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attachment A

SUBCOMMITTE ON RESEARCH AGENDA

REPORT TO THE AGENT ORANGE WORK GROUP (AOWG)
Dec. 15, 1982

BACKGROUND

As a result of discussions at AOWG meetings, the AOWG acting chair appointed a subcommittee in June, 1982 to investigate the question of "a research agenda for federal research on long-term health effects of [Agent Orange]". (See attachment A for text of original charge and subsequent modifications.)

The subcommittee held three formal meetings, summaries of which constitute Attachment B.

This report summarizes the position of the subcommittee vis a vis the items in the charge. The summaries of the meetings of the subcommittee contain further insights into our outlook, together with specific suggestions for a research agenda which, we believe, should address the following questions:

A. Where are we?
B. Where do we want to be at some future time?
C. What needs to be done to get from A to B?

CONCLUSIONS REGARDING ISSUES RAISED IN CHARGE TO SUBCOMMITTEE

1. There is a need for a research agenda of Federal activities directed at resolving the issue of alleged connections between exposure to Agent Orange exposure in Vietnam and adverse health effects.

   Rationale

   This need arises from

   a. The complexity of the problem
   b. The number of research projects--in progress or planned
   c. The cost of these projects--both visible and hidden costs
   d. The limited resources available

2. The development of a research agenda is feasible.

   Rationale

   a. As one of its first actions, the Science Panel of the predecessor of AOWG issued an interim research agenda (Attachment C), demonstrating the feasibility.
   b. It was pointed out that developing a full-blown research agenda can be a large, time- and resource-consuming exercise. Such has indeed been the case in instances in which detailed analysis and careful directions have been given. For the AO situation, however, the subcommittee envisions something of a more

general nature which would, like the first interim agenda, provide descriptive guidance, rather than prescriptive detail. Areas would be identified that require additional information; and in some cases, suggestions might be included as to how that information might be gathered. Such an approach would not be costly in terms of time or resources.

c. In fact, the elements of the agenda already exist.
   i. The Science Panel has written one some time ago, portions of which are still relevant. (See annotations on Attachment C.)
   ii. Attachments D1 and D2 is a draft analysis of the on-going research that constitutes the present, operational agenda.
   iii. Attachments E1 and E2 are examples of what some other groups conceive an agenda to be.

3. The purpose of a research agenda is to serve as guidance document and point of reference for AOWG, Congress, the states, and the public.

Rationale

a. As mentioned above, the research agenda envisioned by the subcommittee would be descriptive, not prescriptive. It would be a document that would evolve over time and would be the subject of continual review by AOWG. At the same time, however, it would serve as a somewhat steady compass bearing, by which the many possible activities of AOWG and others could be evaluated.

b. Such an agenda would serve to articulate succinctly the thrust of Federal efforts and provide a gauge by which progress could be measured.

c. Broad distribution of the agenda would serve to catalyze communication on a substantive level with Congress, the states, and the public.

4. The scope should be sufficiently broad to assure collection of information needed to resolve the central issue: What is the alleged connection between exposure to Agent Orange in Vietnam and adverse health effects?

Rationale

While there is probably no limit to the number of health effects which might be alleged in connection with Agent Orange exposure, it is probably too early to limit the areas of investigation. In fact, establishing the specific health effects of concern might well be a part of an agenda.

5. A possible form of an agenda is included in Attachment F.

Rationale

The subcommittee recognized its own limitations in

the area of developing a formal research agenda to deal with the issue. However, the members felt that it would be important to submit a "straw man" to serve as a point of discussion; hence, Attachment F.

What is missing at this stage is a narrative link between (a) the final goal ("Resolution of the alleged connection between exposure to AO in Vietnam and advverse health effects") and (b) each element of the agenda. In any final agenda such links should be clearly articulated as a way of justifying inclusion of each element in the agenda.

6. The agenda would be useful in a number of important areas.

Rationale

a. This item is addressed in a number of the rationales for previous points.

b. The states are becoming increasingly active actors in the scientific arena. An agenda would serve to inform them of the areas that should be addressed. By comparing the list of on-going Federal (and, hopefully, state projects (see Recommendation B below)) with their own resources and capabilities, the states are more likely to contribute in a positive, and perhaps unique, way to the overall effort.

