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DRAFT

Science Panel Review of Epidemiological Studies Proposed by the National Institute for Occupational Safety and Health Based on a Registry of Workers Known to Have Been Exposed to Polychlorinated Dibenzo Dioxins

The Science Panel of the Agent Orange Working Group met on May 29, 1984 from 10:00 a.m. to 1:00 p.m. in Washington, D.C., to discuss two protocols prepared by the National Institute for Occupational Safety and Health (NIOSH). The members present at this meeting were as indicated on the attached list of attendants (Tab A) and included two of the NIOSH investigators who had been instrumental in the preparation of the protocols which were reviewed. Several Science Panel members had prepared written comments which are included at Tab B of this review. A brief summary of the review with recommendations to the Agency for Toxic Substances and Disease Registries was prepared immediately following the meeting and is included at Tab C.

The proposed studies include a Mortality Study, a Morbidity Study and a Reproductive Outcome Study associated with the Morbidity Study. The brief description and comments on each of these studies which follows is based on individual reviewers' written comments and discussions among reviewers during and following the May 29, 1984, meeting. The presence of two of the NIOSH investigators (Drs. Fingerhut and Moody) at the meeting was very helpful in clarifying a number of issues and providing additional information on the current status of these studies.

Review of Draft Protocol for a Mortality Study of Workers Exposed to Dioxin

DRAFT

Description

Investigators at the National Institute for Occupational Safety and Health (NIOSH) have identified 15 manufacturing facilities in the United States which have produced products likely to be contaminated with polychlorinated dibenzo dioxins (PCDD) during the last 40 years. Manufacturing practices and personnel records exist for 13 of these which involve approximatley 6000 workers with some likelihood of having been exposed to these chemicals. Most of these workers have been identified and demographic information, work histories, and medical information obtainable at the manufacturing facilities are being assembled.

Several classes of workers will be included in a Dioxin Registry Cohort to be followed for mortality experience and cause of death. These include production workers and formulators in departments which made or formulated pentachlorophenol (PCP) and trichlorophenol (TCP) and its derivatives, maintenance and salaried workers known to have been assigned to these departments, all workers in plants whose total or predominant output was phenoxy acids or chlorophenol and workers present during explosive release of a TCP reactor or who were involved in the cleanup process. Vital status will be determined by standard methods and overall cause-specific mortality ratios will be computed using life table methods and United States mortality rates as the standard for comparison. Eighty-nine causes of death will be examined, including those of obvious interest at this time. Analyses will include race and sex specific comparisons as well as the effects of latency and duration of exposure.

In addition to an analysis of the entire Registry cohort, some attempt will be made to do separate analyses on subgroups experiencing different dioxin

exposures. These may include workers from different plants, those producing different products or involved in TCP accidents and other estimates of varying exposure including the presence of chloracne. Some attempt will be made to control for potential confounding chemicals such as 2,4-D, MCPA and chlorinated benzenes in so far as company records of work histories will enable this to be done.

Discussion

The investigators have already done an excellent job of identifying workers who may have been exposed to PCDD. Following these to determine vital status and obtaining death certificates can be done and should be encouraged on a continuing basis. It is not clear, however, what other population data will be most useful for comparison at this time.

Cause-of-Death-Specific Mortality rates based on death certificate diagnoses are available for the general population of the United States and will be compared with those of registrants. If death rates are lower among registrants than expected from the general population, this will be interpreted as the "Healthy Worker Effect." If death rates are higher among registrants, it will be tempting to interpret this as "due to" exposure to PCDDs. Unfortunately, these two opposing effects can cancel each other, particularly with the limited number of registrants available for follow up.

One of the ways in which this problem might be handled is to develop the possibility for determining if there exists a dose-response relationship. The investigators have obtained information on duration and type of job assignment for many of the registrants and are currently refining their estimate of duration and level of exposure based on these data. Science Panel reviewers

strongly urge support for this activity with an attempt to quantify exposures where possible. Results of this study would be most useful if particular types of exposure, such as persons present during or following an explosive release of a TCP reactor, production workers, formulators, pesticide applicators and other persons in contact with PCDDs could be arrayed in order of exposure for other studies as well.

The NIOSH investigators have indicated that they may separately analyze the several hundered workers who have suffered from chloracne as a particularly highly exposed group. The Science Panel feels that this could be misleading since a number of other chemical compounds are also chloracnigens and individuals vary in their susceptibility to chloracne. The Panel suggests that the investigators reserve comparing the relative rate and severity of chloracne among different groups as confirmation for an exposure index based on other data.

