T being re-registered.

Sincerely,

Gaston Rose
Vice President

:kh

cc Wendell Ford
Walter Huddleston
Carol Hubbard
William Natcher
Romano Mazzoli
Gene Snyder
Dr. Tim Lee Carter
John Breckinridge
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LETTERS RECEIVED

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ASPLUNDH

ASPLUNDH TREE EXPERT CO.

BLAIR MILL ROAD, WILLOW GROVE, PA. 19090 • AREA CODE 215 • TELEPHONE: 784-4200

1034 West Street, Amherst, MA 01002

DOW9135538

October 13, 1978

Federal Register Section
Technical Service Division (WH-569)
Office of Pesticide Programs, EPA
Room 401 East Tower
401 M. Street, SW
Washington, D.C. 20460

ATTN: OPP 30000/26

Gentlemen:

As a Division Manager and Vice President of ASPLUNDH TREE EXPERT COMPANY, I wish to acquaint you of my concern regarding the study by the Environmental Protective Agency on the re-registration of the Herbicide 245T.

I, as an employee and user of 245T, have worked closely with this material since 1949.

I have had the responsibility of applying this material and assisting people in making decisions about its use.

As an applicator who has used 245T to treat undesirable woody growth on Utility Rights of Way over a period of 28 years covering many thousands of acres of brush, I feel that you should be aware that during this period I have not received a claim from an employee or ex-employee of any health problem or am I aware of any that existed.

I am sure that you are aware of the many discrepencies that exist in the newspaper, radio and television reports with unsubstantiated claims of health hazards.

245T, when properly used in the control of unwanted vegetation on utility company's Rights of Way, offer a substantial savings to the maintenance budgets. The alternative measures of control would multiply maintenance costs and thereby be directly reflected in utility rates.

At this point in time, I am not aware of other chemicals or mechanical control measures that offer the benefits achieved by the use of 245T.

DOW913539

As an active member of the International Society of Aboriculture, Western Mass. Shade Tree Association, Massachusetts Tree Wardens and Foresters Association and the Maine Arborist Association, I sincerely request that you give serious consideration to the positive aspects of the use of the herbicide and use your influence to keep 245T as a tool for Right of Way brush control.

Respectfully yours,

Joffre G. Schnarr
Vice President

pc: Hon. Paul Tsongas
Hon. Edward Brooke
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Hon. Edward Boland
Hon. Joseph Early
Hon. Robert Drinan
Hon. Edward Markey
Hon. Thomas O'Neill
Hon. John Moakley
Hon. Gerry Studds

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CONTRACTORS

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#	CONTRACTOR	Phone	Name-Title of Person	No	Out	Yes	AES Copy	Date
1	Walgren Tree Experts, Inc.	203-249-5266	Bruce Walgren			x	x	8-18
2	Farrens Tree Surgeons	904-743-2622	Gerald Farrens			x	x	8-18
3	Georgia ROW Construction	404-278-6905	James H. Hicks			x	x	8-18
4	N. G. Gilbert Corp.	404-294-5490	Bob Bowen			x	x	8-18
5	Davey Tree Expert Co.	216-673-9511	Dick Abbot (sent previously)			x	x	8-18
6	Nelson Tree Service Inc.	513-294-1313	Paul Russell			x	x	8-18
7	Townsend Tree	614-593-6037	Dent C. Dailey			x	x	8-21
8	Noxious Vegetation Control	614-486-8994	Sally Watson			x	x	8-18
9	Karl Kuemmerling Assoc.	614-471-4144	Franklin N. Brown			x	x	8-18
10	Funk Bros. Tree Service	419-325-2113	Kenneth H. Funk			x	x	8-21
11	Noxious Vegetation Control	814-623-6351	Walter Grobert			x	x	8-23
12	Bartlett Tree Expert Co.	614-453-0653	Burl B. Shreve		wcb			
13	Utilities Forestry Service	814-765-7115	S. J. Wayrynovic, James Davis			x	x	8-18
14	Bartlett Tree Expert Co.	615-247-2154	Herb Merrill			x	x	8-18
15	Blume System Tree Experts	713-782-9450	H. L. Graves, Gen. Mgr.			x	x	8-23
16	Trees, Inc.	713-692-6371	Thomas Gunning	x	Do not offer spray service			8-25
17	Davey Tree Expert Co.	214-593-3122	Merle Talbot			x	x	8-25
18	The Daltons of Indiana, Inc.	219-267-2460	Lex Dalton			x	x	8-18
19	N. G. Gilbert Corp.	317-284-4461	John Elsesser			x	x	8-24
20	Townsend Tree Service	317-282-1234	Donald F. Townsend			x	x	8-21
21	Asplundh Brush Control Co.	317-482-2041	Fernand Perras			x	x	8-18
22	Shannon Tree Co.	717-296-6351	Walter Shannon, V.P.			x	x	8-21

17246

JTIL... CO.. CTO..

#	CONTRACTOR	Phone	Name-Title of Person	No	Out	Yes	AES Copy	Date
23	Arbor Tree Surgery	805-466-1239	Richard G. Alvares			x	x	8-21
24	Davey Tree Expert Co.	415-443-1723	Eugene W. Haupt	x	See Davey Home Office			8-21
25	Utility Tree Service Inc.	707-443-9794	Jim Fox			x	x	8-21
26	Farrens Tree Surgeons	205-833-9079	Marvin Humphries	x	NOT USING 2,4,5-T			8-21
27	Farrens Tree Surgeons	404-636-1994	J. L. Argo			x	x	8-21
28	Davey Tree Expert Co.	404-451-7913	Tommy Davis			x	x	8-21
29	Wright Tree Service, Inc.	515-277-6291	Roy Gunson			x	x	8-21
30	Phillips Tree Experts Inc.	606-528-4145	Ray Phillips		wcb			
31	John Lucas Tree Expert Co.	207-797-7294	Henry Thibedeau			x	x	8-22
32	Bartlett Tree Expert Co.	703-343-9376	C. L. Gregson			x	x	8-21
33	Nelson Tree Service	906-265-2618	Frederick Gault	See Main Office				9-1
34	Tree Preservation Co., Inc.	914-941-2600	David Franklin			x	x	8-21
35	Lewis Tree Service, Inc.	716-684-0120	Robert Howard			x	x	8-21
36	Monroe Tree & Landscape Service	716-436-2900	Steve Kubber			x	x	8-22
37	J. Taylor Tree Surgery	914-895-3495	James W. Taylor		cb			
38	Davey Tree Expert Co.	312-437-0911	Herbert J. Winters			x	x	8-22
39	F. A. Bartlett Tree Expert Co.	203-323-1131	Robert A. Bartlett, Jr.			x	x	8-22
40	F. A. Bartlett Tree Expert Co.	215-664-3200	David G. Poe	x	NOT USING CHEMICALS			8-23
41	Black Industries, Inc.	919-4770485	Craig M. Black			x	x	8-22
42	Davey Tree Expert Co.	704-596-8066	Gene Efird			x	x	8-22
~~43~~	Stackhouse, Inc.	919-735-1784	James B. Edmondson	x	DO NOT USE 2,4,5-T			8-24
44	W. D. Poole Construction Co.	919-273-6927	W. D. Poole	x	DO NO SPRAY WORK			8-22

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DOW91353Z

UTILITY CONTRACTORS

#	CONTRACTOR	Phone	Name-Title of Person	No	Out	Yes	AES Copy	Date
45	Asplundh Tree Expert Co.	617-832-5721	Patrick V. Smith			x	x	8-23
46	Bartlett Tree Expert Co.	606-324-9414	Elmer W. Reynolds			x	x	8-22
47	Henkels & McCoy, Inc.	215-646-8000	John J. Burns		yes	for PE stumps x	x	8-25
48	Southern Utility Const.	205-871-0410	Melvin J. Hornberger			x	x	8-22
49	Nelson Tree Service, Inc.	419-433-6471	Herb Dotson, Mgr.			x	x	8-22
50	Henkels & McCoy, Inc.	301-658-5522	Joseph B. Dugan			x	x	8-24
51	Agricultural Services, inc.	612-338-5801	Ted Weidenfeller		wcb			
52	Davey Tree Expert Co.	803-543-3829	Ray Bannister & J. D. Brooks			x	x	8-22
53	Asplundh Tree Expert Co.	414-931-1610	Robert Wakeford			x	x	8-24
54	CUSCO	703-362-9210	Mr. Bob Sayre			x	x	8-24
55	Love & Associates, Inc.	804-372-4941	William Keel			x	x	8-25
56	Westvaco Corp.	804-823-2257	John (Jack) Gnegy (sent previously)			x	x	8-23
57	Chem-Spray	318-425-8671	R. A. Rains			x	x	8-24
58	Industrial Weed Control	318-233-3356	J. O. Richard		cb			
59	Reeds, Inc.	312-448-5677	John Waronich	x	DO NOT USE 2,4,5-T			8-24
60	Parker Layne Tree Service	615-837-6565	John P. Layne (sent previously)			x	x	8-24
61	McKibben & McKibben	717-323-8285	Bill McKibben		cb	x	x	9-1
62	Chem-Trol, Inc.	913-342-3006	Bob Tolman (sent prev.)			x	x	8-25
63	Madison Spraying Service	405-237-0294	Wesley Madison			x	x	8-24
64	Gute Tree Service	712-792-9009	L. J. Gute			x	x	8-24
65	J. I. Brown Tree Expert Co.	615-837-6565	John P ("Parker") Layne (sent previously)			x	x	8-24
66	Nelson Tree Service	815-725-7269	Chuck Kaseno		cb			

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UTILITY CONTRACTORS

#	CONTRACTOR	Phone	Name-Title of Person	No	Out	Yes	AES Copy	Date
67	Chem-Ag	318-981-0349	Russel Mier		cb			
68	Nelson Tree Service (Main office)	313-727-7557	Vic		cb			