7. At this stage, there is no need to establish priorities within the research agenda. In addition, it would not be feasible to do so.

Rationale

a. As mentioned above, the agenda should provide guidance, not directives. The complexity of the issue is sufficient that it counsels against definitive statements. There is room for innovative approaches which might not be envisioned by a central group.

b. Many of the agency projects which impact on the AO issue are, in fact, parts of efforts directed at other questions of programmatic importance to the agencies themselves. Setting priorities might inadvertently reflect poorly on good projects which are being conducted primarily for other purposes. Consequently, the setting of priorities could be a stressful exercise and simply not worth the effort.

RECOMMENDATIONS

The AOWG, through its Science Panel, should take the lead (either directly or by delegating to some other agent) in

A. Assembling "one-pagers": brief, technical descriptions of current Federal research projects related to the mission of AOWG.

B. Serving as an exchange point for information on the progress of AO-related research at the state, Federal,

and international level.

C. Developing, publicizing, evaluating, and updating a research agenda directed at resolving the issue of the connection between exposure of Agent Orange in Vietnam and adverse health effect. As a first step in this direction, the Science Panel could appoint a small subcommittee to prepare a draft agenda for review by the entire Panel in January.

Donald G. Barnes, Chair
Jerome G. Bricker
Phillip G. Brown
Lawrence B. Hobson
Phillip Kearney
Carl Keller

THE MISSION OF THE SUBCOMMITTEE

Original Charge (June 11, 1982)

The AOWG Research Subcommittee is charged with assessing the need for, and the feasibility of, preparing a research agenda for federal research on long-term health effects of phenoxy herbicdes. The subcommittee will examine the purpose and scope of such an agenda, the possible forms such an agenda might take, and how it might be useful to scientists and policy makers. The subcommittee is also charged with assessing the need for, and the feasiblity of, establishing research priorities in this area. The sub committee is asked to report to the AOWG by August, 1982.

Subsequent Modifications

At the July meeting AOWG indicated that the concern of the subcommittee should be limited to Agent Orange, with an emphasis on its use in Vietnam.

Further communications with AOWG indicated that the subcommittee should take steps to develop an agenda.

ATTACHMENT B

SUMMARY OF THOUGHTS/ACTIVITIES FROM
OF RESEARCH AGENDA SUBCOMMITTEE MEETINGS

June 30,1982

1. There is a need to focus research on those topics that will generate data useful in making a decision on the AO/Vietnam problem. This does not mean that research must be limited to veteran populations.
2. There is not a limitless source of funds somewhere to support research related to this problem.
3. A clearly articulated research agenda would serve as a constant point of reference for AOWG, the Congress, et al and could serve to focus efforts of the states.
4. There needs to be some group that maintains a continual monitoring and updating of any research agenda.
5. The experience of the group which dealt with low level radiation suggests that the agenda simply be a widely circulated set of recommendations that are continually reviewed and updated; i.e., no attempt made to direct research resources or activities.
6. A research agenda should be derived from a consideration of
    a. Where we are
    b. Where we want to be at a giveng time
    c. What needs to be done to get us there
7. In accordance with our charge we will focus on item 6a.

Homework: Classify on-going research activities. Identify gaps.

August 30, 1982

1. VA has done a fine job of classifying human, laboratory, and other studies which have been identified by AOWG. Some small errors should be corrected.
2. There is a need for more definitive information on each of these studies; e.g., a succinct scientific summary, together with the name and telephone number of a person to contact for more details and update information.
3. Previous groups have examined the larger chlorinated dioxins and phenoxy acid question. We should compare their research recommendations with current activities.

Homework:
- a. Obtain from the individual agencies the information called for in 2. Enlist the assistance of AOWG.
- b. Review research recommendations from such groups as
    - i. The Second International Symposium on Chlorinated Dioxins and Related Compounds
    - ii. The VA literature survey report.