Finally, there is concern that some rare cancers, particularly soft tissue sarcoma, cannot be accurately identified from death certificates. The NIOSH investigators' own experience has already indicated as much among some of the same subjects which will be included in the mortality analysis. Unfortunately, the special review of pathologic specimens and clinical materials which is needed to make a more accurate assessment of cell types is not available for the general population. Since the creation of a reference population is a formidable undertaking, using a minimally exposed subgroup of the Registry as an internal standard appears to be the most feasible approach at this time. Even this will require 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. Also, this further emphasizes the need for a carefully constructed exposure index.

JKH7

Review of a Protocol for a Study of Persistent Health Effects in Chemical-Herbicide Workers and in Community Residents of Unknown Exposure Status and Review of Draft Protocol of Adverse Reproductive Outcomes Among Chemical Workers and Community Residents Participating in a Morbidity Study

Description

Within the Dioxin Registry briefly described in the "Review of Draft Protocol for a Mortality Study of Workers Exposed to Dioxin" are two subgroups which have been considered suitable for studying long-term morbidity: a New Jersey plant producing phenoxy herbicides between 1951 and 1969 with about 500 workers, approximately 100 of whom had chloracne, and a Missouri plant with about 80 workers producting 2,4,5-T and hexachlorophene between 1968 and 1971. As many as possible of the 447 surviving and locatable employees from these two plants will be questioned and examined along with a set of neighborhood controls of about equal size. It is the aim of the study to "provide useful information about the persistence of biologically significant medical effects and reproductive outcomes" which may be related to exposures to dioxin among workers. The comparison group will be matched for age, sex and race as well as length of residence in the community ($\pm$ 5 years). It is also proposed to offer a financial incentive of $100 to all participants and to abandon the study if less than 75% of locatable subjects and their controls agree to participate. Some additional information on potential confounding exposures to other chemicals will be obtained from company records and employee histories and dealt with during analysis. It is anticipated that the study will be pretested and piloted among 50 New Jersey workers and their controls.

The Reproductive Outcome Protocol states that "the objective of this study is to determine if occupational exposure to dioxin . . . is associated with decreased fertility, spontaneous abortions, stillbirths or congential malformations in the offspring of male workers." The study will be part of the

morbidity study previously described and will entail a retrospective cohort design based on interviews of male workers and their wives. It is also planned to collect birth, fetal death and infant death certificates for verification of reported reproductive outcomes.

Discussion

One of the first questions which arises in reviewing these protcols is why the New Jersey and Missouri plants were selected as sources for the study population. The investigators stated that the New Jersey plant was fairly large and apparently quite contaminated as indicated by the fact that 20% of the workers are reported to have had chloracne. Strong local interest in studying this problem in both New Jersey and Missouri, however, seem to have been at least as instrumental in the selection, and may enhance participation if this interest can be exploited.

The protocol includes a discussion of several possible choices for selecting comparison subjects and concludes that neighborhood controls matched on age, sex, race and length of residence, are most appropriate. Members of the Science Panel feel that this may introduce selection bias in that motivation for participation will be different, particularly among subjects currently living at some distance from the examination sites. The Science Panel suggests study subjects (and their controls) include only persons currently residing in New Jersey and Missouri, or in close neighboring areas. The investigators have indicated that approximately half of the New Jersey subjects no longer live in New Jersey and currently reside in some 38 different states. If additional subjects are needed to increase the statistical power of the study, another plant should be selected for inclusion. This would enhance the study if a plant is selected which can contribute unexposed in-plant comparison subjects as well as neighborhood controls.

Although not included in the protocol, the investigators intend to verify reproductive events through medical record review. This will be particularly important for those items not reliably reported on vital records, such as birth defects, spontaneous abortions and early miscarriages. Another procedure which the Science Panel strongly recommends is that former wives be interviewed for reproductive outcomes. In order to maximize the number of reproductive events for analysis and cover the younger ages, pregnancies engendered during the entire reproductive period should be included. This is particularly important considering the large proportion of short-term workers and the length of time (well over 10 years) since any of them were employed at these plants.

As is indicated in the protocol, in order to make a meaningful interpretation of results from the detailed health examinations and tests on these subjects, it will be essential that an accurate assessment of exposure is available. Records of job assignments from the New Jersey plant appear to be useful for this purpose, but the comparisons will have no such records and must rely on occupational historical data. Of concern are possible differences in exposure to chemicals other than dioxin among both groups. This is a good reason for including an additional plant with both exposed and unexposed chemical workers in the study. Job assignment records might then be used to construct an index of exposure to a number of chemicals in addition to those likely to be contaminated with dioxins.

Other suggestions, not included in this discussion, can be found among individual reviewers' comments.

