Monsanto

PX 1463

MES

FROM (NAME—LOCATION—PHONE): Dept. of Medicine & Environmental Health M.E.Strauss G2WE 4-8856

DATE: August 14, 1984

SUBJECT: Zack/Gaffey verbatim and critique

REFERENCE:

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TO: A. M. Ford (c/o Bowles, McDavid Graff & Love)
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Enclosed is a verbatim and critique of the Zack/Gaffey all plant mortality study. Please let me know if you suggest any changes to the text.

Marcie E. Strauss

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ajn

Attachments

CONFIDENTIAL
SUBJECT TO PROTECTIVE ORDER

C04192

VERBATIM AND CRITIQUE OF
ZACK/GAFFEY MORTALITY STUDY

VERBATIM

Zack, J.A. and Gaffey, W.R., A Mortality Study of Workers Employed at the Monsanto Company Plant in Nitro, West Virginia, Environ. Sci. Res. 26, 1983.

A study cohort was developed from the Nitro plant consisting of employees active on or after January 1, 1955 with one or more years of employment on the hourly roll prior to December 31, 1977. Salaried personnel who had never worked on the hourly roll were excluded from study because many of these employees had no appreciable exposure to the plant environment and, for the most part, their exposure cannot be determined from plant records. Females and non-white males were also excluded because of their small numbers.

The cohort was assembled using government earnings reports, independent of the plant work history records. Annual earnings reports were available on a computer file from 1951 through 1977. Names and social security numbers were identified from this source. Work history records were used to supplement the earnings records. Information on race, sex, date of birth, date of hire, date of separation, and, if deceased, 2,4,5-T exposure was abstracted from these records. Ascertainment of 2,4,5-T exposure was confined to decedents only because it was too tedious to do for the entire cohort. The information from the work history records was used to determine which names identified from the annual earnings records met the cohort entrance criteria. Employees identified from the earnings records who terminated prior to 1955 were not included in this study because work history records for all such employees were not retained prior to this date.

Exposure to 2,4,5-T was determined by assignment to a 2,4,5-T operation based on the work history records. 2,4,5-T exposure was determined for all but one decedent. Employees holding a job having plant-wide responsibilities with the potential for exposure to 2,4,5-T were, for the purposes of this study, considered to be non-exposed.

The vital status of each member of the study cohort was determined using standard follow-up techniques and ascertained as of December 31, 1977. Death certificates were coded by an independent nosologist for the underlying cause of death, according to the rules of the Eighth Revision of the International Classification of Diseases, Adapted.

VERBATIM AND CRITIQUE OF ZACK/GAFFEY
MORTALITY STUDY

CRITICISMS

1. Are there discrepancies in the tables of the Zack/Suskind report and the Zack/Gaffey report?

No. The plaintiff's lawyer contests that one person acutely exposed in Table 2 of the Zack/Suskind report is also noted as chronically exposed in Table 10 in the Zack/Gaffey report. Further, he contests that there are four people in Table 2 of the Zack/Suskind report who are also in Table 11 of the Zack/Gaffey report. He, therefore, claims a willful manipulation of the data. However, these "discrepancies" totally reflect the two separate types of exposure that a single individual could have experienced. Exposure in the Zack/Suskind report is defined as stated above as those involved in the TCP process accident in 1949. In the Zack/Gaffey report, the cohort is assembled from a group who from 1955 to 1977 worked for at least one year and at some time were exposed to TCDD. If there are potentially two different mechanisms for the development of the outcomes of interest, one based on a single acute exposure and the other based on a chronic exposure, what has been done seems perfectly proper from an epidemiologic and statistical view. It might have been optimal to exclude all of those acutely exposed in the Zack/Suskind report from the Zack/Gaffey analysis. However, there is no justification to do as the plaintiff suggests and include everyone with chloracne.

Attachment I lists the nine employees who died of malignant neoplasms in the Zack/Suskind study and how they were classified in the Zack/Gaffey study. Attachment II accounts for other 'discrepancies' between the Zack/Suskind and Zack/Gaffey studies. Table 1 lists the people who were included in the Zack/Suskind study, but excluded from the Zack/Gaffey study. Table 2 lists people who were counted as deceased in the Zack/Suskind study but as living in the Zack/Gaffey study. Table 3 lists the name of an employee who should have been included in the Zack/Gaffey study, and the people who were misclassified into the wrong exposure categories.