December 8, 1982

1. It was reported that representatives of state AO efforts would like to have brief, but somewhat technical, discussions of individual research projects. This exercise would ideally include projects at the state, as well as Federal, level. The representatives indicated a need for a coordinating body to serve as a focal point for information exchange, updates, overall perspective, etc.
2. The group's deliberations followed the outline of item 6 in the June 30, 1982 meeting:
   a. Where we are
      i. After some modifications, the VA analysis of on-going Federal research will serve as a good thumbnail summary of activities.
      ii. The VA analysis needs to be supplemented by semi-technical "one-pagers" which will provide the interested technical observer/participant with relevant details on the projects and the name and number of a specific contact for each project.
      iii. Some group needs to have the responsibility of remaining current all of these projects. That group would serve the vital function of coordination through communication, rather than through control.
   b. Where we want to be at a given time
      i. The group decided that the research mission associated with the AOWG effort could be summarized in the following way:
         To resolve allegations on the connection between AO exposure in Vietnam and adverse health effects.
      ii. The question of timing should be addressed.
   c. What we need to do to get use there
      i. In the short time remaining during the meeting the group came up with the following ideas:
         (a) Establish the existence of any links between AO exposures and adverse health effects
         (b) Quantitatively investigate aspects of the exposure question; e.g.,
            (i) Estimate maximum likely exposures in Vietnam.
            (ii) Use simulation exercises to augment estimates.
            (iii) Investigate absorption of toxicants from various routes of exposure.
            (iv) Investigate degradation of toxicants under Vietnam-like conditions.
            (v) Compare possible Vietnam exposures with those resulting from any background levels of toxicants in the US.
         (c) Analytical chemistry
            (i) Develop agreed-upon protocols for

analsyis in various matrices.

(ii) Gather the information on the background of toxicants in the US environment and population for comparisom with similar values in Vietnam veterans.

Recognize the need to link these activities closely with those in (a) so that some sort of answer can be provided to the "So what?" question.

ii. Research suggestions from the VA literature search report and the from the 2nd International Symposium on Chlorinated Dioxins and Related Compounds were distributed to stimulate further ideas.

iii. The group reviewed the original Interim Research Agenda of the WGILTHEPAHTC (!) (attached). Each item on that agenda was reviewed as to its current relevance and status.

3. The group decided that a draft report will be presented to AOWG at the Dec. 15 meeting. The report will follow the outline of 2, immediately above. In addtion, it will include a recommendation that the Science Panel adopt a strong role in designing, monitoring and coordinating a research agenda which will accomplish the mission set before us.

Homework:

a. The subcommittee members should look over the distributed materials to find items they would recommend adding to an agenda.

b. The subcommittee chairman will draft the report to the AOWG and will distribute it for comments, additions, deletions on Monday, Dec. 13.

INTERAGENCY WORKING GROUP TO STUDY THE POSSIBLE LONG-TERM HEALTH EFFECTS OF PHENOXY HERBICIDES AND CONTAMINANTS

INTERIM RESEARCH AGENDA

Still relevant, in 1982.

I. Sources of Exposure

1. Identify chemicals known to be contaminated with TCDD, TCDF, other dioxins and dibenzofurans. No

2. Determine the stages in the production process at which contamination occurs. No

3. Quantify the magnitude of contaminant levels. No

4. Consider the significance of other means of dioxin or dibenzofuran formation. No

Concern is only AO + this info is known for AO

II. Chemical Analyses

1. Determine the quantitative and qualitative reliability of methods, including human tissue analysis. Yes

2. Estimate the quantitative limits of detection required in analyses of selected samples. Yes

3. Determine the analytical standards required and procedures for their procurement. No

Concern is only 2,3,7,8-TCDD + standard is already available

III. Human Health

1. Accidental or Occupational Exposures

A. Evaluate the adequacy of ongoing or completed studies in assessing toxicities associated with exposures. Yes

B. Attempt to obtain more current information on health status of individuals involved in previous U. S. and foreign exposures. Yes

2. Characterization of the Disease

A. Determine the symptomology and clinical findings consistently associated with exposure. Yes

B. Identify the toxicity parameters that may be associated with exposures. Yes

C. Adjust the time frame from exposure that toxic symptoms appear and persist. Yes

D. Consider whether dose response parameters can be developed. Yes

3. Vietnam Veterans

A. Collate the alleged disease parameters. Yes?

B. Assure that epidemiology study designs will assess possible increases in alleged disease patterns, disease parameters associated with occupational or accidental exposures and selected toxicity parameters identified in laboratory toxicity experiments. Yes

