Uploaded to VFC Website

November 2012

This Document has been provided to you courtesy of Veterans-For-Change!

Feel free to pass to any veteran who might be able to use this information!

For thousands more files like this and hundreds of links to useful information, and hundreds of "Frequently Asked Questions, please go to:

Veterans-For-Change

Veterans-For-Change is a 501(c)(3) Non-Profit Corporation
Tax ID #27-3820181

If Veteran's don't help Veteran's, who will?

We appreciate all donations to continue to provide information and services to Veterans and their families.

https://www.paypal.com/cgi-bin/webscr?cmd=_s-xclick&hosted_button_id=WGT2M5UTB9A78

Note: VFC is not liable for source information in this document, it is merely provided as a courtesy to our members.

Item ID Number	05739 ☐ **Not Scanned**
Author	
Corporate Author	
Report/Article Title	Response to the AOWG Science Panel Review of the NIOSH Draft Protocol for a Mortality Study of Workers Exposed to Dioxin
Journal/Book Title	
Year	0000
Month/Day	
Color	☐
Number of Images	0
Description Notes	

RESPONSE TO THE AOWG SCIENCE PANEL REVIEW OF THE NIOSH DRAFT PROTOCOL FOR A MORTALITY STUDY OF WORKERS EXPOSED TO DIOXIN

We are grateful to the members of the Science Panel for their careful review of our protocol and for their constructive and supportive comments. We respond here to the comments received.

A. Points Raised in the Summary Statement of the Science Panel.

1. The reviewers endorse the value and utilization of our exposure index, recommending that it be carefully constructed, that it quantify exposure if possible, and that it be used to create categories which will allow us to evaluate a dose-response relationship.

   We agree with the Panel's assessment of the value of the exposure index. We are working hard to make it quantifiable and to ensure its accuracy. It is our intention to use it to assess a dose-response relationship. We are scheduled to finalize the structure and use of the exposure matrix with our NIOSH Special Peer Review Panel by March, 1985.

2. The reviewers recommend that we should not separately analyze the chloracne workers as a single highly exposed group. They believe this may be misleading since compounds other than dioxin are chloracnegens and because individuals vary in their susceptibility to chloracne. Additionally, the Panel recommends that we reserve the comparison of

chloracne among different subgroups of workers as confirmation for an exposure matrix which is based on other data.

We have not yet finalized a method for utilization of the person known to have chloracne. We are scheduled to develop this section of the protocol and present it to our NIOSH peer review panel by March, 1985. We plan to analyze the chloracne subcohort as a group with highly probable exposure. We have collected information at each company about the presence of other potential chloracnegens. Since the known chloracnegens are very few, we believe we can exclude from the chloracne group those persons with potential confounding exposures.

Following the suggestion of the Science Panel and also of several NIOSH peer reviewers, we will use the chloracne group as confirmation for the exposure index rather than as a component in its construction.

3. The reviewers supported our concern that soft tissue sarcomas cannot be identified accurately from death certificates, and noted the absence of population rates based on pathologically reviewed specimens. The Panel suggested that the creation of a reference population is a formidable undertaking and recommended that a feasible approach at this time may be to use a minimally exposed subgroup of the Registry as an internal standard. The Panel points out that even this approach will require a considerable review of pathological specimens and clinical records, and will have low power for rare tumors unless there is a very steep dose-response gradient.

We appreciate the recommendation. We believe that there will be too few deaths in this study to use the low exposure group to generate comparison rates for soft tissue sarcoma. We have not yet completed our efforts to ascertain whether we can identify any useful population-based data or whether we can conduct a useful pathology review to generate stable comparison rates. Our current priority is to complete the analysis of the study as it was designed, using the NIOSH Life Table Analysis System, which is based on death certificate data. We will then complete a more appropriate and thorough analysis of the soft tissue sarcoma outcome. A protocol for this effort will be prepared for review by the NIOSH Special Peer Review Panel.

B. Individual Reviewer Comments.

The Science Panel members brought their written comments to the meeting of May 29, and most of their questions and suggestions were addressed during our lengthy discussion at that time. One remaining question is considered here.

What is the schedule for completion of open-ended items in the protocol and for meeting with the NIOSH Special Peer Review Panel?

We are currently working on the two major items not yet detailed in the protocol: development of the exposure matrix and determination of a methodology for use of the "chloracne subcohort". Our NIOSH peer reviewers are working with us on an "as needed" basis. We will revise the

1982 draft protocol using the comments we have received from our NIOSH reviewers and the Science Panel, and we will hold a meeting in March, 1985 with our NIOSH Special Peer Review Panel to finalize the protocol. At this meeting the Panel also will review our analytic methods, because the group has been charged also with a continuing review of our data collection, analysis of data, and generation of draft and final reports. The reviews will be accomplished in scheduled meetings and on an "as needed" basis.