AOWG Science Panel
Meeting - May 29, 1984 170 A 10 AM

Vernon N Houk	CDC/PHS/HHS	236 4166
LtCol Robert Capell	AF/SGES	767-5078
Miriam Davis	OASH	245-6301
Han Kang	VA/AOPO	389-5534
Lawrence B. Hobson	VA/AOPO	389-5534
Lynne Moody	NIOSH (IWSB/DSHEFS)	684-4207
Marilyn Fingerhut	NIOSH	684-4207
D Rall	NIEHS	8-629.3201
Peter A. Flynn	OASD(HA)/DoD	697-8973
Don Barnes	EPA	382-2897
Douglas L. Clark	Army	653-1829
Dick Christian	Army	653-1828
Rob Lipnick	Army	653-1866
Carl Keller, Chair	NIEHS	496-3511
[illegible]	Comair	576-1414
Michael Gough	OTA	226-2070

Individual Reviewers'

Comments on "Draft Protocol for a Mortality Study of Workers Exposed to Dioxin"

Reviewer #1

I have reviewed the two epidemiological research protocols for studies of occupational exposure to dioxin. Both are meritorious and needed. The mortality study, which is already in progresss, unquestionably warrants additional funds for completion. I concur with the previous reviewers of this study.

Reviewer #2

The investigators have already assembled a cohort of workers possibly exposed to a chemical(s) which has no commercial value and for which no records exist. There seems to be every reason to compare mortality experience of this group with an appropriate comparison group given the known high toxicity of the chemical under consideration and the length of follow up which can be achieved--now and in the future.

Several matters of concern may improve the usefulness and interpretation of mortality and other studies based on the Dioxin Registry included in the Protocol for a Mortality Study. Primary among these is a method for assigning exposure status to members of the cohort. While it is clear that the investigators are attempting to do this, there is little in the protocol to indicate how or even whether this can be done. It may not be possible to make such an estimate for every member of the Registry, but for those which can be so assigned, this should become part of their record(or at least some estimate of relative exposure). As suggested by other reviewers, this should probably not be based on the presence of chloracne, but rather "tested" by the rate or severity of chloracne.

Another item is the choice of the U.S. population mortality rates for comparison. This will certainly confound the healthy worker effect which was found, for example, in the Project Ranch Hand II Mortality Results. Unless more appropriate comparison mortality rates are used, it becomes even more important to use internal comparisons--and thus estimate at least relative exposure among different groups in the cohort.

The Investigators should be complimented for the difficult job already accomplished. Further suggestions for improving these studies are expected to be continuing activities and will depend on the collection of information already underway.

Reviewer #3

1. The draft protocol for the above study, the "Description of the Dioxin Registry Sites," the accompanying memoranda and the reviewers' comments were examined by . The draft protocol was prepared in late 1982 and undoubtedly has been modified since then. Our comments, therefore, may be outdated and our suggestions may well have been taken before they were made.

2. The study proposes to compare the number of deaths in the exposed workers to the expected number of deaths generated from U.S. mortality rates for 89 causes of death including soft tissue sarcoma. This is, of course, the usual modified life table method for analysis of data on mortality. Although it is not described in the draft protocol, the author recognized elsewhere the pitfall of using death certificate information for a mortality study, especially soft tissue sarcoma. It is well known that a substantial portion of the soft tissue sarcoma deaths coded on the death certificates were not confirmed by hospital records (Percy et al, 1981). In light of this problem of misclassification of disease and lack of readily accessible mortality data from industrial population (e.g., age, sex, race, calendar year, and cause -- specific mortality data), it is desirable to have an additional comparison group developed from an industrial population. There may be practical reasons (legal, logistic, budgetary) for not pursuing this. But if the author plans to review the hospital records or pathology of cancer deaths, it is necessary to apply the same criteria to the comparison group in order to improve the comparability.

3. No mention is made of going beyond the death certificate to determine the cause of death. It certainly would be advisable to confirm the reported causes at least by review of the medical records. Russell emphasizes the need for confirmation of the diagnosis of soft tissue sarcoma by recognized experts. This would avoid false positives. We suggest that an expert pathologist review tissues and/or slides from any malignancy that is not clearly a carcinoma. This would reduce the chances of false negatives and would provide confirmation for the diagnosis of malignant lymphoma as well. Pathology reviews would also provide classification by tissue type with little extra effort.

4. It may be important to consider separately individuals exposed during, or as a consequence of, an explosion (p. 18, "third definition"). Both the intensity and the duration of exposure from these episodes would be very different from the chronic exposure to lower amounts of chemicals during manufacturing.