2. Should these two series have been combined to give a more accurate assessment of the health hazards of exposure to TCP?

No. Such a combination of the data for analysis might lead to bias. If, for example, there were cases of chloracne which developed secondary to the industrial accident and also cases of chloracne which developed secondary to other means of exposure to TCDD, the combination of all cases of chloracne in the analysis could lead to a biased overestimate of the danger from the acute exposure. This would be a particular problem if in fact an acute exposure caused little or no effect and a

chronic exposure increased the likelihood of adverse outcomes. In fact, this situation does have an excellent analogy with regard to carcinogenesis in which acute and chronic exposures should not be linked. For example, if a large group of people were exposed to smoking several cartons of cigarettes in one day, there is little or no evidence that this would lead to long term carcinogenic consequences. Nonetheless, if these people were exposed to one pack of cigarettes per day over a 20 year period, they would clearly develop 20 to 30 times the risk of lung cancer. Thus, pooling these two groups of people together might lead to a biased estimate that a single acute exposure caused cancer, when in fact it requires long exposure and long latency periods to develop such outcomes.

3. Would the results and conclusions of the PMR study be altered if the employees from the TCP incident were excluded from the analysis?

We redid the analysis by removing the TCP employees from the non-exposed group (see Attachment III). The PMR for lung cancer decreased from 125 (8 observed vs. 6.42 expected) to 76 (4 observed vs. 5.26 expected) for the unexposed group. This is compared to a PMR of 168 (6 observed vs. 3.57 expected) for the exposed group. According to a publication of cancer mortality rates and trends by the Environmental Protection Agency,[1] Morgan county, West Virginia has a high background mortality rate for lung cancer. The rate for 1970-79 was 46 percent higher than the rate for the United States, (93.2 and 64, respectively). This high background mortality may be partially responsible for the high PMR for the exposed group.

The large discrepancy between the exposed and unexposed groups still needs to be explained. Both of these PMRs are not statistically significant. In addition, since the number of observed cases are small, they are very sensitive to misclassification errors. While auditing the data, I discovered six exposure misclassification errors (see Attachment II, page 4). Thomas Davis (SSN:236-16-3469) died of lung cancer and was incorrectly counted in the exposed category. If he was reclassified in the PMR analysis, then the number of exposed lung cancers would decrease by one and the number of nonexposed lung cancers would increase by one. The lung cancer PMR would then change to 140 for the exposed group and to 95 for the unexposed group. This would also increase the significance level of the chi-square value, meaning that there would be a greater probability that the lung cancers occurred by chance.

[1] NCI and EPA, *U.S. Cancer Mortality Rates and Trends*, 1950-1979, Vol. II, September 1983.

This modified analysis did not have a major effect on the PMR for arteriosclerotic heart disease (AHD). This PMR decreased slightly from 131 (52 observed vs. 39.68 expected) to 128 (43 observed vs. 33.63 expected) in the unexposed group. The PMR for the exposed group is 137 (27 observed vs. 19.72 exposed) and is not significantly higher than expected.

4. Was there any bias in the Zack/Gaffey method of categorizing exposure?

No. Determination of exposure was based on information from work history records. A person was categorized as exposed if he worked as a production worker in any one of the departments listed on the attached list (see Attachment IV) during the specified time period. However, people holding jobs with plant-wide responsibilities (i.e., maintenance workers) with the potential for exposure were considered to be unexposed, since their employee histories did not mention a specific work area. In some cases, the work record did indicate that the employee died while active, but there was no way to determine cause of death. Certainly the claim of the plaintiff's lawyer and their expert witness that the people who developed disease should have been categorized retroactively as exposed would lead to a bias since comparable information on exposure would not be available on other members of the group who did not develop disease.

5. Why weren't people who terminated prior to 1955 included in the study? After all, these people were more highly exposed since they worked during the early years of the process, and they were sicker since they terminated early. This also means that some chloracne cases were not included in either the TCP study or the Zack/Gaffey study.