C. Review ongoing or completed activities, i.e., Ranch Hand; selection of appropriate ground troop population; tissue analyses, etc. Yes

D. Determine the most reliable or acceptable means of presuming herbicide exposure: Yes

E. Consider the significance of herbicide and contaminant exposure of military personnel not stationed in Vietnam. Yes

IV. Laboratory Toxicology

1. Collate the comparative toxicity data for the dioxins and dibenzofurans; identify data gaps. No?

2. Consider comparative studies that correlate dose and duration of exposure with sequential development of toxic symptoms. Yes

3. Reevaluate chemical disposition data as to adequacy. Huh?

tember 7, 1982

FEDERALLY SPONSORED HUMAN STUDIES RELATED TO AGENT ORANGE

NCY	TYPE OF STUDY					STATUS		
STUDY TITLE	Mortality	Morbidity	Cancer	Reproduction	Analytical	Completed	Ongoing	Estimated Completion Date
ERANS ADMINISTRATION								
'A Epidemiologic Study of Ground :roops Exposed to Agent Orange uring the Vietnam Conflict	X	X	X	X			X	1987
/ietnam Veteran Mortality Studies	X						X	Late 1984
/ietnam Veteran Identical Twin Studies		X		X			Protocol	Initial 1984
Survey of Patient Treatment File for Vietnam Veteran In-patient Care		X	X				X	Initial 1983 Survey
Agent Orange Registry Examinations		X	X				X	Indefinite
TCDD in Body Fat of Vietnam Veterans and Other Men		X			X	X		Publication Preparation
Retrospective Study of Dioxins and Furans in Adipose Tissue of Vietnam-Era Veterans					X		X	198
:PARTMENT OF DEFENSE								
Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicide Orange (Air Force Health Study)	X	X	X	X			X	Baseline 198 Complete 199

FEDERALLY SPONSORED HUMAN STUDIES RELATED TO AGENT ORANGE

CY	TYPE OF STUDY					STATUS		
TUDY TITLE	Mortality	Morbidity	Cancer	Repro-duction	Analytical	Completed	Ongoing	Estimated Completion Date
RTMENT OF DEFENSE								
med Forces Institute of thology Agent Orange gistry of Vietnam Veteran opsy Tissues			X				X	Indefinite
RTMENT OF HEALTH AND AN SERVICES								
C Birth Defects and litary Service in etnam Study				X			X	Late 1983
IOSH Dioxin Registry	X	?	X	?			X	Indefinite
IOSH Establishment and intenance of an International gister of Persons Exposed to enoxy Acid Herbicides and ntaminants	X		X				X	Indefinite
IOSH Soft Tissue Sarcoma nvestigation			X				X	Indefinite
CI Case Control Study of mphoma and Soft Tissue Sarcoma			X				X	Indefinite
CI Study of Mortality Among esticide Applicators from lorida						X		Publication in Press

FEDERALLY SPONSORED HUMAN STUDIES RELATED TO AGENT ORANGE

NCY	TYPE OF STUDY					STATUS		
STUDY TITLE	Mortality	Morbidity	Cancer	Repro-duction	Analytical	Completed	Ongoing	Estimated Completion Dat
PARTMENT OF HEALTH AND MAN SERVICES								
NIOSH Investigation of Leukemia Cluster in Madison County, Kentucky Allegedly Associated with Pentachlorophenol Treated Ammunition Boxes			X			X		Publications i Press
VIRONMENTAL PROTECTION AGENCY								
Report of Assessment of a Field Investigation of Six-Year Spontaneous Abortion Rates in Three Oregon Areas in Relation to Forest 2,4,5-T Spray Practices				X		X (Published)		
National Pesticide Monitoring Project of Human Adipose Tissue					X		X	Indefinite (Annual Repor
PARTMENT OF AGRICULTURE								
A Case Control Study of the Relationship Between Exposure to 2,4-D and Spontaneous Abortions in Humans				X		X		