Executive Summary: Response to the AOWG Science Panel Review of Protocols for NIOSH Dioxin Morbidity and Reproductive Studies

1. CHOICE OF PLANTS FOR STUDY

Plants in Missouri and New Jersey plants were chosen for study for several reasons, including requests from the States for assistance in evaluating those workers. The New Jersey cohort can readily be justified on scientific grounds because of the high proportion of workers with documented chloracne (about 20%) and therefore evidence of exposure. Because a pilot study will be required, we suggest that a reasonable approach will be to use the Missouri plant as a pilot effort, with the New Jersey cohort serving as the major study plant.

2. REFERENT GROUP

Neighborhood referents will be chosen only for exposed workers still living in-state (or in the surrounding geographic area), although all exposed workers will be invited to participate in the study. In-state workers appear to be similar to those who moved out of state with respect to date of birth, date of hire, and duration of employment.

Logistical obstacles to obtaining an industrial referent group outside the Registry remain daunting.

3. POWER

The power of the morbidity study using in-state/contiguous geographic area workers from New Jersey appears to be adequate to detect statistically significant excesses of several major outcomes of interest detected in the recent studies of the Nitro, W.Va. cohort, including ulcer disease, abnormal pulmonary function, neuropathy on physical exam, and decreased libido (providing background prevalences and prevalence rate ratios are roughly similar to those in the Nitro, W.Va. workers). It will not be adequate to detect subgroup excesses of outcomes such as coronary heart disease or impotence. Power calculations show that two additional larger plants would have to be studied in order to detect excesses of these outcomes.

4. STAFF AND FUNDING

Even if funding is forthcoming to study the Missouri and New Jersey workers, NIOSH does not currently have adequate staff positions to carry out the work. Any directive to proceed with this or an expanded study should be made with the recognition that a larger staff will be necessary if we are to proceed.

5. REPRODUCTIVE STUDY

The study of New Jersey workers will probably be adequate to permit

detection of a 2.5-fold increase in spontaneous abortions. However, the study size is totally inadequate to study either all major birth defects or neural tube defects. The question of whether the Registry population is an appropriate group for a birth defects study is a separate matter from that presented here. If a reproductive study of the entire Registry is desired, its feasibility and power to detect the desired outcomes should be evaluated at a later time. Design, efficiency, and cost considerations suggest that such a Registry-wide study be done as a separate and independent piece of research.

RESPONSE TO THE AOWG SCIENCE PANEL REVIEW OF THE NIOSH PROTOCOL FOR A STUDY OF PERSISTENT HEALTH EFFECTS IN CHEMICAL-HERBICIDE WORKERS AND IN COMMUNITY RESIDENTS OF UNKOWN EXPOSURE STATUS AND PROTOCOL FOR A STUDY OF ADVERSE REPRODUCTIVE OUTCOMES IN THE SAME STUDY POPULATION

This response to the AOWG Science Panel's review of our protocols for the Medical/Morbidity and Reproductive studies first addresses the major points raised in the Science Panel summary "Discussion" and then selected points raised by the individual reviewers.

Points raised in the "Discussion":

1) Choice of plants for study

We recognize the concern of the Science Panel over whether Missouri and New Jersey are the most suitable plants for study, and we wish to reiterate again the history of events that lead to their choice. In the spring of 1983, public concern over environmental dioxin contamination became urgent first in Missouri and then in New Jersey, and the state health departments approached NIOSH for assistance in evaluating workers who had been exposed to dioxin-contamininated processes. Because NIOSH had for several years envisioned a morbidity study of one, several, or many plants in the NIOSH Dioxin Registry, the request for assistance from two of the states in which two plants from the Registry were located provided an opportunity both to do research and to provide a public health service.

As we discussed in the meeting with the Science Panel, the choice of the New Jersey plant can readily be justified on purely scientific grounds: of approximately 480 workers employed at the plant during its 20 years of operation, there were more than 100 cases of chloracne or suspected chloracne (industrial dermatitis). We can be certain that exposures to 2,3,7,8-TCDD existed, since there were no other known chloracnegens at this plant. Hexachlorobenzene, a confounder for both the porphyrinogenic and neurotoxic effects of dioxin, and in production and use in this plant and in the Missouri plant, has never been associated with chloracne. The Missouri plant had fewer workers (84), no documented chloracne, and briefer potential exposure periods. As noted in the Panel's review and in the history recounted above, however, "strong local interest" was "instrumental" in its selection.