5. The necessity for determining the duration and level of exposure to 2,3,7,8-TCDD is emphasized in the protocol and in the reviewers' comments. The inaccuracies in attempting to do this are also recognized. Even the use of chloracne as an indicator of exposure (page 26) is questionable since other chlorinated organic chemicals also produce the skin changes (page 15) and the condition is often confused with acne vulgaris. One source of information about exposure may be used but is not specifically mentioned. Chemical engineers and production chemists are usually aware of details of the processes used, of the adequacy of controls and safety measures, and of the likelihood of exposure during operations.

6. As indicated by the author (p. 28) the power to detect outcomes of certain rare causes of death is inadequate. Unless the true risk of dying from soft tissue sarcoma, liver cancer, or stomach cancer is greater than four fold, the study may not be able to detect the excess.

7. Despite the unavoidable difficulties and limitations, the Dioxin Registry Mortality Study should yield valuable information on the effects of chemical exposure.

Reviewer #4

Considering the massive amount of data already accumulated and the urgent need to shed light on the soft tissue sarcoma relationship with dioxins, this member would recommend continued funding of the program to completion.

The following comments are provided with respect to the Draft Protocol and reviewer comments:

1. On page 18, lines 8-10, of the draft Protocol it states that if no record of assignment exists, but the primary production of the company was phenoxy acids or chlorophenol, all males will be considered as exposed. This may be a flawedassumption leading to a dilution of truely exposed persons especially when the worker was employed for a short period at that production facility. Similarly on lines 19-22 of the same page, it is stated that for two sites, incomplete records exist which only list a job title held at one point in time. In this case, the individual will be assumed to have held that job throughout the term of his employment with the company. In this assumption it would seem that an unusally long exposure time might result when such was in fact not the case. It would seem better to limit subjects to those in which we had valid employment records covering their entire period of employment.

2. On page 19, second paragraph states that an effort will be made to develop a model predicting probable levels of exposure for each type of worker. Factors in this model are then listed. This seems to be a very worthwile effort when one considers the great possible significance of this NIOSH study.

3. Page 20 of the Protocol contains a discussion of potential confounding exposures which may exist. It would improve the discussion by including the types of cancers produced in animals by the dichloro-isomer found in 2,4-D. The same comment applies to 2,4-D and MCPA and their effect on increasing the risk of cancer in humans. We agree with the concluding sentence on the page which states that potentially confounding exposures will be difficult to assess. Therefore, every effort should be made to obtain detailed employee work histories. Dr. Enterline in his comments of Dec. 14, 1982 shares in a manner our concerns in his comments numbered 1 and 5. His point of "never categories of exposure" covered in comment 6 also has merit because of the unusually low mortality rate of chemical workers.

4. The comments provided by Dr. Thomas J. Smith in numbered paragraph 2 states our concern very succintly with respect to any dose-response relationship for TCDD and cancer risk. Finding these highly TCDD exposed workers may be a difficult task.

5. In numbered comment 4, Dr. Smith clearly expresses a concern which we have shared regarding other isomers of dioxin being aggressive human carcinogens and that one or more of the other substances such as the herbicides might be synergists or antagonists of TCDD's action. We do not want to lump improper categories of exposure and end up with suspect results.

Reviewer #5

I understand that this study has been referred to, if not critically examinined, by the AOWG for a number of years. We all have the feeling that this study will be useful, but a review the documents provided to the Science Panel does raise some questions:

1. The extent of previous review is not clear. The documentation refers to a panel of 6 outside reviewers which was convened on Dec. 16, 1982, to receive and discuss comments and issues associated with a Dec. 1, 1982 draft. A March 23, 1983 memo summarizes this meeting, which is referred to as the "first" meeting. The memo also notes the unanimous agreement to meet again after the protocol had been modified. There is no indication as to whether or not these planned events actually occurred.
   The concern is how and whether the comments of these reviewers have been addressed. The reaction to a number of the comments could be critical to the final results.
   Is there a more current protocol than one we received?

2. Has any progress been made in handling the multiple comparison question? The study sets forth four diseases as hypothetically linked to "dioxin" exposure, and yet the protocol indicates that comparisons will be made on 89 causes of death.
   In animal studies researchers often use the Bonferroni correction factor when considering multiple comparisons. Would this not be appropriate in this case also?

3. Given that the power of the study to successfully test the hypotheses was admittedly very low, what prompted continuation of the study?

4. The protocol mentioned a July, 1985 review by the Special Peer Review Panel, which is presumably the panel of six who reviewed the Dec. 1979 protocol. What role is there in the review loop for the Science Panel and/or the oversight committee for the Ranch Hand Study? Given the import and impact that this study is likely to have, I would suggest that the AOWG be closely involved.