There were many work histories prior to 1955 which were missing from the plant files; therefore no demographic information was available for these people. In addition, there was no way to classify their exposure. It is also possible that some chloracne cases weren't included in either study.

6. Doesn't the excess of soft tissue sarcomas (STS) from four U.S. cohorts exposed to 2,4,5-T prove that dioxin causes cancer?

Between 1980 and 1983, four studies (the two Nitro studies and two Dow studies) were conducted in U.S. manufacturing plants of workers exposed to the herbicide 2,4,5-trichlorophenoxy acetic acid (2,4 5-T) and/or its chemical precursor, trichlorophenol (TCP). The dioxin isomer contaminating these products is the most toxic form, 2,3,7,8

tetrachlorodibenzodioxin (2,3,7,8-TCDD). None of these four studies found any statistically significant excess in total mortality or death from cancer which was attributed to dioxin exposure. However, each cohort was small and had insufficient power to adequately evaluate rare causes of death.

In 1981, P. Honchar, from the National Institute of Occupational Safety and Health, reviewed deaths in these four industrial cohorts, and found that 9 (2.9 percent) of the total 105 deaths in the merged cohorts were attributed to soft tissue sarcoma. Based on national statistics, only 0.07 percent of deaths were expected to be due to this cause. Subsequently, Dr. Ralph Cook of Dow Chemical Company reported a fourth, living person in one of these cohorts as having a soft tissue sarcoma, who is is now deceased. Dr. Moses of Mt. Sinai reported an additional case of soft tissue sarcoma in an individual employed at the Nitro plant. Subsequently, two additonal persons from the Krummich plant were reported to have soft tissue sarcomas.

NIOSH later on did an extensive review of the medical and exposure records, and pathology specimens of these seven individuals. Of four individuals with employment records of assignment to production of TCP and 2,4,5-T, the review suggests that only two are cases of soft tissue sarcoma. Three additional cases who are confirmed as having soft tissue sarcoma had no record of assignment to these departments. However, one person worked briefly in the production of pentachlorophenol, which is contaminated with other isomers of dioxin. The authors concluded that identification of cases of soft tissue sarcomas through either death certificates alone, or through pathology records can lead to errors of ascertainment (from Fingerhut, M., et al., Review of Exposure and Pathology for Seven Cases Reported as Soft Tissue Sarcoma Among Persons Occupationally Exposed to Dioxin Contaminated Herbicides, NIOSH and North Ridge General Hospital and Cancer Foundation, Unpublished report).

Three of the seven soft tissue sarcoma cases mentioned above were from the Nitro plant. Herman Moore (SSN:234-24-0050) was a decedent in the Zack/Suskind mortality study and was found to be correctly classified as having exposure to 2,4,5-T and dying from a malignant fibrous histiocytoma. The second decedent was Earl Harris (SSN:233-22-9240) who, according to the NIOSH report, had exposure to 2,4,5-T. Two out of three pathologists, however, reclassified his soft tissue sarcoma as a poorly differentiated carcinoma. The third person who died from a STS from Nitro was Jesse Ray Johnson (SSN: 236-24-9748). His death certificate said he died of a carcinomatosis on 11/30/80, but his pathology report said that the cause of death was a malignant Schwannoma (which is a connective tissue disease of the nervous system). The only time he may have had exposure to 2,4,5-T was when he was an instrument

mechanic which was from 09/30/68 through the time that 2,4,5-T production was discontinued on 08/26/70. As an instrument mechanic, he would not have had much exposure to 2,4,5-T since he would have spent most of his time in either the shop or the control room.

7. Was the study of inadequate power to detect any effects?

No. The study did show a statistically significant excess of bladder cancer, probably attributable to PAB exposure. This implies that other large effects to TCP exposure would have emerged from these data. Whereas it is true that the study has low statistical power for small to moderate effects because of small sample size and few observed deaths, it must be emphasized that the only available data were those which were analyzed. In such a situation, one could look for trends within the data or if other studies were done, the consistency of findings in various types of investigations. In the former case there appear to be no trends that suggest that these adverse health outcomes are related to the accident per se or chronic long term exposure. In the latter instance, the findings of these two reports are consistent with each other as well as other published reports.