In view of this, we believe that the following approach to the study of these two plants is reasonable. Because a study even of the magnitude of that proposed will require a pilot study, and because it is customary to exclude "pilot study" subjects from the main analysis, we propose that we study both plants, but that the pilot study be conducted in Missouri rather than in New Jersey. In this way, the Missouri workers will be fully studied and their data can be separately analyzed. On the basis of this pilot effort, we can assess participation rates, locating and sampling methods for the referent group, and a number of methodological and logistical matters such as questionnaire acceptability, scheduling of participants, quality control of examination protocols, etc. Although this will not be an ideal pilot, it will provide valuable experience and still allow a full study of the Missouri plant

within the context of this project. The main study (or its first phase) can then be conducted in New Jersey on that larger group of workers, and no data from New Jersey will be lost because it was dedicated to the pilot study.

2) Choice of the referent group

a. Neighborhood referents
(and studying only exposed workers still resident in the state or surrounding area

In addition to concern over the choice of these two plants, there is the added knotty problem of the appropriate referent group. As noted by the reviewers, we propose to use neighborhood referents matched on age, race, sex, and duration-of-residence-in-current-community, a proposal found acceptable by two of our epidemiological reviewers, Dr. Brian MacMahon and Dr. Clark Heath. However, because about a third of the New Jersey workers now reside out of state, the Science Panel reviewers expressed concern that it may not be feasible to obtain neighborhood referents for the workers no longer in the area and to persuade them to travel to a distant examination site. Participation rates may suffer accordingly. Therefore, we propose to adopt the Panel's recommendation and Dr. MacMahon's independent proposal that we focus our study on those exposed workers still residing in the States of Missouri and New Jersey (and surrounding areas within a reasonable travel

distance, e.g. 100 miles). We would obtain neighborhood referents only for this in-state group. We can also study those out-of-state exposed persons willing to participate, but we will not attempt to obtain out-of-state "neighborhood" referents for that group. Thus for each plant, we would have three groups in the study: in-state exposed, their neighborhood referents, and out-of-state exposed. This would permit comparisons among the three groups. Even though the neighborhood referents will be matched to the exposed, the matching can be broken if necessary, since the abandonment of matching in a cohort study will decrease efficiency but will not compromise validity.

A related matter which should be examined before deciding whether it is a reasonable approach to study the in-state exposed groups is a consideration of the similarities and differences between the groups that remained in-state and those moving out-of-state. We examined frequency distributions for in- and out-of-state exposed persons with respect to decade of birth, decade of hire, and duration of employment. Because we examined only those entries with correctly coded social security numbers, date of birth, etc., the total number of living, located workers is 431 (instead of 447), 355 of whom were from the New Jersey plant. According to this run, there were 254 (72%) of surviving New Jersey workers still residing in New Jersey, New York, or Pennsylvania (with 101 living elsewhere), and 59 (78%) of surviving Missouri workers residing in Missouri, with 17 residing elsewhere.

The accompanying histograms show this comparison for the New Jersey plant. As can be seen from the histograms (Figures 1-3), the workers who moved out of

the geographic area were a bit younger and started their employment a bit later. Although a larger proportion of the out-of-state group (19%) than of those remaining in-state (13%) worked more than ten years, the absolute number of persons working more than ten years was greater in the group remaining in the New Jersey area (32 in-state vs 19 out-of state). Overall, the groups appear fairly similar, at least according to these parameters.

b. Industrial referents

We are reluctant to embark on trying to obtain a separate industrial cohort (a plant which is not part of the Registry) as a comparison group, for the reasons outlined in the protocol. To summarize those reasons: a suitably large plant without obvious confounding exposures and which operated during the same time period as the New Jersey plant (1951-69) would have to be identified in the Newark or northern New Jersey area (and perhaps for the Missouri workers as well, which should prove more difficult). We would then have to gain access to the plant and its personnel records solely for the purpose of obtaining a "control" group, something which has never been done for a large NIOSH study. Follow-up procedures to determine vital status and address, through social security, IRS, and special search agencies, would be the same as for the exposed plant and will take up to a year to accomplish. (With this method, it may not be possible to identify short-term workers who left the company.) Once identified, workers still living in the area would have to be evaluated to see that the age, race, and sex distribution of the workforce is comparable to that of the exposed cohort of workers still living

in the New Jersey area. If not comparable, a different comparison group would have to be sought. If deemed comparable, the workers would then be approached to request their participation in the study. The cooperation of both the company management and the union would be required. Depending on the nature of the company and its management, and on the possibilities for future litigation by workers if ill health effects are discovered in the "control" group, resistance to allowing NIOSH access to its personnel records may be considerable. In addition, unexpected confounding exposures in the selected referent plant may bias the results or even make comparisons impossible because of irreducible confounding.