TAB B2

Individual Reviewers'
Comments on "Protocol for a Study of Persistent
Health Effects, etc." and Draft Protocol for
"Adverse Reproductive Outcome's, etc,"

Reviewer #1

The morbidity and reproductive outcome study is an ambitious and important project. The purpose is to perform a careful evaluation of workers who were occupationally exposed to dioxin. The reviews and the authors' response to the reviews have addressed all of my concerns which centered on type of control population, exposure indices, and confounding exposures. The authors do an excellent job of responding to the reviewers' comments.

I have little to add beyond what has already been written. First, I wish to know what is the status of the planned neurological testing. I believe that this aspect of the study is critical, particularly in light of the frequently reported neurological and behavioral changes in the Vietnam Veteran population. It is my suggestion that neurologists, rather than "neurologist-surrogates", be actively involved in the examination of the study population. Second, I would like to know what the authors mean when (in their response to reviewers) they write that, in the event that the study is abandoned because of poor participation rates, "an alternative 'public health survey' of workers who wish to be examined may have to be conducted, for public health and public credibility reasons."

Reviewer #2

The discussion of background information on possible health effects and the rationale for examination procedures are adequate, although a detailed discussion of how and where the examination will be conducted is lacking. This may have some relevance to participation rates.

The sample which appears likely to be available for study appears rather small. An important consideration is whether detectable biological and health differences between dioxin exposed workers and controls are likely to occur. It was of great concern during review of the Air Force Project Ranch Hand II Study whether twelve hundred Ranch Handers were sufficient to detect meaningful health differences. Perhaps some consideration should be given to the expected outcome of various test results and the possibility of expanding the cohort size by adding additional groups.

One of the variables which should be considered for matching has to do with employment history. Something like a healthy worker (or unhealthy non-worker) effect may be introduced if the comparison group has a sufficiently different employment experience. This would be in addition to possible chemical exposure effects which might be included among the controls. The investigators' discussion of the problems associated with the choice of various possible alternative control groups is welcomed but should be supplemented with the likely effect of the various alternatives including the use of neighborhood controls.

Reproductive Outcome

Although the stated objective of this study includes an assessment of spontaneous abortions and congenital malformations, a lack of medical confirmation of these events makes it unlikely that useful information will be obtained. For that information which can be derived from vital certificates, it is unlikely that wives need be interviewed at all. This study probably can best be incorporated into the Morbidity Study with only a slight modification involving more rigorous ascertainment of reproductive events and obtaining vital records.

Reviewer #3

1. In these comments, we consider the "Protocol for a Study of Persistent Health Effects in Chemical-herbicide Workers and in Community Residents of Unknown Exposure Status," dated April 1984 (referred to as "health effects protocol") and the draft protocol for "Adverse Reproductive Outcomes Among Chemical Herbicide Workers and Community Residents Participating in a Morbidity Study," dated March 1984 (referred to as "reproduction protocol"). The material submitted included the comments of prior reviews and the investigators' responses. It did not include the questionnaires, physical examination details, the clinical chemistry determinations, nor the ancillary tests to be performed. There may also have been revisions of the protocols to include some suggestions made here.

2. It is difficult, if not impossible, to form an accurate, comprehensive opinion concerning protocols for clinical-epidemiological studies when so much operational material is not available. I comment on the protocols with this reservation.

3. The health effects and reproduction studies share certain difficulties, including the likelihood that estimates of exposure to TCDD will be inaccurate and that the subjects will have been exposed to varying and often unknown amounts of other biologically active chemicals. The small sample size will also limit the significance of many negative findings. These difficulties beset all studies of phenoxy herbicides and dioxins that attempt to examine exposed individuals in detail.

4. The quality of the control group is debated by prior reviewers but the use of neighborhood cohorts remains questionable. A group of chemical workers not exposed to dioxin offers enough advantages to make it worthwhile to consider it as an alternate or an additional control cohort.

5. In the health effects study, major considerations center around particulars of the questionnaire, the manner of performing and recording the physical and psychological examinations, and the other tests. It is extremely important to confine the laboratory testing to meaningful determinations that are readily standardized, non-experimental, and detect significant abnormalities. The latter do not include well-known physiological variants, possible causal mechanisms for adverse effects that are not yet established, or changes known to be produced by common activities such as smoking, drug abuse, or dehydration. The testing will produce an enormous amount of data and the attempts to sort out confounders such as drug effects or dehydration can confound the statisticians.

3. Page 17 of the Protocol relates that production of phenoxyherbicides at the Missouri plant only took place for seven months (May-November) in 1968. This would seem to be a short term exposure period with many years following in which the workers could have had other work exposures and other effects such as from alcohol and drugs could assume importance. Therefore bias may be introduced from this small short duration sample of exposed workers.