8. Is there evidence that the data have been willfully manipulated?

No. There is no evidence to suggest that the data had been willfully manipulated. In fact, it is curious to note that although both studies have been challenged as being negative, there is an overall excess of bladder cancer and arteriosclerotic heart disease which is statistically significant, as well as a non-significant excess of lung cancer. It is very possible that for arteriosclerotic heart disease and lung cancer, most if not all of the excess observed could be explained by excess cigarette smoking habits among the exposed compared with the non-exposed population. With regard to bladder cancer, it is not likely that the total excess risk would disappear, but a part certainly would if the smoking habits of those exposed were different than those of the general population, which appears to be the case upon looking at the smoking habits of all the decendents from malignancy. Furthermore, the remaining excess of bladder cancer might well be explained by the existence of other carcinogens in the work place, such as PAB, which has already been discussed.

MALIGNANT NEOPLASM DEATHS IN ZACK/SUSKIND STUDY AND CLASSIFICATION STATUS IN ZACK/GAFFEY STUDY

Counted in Table 10 of Zack/Gaffey Study

Name	SSN	Exposure Class. in PMR Study	Reason	COD
1) Tucker, Russel	239-24-0204	Exposed	Hourly production worker in 2,4,5-T department.	Bronchiogenic carcinoma

Counted in Table 11 of Zack/Gaffey Study.

Name	SSN	Exposure Class. in PMR Study	Reason	COD
2) Farley, Stonewell	236-09-2190	Unexposed	Maintenance worker, not a production worker in a 2,4,5-T department, according to work history.	Lung cancer
3) Hudnall, Howard	235-09-0302	Unexposed	Same as above	Pulmonary carcinoma
4) Westfall, Ralph	232-16-0225	Unexposed	Same as above	Lung cancer
5) Arthur, Robert	236-09-2143	Unexposed	Same as above	Hodgkin's disease

Not Included in Study

Name	SSN	Exposure Class. in PMR Study	Reason	COD
6) Roe, James	416-05-6467	Not included in study	Never on hourly payroll-not eligible for inclusion in study.	Bronchiogenic carcinoma
7) Cochran, Howard	235-09-0261	Not included in study	Transferred to salary payroll 5/17/43 - not eligible for inclusion into study.	Lymphatic leukemia

Included in Zack/Gaffey Study, But Not Included in PHR Analysis

Name	SSN	Exposure Class. in PHR Study	Reason	COD
8) Moore, Herman	234-24-0050	Not included in PHR analysis	Counted as alive in Zack/Gaffey study - died after 12/31/77.	Malignant fibrous histiocytoma of soft tissue.
9) Tidquist, Hugo	512-10-9016	Not included in PHR analysis	Counted as alive in Zack/Gaffey study - died after 12/31/77	Acute myelogenous leukemia

Zack/Suskind Study

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

Study Criteria

Population:	All persons with chloracne which could be attributed to the 1949 TCP process accident.
Start Date:	March 8, 1949
End Date:	December 31, 1978
Exclusions:	Females
Vital Status:	Vital status as of December 31, 1978

Zack/Gaffey Study

"A Mortality Study of Workers Employed at the Monsanto Company Plant in Nitro, West Virginia"

Study Criteria for SMR (Standard Mortality Ratio) Study

Population:	Employees active on or after January 1, 1955 with one of more years of employment on the hourly roll prior to December 31, 1977.
Start Date:	January 1, 1955
End Date:	December 31, 1977
Exclusions:	Salaried personnel who had never worked on the hourly roll Females Nonwhite males
Vital Status:	Vital status as of December 31, 1977

Study Criteria for PMR Study (Proportional Mortality Ratio)

Population:	Deceased employees from Nitro cohorts divided into 2,4,5-T exposure and non exposure cohorts.

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Employees Included in the Zack/Suskind Study But Excluded from Zack/Gaffey Study
(Reason for exclusion: They were not on hourly payroll 01/01/55 or after.)