If, despite these obvious logistical difficulties, the Science Panel feels strongly that the validity of our study will be too severely compromised without the use of an industrial cohort as a referent group, we should reconsider the issue with our Peer Reviewers. Such an addition to the present study will add considerably to the time and expense required before we can begin.

The Science Panel suggested that we consider inclusion of an additional exposed plant from the Dioxin Registry which may have had workers in sufficient numbers to provide an "internal" referent group. While this is an appealing suggestion for methodological reasons, the study of a second or third plant in this phase of the study may not be necessary for reasons of statistical power, according to the results of our power calculations shown in the next section.

(3) Power calculations have been made for important outcomes based on the reduced size of the study if referents are obtained only for the in-state exposed persons in New Jersey (with added calculations to show the power obtained by adding more plants from the Registry as needed).

The outcomes which we plan to study are numerous. They include the following categories:

a. HISTORICAL HEALTH INFORMATION: Medical questionnaires will be used to ascertain the following health outcomes:

Prior physician diagnoses of pneumonia, liver diseases (jaundice, hepatitis, cirrhosis, enlarged liver), coronary heart disease (heart attack or angina), nervous breakdown, neuropathy, ulcer disease, chloracne, adverse reproductive outcomes (miscarriage, abortion, stillbirth, birth defect, infertility) or cancer. As the major illnesses about which there has been the greatest concern, these outcomes will be confirmed by obtaining medical records.

Patient report of a physician diagnosing or treating him/her for elevated lipids, hypertension, pulmonary diseases, genitourinary diseases, allergies, blood diseases, other nervous system disease, arthritides, skin diseases (e.g. eczema, psoriasis), thyroid problem, diabetes, etc. As outcomes which have been reported but for which the evidence is either less compelling, or the outcome alone does not necessarily represent

morbidity, or it represents a confounder, patient reported information will be regarded as adequate for our purposes. No medical records will be obtained.

Current or past symptoms (include symptoms referrable to porphyria, hirsutism, neuropathy, depression, changes in vision, hearing, and taste, emotional lability, sleep disturbances, and chronic bronchitis). No medical records will be obtained.

b. PHYSICAL EXAMINATION (general, dermatologic, and neurologic--the latter including both physician administered and quantitative sensory testing)

c. NEUROBEHAVIOURAL/PSYCHOLOGICAL BATTERY

d. NEUROPHYSIOLOGIC TESTING (nerve conduction testing)

e. PULMONARY FUNCTION TESTS

f. BIOLOGICAL SAMPLES (blood and urine)

Hepatic function/lipids

GGT, SGPT, alkaline phosphatase

cholesterol, triglycerides, HDL-cholesterol

Hematopoetic: CBC with differential and platelets

Metabolic/endocrine

Thyroid screen

Fasting blood sugar, 2 hour post prandial blood sugar

Testosterone and gonadotropins

Urinalysis with microscopic

Urinary porphyrins

D-glucaric acid in urine

To attempt to do power calculations for each of these seems unnecessary, since background prevalences of many possible abnormalities are either unknown, or the isolation of a single biological test (eg, GGT) for power calculations would seem too obsessively narrow a focus. Therefore, we performed power calculations for several important medical and reproductive outcomes which clearly imply major morbidity and for which the background prevalence is known or at which we can guess based on work in other dioxin-exposed cohorts. These include in Table I (1) ulcer disease (physician diagnosis of ulcer disease during or since employment at the exposed plant); (2) abnormal pulmonary function tests in exposed persons who are current smokers, implying some interaction between exposure and smoking to produce chronic obstructive pulmonary disease (FEV_1/FVC less than 80% predicted); (3) heart disease (physician diagnosis of angina or history of myocardial infarction); (4)

neuropathy (sensory neuropathy on physical exam); and (4) impotence and decreased libido. Table II includes power calculations for spontaneous abortion, major birth defects, and for neural tube defects.

The outcomes in Tables I and II are those other than chloracne that were positive in some subgroup of the Nitro, West Virginia cohort (ulcer disease, abnormal PFT's, and CHD), that have been implicated in other studies of occupationally exposed groups (ulcer disease, CHD, neuropathy), or that are of major concern in relation to dioxin without clear evidence in an occupationally exposed cohort (spontaneous abortion, reproductive abnormalities). Power calculations are done including the New Jersey cohort alone (Plant A), and then with the addition of two more plants sequentially. Plants chosen for possible addition are those in the Registry which have not been studied or have not been well studied, and which have the largest appropriate worker populations.