4. It seems possible that the male member of the family could bring home on his body or clothing TCDD and/or dioxin contamination and thus could expose his wife indirectly. Hence why restrict conceptions to those after 11 weeks of employment. His wife could be pregnant when the husband went to work and we could have indirect gestational exposure of the wife.

5. It would seem that as Dr. Richard Hornung points out in his comments that a time-weighted exposure index would be very important if we expect to achieve valid results.

6. Reference the last paragraph of page 24 of the Protocol. Given that the estimates of sample size are crude with respect to conceptions which took place, why have the investigators not already considered the inclusion of other chemical plant sites in the NIOSH registry to make very sure that enough conceptions from exposed workers would be ensured to give results with the needed power?

Reviewer #5

1. Comments common to both protocols

a. The documentation supplied clearly lays out the comments of the reivewers and the investigators' reactions. Some questions may remain, but at least the issues are plainly presented.
It is still not clear, however, whether chlorance be used as an indication of exposure to 2,3,7,8-TCDD or not?
The response to comments suggests that the standardized fertility rates will not be used. The current protocol suggests that they will. This appears to be inconsistent.
The response to comments implies that the reproductive effects of dioxin will be repairable, but suggests that the enzyme induction may not be. Is there a basis for this apparent inconsistency?

b. Is the total amount ($2.036,000) being sought from Superfund? Does such a study fall under the Superfund rubric, since the populations under study are not associated with waste site exposures?

c. Given the acknowledged complexities/difficulties involved:
Limited populations
Problems of recall bias
The expense of the study
Problems with confounders at both plants
The length of time since exposure -- a likely advantage only in the case of cancer, which, itself, should manifest
itself in the Dioxin Registry Mortality study.
The question of comparability of referents
The multiple comparisonsissue
The ambiguities likely to be associated with any results
The lack of comparable populations for confirmatory studies
Problems in determining existence and extent of exposure
Reservations articulated by some of the reviewers
Etc.
it is questionsable whether the results of such a study can justify the expense, particularly in light of other (related,

2. Comments on the Morbidity Study
   a. Studies on nerve conduction velocity and measurements related to the immune system will be conducted. In the former case, apparently there are sufficient data that some investigators feel comfortable in saying that a test population is, or is not, within "normal" ranges. Can the same be said about the immunological measurements? What is one to make of any differences observed? For example, the famed Ward study and the work by Prince have been examined (to the limited extent possible), and there seems to be little one can infer from such results. Will the situation be any different in this study? It would seem that some fundamental research needs to done in this area before gathering additional data on a highly controversial subject that would both beg for, and defy, clear interpretation.
   b. Could the question of the PCB fingerprint be treated by a phased approach? That is, the GC/MS analysis would be done only if the enzyme patterns differed remarkably between the two groups.
   c. Reference is made to determining referent exposure status on the basis of questionaire data. Without seeing the questionaire it is difficult to determine whether this is likely to successful. Is the implication that the exposure status of the exposed group should also be determined from questinaire data "for reasons of comparability"? Taken literally, the approach does not seem reasonable for the exposed group, where employment records provide a more objective testimony.

3. Comments on the Reproductive Study
   a. It is unclear whether there are particular hypotheses being tested or not. Some of the commenters and the response to those comments suggest that the study is really a hypothesis generating study, rather than a hypothesis testing study. In such a case, the population size, power, etc. considertions are of less importance. And yet, the protocol seems to return to the idea of testing various hypotheses. Which is it?
   b. The high turnover rate, especially at Plant 01 (more than 70% of those in their "primary reproductive years" employed for less than 3 months), raises questions about attributing any observed effects to this particular chemical exposure; particularly for pregnancies which occur years later--perhpas after one or more successful pregnancies.
   c. The wives' telephone interviews will be conducted with the current wife. From a biological plausability point of view it would be the wife at the time of exposure that would have the greatest knowledge of the pregnancies of greatest interest. The protocol explicitly rules out such interviews. What are the implications for the study? What happens in the case of widowers? What would be the implications for the study if one of the groups had longer term marriages than the other; i.e., more "relevant wife" interviews than the other? Is sufficient information be gathered on the wives to detect possible problems there; e.g., congenital, familial, hereditary, etc. problems?
   d. The protocol treats "habitual aborters" (defined as 3 or more consecutive fetal losses) differently. Is this a generally agreed upon definition? Why not two consecutive losses? Why not three losses total? This definition might, in fact, be throwing out the most signficant evidence of a longer term effect.

6. No details are given about the data collection or the handling, processing and protecting of the information from disclosure. Quality control measures in these areas will be important because of the great numbers of data. The quality control will be especially important if the examinations are to be conducted by two sets of examiners, i.e., in New Jersey and Missouri.