FEDERALLY SPONSORED HUMAN STUDIES RELATED TO AGENT ORANGE

ENCY	TYPE OF STUDY					STATUS		
STUDY TITLE	Mortality	Morbidity	Cancer	Repro-duction	Analytical	Completed	Ongoing	Estimated Completion Da
PARTMENT OF AGRICULTURE								
Exposure Measurements of Mixers, Loaders and Applicators of 2,4-D on Wheat					X		X	198
Exposure of Forest Workers to Ground Applications of 2,4-D					X		X	198

September 7, 1982

FEDERALLY SPONSORED LABORATORY STUDIES AND LITERATURE SURVEYS RELATED TO AGENT ORANGE

AGENCY	TYPE OF STUDY				STATUS		
STUDY EFFORT	Animal	Environmental	Analytical	Literature	Completed	Ongoing	Estimated Completion D
VETERANS ADMINISTRATION							
Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins				X	Published 1981		Annual Updat Approved
Urinary 6-Hydroxy Cortisol: Physiological and Pharmacologic Studies (Including Agent Orange)	X					X	19
Effect of TCDD on Lipid Metabolism	X					X	19
Mechanisms of Dioxin Induced Toxicity Using the Chloracne Model - Phase I	X				X		Publication press
Behavioral Toxicity of An Agent Orange Component 2,4-D	X					X	19
Effects of 2,3,7,8-Tetrachloro-dibenzodioxin on Hepatobiliary Function in Animals	X					X	19
Mechanism of TCDD Absorption and Toxicity on Lipid and Lipoprotein Metabolism	X					X	19
Metabolism of the Herbicides Present in Agent Orange and Agent White	X					X	19
TCDD Exposed Rhesus Monkeys: Effects on Behavior and Stress Hormones	X					X	19
Neuromuscular Toxicity of Agent Orange	X					X	19

FEDERALLY SPONSORED LABORATORY STUDIES AND LITERATURE SURVEYS RELATED TO AGENT ORANGE

ENCY	TYPE OF STUDY				STATUS		
STUDY EFFORT	Animal	Environmental	Analytical	Literature	Completed	Ongoing	Estimated Completion D
ETERANS ADMINISTRATION							
Mechanisms of Dioxin Induced Toxicity Using the Chloracne Model - Phase II	X					X	19
Effects of Low Dose TCDD on Mammalian Chromosomes and Liver Cells	X					X	19
Mechanism of Porphyria Caused by TCDD and Related Chemicals	X					X	19
Effects of Agent Orange on Sleep	X					X	19
JEPARTMENT OF HEALTH AND HUMAN SERVICES							
Bioassay of Octachlorodibenzo-p-dioxin	X					X	
Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in Swiss Webster Mice	X					X	
Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in Osborne-Mendel Rats and B6C3F1 Mice	X				X		
Bioassay of a Mixture of 1,2,3,6,7,8- and a Mixture of 1,2,3,6,7,8-Hexachlorodibenzo- p-dioxins for Possible Carcinogenicity	X					X	

FEDERALLY SPONSORED LABORATORY STUDIES AND LITERATURE SURVEYS RELATED TO AGENT ORANGE

ENCY	TYPE OF STUDY				STATUS		
STUDY EFFORT	Animal	Environmental	Analytical	Literature	Completed	Ongoing	Estimated Completion Da
PARTMENT OF HEALTH AND HUMAN SERVICES							
Comparative Species Evaluation of Chemcial Disposition and Metabolism of 2,3,7,8- Tetrachlorodibenzofuran (TCDF) in Rat, Monkey, Guinea Pig and Two Strains of Mice	X					X	
Neurotoxicity of 2,4-D in Rodents	X				X		
Studies of the Chemical Disposition and Metabolism of Octachlorodibenzodioxin (OCDD)							X
Effects of Agent Orange Components on Male Fertility and Reproduction	X				X		
Mutagenicity Studies of TCDD, 2,4-D; 2,4,5-T and Esters of 2,4-D and 2,4,5-T	X					X	
Implications of Low Level Exposure to Dioxins	X					X	
Mechanisms of Toxicity of the Chlorinated- p-dioxins	X					X	
Research Toward Understanding the Molecular Level Mechanisms of Toxicity of TCDD and Related Compounds	X					X	
Synthesis of Selected Tetrachloro-dibenzo-p-dioxins and Related Compounds as Analytical Standards			X			X	