Name	SSN	Date of Birth	Cause of Death	Date of Term. From Hourly	Date of Death
Blackwell, John E.	235-01-0079	07/31/05	410.9	--	04/15/53
Cochran, Howard W.	235-09-0261	10/09/07	204.9	05/17/43	11/28/71
Cooper, Robert H.	235-09-0379	08/09/07	412.4	(Never an hourly worker)	01/11/77
Fletcher, James A.	235-09-0276	11/30/01	250.9	05/29/53	01/29/73
Hudnall, Berry	236-07-4320	09/15/89	433.9	09/30/54	01/26/64
Ingram, Albert C.	233-07-3788	12/12/86	412.3	01/01/52	11/07/78
Jeffers, Robert	236-07-6061	03/31/91	881.0	01/26/50	01/26/50
Lloyd, John P.	235-03-7914	01/22/86	410.0	02/01/54	06/29/73
McKone, Charles J.	206-07-5877	03/29/14	431.0	02/28/50	05/18/66
Nelson, George O.	032-07-1132	09/19/18	410.0	09/30/50	03/25/59
Roe, James F.	416-05-6467	06/25/11	162.1	(Never an hourly worker)	06/09/64
Saffel, Delbert	235-09-0340	03/19/99	436.9	04/01/45	12/24/70
Shank, Lawrence L.	235-09-0342	02/16/05	410.9	09/01/44	07/16/72
Woods, Frank	235-09-0371	07/10/94	410.9	04/01/45	01/02/57

These employees were counted as deceased in the Zack/Suskind study but as living in the Zack/Gaffey study. The cutoff date of the Zack/Suskind study was 12/31/78, while the cutoff date of the Zack/Gaffey study was 12/31/77. All these employees were living as of 12/31/77.

Name	SSN	Date of Death	Cause of Death
1) Hanna, Cecil	232-18-9308	06/11/78	412.4
2) Moore, Herman	234-24-0050	11/10/78	173.9
3) Tidquist, Hugo	512-10-9016	11/13/78	205.0
4) Wolf, Leslie	235-01-4008	01/27/78	519.3

I. Not included in Zack/Gaffey study and should have been.

1) Johnson, Warner 224-52-5989

II. 2,4,5-T exposure category was incorrectly classified in Zack/Gaffey PMR study.

A) Counted as unexposed - should have been exposed.

Name and SSN	COD	DOD	DOH	DOT	EXP
1) Johnson, Warner 224-52-5989	819.9	04/02/76	03/21/66	04/02/76	Y
2) Simmons, William 234-34-2228	410.9	05/05/69	02/05/44	05/05/69	Y
3) Workman, John 233-32-4578	151.9	08/30/71	04/11/50 (medical record says he was exposed)		Y

He shouldn't be counted as exposed because information came from the medical record, not the work history

B) Counted as exposed - should have been unexposed.

Name and SSN	COD	DOD	DOH	DOT	EXP
1) Davis, Thomas 236-16-3469	162.1	04/15/68	10/24/46	04/15/68	N
2) Eads, Martin 236-16-4813	782.4	01/06/64	01/03/44	01/06/64	N
3) Vintroux, James 234-28-8198	924.0	04/16/57	07/01/45	04/16/57	N
4) Winter, James E. 235-05-3054	188.0	12/25/68	11/21/44	12/25/68	N

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INCLUDING DEATHS FROM TCP INCIDENT

Table 9. Observed and Expected Number of Deaths During 1955-1977 by Cause and 2,4,5-T Exposure Category Showing Proportional Mortality Ratios (PMR'S)