DOW 913534

17239

#	ASPLUNDH REGIONAL MANAGERS	Phone	Name-Title of Person	No	Out	Yes	AES Copy	Date
1	ATE (Conn.)	#47	Bill Neidig, V.P. (sent previously)	-----		x	x	7-25
2	ATE (N.Y.)	#30	Ed Regan, V.P			x	x	8-3
3	ATE (Georgia)	#52	Conrad Bostock, V.P.			x	x	8-3
4	ATE (Texas)	#58	Richard A. Bates, V.P.			x	x	8-3
5	ATE (Virginia)	#42	Dan Cole, V.P.			x	x	8-4
6	ATE (Maryland)	#35	Bob Collier			x	x	8-4
7	ATE (Mass.)	#45	Ed Cummings, V.P.			x	x	8-3
8	ATE (California)	#75	Jack Curtin	x	DO NOT USE 2,4,5-T			8-4
9	ATE (Maryland)	#38	Charles Dalton, V.P.			x	x	8-4
10	ATE (Florida)	#54	Rick Dannenmiller			x	x	8-3
11	ATE (Connecticut)	#46	Harold Duncan (Car #614)			x	x	8-7
12	ATE (Pennsylvania)	#22	Bill Eggers, Jr.			x	x	8-3
13	ATE (Pennsylvania)	#34	Jerry Erickson, V.P.			x	x	8-4
14	ATE (Minnesota)	#65	Paul Erickson			x	x	8-4
15	ATE (North Carolina)	#50	Norman Hope, V.P.	x	MOWING			8-7
16	ATE (Ohio)	#61	Dudley W. Jordan, V.P.			x	x	8-21
17	ATE (Oklahoma)	#70	Howard Kidder, V.P.			x	x	8-4
18	ATE (D.C.)	#40	Werner (Dutch) Lange			x	x	8-3
19	ATE (New York)	#32	Fred Mehre			x	x	8-8
20	ATE (Tennessee)	#57	Ray Muse, V.P.			x	x	8-4
21	ATE (Illinois)	#66	Earl Reynolds, V.P.			x	x	8-4
22	ATE (Kentucky)	#59	Gaston Rose, V.P.			x	x	8-3

DOW 913535

17250

#	ASPLUNDH REGIONAL MANAGERS	Phone	Name-Title of Person	No	Out	Yes	AES Copy	Date
23	ATE (Massachusetts)	#44	Joffre Schnarr, V.P.			x	x	8-9
24	ATE (California)	#78	Mel Sease, V.P.	x	NOT USING	CHEMICAL		8-3
25	ATE (Florida)	#55	Dallas Schiver, V.P.			x	x	8-3
26	ATE (Louisiana)	#58	Ray Spencer, V.P.			x	x	8-3
27	ATE (Indiana)	#60	Bob Spudis, V.P.			x	x	8-3
28	ATE (Texas)	#69	Dick Troxell	x	NOT USING HERB	CIDE		8-4
29	ATE (New Jersey)	#27	Milton Walsh, V.P.			x	x	8-3
30	ATE (Florida)	#56	Sam Sandlin			x	x	8-18
31	ATE (Pennsylvania)	#23	Merle Welty, V.P.			x	x	8-4
32	ATE (Texas)	#71	Dwight Watkins			x	x	8-8
33	ATE (Utah)	#73	Lloyd Egemo			x	x	8-3
34	ATE (Washington)	#72	Donald Kuhn			x	x	8-9
35	ATE (Michigan)	#64	O. Dan Stewart			x	x	8-8
36	ATE (Alabama)	205-633-9037 (off.)	Roger Ferry			x	x	8-9

17251

DOW91336

95th CONGRESS
2nd Session

H.R. .....

(Original signature of Member)

IN THE HOUSE OF REPRESENTATIVES

March 13, 1978

Mr. Evans of Georgia introduced the following bill; which was referred to the Committee on .....

A BILL

To abolish the Environmental Protection Agency

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Section 1. The Environmental Protection Agency is hereby abolished. All functions, activities, powers, and duties of the Environmental Protection Agency are terminated and shall not be transferred to any agency or instrumentality of the United States. Notwithstanding any other provision of law, all regulations, orders, rules, determinations, contracts, certificates, licenses, and privileges issued, made, granted, or allowed to

3/27/78

DOW 913528

become effective by the Environmental Protection Agency on or before the date of the enactment of this Act shall cease to have effect.

Sec. 2. The Director of the Office of Management and Budget shall take such action as he deems necessary, in accordance with applicable laws and regulations, to conclude the outstanding affairs of the Environmental Protection Agency, including matters affecting personnel, contracts, assets, liabilities, property, and records of the Environmental Protection Agency.

Sec. 3. Unexpended balances of appropriations, authorizations, allocations, or other funds related to the Environmental Protection Agency shall be available for use by the Director of the Office of Management and Budget until the end of the fifth fiscal year after the fiscal year in which this Act is enacted. Such use shall be for the purposes for which the appropriations, authorizations, allocations, or other funds were originally made available, but only to the extent required to conclude the affairs of the Environmental Protection Agency pursuant to Section 2. After the period specified in the preceding sentence, any unexpended balances remaining shall be returned to the general fund of the Treasury.

COMMITTEE

DOW913526

June 28, 1978

COPY

Mr. Tom Price
KIRBY FOREST INDUSTRIES
P. O. Box 577
Silsbee, Texas 77657

Dear Tom:

In compliance with your request, please find listed below the statistical information of Campbell Air Service, Inc. for the past 12 years or seasons, as regards to the use of 2,4,5-T for Rights-of-Way Brush Control and Forestry Pine Release:

Rights-of-Way Brush Control

1)	Average work days per crew per year	71
2)	Average flight hours per crew per day	2.51
3)	Average hours per day each crew member is in direct contact with chemical, including mixing and loading	4

Forestry Pine Release

1)	Average work days per crew per year	41
2)	Average flight hours per crew per day	2.25
3)	Average hours per day each crew member is in direct contact with chemical, including mixing and loading	4

Please note that one crew working both rights-of-way and forestry would average 112 days per year and in our experience the maximum would not exceed 120 days or 4 months.

For your further information Campbell Air Service, Inc. has not experienced any injuries, nor ill effects, to any employee, as a result of chemical useage in our operations. Every precaution is taken to prevent spillage and leakage by maintaining a strict schedule of inspections and maintenance. The chemical is transferred from its original container to closed mixed tanks by means of suction pump and hose, where it is mixed with water and subsequently delivered to saddle tanks on the helicopter, also by means of pump and hose.

Also, I would like to add that I personally have been using and in direct contact with this chemical for the past 26 years, and have experienced no ill effects, whatsoever. I have 2 children and each of them have children, and there are no ill effects to any, as a result of my experiences with the chemical.

I conclude, that after seeing first-hand the tremendous accomplishments thru the use of this chemical, that to question its use is utterly ridiculous.

Yours very truly,

CAMPBELL AIR SERVICE, INC.

W. B. Rowe, Sr., President

WBRSR:jw

C O P Y

DOW0135227

CAMPBELL AIR SERVICE, INC.

P. O. BOX 872 • VIVIAN, LOUISIANA 71082
PHONE A/C 318 - 375-3207, 425-8218

934

MESSAGE REPLY

TO Mr. Jim Skelton

ASPLUNDH ENVIRONMENTAL SERVICES
Blair Mill Road
Willow Grove, Penna. 19090

DATE 8/2/78

DATE

DOW 9135525

Dear Mr. Skelton:

In response to your telephone conversation of this date, enclosed please find a copy of one of our letters to our customer, concerning the use of 2,4,5-T. Also, enclosed is a copy of a Bill introduced by Mr. Evans of Georgia. His Bill abolishing the EPA, might be what we need.

Hope this information will assist you and if we can be of any further assistance, please do not hesitate to call on us.

Regards,

BY J. G. Eakin, Sec.-Treas.

SIGNED

Form N-772 The Drawing Board, Inc. Box 502 Dallas, Texas

INSTRUCTIONS TO SENDER: 1. KEEP YELLOW COPY. 2. SEND WHITE AND PINK COPIES WITH CARBON INTACT

INSTRUCTIONS TO RECEIVER: 1. WRITE REPLY. 2. DETACH STUB. KEEP PINK COPY. RETURN WHITE COPY TO SENDER

17256

EASTERN SHORE NATURAL GAS COMPANY
P. O. BOX 615
DOVER, DELAWARE 19901

935

August 23, 1978

DOW913524

Asplundh Environmental Services
Mr. Jim Skelton
Benefits Letter Coordinator
Blair Mill Road
Willow Grove, PA. 19090

Dear Mr. Skelton:

We do not use 2,4,5-T RPAR.

Sincerely yours,

EASTERN SHORE NATURAL GAS COMPANY

Wayne Morris

Wayne Morris
Project Designer

WM/kd

17257

DOW 913522

LETTERS RECEIVED

ARCO Pipe Line Company
ARCO Building
Independence, Kansas 67301
Telephone 316 331 1600

G. E. Clapp
Coordinator, Environmental
Protection/Security

September 15, 1978

DOW913523

Mr. Dennis Holewinski, Manager
ASPLUNDH Environmental Services
Blair Mill Road
Willow Grove, Pennsylvania 19090

Re: 2, 4, 5 - T (RPAR)

Dear Sir:

This letter has been prepared in accordance with your letter of August 4, 1978, regarding re-registration by EPA of 2, 4, 5 - T formulations.

ARCO Pipe Line Company has not used this material extensively in weed control on our pipeline rights-of-way, however it has been used on our pipeline station properties very effectively in control of broadleaf vegetation over the last few years.

Alternatives to the use of 2, 4, 5 - T formulations on our station properties would include the less effective use of diesel oil.