CONDITIONS AND ASSUMPTIONS GOVERNING THE POWER CALCULATIONS IN TABLE I

The Suskind study of the Nitro, West Va. cohort (JAMA, 251(18):2372-2380, 1984) showed a statistically significant, three-fold increase in ulcer disease in the exposed group overall, with a background prevalence in their unexposed group of nearly 6%. That study found a statistically significant excess of abnormal pulmonary function in current smokers who had been exposed (26% in exposed current smokers, 6.7% in unexposed current smokers). The Suskind study also showed a six-fold excess of angina in the exposed group less than

fifty years of age (with a prevalence in the unexposed of 1%, and an excess (2% in the exposed, 0% in the unexposed) of "coronary artery disease", which was not defined further. Impotence and decreased libido occurred as a four-fold excess in the under-50 age group, with backgound prevalences in the unexposed group of 2% and 5%, respectively. Moses' study of the Nitro workers (AJIM, 5(3):161-182, 1984) showed a 3-4 fold excess of myocardial infarction and angina in the under 60 year old age group of those with chloracne, compared with those without chloracne (background prevalence=4%). Moses also found an 18% prevalence of sensory neuropathy on physical exam (decreased sensation to pinprick in the lower extremities) in those with chloracne, and a 0% prevalence in those without chloracne.

The power calculations shown in Table I are based on the background prevalences in the studies described above, and also utilize the following assumptions: 50% of the cohort will be alive, locatable, and still remaining in the surrounding geographic area (as was the case in New Jersey). Eighty percent of that group will participate. Thirty percent of the group will be under fifty years old, and 55% will be under 60 (as in New Jersey). Twenty percent of the cohort will have had chloracne (based on our knowledge of New Jersey, although the prevalence was higher in the Nitro cohort), and 35% will be current smokers (as in the Nitro cohort).

The Missouri plant is not included in Table I, since it will serve as the pilot. Plant A is the New Jersey plant, and Plants B and C are the two plants from the Registry which would seem the best candidates for a medical study.

The overall plant populations are given in parentheses next to each alphabetical designation. The potential study group size from each plant for each outcome is given in parentheses (n=) beneath the power achieved by using the additional population from that plant. The alpha level chosen is .05 (one-tail test), and the Rothman-Boice Hewlett Packard program for study size and power calculations was employed.

TABLE I

ESTIMATED POWER FOR SELECTED MEDICAL OUTCOMES

	POWER		
	Plant A (490)+	Plant B (325)+	Plant C(2194)
OUTCOME			
(Based on Suskind study--exposed vs. unexposed)			
Ulcer PRR*=3	99%		
	(n=190)		
Abnl PFT's PRR=3+	96%		
	(n=65)		
Impotence PRR=4	40%	60%	99%
	(n=60)	(n=40)	(n=260)
Libido PRR=4	83%		

*PRR=prevalence rate ratio

Table I (continued)

OUTCOME (Based on Suskind study)			
Angina (under 50 yrs)	PRR=6 (n=60)	40% (n=40)	63% 99% (n=260)
Coronary artery disease (under 50 yrs)	PRR=20 (n=60)	7% (n=40)	21% 98% (n=260)

(Based on Moses study--chloracne vs. no chloracne as exposure indicator)

Neuro. (Even if the prevalence in the exposed or chloracne group is only half that seen by Moses, i.e. 9% instead of 18%, the power would still be 86% using the New Jersey plant alone, although this assumes the same distribution of confounders in the exposed and referent populations.)	PRR=18+	100%	
Myocardial infarct. (under 60 yrs)	PRR=3+ (n=20)	23% (n=14)	37% 87% (n=96)
Angina (under 60 yrs)	PRR=3+ (n=20)	30% (n=14)	50% 96.5% (n=96)

CONDITIONS AND ASSUMPTIONS GOVERNING THE POWER CALCULATIONS IN TABLE II

The power calculations shown in Table II are based on the same basic assumptions used in Table I which were that 50% of the cohort will be alive, locatable and living in the surrounding geographic area and 80% will participate. In addition, we assumed that 20% of the cohort worked a minimum of 5 years, was less than 50 years old at the time of hire, and each had an average of 1.5 children.

Very few studies have been conducted which examine paternal exposure as a risk factor for adverse reproductive outcomes. The few studies that have been done, which include anesthetic gases and vinyl chloride, have shown risks of two-fold or below for spontaneous abortion and of less than 1.5 fold for congenital malformations.