FEDERALLY SPONSORED LABORATORY STUDIES AND LITERATURE SURVEYS RELATED TO AGENT ORANGE

ENCY	TYPE OF STUDY				STATUS		
STUDY EFFORT	Animal	Environmental	Analytical	Literature	Completed	Ongoing	Estimated Completion Da
PARTMENT OF HEALTH AND HUMAN SERVICES							
Matrix Effect and Sub Parts-per-billion Quantitative Analysis of TCDD by Mass Spectrometry - With Special Reference to Milk	X		X			X	
Toxic Actions of Tetrachloroazobenzene Dioxins	X					X	
Xenobiotic Induction of Pleiotropic Responses in Liver	X					X	
Molecular, Biochemical Actions of Chlorinated-p-dioxins	X					X	
Mechanism(s) for Toxicity of Chlorinated Dibenzodioxins	X					X	
VIRONMENTAL PROTECTION AGENCY							
Evaluation of Large Scale Combustion Sources		X	X			X	
Evaluation of Municipal Waste Combustors		X				X	
Bacterial Decomposition of TCDD		X				X	
Investigation of Bioavailability to Fresh Water Fish of TCDDS in Fly Ash	X	X				X	
Analysis of Environmental Samples for PCDDs and PCDFs		X	X			X	

tember 7, 1982

FEDERALLY SPONSORED LABORATORY STUDIES AND LITERATURE SURVEYS RELATED TO AGENT ORANGE

NCY	TYPE OF STUDY				STATUS		
STUDY EFFORT	Animal	Environmental	Analytical	Literature	Completed	Ongoing	Estimated Completion Dat
ARTMENT OF AGRICULTURE							
urvey of Phenoxy Herbicide Use by gricultural Commodity				X		X	
urvey of Phenoxy Herbicide iterature				X		X	Annual Biblio-graphies Published
hotolysis of 2,4,5-T			X			X	
iological and Economic Assessment of ,4,5-T and Silvex				X		X	
CDD Residue Monitoring in Deer	X	X			X		Report in Preparation
ARTMENT OF DEFENSE							
nvironmental Chemistry of erbicide Orange and TCDD		X	X			X	Indefinite

From VA Lit Survey. Vol I.

occur among spray operators and RANCH HAND aircrews (Young et al., 1978; GAO, 1979b), little can be said about the quantity and quality of such exposures.

Many variables alter the rate of absorption of 2,4,5-T by workers. Some of these factors, including type of occupation, rate of spraying, type of protective clothing, and rates of absorption by both dermal and inhalation routes, were considered in developing a model for estimating potential dosages of 2,4,5-T absorbed by workers (RPAR Assessment Team, 1979). The Assessment Team used several different values for each parameter, based on assumptions regarding the conditions of exposure. They then performed exposure assessments for occupational situations. However, Lang (1978) has challenged some of the assumptions used by the RPAR Assessment Team to calculate their exposure assessment, including the extent of skin exposure and dermal absorption rates. Nisbet (1980) has also presented estimates of human exposures in the general population. Since the assumptions used for these exposure assessments apply to occupational use of herbicides, but not military use, the results are not necessarily related to assessments of potential exposure in Vietnam.

The General Accounting Office (1979b) further attempted to estimate troop deployment in spray areas, and aborted missions and dumped herbicide cargos have also been reported. Once again, it is apparent that ground troop exposures occurred in Vietnam, but it is beyond the scope of this report to attempt to assess the magnitude and duration of such exposures; this work must be carried out by others.

1.4 CONCLUSIONS AND GAPS IN CURRENT KNOWLEDGE

This section presents summary statements of the conclusions supported by the available literature and gaps in current knowledge identified during the literature review. These summary statements are arranged by topic areas addressed in subsequent chapters of this report:

- Metabolism
- Human exposure to TCDD
- Acute toxicity
- Subacute and chronic toxicities
- Reproductive toxicity
- Mutagenicity
- Carcinogenicity.