If 2, 4, 5 - T should not be re-registered, the economic consequences would amount to the lower cost of diesel oil but result in the greater cost of labor in killing the weed roots which the diesel would not do.

Sincerely,

G. E. Clapp

GEC:vrr

ARCO Pipe Line Company

Approval	☐	To: Mr. Dennis Holewinski
Handling	☐	
Comments	☐	We have not sent copies of this letter to EPD or State Representatives or Senators. You may do so if you believe that our comments are appropriate.
Information	☐	
Signature	☐	
File	☐	
Note & Return	☐	
As Requested	☐	
Contact Me	☐	

From: G. E. Clapp | Date: 9-15-78

17259

DOW9135I5

PIPELINES

PIPELINE/CONTRACTOR

#	Pipeline or Contractor	Phone	Name-Title of Person	No	Out	Yes	AES Copy	Date
1	Buckeye Pipe Line	215-967-3131	F. Romaker, Reg. Mgr.			x	x	7-28
2	ARCO Pipe Line	215-678-8005	P. Christman, R/W	x	No experience			7-28
3	Consolidated Gas Supply	304-623-3611	J. Rine, Environmental	x	DO NOT USE 2,4,5-T			7-28
4	Laurel Pipe Line	717-737-8611	J. E. Johnson			x	x	8-2
5	Columbia Gas Transmission'	304-346-0951	B. Ollice; Eng.			x	x	7-28
6	Transco Companies Inc.	201-862-8600	Jim Houston		cb			
7	ARCO Pipeline Co.	316-331-1300	Geo. Clatp, Env. Eng.			x	x	7-28
8	Acorn Pipe Line Co.	713-923-3300	H. I. Mayes	x	OWN NO ROWS			7-28
9	Aker Oil & Gas Company	918-743-9148	Donald F. Baker	x	NO CHEMICALS			8-2
10	Alabama-Tenn. Natural Gas Co.	205-383-3631	J. W. Solomon			x	x	7-28
11	Algonquin Gas Transmission Co.	617-254-4050	Wm. Lawson			x	x	8-2
12	Allied Materials Corp.	405-842-4403	Truman Peek	x	DO NOT USE 2,4,5-T			7-28
13	American Natural Gas Service Co.	313-965-8300	Vince Lajiness, Env.	x	DO NOT USE 2,4,5-T			8-4
14	Amoco Pipeline Co.	312-856-5111	Wm. Domax	x	ROW on Farmlands			8-7
15	Apollo Gas Co. & Carnegie Nat'l. Gas	412-462-7121	B. F. Morton	x	DO NOT USE 2,4,5-T			8-2
16	Arkansas Louisiana Gas Co.	318-425-1271	J. A. Irvin			x	x	8-2
17	Cambell Air Service	318-425-8218	Jim Eakin	(sent prev.)		x	x	8-2
18	American Petrofino Pipe Line Co.	915-263-7661	Wayne Bartlett	x	NO CHEMICALS			8-3
19	Aminoil U.S.A. Inc.	713-686-9261	Harold Nissen	x				8-7
20	Amoco Gas Co.	713-948-2501	Mr. Castille, Envir. DOW91351E	x	DO NOT USE 2,4,5-T			8-2
21	Anadarko Production Co.	713-526-5421	Richard Gains, or Clyde Anthen	x	NO CHEMICALS			8-4
22	Apco Pipe Line, Inc.	316-442-3620	H. R. Ledeker	x	Use Lance Weed Cont.			8-7

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PIPELINE CONTRACTOR

#	Pipeline or Contractor	Phone	Name-Title of Person	No	Out	Yes	AES Copy	Date
23	Arapaho Pipeline Co.	303-842-2881	Mr. A. G. Sprawka	x				8-4
24	Arbuckle Pipeline Co.	918-560-6357	Charles Hoffman	x	DO NOT USE 2,4,5-T			8-3
25	Arkansas-Oklahoma Gas Corp.	501-783-3181	Lewis Belcher	x	No Spray Prog. Use Brush-Hog			8-2
26	Arkansas-Western Gas Co.	501-521-5400	James Walker	x	Use Brush-Hogs			8-2
27	Ashland Pipeline Co.	606-329-3333	Clarence A. Clark	x	Use Brush-Hogs			8-2
28	Badger Pipeline Co.	312-439-0270	Merle Helgland	x	Mechanica			8-2
29	Belle Fourche Pipeline Co.	307-756-3292	Lyle Sessions, Supt.	x	DO NOT USE 2,4,5-T			8-4
30	Bigheart Crude Oil Corp.	918-582-7211	Ralph Eaton	x	NO CHEMICALS			8-2
31	Black Lake Pipeline Co.	316-331-1300	John R. Sebastian			x	x	8-2
32	Black Mesa Pipeline, Inc.	602-774-5076	J. G. Montfort	x	DO NOT USE 2,4,5-T			8-2
33	Crystal Oil Company	318-222-7791		x	No one knows about 2,4,5-T			8-2
34	Burro Pipeline Corp.	505-398-6308	C. A. Norvell	x	DO NOT USE 2,4,5-T			8-2
35	Butte Pipeline Co.	915-684-5511	Jim Waddell	x	Up to Individual Foreman			8-4
36	Cra, Inc.	918-333-4111	George Todd	x	DO NOT USE HERBICIDES			8-2
37	Cra, Inc.	913-434-4832	Joe Hicks	x	DO NOT USE CHEMICALS			8-2
38	Cabot, Corporation	806-669-2581	R. A. Keagy	x	DO NOT USE HERBICIDES			8-2
39	Calney Pipe Line Co.	714-877-2414	J. R. Scruggs, Maint. Supt.		cb			
40	Carolina Pipeline Company	803-788-3220	Skip MacInnis, P.L. Supt.			x	x	8-2
41	Cenex Pipeline	406-252-9326	Mr. Bratlie	x	ROW on cropland			8-2
42	Central Florida Pipe Line Co.	813-248-2148	R. P. Brunck	x	Maintain no ROWs			8-2
43	Champlin Petroleum Co.	405-233-7600	Robert Crews	x	No Experience			8-7
44	Chandeleur Pipe Line Co.	502-587-7531	Mr. Ingles	x	Not Familiar			

17262

NOV 91 1357

PEL[illegible]CO[illegible]TOR

#	Pipeline or Contractor	Phone	Name-Title of Person	No	Out	Yes	AES Copy	Date
45	Charter Gathering Co.	713-923-3404	Aubrey Williamson, Frank Smith	x	"use Chem Spray"			8-7
46	Chase Pipeline Co.	316-321-6380	Andy Hendricks	x	DO NOT USE 2,4,5-T			8-4
47	Chevron Pipeline Co.	801-359-7761	Jerry Brower, Sr. Eng.	x	DO NOT USE HERB CIDES			8-4
48	Cheyenne Pipeline Co.	307-634-2064	C. E. Siemers	x	ROWS on Pasture & Farms			8-7
49	Chicap Pipeline Co.	312-885-5411	Mr. Ed. Scott	x	DO NOT USE 2,4,5-T			8-7
50	Cities Service Gas Co.	405-236-0601	Mr. Turney	x	DO NOT USE 2,4,5-T			8-7
51	Cities Service Pipeline Co.	918-586-3750	Mr. Ansal Neal			x	x	8-7
52	Citronell-Mobile Gathering, Inc.	205-433-6167	Don Smith	x	Mowing and Hand Cutting			8-8
53	Clajon Gas Co.	915-336-3379	Chas. Moody		cb			
54	Clear Creek, Inc.	316-263-8145	Dalton Alspaw		cb			
55	Coastal States Gas Producing	713-627-3700	J. C. Baker	x	Own No ROWs			8-7
56	Chem Spray	713-486-1891	Steve Crosby	x	DO NOT USE 2,4,5-T			8-9
57	Collins Pipeline Co.	713-757-2131	J. L. Solomon	x	No Maintenance			8-7
58	Colonial Pipeline co.	404-261-1470	F. J. Collins, Mgr. ROW		cb			
59	Colorado Interstate Gas Co.	303-473-2300	W. I. Blount		cb			
60	Columbia Gas Transmission	412-228-3200	Geo. Walz	x				8-7
61	Commonwealth Natural Gas Corp.	804-644-2931	R. J. Godfrey	x	No Spraying Mow 1x/year			8-7
62	Continental Pipeline Co.	713-956-1130	Don Butter	x	DO NOT USE 2,4,5-T			
63	Cosden Pipeline Co.	915-263-7051	D. M. Bardwell		cb			
64	Crown-Rancho Pipeline Corp.	713-224-8550	J. D. Winzeried	x	NO CHEMICALS			8-7
65	Cullman-Jefferson Counties Gas.	205-734-1911	E. W. England	x	No HERBICIDES			8-7
66	DeKalb-Cherokee Counties Gas Dist.	205-845-3731	Wm. A. Wright		No R[illegible]			