7. The Ranch Hand investigators found that it was highly desirable to have a physician review directly with the subject or control the results of the health examination. This could be done by telephone if the persons are unable to return for their results when laboratory data are available.

8. The reproduction protocol introduces a number of methodological questions. It is possible to elicit very "sensitive" reproductive information during questioning by a physician. There would seem to be adequate reasons for including data about pregnancies caused by a man outside wedlock, about induced abortions whether legal or not, about sterilizing infections such as gonorrheal salpingitis, and about children born outside of wedlock. Details about impotence and the use of contraceptive techniques have been easy to obtain during medical questioning. In as much as these issues all bear on the question of fertility and reproductive failure they should be included. The confidentiality of the information must be assured, of course.

9. Consideration should be given to obtaining information from former wives and consorts.

10. Apparently no attempt will be made to confirm birth defects, late abortions or stillbirths by reference to hospital and pediatricians' records. Such confirmatory information has proved valuable if somewhat troublesome to obtain.

11. There have been few opportunities to study women who have been exposed to TCDD. The Registry contains at least 60 and it would seem advisable to examine all of them, especially with reference to possible reproductive effects. Indeed, this would be more valuable than the proposed study of the male workers since it was the women in Vietnam who claimed the most pronounced effects after exposure to Agent Orange. Further, there is no good evidence that male animals or men are reproductively abnormal as a specific effect of TCDD. The reproductive disturbance from TCDD in the laboratory has resulted from exposure of female animals.

Reviewer #4

The following comments are provided with respect to the Protocol for a Study of Persistent Health Effects in Chemical-Herbicide Workers and in Community Residents of Unknown Exposure Status:

1. On page 30 of the Protocol it states that the sample of exposed workers should be about 300 (this number includes 90% follow-up, an estimated 123 dead, and 75% of the remainder). Based on this assumption and the cost proposal total of $2,036,00 (includes inhouse and contract costs) we would have an exposed individual cost of $6,787.00 per person. This seems to be a very expensive study when so many potential unknowns enter into the real exposure of the worker to TCDD. Our concerns will be discussed in the following comments.

2. On page 28 of the Protocol there is a discussion of the fact that hexachlorobenze was manufactured until 1969 at the New Jersey plant and it is both a porphyrogen and a neurotoxin. Similarly ethylene oxide has been used at the Missouri plant for a number of years since 1971 and may potentially affect workers exployed at the plant after 1971. Ethylene oxide is known to have adverse reproductive effects and is a neurotoxin. Thus three of the effects to be surveyed in the dioxin exposed workers may also be affected by these two other chemicals. Why then have we not selected other plants and other worker groups as a basis for exposed workers? We seem to be asking for confounding effects with this cohort selection. Further, on page 21 of the Protocol, it states that there is no documentation of chloracne in the Missouri plant population and (on page 23) the statement is made that there is no other group of chemical workers in the local area with which a comparison can be made.

3. The Protocol discusses the estimation of exposure status on page 46. We fully agree with the first sentence which reads: "Estimation of exposure status will be difficult, since measurements of actual TCDD levels are rare or non-existent." Further on it states that chloracne can serve as an index of a given group's exposure level. We disagree as several other chemical compounds can cause chloracne and hence TCDD may not have been the cause of the condition. It would seem that true exposure variations including concentration and duration of exposure may be impossible to obtain because of the lack of or poor quality of the employment records as has been discussed in other parts of the Protocol. The results of the study may thus be subject to serious challenge especially if the findings are marginal in nature.

4. On page 49 of the Protocol, 1st paragraph it states that the investigators have decided to present the study not as one of dixoin exposure, but of workers exposed to chemicals and herbicides, using Agent Orange as an example, and of community residents. Why does Agent Orange have to be mentioned at all? The study will not measure the effects of Agent Orange as the workers were certainly not exposed to Agent Orange in its final formulation and dissemination manner. Will some of the subjects even know what Agent Orange is? Why not relate the study to chlorine containing pesticides and let it go at that?

5. No mention was found in the Protocol of any consideration of whether the exposed subjects or control subjects would be checked out for military service including servie in Vietnam. It would seem possible that some of these people may have been in military service and could have been exposed to Herbicide Orange while in the service. Similarly many of the control population could have used TCDD containing commercial weed killers on their farms or in their gardens. This might especially be the case in the controls around the Missouri plant which is in a farming area.