Cause of Death	2,4,5-T Exposure Category: Exposed Observed	Exposed Expected	Exposed PMR	Non-exposed Observed	Non-exposed Expected	Non-exposed PMR
All malignant neoplasms	9	10.94	82	25	~~20.43~~ 17.19	122
Buccal cavity and pharynx	0	0.38	0	0	.52 ~~0.64~~	0
Digestive organs and peritoneum	0	2.80	0	3	4.86 5.74	52
Stomach	0	0.52	0	0	.9 1.06	0
Liver	0	0.19	0	0	.34 0.39	0
All other digestive organs	0	2.09	0	3	3.62 4.29	70
Respiratory system	6	3.78	159	8	5.58 6.81	117
Lung	6	3.57	168	8	5.26 6.42	125
All other respiratory organs	0	0.21	0	0	.32 0.39	0
Skin	0	0.29	0	0	.30 0.35	0
Genitourinary organs	2	0.96	208	10	2.39 2.70	370*
Bladder	2	0.22	909	7	.56 0.65	1077*
All other genitourinary organs	0	0.74	0	3	1.83 2.05	146
Lymphatic and hematopoietic tissue	0	0.35	0	1	1.79 2.07	48
Other sites	1	1.38	72	3	1.12 2.12	142
Diseases of the nervous system and sense organs	0	0.61	0	0	.72 0.83	0
Diseases of the circulatory system	31	26.48	117	61	47.33 35.34	110
Arteriosclerotic heart disease, including CHD	27	19.72	137	52	35.63 39.68	131*
All other diseases of the circulatory system	4	6.76	59	9	13.74 15.66	57
Diseases of the respiratory system	2	2.67	75	4	5.66 6.49	62
Diseases of the digestive system	1	3.70	27	4	4.06 4.93	81
All other diseases	3	4.31	70	2	6.70	30
External causes of death	12	9.29	129	8	8.23 9.28	86
Total number of deaths:	58	58.00		104	104.00	

*p < .05

SUBJECT TO PROTECTIVE ORDER

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586

J.A. ZACK AND W.R. GAFFEY

Table 9 Observed and Expected Number of Deaths During 1955-1977 by Cause and 2,4,5-T Exposure Category Showing Proportional Mortality Ratios (PMRs) (Not Including Deaths from TCP Incident[§] who were not otherwise exposed-from press

	Exposed			Non-Exposed		
Cause of Death	Observed	Expected	PMR	Observed	Expected	PMR
1 causes of death	58	58.00	100	89	89.00	100
1 malignant neoplasms	9	10.94	82	21	17.19	122
Buccal cavity and pharynx	0	0.38	0	0	0.52	0
Digestive organs and peritoneum	0	2.80	0	3	4.86	52
Stomach	0	0.52	0	0	0.90	0
Liver	0	0.19	0	0	0.34	0
All other digestive organs	0	2.09	0	3	3.62	70
Respiratory system	6	3.78	159	4	5.58	72
Lung	6	3.57	168	4	5.26	76
All other respiratory organs	0	0.21	0	0	0.32	0
Skin	0	0.29	0	0	0.30	0
Genitourinary organs	2	0.96	208	10	2.39	370*
Bladder	2	0.22	909	7	0.56	1077*
All other genitourinary organs	0	0.74	0	3	1.83	146
Lymphatic and hematopoietic tissue	0	1.35	0	1	1.78	48
Other sites	1	1.38	72	3	1.76	142
seases of the nervous system and sense organs	0	0.61	0	0	0.72	0
seases of the circulatory system	31	26.48	117	52	47.37	110
Arteriosclerotic heart disease, including CHD	27	19.72	137	43	33.63	128
All other diseases of the circulatory system	4	6.76	59	9	13.74	57
seases of the respiratory system	2	2.67	75	4	5.66	62
seases of the digestive system	1	3.70	27	2	4.06	49
1 other diseases	3	4.31	70	2	5.77	30
ternal causes of death	12	9.29	129	8	8.23	86

analysis showed 65 deaths.

P<.05

ATTACHMENT IV

Chronology of 2,4,5-T and NaTCP Production Activities at Nitro Plant

Bldg.No./Dept.	Subarea	Exposure	Start Date	End Date
32	00 (Pilot Plant)	NaTCP & 245T	7/48	10/48
	08	245T	"	"
	09	NaTCP	"	"
34 (old)	00	not specified	11/48	12/52
	01	245T	"	"
34 (new)	00	not specified	1/53	8/63
	01	245T	"	"
16	00	245T drying	10/48	11/52
21	00	"	"	"
46	00	"	"	"
79	00	"	"	"
41	00	not specified	11/48	3/50
	01	NaTCP	"	"
51	00	not specified	2/51	6/63
	01	NaTCP	"	"
52	00	not specified	8/63	8/71
92	01	245T	"	"
	02	NaTCP	"	"
P(Production)	00	not specified	7/48	8/71