17263

8T33T6MOd

PIPELINE/CONTRACTOR

#	Pipeline or Contractor	Phone	Name-Title of Person	No	Out	Yes	AES Copy	Date
67	Eastern Shore Natl. Gas Co.	302-734-7443	Wayne Morris			x	x	8-8
68	Eastern Tennessee Nat'l. Gas Co.	615-693-3501	Robt. Rader		wcb			
69	Dixie Pipeline Co.	404-237-4636	Jim McGaha	x	DO NOT USE CHEMICAL			8-8
70	Derby Refining Co.	316-267-0361	D. B. Adkins	x	NO BRUSH CONTROL			8-10
71	Delhi Gas Pipeline Corp.	214-747-8341	Pete Dickens	x	USE NO CHEMICALS			8-8
72	Everglades Pipeline Co.	305-522-8464	D. J. Stack	x	USE CONTRACTOR			8-8
73	Cities Utilities Construction Co.	305-525-7025		x	Supply Only Labor			8-8
74	Eureka Pipeline Co.	304-485-5548	Bill Lytle		cb			
75	Equitable Gas Co.	412-471-7600	Jim Noel	x	No HERBICIDES On ROWs			8-8
76	El Paso Natural Gas. Co.	915-543-2600	D. N. Canfield	x	Don't Know about 2,4,5-T			8-8
77	El Paso Products Co.	915-337-2811	John J. Strojek	x	Use Contractor			8-8
78	Enterprise Pipeline Co.	713-658-8180	Harold Lee	x	Don't Know About 2,4,5-T			8-9
79	Explorer Pipeline Co.	918-743-5393	G. V. Shaw	x	Use Brush Hogs Some Tordon 10-K			8-9
80	Exxon Pipeline Co.	713-656-3636	Joe Hollmer	x	Use Contractors			8-9
81	Farm Bureau Oil Co.	812-838-4341	John Adams			x	x	8-9
82	GETTY Pipe Co.	717-455-5588	W. F. Tucker	x	Handled by Foremen			8-9
83	Florida Gas Transmission Co.	318-942-6535	Carroll Richard			x	x	8-9
84	Four Corners P.L. Co.	713-241-6161	Mr. Joe Mims			x	x	8-9
85	Frio Pipeline Co.	713-223-4901	W. H. Heisler, Jr.	x	No Maintenance			8-9
86	Golden Eagle Refinig Co.	213-777-8951	Emnett Cooper		wcb			
87	Great Lakes Gas Transmission	313-965-9400	Richard Spence		wcb			
88	Great Yellowstone Corp.	918-749-1668			Do Not Maintain ROW			

1726

PIPELINE CONTRACTOR

#	Pipeline or Contractor	Phone	Name-Title of Person	No	Out	Yes	AES Copy	Date
89	Sante Fe (Gulf Cnetral) Pipeline	918-585-2631	Mr. Filer or W. R. Keathly	x	Use Brush Hogs			8-9
90	Hess Pipeline Co.	601-425-1496	Billy Green		cb			
91	The A. S. Helbig Co.	216-376-8116	Robt. Helbig, Sr.		cb			
92	Gulf Energy & Development Corp.	512-828-0501	M. B. Parks		cb			
93	Gulf Refining Co.	713-226-3448	Bill Traylor		cb			
94	Houston Pipeline Co.	713-654-6161	Robt. Newell	x	Use Mowing			8-9
95	High Plains Natural Gas. Co.	806-323-6464	Paul Wilson	x	Only Pasture and Farm and			8-9
96	Husky Pipeline Co.	307-587-4711	Mr. Spear	x	N o Brush		!	8-9
96	Hydrocarbon Transportation Inc.	402-348-5371	(see regional offices)					
98	" "(Minneapolis)	612-884-2204	Mack Mickelberg, Eng.			x	x	9-10
99	" "(Midland, TX)	915-682-7964						
100	" "(Liberal, KS)	316-624-1911						
101	" "(Great Bend, KS)	316-792-2161						
102	" "(Des Moines, IN)	515-243-6139						
103	Standard Oil (Ohio)	513-898-3971	Mr. Henman	x	DO NOT USE 2,4,5-T			9-9
104	Standard Oil (Texas)	214-757-3110	Jim Goodwin	x	DO NOT USE 2,4,5-T			9-9
105	Inland Gas Co., Inc.	606-324-3171	T. Moore	x	DO NOT USE 2,4,5-T			9-10
106	Interstate Storage & Pipeline Corp.	609-267-9100	Mr. Sampson	x	NO BRUSH PROBLEM			9-10
107	Jayhawk Pipeline Corp.	316-267-0361	B. E. Ashford	x	NO Brush Control			9-10
108	Kaneb Pipeline Co.	316-262-1408	James A. Stricland		cb			
109	Kansas-Nebraska Nat'l Gas Co	402-462-2441	James Asbury	x	ROWs on Cropland			9-10
110	Kentucky West Virginia Gas Co.	606-886-2311	Philip Jenkins	x	MANUAL CUTTING			9-10

5924

PIPELINE/CONTRACTOR

#	Pipeline or Contractor	Phone	Name-Title of Person	No	Out	Yes	AES Copy	Date
111	Kaw Pipeline Co. (See Texaco)	713-666-8000	R. W. Olbrich		cb			
112	Kenai Pipeline Co. (see Chevron)	415-894-0773	Chas. Stevenson		cb			

17265

TICKLE DATE _____

0310-0260-7440 (744)

June 22, 1978

938

DOW913514

Office of Pesticide Program
Technical Service Division
Environmental Protection Agency
401 M Street, S.W.
Washington, D. C. 20460

Gentlemen:

The Pennsylvania Department of Transportation has used 2,4,5-T for many years without serious problems. 2,4,5-T has proven to be an economical and effective control for undesirable trees and shrubs growing along the Department's 45,000 miles of highways.

Applications of 2,4,5-T include foliage brush spraying and dormant basal application.

Without 2,4,5-T, the Department would be forced to use other herbicides which have not had as widespread and varied use as 2,4,5-T. Substitute herbicides, in every case, would cost the Department more money to achieve the same results as 2,4,5-T.

Sincerely,

Robert S. Ross, L.A., Chief
Roadside Environment Division
Bureau of Maintenance

460/EHI/clb

6/28/78
DATE

SUBJECT: RPAR AGAINST 2,4,5-T

Your comment concerning this subject has been received, and has been forwarded to appropriate personnel in the Office of Pesticide Programs for consideration. Please ensure that any further correspondence on this issue bears the identifying notation OPP-30000/26

Thank you for your interest in the Office of Pesticide Programs' activities.

Federal Register Section
Information Branch
Technical Services Division (WH 569)
Office of Pesticides Programs, EPA

17287

STATE OF MAINE
DEPARTMENT OF TRANSPORTATION
STATE OFFICE BUILDING AUGUSTA, MAINE 04333

ROGER L. MALLAR
Commissioner

939

May 25, 1978

DOW913511

Douglas Castle, Administrator
for Pesticide Programs
US Environmental Protection Agency
Washington, D.C. 20460

COPY

Dear Sir:

It is my understanding that an RPAR will be held in the near future involving the continued registration of 2,4,5-T.

I also understand that arguments are being presented for and against the suspension of the use of 2,4,5-T during the RPAR period.

I wish to be placed on record as opposing any suspension of the RPAR period and request that your actions on this product be limited to an RPAR review.

Thank you for your consideration.

Very truly yours,

Department of Transportation
Roger L. Mallar, Commissioner

By: _____
Martin C. Rissel
Engineer of Maint. & Operations

MCR/low

cc: T. Stone

17268

STATE OF MAINE
DEPARTMENT OF TRANSPORTATION
TRANSPORTATION BUILDING AUGUSTA, MAINE 04333

ROGER L. MALLAR
Commissioner

950

DOW913510

August 3, 1978

Mr. Jim Skelton
Asplundh Environmental Services
Blair Hill Road
Willow Grove, PA 19090

Dear Sir:

As requested in your telephone call, I have attached copies of the Maine Department of Transportation letters to EPA regarding the RPAR on 2 4 5-T.

Sincerely yours,

Theodore M. Stone
Landscape Architect
Bureau of Highways

TMS:mc
attachments

17269

IOWA DEPARTMENT OF TRANSPORTATION

951

DOW913509

August 3, 1978

600

Federal Register Section
Technical Service Division (WH-569)
Office of Pesticide Programs, EPA
Room 401 East Tower
401 M. Street, SW
Washington, D.C. 20460

ATTN: OPP 30000/26

Gentlemen:

The Highway Division of the Iowa Department of Transportation has a positive program governing right of way maintenance which recognizes the benefits accruing to the public in beautification, compliance with state law regarding control of noxious weeds, and prevention of vegetative growths which would adversely effect drainage, sight distance and snowfall. As Chief Engineer with administrative responsibility over 10,000 miles of state highways requiring a maintenance budget of $41 million, judicious expenditure of funds for right of way preservation is necessary.

Our brush control program formerly utilized 2, 4, 5-T principally to control volunteer growth after cutting brush. However, when it was indicated that 2, 4, 5-T might be removed from the list of registered herbicides, we elected to discontinue the purchase and use of that chemical.

For the past six years Tordon 10-K pellets, Hyvar X-L or Krenite has been utilized for brush control. The substitute chemicals are effective and acceptable.

Under present circumstances no reason appears to exist for revising present maintenance practices, even if 2, 4, 5-T is re-registered.

Very truly yours,

PHG:ckw

bcc: Dennis Holewinski, Mgr.
Asplundh Environmental Services
Blair Mill Road
Willow Grove, PA 19090

R. H. Given
Chief Engineer

17270

4738 Wildrye
Boise, Idaho 83705
August 7, 1978

DOW913508

Federal Register Section
Technical Services Division (WH 569) Code No. 30000/76
Office of Pesticide Programs
Environmental Protection Programs
Environmental Protection Admin.
Room 401 East Tower
401 M St. S.W.
Washington, D.C. 20460

Dear Sirs:

My first experience with the use of 2,4,5-TP was in the years between 1952-58 when I was working for the Federal Government with responsibilities which included range-land improvement. We were able to increase carrying capacity as much as 400% with the use of the 2,4-D, 2,4,5-T sprays, usually applied by airplane. The Conservation Cost-Share Program of the government paid for about 50% of the cost of this woody plant control. Prior to this, our only method was by mechanical beating, etc. at a much greater cost while obtaining a much poorer quality job.

Many thousands of acres were improved in this manner and I have remained in the area since and have not observed any detrimental effects whatsoever, nor have I even heard the hint of any.

At the present time I am responsible for right-of-way vegetation control. My estimate is that should we lose our use of 2,4,5-T for woody plant control, the cost would increase dramatically, about 1,000%. This would cause a very serious cost situation and could very well bring about unsafe conditions and deaths as a result.