6. Page 51 of the Protocol provides a very truthful statement which is the basis of our concern for the expediture of so much money on so few possibly dioxin exposed persons. It reads as follows: "Finally, misclassification of exposure is a potential source of bias, which if not differentially distributed between exposed and unexposed groups will invariably bias results toward the null. If obtained job exposure records on referents is deemed unfeasible, which it almost certainly will be, then exposure status can only be based on questionnaire data when the exposed and referent groups are compared, again for reasons of comparability." (Underlining added by us).
The legal and political implications of the results of this study may be of great significance with respect to the effects of dioxin and more particularly TCDD exposure. Hence completion of a study based on questionable and even unreliable exposure data concerning TCDD concentration and duration may be a disservice to the Nation and its concerned population. We note that Dr. Brian MacMahon of the Harvard School of Public Health shares our view that these studies may be very difficult to carry out and it is very much a question in his mind whether the results will be credible (Comments of Nov 7,1983,para 1.). Dr. William O. Russell of North Ridge General Hospital in his comments of Dec. 14, 1983 points out that "An exposure index of time, job performed, and some knowledge of plant location contaminations are but approximations, and imaging of individual variations that could, on the one hand result in little or not true dioxin exposure for one individual, yet, on the other hand, be more than several times that expected for another. In the equating of results, separate evaluation would be indicated for only the chloracne individuals since this change would be reliable most probably to the longest time exposure."
This statement seems to further substantiate our concern for exposure variability and then finally falls back on chloracne as an idicator of choice. However, chloracne is not produced exclusively by TCDD.

7. Reference the last paragraph of Page 36 of the Protocol.
The Digit Symbol Test subscale of the WAIS measures only a few cerebral functions. The Halstead-Reitan or Luria-Nebraska are better measures of a variety of CNS dysfunctions.

The following comments are provided with respect to the Protocol entitled "Adverse Reproductive Outcomes Among Chemical Herbicide Workers and Community Residents Participating in a Morbidity Study":

1. Page 19, Paragraph 2, states that reproductive history interviews of ex-wives will not be conducted as they would be difficult to obtain. So the interviews may be difficult to obtain, these former wives may be the very spouses that had children from the workers at their highest point of exposure and most recent exposure. Not at least trying to conduct interviews of former wives would make the whole study suspect as very important exposure effects would never be found. The Protocol then points out at the bottom of page 20 that the validity of the father's interview data on previous marriages can only be evaluated if ex-wives are interviewed. So why do we not make a full and devoted effort to interview ex-wifes if we are going to have a credible study?

2. We share Dr. Renate Kimbrough's same concerns as expressed in numbered paragraph 2 of her review comments. We also feel that exposure is not defined very well and it is very possible that the dose received by different persons may very greatly and the time elapsed variations since exposure.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date June 1, 1984

From Carl A. Keller, Chair Pro Tem
Science Panel of the Agent Orange Working Group (Cabinet Council)

Subject Review of NIOSH Studies Based on the Dioxin Registry

To Vernon N. Houk, Assistant Administrator
Agency for Toxic Substances and Disease Registries

Pursuant to your request of May 9 and with instructions from the Chair of the Agent Orange Working Group, the Science Panel met on May 29, 1984, to review protocols for Mortality and Morbidity Studies of Workers Exposed to Dioxin which have been prepared by the National Institute for Occupational Safety and Health (NIOSH). These studies are based on an already identified Dioxin Registry Cohort which includes workers from 13 chemical production facilities in the United States, and who are known to have been exposed to pentachlorophenol or trichlorophenol and its derivatives over the past 40 years.

Members of the Science Panel unanimously agreed that the Mortality Study, which will ascertain the fact and cause of death for all deceased members of the Registry, should proceed as designed and should be updated on a periodic basis. The investigators at NIOSH are strongly encouraged to continue to develop a quantitative exposure index based on available records for all of the identified members of the Dioxin Registry Cohort.

The Morbidity Studies propose to measure current health status and reproductive outcome histories for several hundred workers from two of the facilities included among those in the Registry. These data will be compared to similar measurements on a group of unexposed persons matched for age, sex, race and current neighborhood of residence. The two facilities to be studied were chosen because of local interest in the possible health effects of dioxin exposure as well as the fact that they comprise a group of workers who may have been among the most heavily exposed individuals in the country.

Members of the Science Panel pointed out some of the difficulties in conducting this study, particularly in the recruitment of appropriate comparison subjects, the collection of adequate information on reproductive outcomes and the interpretation of results where there is possible confounding with other chemical exposures. However, the Science Panel as well as NIOSH staff recognize the importance of studying this highly exposed group and recommend that the investigators continue their efforts. Results from the proposed pilot study are expected to resolve some of the difficulties, and as part of its review, the Science Panel is preparing detailed comments and suggestions for the NIOSH investigators which may be useful in conducting the proposed studies.

cc:
Dr. Edward N. Brandt, Jr.
Dr. Marilyn Fingerhut