The background prevalence of spontaneous abortion is approximately 15% of all pregnancies. In calculating power, we assumed a potential risk between 2.0 and 3.0 for spontaneous abortion. The background prevalence of all major congenital malformations is approximately 2.5% of all live births. The prevalence of neural tube defects is, on average, about 0.5%. The CDC study of Vietnam veterans (JAMA 252:903-912, 1984) showed a statistically significant trend for the risk of spina bifida with increasing exposure, with a risk of 2.7 in the high exposure category. Our power calculations are based upon detection of a three-fold risk in the exposed group.

If exposure increases the risk of only a few malformations, we would expect the overall risk for total major malformations to be lower than individual defects. We therefore selected a two-fold risk as reasonable.

Table II

ESTIMATED POWER FOR REPRODUCTIVE OUTCOMES

		PLANT		
OUTCOME		A(51*)	B(86)	C(323)
Spontaneous Abortion	RR=2	43%	62%	99%
	RR=3	82% (n=60)**	96% (n=101)	(n=380)
All Major Birth Defect	RR=2	14%	19%	48%
Neural Tube	RR=3	9%	13%	33%

* - estimated number of live births
** - estimated number of pregnancies
Z_{alpha} = 1.645 (one tailed)

COMMENTS:

As can be seen in the preceding tables, ulcer disease, abnormal pulmonary function in smokers, sensory neuropathy on physical examination, diminished libido and spontaneous abortion may all be detectable in the New Jersey plant workers alone. Thus, in the study as presently designed, we have a reasonably good chance of finding a number of important outcomes, assuming some similarities to the Nitro cohort. However, since there are inconsistencies even within the two studies of the West Virginia workers, we may expect that our findings will be somewhat different (for example, Suskind reported no abnormal neurological findings on physical exam in his group, while Moses reported a high prevalence of sensory neuropathy among chloracne victims). Should the prevalences of these various outcomes when verified by physician records and our examinations be less than those in the Nitro workers, our power will decrease as well, and a larger study may be required. However, we should expect to see some indication of excess, even if statistically significant excesses are not found. If this is the case, additional plants may then be studied.

The detection of impotence and coronary heart disease events will require the addition of at least two more plants from the Registry. A benefit of adding other plants from the Registry at a later time would include not only increased power but "internal" referent groups from some of the larger plants in the Registry (such as Plants B and C).

The reproductive component, which is a small part of the medical study, may have adequate power to detect an excess of spontaneous abortions. It is totally inadequate for the study of birth defects, in particular neural tube defects. This study was not designed to investigate primarily reproductive outcomes. We have not, therefore, presented power calculations for reproductive outcomes for the total Registry population. The question of whether the Registry is an appropriate cohort for investigation of birth defects is a separate matter from that presented here. If a reproductive study of the entire registry is feasible, efficiency and cost considerations dictate that it be done as an independent study utilizing telephone interviews for data collection.

PROPOSAL: As noted earlier in this memo, we believe that a practical approach would be to study the Missouri and New Jersey plants, with the modifications in approach proposed above (i.e., utilize the Missouri plant as a pilot; study exposed workers from both plants who are still residents of their respective states or surrounding areas, using neighborhood referents, and invite out-of-state exposed workers to participate but without referents). Because our study will obtain medical records to verify important physician diagnoses and will use an age, sex, etc.-comparable referent group, we may anticipate somewhat more reliable results than have been obtained by other earlier occupational studies.

In view of our power calculations, it would seem unnecessary to plan at the present time to study additional plants, since we may be able to detect several important medical outcomes, with the exception of coronary heart disease events and birth defects. As noted, other plants from the Registry can be added later, using the same protocol, since different study sites will be required in any event.

It must also be stated that, if funds are authorized to carry out the study as planned thus far, NIOSH personnel resources would need substantial augmentation to carry out the study without making deep inroads into other research areas. Positions for additional professional staff are needed before the project even as it is currently conceived can proceed. If the Science Panel feels that the study of additional plants is desirable, since it will clearly afford greater power for some rarer medical events and for reproductive outcomes, this recommendation should be made in recognition of NIOSH's need for additional financial and staff resources to carry out both the currently planned and extended studies.

Additional Comments from Science Panel Members

Since the Science Panel members brought written comments to the meeting of May 29, 1984, many of their concerns were discussed during that meeting. Other major comments were discussed in the preceding pages. We respond here to several comments from reviewers which may have been partially or fully discussed but which reviewers may wish to have in written response form from us.