We have struggled very hard to hold down costs and my hope is that the unfounded rumors, started probably by some uninformed or hysterical persons, will not deprive us of this valuable material that we have worked with so very successfully over so many years.

Gentlemen, please allow common sense and sound scientific reasoning, rather than fear, to prevail on this 2,4,5-T, RPAR issue.

Very truly yours,

J. E. RINARD

. . Number of acres in your system 42,000 T 2. Number of miles in your system 15,000

3. States in which you have right-of-way areas N.C. S. Carl 993

Percentage of your total right-of-way acreage that is under some form of vegetation management program 42,000 T

Number of right-of-way acres that were treated during 1977 5 thousand 2-4-5-

6. MECHANICAL METHODS USED FOR VEGETATION MANAGEMENT

a. Approximate percentage of total ROW acreage that is treated by mechanical methods 42,000 T

b. Percentage of these mechanically treated areas that were treated by the following methods:

	% of all mechanically treated acreage treated with each method below	approximate cost per acre
Roller chopping		
Brush raking		
Sheardozing		
Brush hog		
Mowing	42,000 T	
Other methods		

DOW913507

7. MANUAL METHODS USED FOR VEGETATION MANAGEMENT

a. Approximate percentage of total ROW acreage that is treated by manual methods very li

b. Percentage of these manually treated areas that were treated by the following methods?

	% of all manually treated acreage treated with each method below	approximate cost per acre
Chain saw cutting		
Trimming	We cut brush for sight distance	
Girdling	maintenance to keep tree and the	
Other methods		

8. CHEMICAL METHODS USED FOR VEGETATION MANAGEMENT

a. Approximate percentage of total ROW acreage that is treated with brush control chemicals Undercut T

NOTICE: POOR COPY DUE TO DEFICIENT ORIGINAL

Detroit
2000 Second Avenue
Detroit, Michigan 48226
(313) 237 8000

1018

DOW 913424

June 1, 1978

Federal Register Section
Technical Services Division (WH-569)
Office of Pesticide Programs, EPA
Room 401 East Tower
Washington, DC

RE: 2,4,5,T - Notice of Rebuttable Presumption
43FR17116, et. seq., April 21, 1978

Dear Sir:

The Detroit Edison Company has reviewed EPA's rebuttal presumption against registration of 2,4,5,T. The Detroit Edison Company contends that the studies referred to in the April 21st Federal Register Notice do themselves sustain the burden of proof that under commonly recognized practices of use, the anticipated exposure of 2,4,5,T, as it is now formulated, to applicators, users and local populations is not likely to result in any significant acute adverse or chronic effects.

Detroit Edison contends that the EPA's determination is in error. Furthermore, Edison contends that 2,4,5,T is an economic and uniquely effective tool in controlling the growth of high growing tree species since it does not impact the growth of low growing trees, shrubs, herbs, and grasses. The Detroit Edison Company knows of no other herbicide which controls tall growing species while preserving a well-balanced monocotyledonous environment. The banning of 2,4,5,T would have significant adverse impacts on both the costs of controlling tall growing species and on the aesthtics of rights-of-way controlled in some other manner.

The studies referred to in the April 21st rebuttal sustain the burden-of-proof that under commonly recognized practices of use, the anticipated exposure of 2,4,5,T, as it is now formulated, to applicators, uses and local populations is not likely to result in any significant acute adverse of chronic impacts. I refer to the bulk of the studies in the presumption rebuttal. These studies demonstrate that 2,4,5,T which contains less than .1 ppm of TCDD (as required by current U.S. Specifications) when applied or dosed to laboratory animals at rates comparable to the dosage and exposure of humans is not likely to result in any significant adverse effects. The data presented (pg. 17119 F.R.) indicate that 2,4,5,T is not

DOW013425

persistent and is readily metabolized by mammals. The data presented (pg. 17120 F.R.) indicate that there is no major problem of bioaccumulation of 2,4,5,T since it is neither strongly lipophilic nor hydrophilic.

The EPA has errored in its conclusion that 2,4,5,T exceeds certain criteria for risks. The error lies in the use of inappropriate data as "effect" levels. Test animals are exposed to more 2,4,5,T/TCDD than would be expected as a normal exposure. Also, assumptions are made regarding application practices which are contrary to commonly recognized practices of use. The State of Michigan requires that applicators of any herbicide or pesticide be fully clothed. We know of no application of 2,4,5,T done by persons having bare arms, hands, or legs. Examples of the use of inappropriate data are:

1. Third Summary of Scientific Evidence Relating to Rebuttable Presumption - Part 1(a) under oncogenic effects (pg. 17124 F.R.) In this study, The test organisms (mice) were fed higher levels than usual to assume for human consumption, since 2,4,5,T is not used on consumable crops.

2. In the same section, Part B (pg. 17125 F.R.) the test organisms (mice) were exposed to higher levels of TCDD (3X) than the current formulations of 2,4,5,T contain. Therefore, the use of this study is unrealistic in looking at oncogenic effects.

3. In the same sections, Part 2 (pg. 17126 F.R.) acute mortalities to control organisms (rats) were higher than test organisms exposed to several concentrations of TCDD. Therefore, the test is not valid since the source of control mortality and subsequent test oncogenic responses may be due to pre-test history of the test organisms, or to poor holding techniques.

4. In the same section, Part 3 "Exposure Analysis", the hypothetical exposure analyses set up a list of criteria which "a priori" result in a rebuttable presumption. The use of a woman's weight as the standard increases the potential exposure on a dose per weight basis. The exposed person is assumed to have bare arms, hands, head, and sometimes legs. In addition, the aforementioned inappropriate data are used as "effect" levels. Lastly, the basis of the margin of safety is not explained and appears to be only a subjective appraisal of quantitative information.

DOW913426

In light of the facts that 2,4,5,T does not appear to result in any significant adverse effects and that the banning of 2,4,5,T would have significant adverse economic and aesthtic consequences, The Detroit Edison Company contends that the benefits from the use of 2,4,5,T far out-weights the risks associated with use and a presumption against registration (and use) should not be established.

Sincerely,

Dennis A. Leonard
Environmental Affairs

bcc: J. J. Gessner
A. Heidrich, Jr.
J. E. Knight
P. J. Eisele

DOW913421

West Penn Power Company
Part of the Allegheny Power System
Cabin Hill, Greensburg, Pa. 15601 (412) 837-3000

June 2, 1978

Environmental Protection Agency
Office of Pesticide Program
Technical Service Division
WH-569
401 M Street, S.W.
Washington, DC 20000

2,4,5-T Herbicide Review

Dear Sirs:

In response to your "Environmental News Release" of April 12, 1978, I will state the benefits of the present registered uses of 2,4,5-T by outlining the field problems that would result if the use of this herbicide was eliminated.

Without the availability and use of 2,4,5-T as the backbone herbicide of the brush control program on the West Penn Power Company System, the effectiveness of herbicide solutions would be reduced. The hydraulic ground foliage method of applying herbicides containing 2,4,5-T in a water carrier will result in 95% or better kill of tall-growing tree species. Basal bark methods utilizing oil products as a carrier for 2,4,5-T can result in similar results where low brush density allows these methods to be used. Without the ability to use 2,4,5-T, the effectiveness of these methods would be reduced 30% to 50%, resulting in unsatisfactory brush control. The use of alternative chemicals presently available would result in higher rates per acre and a greater use of more persistent materials. This course of action could easily increase off right-of-way damage along the edges of rights-of-way and would force the unnecessary introduction of a larger amount of herbicides into the environment.

The cancellation of 2,4,5-T for use on rights-of-way will result in higher maintenance costs to obtain a lesser degree of control. The results obtained through the use of alternative herbicides could dictate returning to hand clearing. As a consequence, our present total annual vegetation control budget of $3.5 million would increase to $6.5 million if we were to hand clear those areas scheduled for spraying. This increase in expenditure would be compounded due to returning every six years to clear the brush. An example of typical charges following initial clearing is as follows:

DOW913422

	Herbicide Treated	Hand Cleared With Equipment
1973	Cleared	Cleared
1975	$100	--
1979	80	$ 400
1985	--	400+
1991	--	400+
1993	80	--
	$260	$1,200

Over the above 20-year portion of the line, the annual cost per year with herbicides is the total cost of $260 divided by 20 years = $13/year. Without herbicides, the total cost of $1,200 divided by 20 years = $60/year. The differential of $47 when applied to the total acres underneath our transmission and distribution system would approximate an annual increase in expenditures of $4 million. Assuming this amount of money was available, it would be highly questionable whether enough men and equipment would be available to perform this type of work. In addition, with each clearing the wildlife population and habitat will be adversely affected. It is interesting to note that workman's compensation rates for brush cutters and tree trimmers are approximately three times greater than the rates for herbicide spraymen, indicating a higher risk in using saws than in using herbicides.

Utility right-of-way brush control depends largely on the use of 2,4,5-Trichlorophenoxyacetic acid alone or in combination with other herbicides. Therefore, the necessity for the continuation of the registered uses of 2,4,5-T is important to the safe, economical, and uninterrupted transmission and distribution of electrical energy.

In working in the herbicide field as a research forester, in railroad vegetation control, and in my present capacity for a total of 15 years, I have not become aware of any toxic effects to man or animals attributable to 2,4,5-T when used according to the label. As a practical observation, I have noticed the red-tailed hawk population increases around herbicide treated utility right-of-way. The increase in population and increasing number of nests on our structures indicate a high small animal population is present to support the increase in the hawk population.

It is my sincere hope that facts such as those mentioned above, magnified by similar conditions in 3,600 U. S. electric utilities, present the Environmental Protection Agency with a true picture of the potential economic and environmental repercussions which could result from cancelling the registration of 2,4,5-T.

Very truly yours,

Peter E. Spangler
System Forester

DOW913423

CC: Mr. Douglas Costle, Administrator, EPA
Mr. Edwin L. Johnson, Deputy Assistant Administrator for Pesticide Programs, EPA
Dr. Rupert Coulter, USDA
Sen. Richard S. Schweiker
Sen. H. John Heinz, III
Rep. Joseph S. Ammerman
Rep. John H. Dent
Rep. Joseph M. Gaydos
Rep. William F. Goodling
Rep. William S. Moorhead
Rep. Austin J. Murphy
Rep. John P. Murtha
Rep. Gary A. Myers
Rep. E. G. Shuster
Rep. Douglas Walgren

BCC: Charles Beckwith, Dow Chemical
Paul H. Johnston, Asplundh
JOHN WALDRUM AMCHEM
DON LOUTZENHISER AMCHEM

1706

May 31, 1978

TO: PROPONENTS OF PHENOXY HERBICIDES

DOW 9143 14
MN001665

SUBJECT: GROUP MEETING TO COORDINATE EFFORTS ON RPAR FOR 2,4,5-T

MEETING TIME AND PLACE: June 7, 1978 - 9:00 a.m.

Ramada O'Hare
6600 Mannheim Rd.
Des Plains, Illinois
Tel. (312) 827-5131

2,4,5-T is a useful and necessary tool for the following:

1. Right-of-way brush control
2. Rangeland brush control
3. Forestry
4. Weed control in rice

In order to better coordinate the activities of these interests, it was thought desirable to assemble a group of individuals that could mobilize the necessary effort to respond to the RPAR.

Reasons for the meeting:

1. Establish lines of communications among the key groups present.
2. Determine capabilities of each organization in regards to making key political and user contacts.
3. How to achieve maximum effect with the news media on forthcoming benefit statements from user groups.
4. Review of RPAR process and the necessary jobs that need to be done.
5. Review of legal actions in various states regarding 2,4,5-T.

Come prepared to participate by reporting what work your organization has underway and difficulties encountered to date.

We will see you June 7.

J. H. Davidson
Agricultural Products Department

nc

THE DOW CHEMICAL COMPANY

MIDLAND, MICHIGAN 48640

July 5, 1978

DOW 910243 MN05T997

D. D. McCollister
L. L. Smith
M. L. Leng
J. H. Davidson
M. J. Traynor, 2020
J. A. Gray, 2030

POLICY QUESTIONS ON THE ORGANIZATION OF THE 2,4,5-T RPAR REBUTTAL

I am organizing the assembly of the RPAR document and have a couple of questions which must be answered by Friday noon, July 7th in order to schedule our personnel needs.

1) Do you wish to include in the RPAR submission copies of the documents referenced in the RPAR position document when they are also referred to in our paper? We could instead give the bibliographic reference and cite the Position document reference number.

2) Do you wish to submit copies of references not directly cited in our papers? We can prepare a list of additional references which EPA would then be able to request and which we would likely be free to discuss if appropriate topics came up.

We will need to know the overall organization of the document by the end of next week (July 14th), in order to answer such questions as:

a) Should the references for each section immediately follow that section, or should all references be compiled at the end? The former arrangement will allow us to compile whole volumes as the collections are completed. We can number pages using the section designation.

no large paper + large refs

b) Since the sections will vary in size, I do not believe we should tie our volume numbers and our section numbers too tightly together as some sections may require two volumes.

I suggest using Roman numerals for the volumes and capital letters for the sections. We can number our references D.r.1, D.r.2., etc.

Attached is the proposed compilation schedule.

Please reserve the morning of August 2nd to help us verify the accuracy of the 10 complete copies.

Alice

Alice H. Morgan
Government Registration
Health & Environmental Research

Attachment

ebg

17280

1060

DOW 798866

EVALUATION OF THE MUTAGENIC POTENTIAL OF 2,4,5-T AND TCDD IN RESPONSE TO A RPAR ON 2,4,5-T

By

B. A. Schwetz, D.V.M., Ph.D.
Research Manager

and

K. S. Rao, D.V.M., Ph.D.
Research Specialist

Toxicology Research Laboratory
Health and Environmental Research
Dow Chemical U.S.A.
Midland, Michigan 48640

17281

798867

Rodenticide Act (FIFRA), the basic environmental standard for major regulatory determinations is "unreasonable adverse effects on the environment". The term is defined in Section 2 (bb) of the act to mean "any unreasonable risk to man or the environment taking into account the economic, social, and environmental costs and benefits of the use of any pesticide". The Environmental Protection Agency's registration guidelines establish the data requirements for registration of a pesticide. Sections 162.84-1 to 162.84-5 of these guidelines establish the requirements for testing to establish the safety of compounds for mutagenic effects in order to register a compound. In making the determination that a rebuttable presumption has arisen, the registration regulations require the agency to take into account the type of effect, the statistical significance of the findings, and whether the tests were conducted in accordance with the material requirements for valid tests as recognized by experts in the field. Section 162.3 (y) of the registration regulations defines the term "mutagenic" as "the property of a substance or mixture of substances to induce changes in the genetic complement of either somatic or germinal tissue in subsequent generations". An important aspect of this definition is that the EPA considers the demonstration

humans.

Multi-test evidence is necessary for assessing the mutagenic potential of a test substance since it is well recognized that it is unlikely that a single test system is capable of assessing all potential types of genetic change with sufficient sensitivity and, in addition, incorporate the toxicological concerns relevant to mammalian physiology and metabolism, as well.

Many new test systems have evolved in recent years or are in the process of being developed presently, especially in the area of in vitro short-term tests to evaluate mutagenic and carcinogenic potential. Nearly all of these tests suffer from lack of validation between laboratories and across different classes of chemicals. Until a satisfactory degree of reliability has been demonstrated for these tests, it does not seem appropriate to use the results of such tests for making critical regulatory decisions. For example, in regard to the microbial tests in particular, consideration must be given to the fact that it is impossible to simulate the route of exposure encountered by man in these tests, liver microsomes are not an accurate reflection of

substances through disposal of the material or its metabolites, and the influence of dose level upon response is not interpretable. Therefore, the usefulness of these test systems even for the process of defining the needs for further testing has significant limitations.

toxicity (1). They concluded that there were insufficient data on the mutagenic potential of 2,4,5-T and TCDD, and that further testing was needed. Mutagenicity was not a trigger for the RPAR.

The results of the laboratory tests to assess the mutagenic potential of 2,4,5-T and TCDD are summarized in Tables 1 and 2, respectively. Our review of the literature revealed considerable additional information to that included in the RPAR Position Document 1.

TESTS IN NON-MAMMALIAN SYSTEMS

Negative results were reported by Anderson et al. (2) in spot tests with salmonella; ten different phenoxyalkanoic acids and five commercial formulations containing these compounds did not increase the frequency of back mutations. A group of 110 different herbicides was evaluated for their ability to induce point mutations in one or more of four different microbial systems using histidine-requiring mutants of Salmonella typhimurium. The amount of 2,4,5-T used in the test plates was not indicated.

2,4,5-T was found to be "doubtfully mutagenic only after activation". In the absence of enzyme activation, 2,4,5-T was not mutagenic in any of the five strains of organisms (TA-100, TA-1535, TA-98, TA-1537, or TA-1538). In the presence of enzyme activation, there was no increase in the number of revertants in the frameshift strains (TA-98, TA-1537, or TA-1538); the increase in the number of revertants in the base substitution strains (TA-100 or TA-1535) was less than two-fold. This increase of less than a two-fold magnitude was referred to by the authors as a doubtful mutagenic effect; increases less than two-fold are generally not considered to represent a positive response in this test.

Seibert and Lemperle (4) tested 32 herbicides for their ability to induce mitotic gene conversion in a diploid strain of the yeast, Saccharomyces cerevisiae. The culture medium contained 1000 ppm 2,4,5-T; no evidence of mutagenic activity was found for 2,4,5-T. Shirasu and co-workers (5) conducted tests with the REC-assay procedure using H17 REC^+ and M45 REC^- strains of Bacillus subtilis. The "dose" of 2,4,5-T was 20 µg/plate; no evidence of mutagenicity was found.

not described in sufficient depth to critically review the procedures used. Another study in Saccharomyces cerevisiae RAD18 has recently been reported by Zetterberg (7). 2,4,5-T was found to be mutagenic at an acidic pH but not in solutions with neutral pH. 2,4,5-T concentrations in the range of 0.02-0.06 mg/ml were evaluated over a range of pH values. The authors concluded that while 2,4,5-T caused mutations in acidic conditions, it was unlikely that mutations would be induced at neutral pH, such as would be found in gametes. Cells would apparently not take up the dissociated form of 2,4,5-T.

Numerous mutagenicity studies have been conducted in the fruitfly, Drosophila melanogaster. In a study by Davring and Sunner (8) chromosomal defects in oocytes and nurse cells of Drosophila females were reported at very low concentrations of a commercial formulation of 2,4,5-T butoxyethyl ester. The significance of these observations

Several sex-linked recessive lethal studies have been reported in Drosophila. In a study reported by Mujumdar and co-workers (10), Drosophila were given 2,4,5-T at concentrations of 250 or 1000 ppm in their diet. A slight increase in sex-linked recessive lethals was found at the high concentration, 1000 ppm. In contrast to these positive findings, Vogel and Chandler (11) found no effect on the incidence of sex-linked recessive lethals in Drosophila given 2,4,5-T at concentrations of approximately 1000 and 2000 ppm in their diet. As already indicated above, Magnusson (9) found an increase in the incidence of direct recessive lethals in Drosophila given 1000 ppm 2,4,5-T in their diet. This was not accompanied by cytogenetic changes in the insects.

is based on forward mutations in the inserted DNA. There was no evidence of mutagenicity at 100 ppm of 2,4,5-T.