4) Verification of reproductive outcomes

All adverse reproductive events will be verified through medical records review, in addition to verification of major medical conditions.

5) Interviews with ex-wives

Former wives of exposed and unexposed subjects will be contacted and interviewed about their reproductive history, as suggested by the Science Panel.

6) Reproductive histories

Study participants will be asked about their complete reproductive histories.

7) Obtaining sensitive information

Data on induced abortions, contraception, infertility, and impotence will be obtained. Since the wives will be interviewed about their entire reproductive histories, data concerning children born out of wedlock will be included in the data collection.

We believe that these responses address the major concerns of the Science Panel members.

FIG. 1 PERCENT OF WORKERS FROM PLANT 01 BY CURRENT AGE

(COMPARES PERCENTAGES IN GROUP STILL RESIDING IN NJ AREA WITH GROUP RESIDING ELSEWHERE)

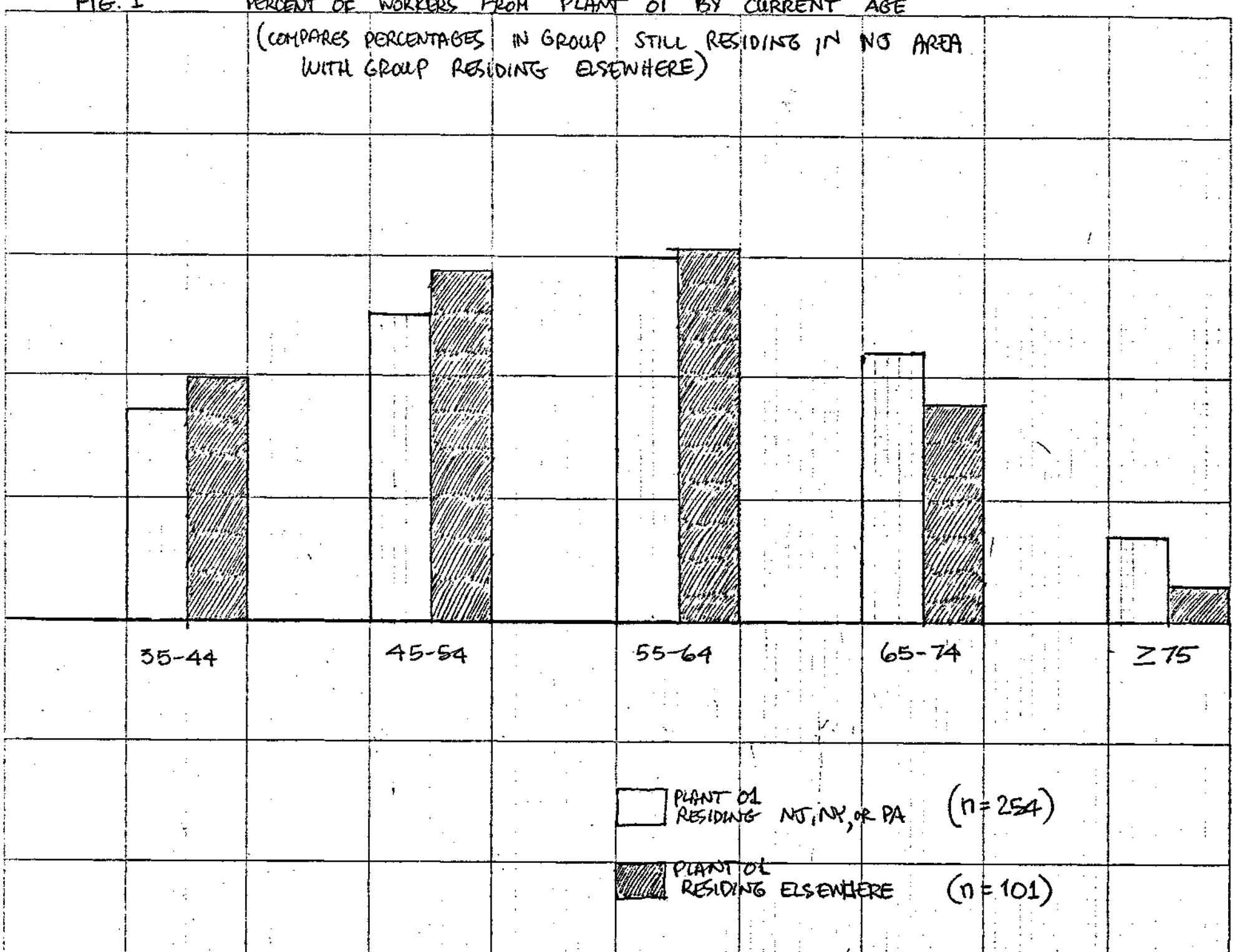
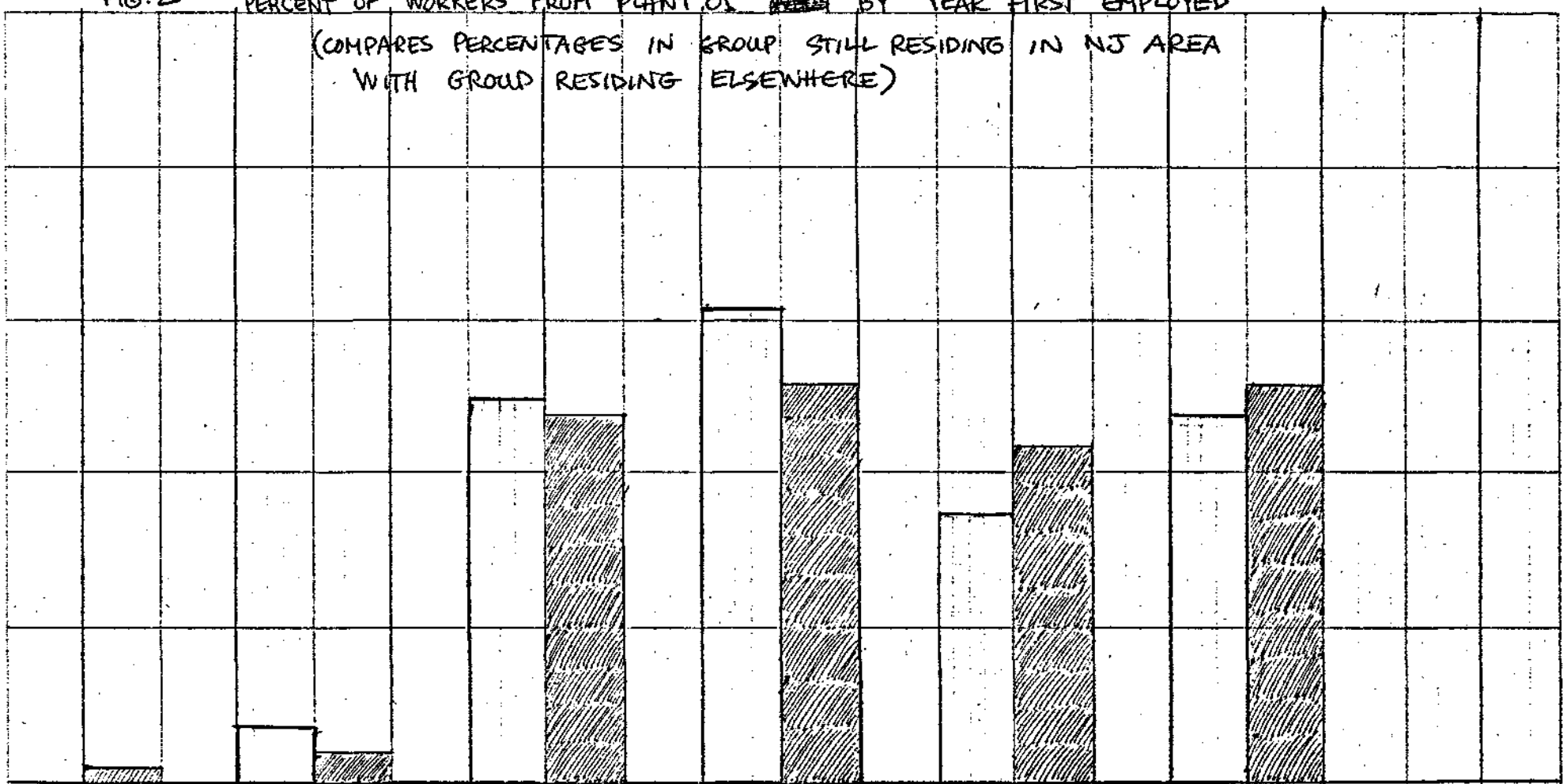


FIG. 2 PERCENT OF WORKERS FROM PLANT 01 BY YEAR FIRST EMPLOYED

(COMPARES PERCENTAGES IN GROUP STILL RESIDING IN NJ AREA WITH GROUP RESIDING ELSEWHERE)



1940-44 1945-49 1950-54 1955-59 1960-64 1965-69

PLANT 01 RESIDING ELSEWHERE

PLANT 01 RESIDING NJ, NY, PA