TESTS IN MAMMALIAN SYSTEMS

In addition to the above tests in non-mammalian systems, numerous tests have also been conducted in mammalian systems. Dominant lethal tests were performed in mice by Buselmaier (13) by injecting 100 mg 2,4,5-T/kg intraperitoneally. The males were subsequently mated during six weeks after treatment with untreated females in order to assess all stages of spermatogenesis. There was no indication of an increased pre- or postimplantation loss. Buselmaier (13) also tested for point mutations in the host-mediated assay using Salmonella typhimurium and Serratia marcescens. 2,4,5-T caused no effect at a dose level of 500 mg/kg. Thus, 2,4,5-T was found to be negative in both the dominant lethal test and the host-mediated assay.

host-mediated assay by Styles (15), serum from rats treated with 2,4,5-T was used with *his* mutants of Salmonella typhimurium. No increase in the number of mutants was observed.

The results of several cytogenetic studies appear in the 2,4,5-T literature. In a study by Yefimenko (16) rats were administered 2,4,5-T at dose levels of 0.001-1 mg/kg. Chromatid aberrations and chromosome adhesions were reported after a dose of only 0.01 mg/kg of the butylester of 2,4,5-T to male rats. This interpretation is based on the information contained in an English abstract and a translation of the original article from the Russian literature. In a study translated from the Japanese literature (Fujita, 17), the effect of 2,4,5-T on cultured human lymphocytes is reported. The concentrations of 2,4,5-T ranged from 0.025-25 µg/ml. Chromosome and chromatid aberrations were reported, but as mentioned in the RPAR position document 1, it is not possible to distinguish whether this was a toxic effect or a potential genetic effect of 2,4,5-T.

were observed which may have been related to toxic effects rather than mutagenic changes. The judgment of the authors in their classification of aberrations has been challenged (Ramel, 19) and leaves the value of the data reported in this paper highly questionable. Another in vivo cytogenetics study was reported by Davring and Hultgren (20) in which mice were dosed with a commercial 2,4,5-T ester formulation. Chromosomal aberrations were observed in the mouse bone marrow cells in this study but close examination of the data reveals that the effects may well be caused by the solvent and/or emulsifier used in the herbicide preparation and not by the 2,4,5-T itself. The same preparation was used in Davring's experiments in Drosophila (8).

In addition to these published reports on studies of the mutagenic potential of 2,4,5-T, several additional pieces of unpublished data are included. An abstract published by Babbitt and co-workers (21) is attached regarding studies of the effects of 2,4,5-T on two human cell lines - spleen fibroblasts and lymphocytes. No data were included in the published abstract.

in the overall assessment of mutagenic potential. In the case of 2,4,5-T, a study was conducted at the Dow Chemical Company in which Sprague-Dawley rats were maintained on diets providing dose levels of 2,4,5-T of 3, 10, and 30 mg/kg/day for three successive generations (22). Effects were not seen in this reproduction study which were suggestive of mutagenic effects of 2,4,5-T. If 2,4,5-T were a potent mutagen which caused changes which were transmissable to subsequent generations, a reproduction study would reveal the effects of a potent mutagen. The results of this reproduction study, considered together with the rest of the data from all of the mutagenesis studies, indicate that 2,4,5-T is not a potent mutagen. At most, 2,4,5-T might be considered to have weak mutagenic potential.

The results of the mutagenicity studies on TCDD are summarized in Table 2. Hussain and co-workers (23) reported that TCDD was mutagenic by causing intercalation in bacterial systems. An increased frequency of mutations was found in E. coli Sd-4. No effects were seen in Salmonella typhimurium TA-1530, but increased mutation frequencies were seen in strain TA-1532, a

on the effect of TCDD in the Salmonella tester strains developed by Ames (24). No evidence of mutagenic effects was observed in these tests.

Two different mammalian tests have indicated a lack of mutagenic potential for TCDD. Khera and Ruddick (25) reported the results of a dominant lethal study in Wistar rats that were dosed with 4 or 8 µg TCDD/kg/day for 7 consecutive days. The male rats were caged with untreated virgin females for 5 days during 7 sequential mating trials after dosage with TCDD. The dose levels administered were clearly toxic, since 11 of 20 and 2 of 20 male rats died after receiving 8 or 4 µg/kg/day, respectively. No dominant lethal effects were observed. An in vivo cytogenetics study in rats has been reported by Green and Moreland (26). In their study, rats were given 10 µg TCDD/kg orally five times in one week; additional groups of rats were given 5, 10, 15 or 20 µg TCDD/kg as a single dose intraperitoneally. Examination of the bone marrow of these rats revealed no increase in the incidence of chromosomal aberrations relative to control rats. Another unpublished study by Green is mentioned in a

TCDD/kg twice weekly for 13 weeks. An increase in the number of chromosome breaks occurred at dose levels of 2 and 4 µg/kg in male rats and at 4 µg/kg in female rats compared to the frequency of chromosome breaks at the lowest dose level. The results of this latter study are not available for review and inclusion in this response.

The results of the mutagenesis tests on TCDD indicate that under some test conditions, this chemical may be mutagenic in microbes. In whole animal mammalian tests, TCDD has not been found to be mutagenic in the reports of studies that have been available for review. The recent data of Sidney Green's representing rats which were dosed on a subchronic basis with TCDD will need to be examined before a more definitive answer can be given regarding the mutagenic potential of TCDD in mammalian systems.

Based upon the definition by EPA of the term "mutagenic" (the property of a substance or mixture of substances to induce changes in the genetic complement of either somatic or germinal tissue in subsequent generations), the results of studies of the mutagenic potential of 2,4,5-T do not indicate that this herbicide represents a mutagenic hazard.

Heritable mutagenic changes induced by 2,4,5-T have not been demonstrated.

CONCLUSION

In conclusion, numerous studies have been conducted to evaluate the mutagenic potential of 2,4,5-T and TCDD in nonmammalian and mammalian test systems. None of the studies in microbial organisms indicate a significant mutagenic effect for 2,4,5-T. One study in yeast indicated mutagenic changes at acidic pH's but not at a neutral pH as found in mammalian tissues. Positive and negative results were seen in studies in Drosophila. Tests in whole-animal mammalian systems have either indicated negative results (dominant lethal test, host-mediated assay and micronucleus test), or uninterpretable results (cytogenetic studies). Thus, 2,4,5-T is definitely not a potent mutagen and might be classified, at most, as a weak mutagen in some test systems.

Additional data from one laboratory which have not been published are reported to indicate a positive cytogenetic change in rats dosed subchronically with TCDD. The final evaluation of the mutagenic potential of TCDD should take these data into account when they become available.

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TABLE 1

Summary - Laboratory Tests For Mutagenicity of 2,4,5-T

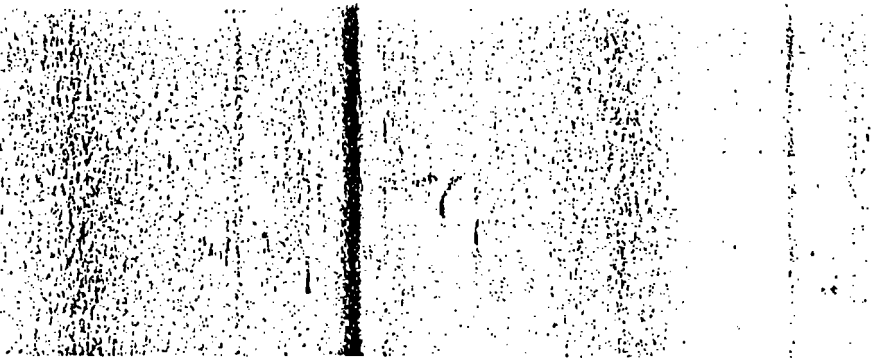
Test System	Dose(s) Tested	Results	Comments	Reference Number	RPAR Reference Number
Ames Test	Not stated	-	110 Herbicides were tested	2	Not listed
Ames Test	4.9 µg/plate	+	Doubtfully mutagenic after activation	3	148
Saccharomyces cerevisiae D_4	1000 ppm	-	32 Herbicides were tested	4	Not listed
Bacillus subtilis	20 µg/plate	-	166 Pesticides were tested	5	Not listed
E. coli (5-MT resistance)	?	-	31 Pesticides were tested, very little description of methods	6	Not listed
E. coli (Gal R^S strain)		-			
Serratia marcescens (a 21 and a 742 strains)	?	-			
E. coli (strep. resistance)	?	-			
Saccharomyces cerevisiae	?	-			
In Vitro Cytogenetics (human lymphocytes)	?	-			
Saccharomyces cerevisiae RAD 18	0.02-0.06 mg/ml	+	Mutations only at pH < 4.5; mutations unlikely at neutral		

1730



Drosophila melanogaster (effect on oogenesis)	250 ppm in diet
Drosophila melanogaster (sex-linked recessive lethal)	250, 1000 ppm in diet
Drosophila melanogaster (sex-linked recessive lethal)	3.6, 7.2 mM (0.92, 1.84 mg/ml)
Drosophila melanogaster (in vivo cytogenetics)	1000 ppm in diet
Drosophila melanogaster (direct recessive lethal)	1000 ppm in diet
Drosophila melanogaster (somatic mutations)	25-200 ppm in diet
Host-Mediated Assay and Dominant Lethal (mice)	100 mg/kg IP
Micronucleus test (mouse)	100 mg/kg
Host-Mediated Assay (salmonella typhimurium)	?
In Vivo Cytogenetics (rats)	0.001-1 mg/kg
In Vitro Cytogenetics (human lymphocytes)	10^{-7} -10^{-4}M) (0.025-25 µg/ml)
In Vivo Cytogenetics (gerbils)	10-100 mg/kg/day
In Vivo Cytogenetics (mice)	Not stated

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+	50% Decrease in fertility at 250 ppm chromosome effects seen; unsubstantiated in other tests	8	172
+	Slight increase in sex-linked recessive lethals at 1000 ppm	10	178
-	No effect on sex-linked recessive lethals	11	Not listed
-	Same sample used by Davring and Sunner (1971)	9	Not listed
+	-	9	Not listed
-	Tested in genetically stable and unstable strains	12	Not listed
-	-	13	Not listed
-	-	14	Not listed
-	Used serum from rats dosed with 2,4,5-T (abstract)	15	Not listed
+	Abstract and translation only	16	151
+?	Not possible to tell if effect was mutagenic or toxic	17	149
+ at 70 & 100 mg/kg	Questionable classification of aberrations	18	169
+	Effect may have been due to solvent or emulsifier	20	171

Test System	Dose(s) Tested	Results	Comments	Number	Number
Ames Test	Not stated	-	110 Herbicides were tested	1	Not listed
Ames Test	4.9 µg/plate	+	Doubtfully mutagenic after activation	3	148
Saccharomyces cerevisiae D_4	1000 ppm	-	32 Herbicides were tested	-	Not listed
Bacillus subtilis	20 µg/plate	-	160 Pesticides were tested	5	Not listed
E. coli (5-MT resistance)	?	-			
E. coli (Sal R^s strain)		-			
Serratia marcescens (a 21 and a 742 strains)	?	-	31 Pesticides were tested, very little description of methods	-	Not listed
E. coli (strep. resistance)	?	-			
Saccharomyces cerevisiae	?	-			
In Vitro Cytogenetics (human lymphocytes)	?	-			
Saccharomyces cerevisiae RAD 18	0.02-0.08 mg/ml	-	Mutations only at pH < 4.5; mutations unlikely at neutral pH, as in gametes	7	Not listed
Drosophila melanogaster (effect on oogenesis)	250 ppm in diet	-	50% Decrease in fertility at 250 ppm chromosome effects seen; unsubstantiated in other tests	9	172
Drosophila melanogaster (sex-linked recessive lethal)	250, 1000 ppm in diet	+	Slight increase in sex-linked recessive lethals at 1000 ppm	17	173
Drosophila melanogaster (sex-linked recessive lethal)	3.6, 7.2 mM (0.92, 1.84 mg/ml)	-	No effect on sex-linked recessive lethals	11	Not listed
Drosophila melanogaster (in vivo cytogenetics)	1000 ppm in diet	-	Same sample used by Davring and Sunner (1971)	7	Not listed
Drosophila melanogaster (direct recessive lethal)	1000 ppm in diet	+	-	7	Not listed
Drosophila melanogaster (somatic mutations)	25-200 ppm in diet	-	Tested in genetically stable and unstable strains	11	Not listed
Host-Mediated Assay and Dominant Lethal (mice)	100 mg/kg IP	-	-	13	Not listed
Micronucleus test (mouse)	100 mg/kg	-	-	14	Not listed
Host-Mediated Assay (salmonella typhimurium)	?	-	Used serum from rats dosed with 2,4,5-T (abstract)	15	Not listed
In Vivo Cytogenetics (rats)	0.001-1 mg/kg	+	Abstract and translation only	16	131
In Vitro Cytogenetics (human lymphocytes)	10^{-7} -10^{-4}M) (0.025-25 µg/ml)	+?	Not possible to tell if effect was mutagenic or toxic	17	149
In Vivo Cytogenetics (gerbils)	10-100 mg/kg/day	+ at 70 & 100 mg/kg	Questionable classification of aberrations	18	174
In Vivo Cytogenetics (mice)	Not stated	+	Effect may have been due to solvent or emulsifier	20	171

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TABLE 2

Summary - Laboratory Tests For Mutagenicity of TCDD

Test System	Dose(s) Tested	Results	Comments	Reference Number	RPA Refer Numb
TCDD: Non-Mammalian Mutagenic Tests					
Ames Test and E. Coli	up to 4.0 µg/plate	+	-	23	24
Ames Test	Not stated	-	A memo to U.S.D.A.	24	Not 1
TCDD: Mammalian Mutagenic Tests					
Dominant Lethal (rats)	0, 4, 8 µg/kg	-	High dose level lethal to some of the males	25	6
In Vivo Cytogenetic (rats)	0, 5, 10, 15, 20 µg/kg	-	Abstract plus text of oral presentation	26	119

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c. Saccharomyces cerevisiae D_4 [illegible] — [illegible] [illegible] Shirasu, Y., Moriya, M., Kato, K., Furuhashi, A., and Kado, T. 1976 Mut. Res. 22, 111-120

d. Bacillus subtilis 20 µg/plate — [illegible] 166 [illegible] Mut. Res. 40, 19-30.

TABLE 1

Summary - Laboratory Tests For Mutagenicity of 2,4,5-T

	Test System	Dose(s) Tested	Results	Positive Mutagen Employed	Comments	Reference
	2,4,5-T: Non-Mammalian Mutagenic Tests					
a.	Ames Test	Not stated	-	Yes	110 Herbicides were tested	Andersen, K. J. et al. 1972 J. Agr. Food ~~Sci.~~ Chem 20, 649
b.	Ames Test	4.9 µg/plate	+	Yes	Doubtfully mutagenic after activation	Ercegovich, C. D. and Rashid, K. A., 1977 (unpublished)
g.	Drosophila (effect on oogenesis)	250 ppm in diet	+	No	50% Decrease in fertility at 250 ppm chromosome effects seen	Davring and Summer, 1971 Hereditas. 68, 115
h.	Drosophila (sex linked recessive lethal)	250, 1000 ppm in diet	+	Yes	Slight increase in sex-linked recessive lethals at [illegible]	Mujumdar, S. K. and Golia, J. K., 1974 Can. J. Genet. Cytol. 16, 465
i.	Drosophila (sex linked recessive lethal)	3.6, 7.2 mM (1.12, 1.84 mg/ml)	—	[illegible]	[illegible]	Vogel, E. and [illegible], J. F. 1974 Experientia 30, 621-622
	2,4,5-T: Mammalian Mutagenic Tests					
m.	Host-Mediated Assay and Dominant Lethal (mice)	500-1000 mg/kg IP	-	No	-	Buselmaier, Von W. et al. 1972 Biol. Zbl. 91, 311
f.	In Vitro Cytogenetics (human lymphocytes)	10^{-7}-10^{-4}M (0.025-25 µg/ml)	?+	No	Not possible to tell if effect was mutagenic or toxic	Fujita et al. 1975 J. Jap. Assoc. Rural Med. 24, 77
n.	In Vivo Cytogenetics (gerbils)	10-100 mg/kg/day	+ at 70 & 100 mg/kg	No	[illegible]	Mujumdar, S. K. and Hall, R. C., 1973 J. Heredity 64, 213
o.	In Vivo Cytogenetics (mice)	Not stated	+	?	[illegible]	Davring and Hultgren, 1977 Hereditas 85, 123-134

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additions to Table 1

	test	dose	result	comment	ref #	RPAR ref #
e)	*E. coli* (5-MT resistance)	?	—	31 pesticides were tested, very little description of methods	+#6	not listed
	E. coli (Gal R^S strain)		—			
	Serratia marcescens (az1 and a742 strains)	?	—			
	E. coli (strep. resistance)	?	—			
	Saccharomyces cerevisiae	?	—			
	in vitro cytogenetics (human lymphocytes)	?	—			
n)	micronucleus test (mouse)	100 mg/kg	—	–	+#14	not listed
o)	host mediated assay (*Salmonella typhimurium*)	?	–	used serum from rats dosed with 2,4,5-T	+#15	not listed
p)	*in vivo* cytogenetics (rats)	0.001–1 mg/kg	+	abstract and translation only	16	151
q)	*in vivo* cytogenetics – *Drosophila melanogaster*	1000 ppm in diet	—	same sample used by Dowring & Sumner (1971)	~~209~~ 209	not listed
r)	*Drosophila melanogaster* (direct recessive lethal)	1000 ppm in diet	+	—	~~209~~ 209	not listed
s)	*Drosophila melanogaster* (somatic mutations)	25–200 ppm in diet	—	tested in genetically stable and unstable strains	+#12	not listed
t)	*Saccharomyces cerevisiae* RAD 18	0.02–0.06 mg/ml		mutations only at pH < 4.5; mutations unlikely at neutral pH as in gametes.	~~227~~ 268864	not listed MOO

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Reference No.	RPAR Reference No.
12	24
13	not listed
14	6
15	119
~~16~~	~~151~~

TABLE 2

Summary - Laboratory Tests For Mutagenicity of TCDD

Test System	Dose(s) Tested	Results	Positive Mutagen Employed	Comments	Reference
TCDD: Non-Mammalian Mutagenic Tests					
Ames Test and E. Coli	up to 4.0 µg/plate	+	No	-	Hussain, S. et al. 1972 Ambio. 1, 32-33
Ames Test	Not stated	-	Yes	A memo to USDA	Ames, B. N., 1974 (unpublished)
TCDD: Mammalian Mutagenic Tests					
Dominant Lethal (rats)	0, 4, 8 µg/kg	-	No	Highest dose level lethal to some of the males	Khera, K. S. and Ruddick, J. A., 1973 Advances in Chemistry 120, 70-84.
In Vivo Cytogenetic (rats)	0, 5, 10, 15, 20 µg/kg	-	No	Abstract ~~only~~ plus text of oral ~~verbal~~ presentation	Green, S., 1975 Toxicol. Appl. Pharmacol. 33, 161
In Vivo Cytogenetics (rats)	0.001 - 1 mg/kg	+	No	Abstract and translation only	Yefimenko, L. P., 1974 Gig. Tr. Prof. Zabol. 18, 24-27.

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