1.4.1 Metabolism (Biodynamics and Biotransformation)

Conclusions

- Pharmacokinetics of 2,4-D and 2,4,5-T in humans have been described.

- Both 2,4-D and 2,4,5-T are cleared rapidly from the blood after they are absorbed, with half-lives for plasma clearance in humans of 12-23 hours.

- Both compounds are excreted by the kidney primarily as the unmetabolized compounds.

- Renal clearance rates for phenoxy acids in animals decrease at high doses that cause nephrotoxicity and saturate the renal transport system.

- The clearance rate of 2,4-D in humans decreases when the urinary pH is low.

- Neither 2,4-D nor 2,4,5-T has been shown to accumulate in animal fat.

- Both compounds reach fetal tissues after they are administered to pregnant animals.

- TCDD is cleared slowly, with half-lives for body clearance of 2-3 weeks in animals.

- TCDD undergoes biotransformation and the metabolites are rapidly excreted in bile.

- TCDD is retained in the liver of the rat, a species that shows an hepatotoxic response to TCDD, to a far greater extent than in the livers of two other species which do not show liver lesions after TCDD administration.

- Diquat is absorbed by the lung, but is not retained in the lung and is rapidly cleared by animals.

- Free radical formation does not appear to be diquat's mechanism of toxicity under conditions of normal oxygen tension.

- Diuron and bromacil undergo biotransformation prior to excretion; diuron is excreted by the kidney.

TCDD Enzyme Induction and Receptor Binding

- TCDD is a potent inducer of various microsomal enzymes; the induced enzymes show elevated levels over a long period of time.

- In certain strains of mice, TCDD binds to a cytosol receptor, the gene product of the Ah locus.

Gaps in Information

Information on the following topics is incomplete or missing in the literature reviewed for this analysis:

- Patterns of biotransformation, distribution, and excretion of TCDD in humans
- The chemical structures of TCDD metabolites in bile
- Differences in distribution and biotransformation of TCDD for a wide range of species
- Differences in TCDD-receptor binding capacity and extent of enzyme induction in a wide range of species
- Pathways for the biotransformation of cacodylic acid and the relative importance of each pathway
- Biodynamics, including pathways and rates of elimination in humans or animals for: bromacil, picloram, dalapon, monuron, tandex.

1.4.2 Incidents of Human Exposure to TCDD

Conclusions

- Chloracne is the most consistently reported health effect of TCDD exposure in humans; in severe cases, chloracne has lasted for 28 years; milder cases have gone undetected or have disappeared in less than a year.
- Neurasthenia, a series of subjective complaints including irritability, fatigue, and insomnia, has been reported after many industrial accidents and exposures; in 1 instance these complaints occurred in the absence of chloracne; a 2-year latency period between TCDD exposure and the onset of neurasthenia has been reported.
- Other neurological disorders (as peripheral neuritis) and hepatic disorders (as hepatomegaly) have been reported after several of the incidents.
- The earlier accidents and exposures were associated with a wider variety of symptoms and more severe symptoms than the later incidents.
- Porphyria cutanea tarda and gastrointestinal problems have not been commonly reported and seem to be associated with long-term exposure.
- An increased risk among exposed people has not been established in mortality studies; increases in any particular cause of death has not been observed for more than 1 study group, so far.

- No data have been systematically collected for a clearly defined study group from Vietnam; health effects are usually claimed by individuals, without documentation by health professionals; exposure to herbicides in Vietnam (and potentially TCDD) is presumed in these studies and exposure levels are unknown; these data have not been compared to any control groups, in general; and symptoms reported often have been nonspecific and may be associated with other factors present in combat situations.

Gaps in Information

The following information is missing from most accounts of human exposure to TCDD.

- The number of exposed people who were not affected
- Health status of exposed workers that did not develop chloracne
- Incidences of conditions other than chloracne and comparison of these data with data from control groups
- Standardization of methods of evaluating symptoms of neurasthenia for purposes of comparison among different studies
- Conditions that could be detected by the examination methods used, but which did not occur (especially for conditions reported in other incidents)
- Sufficient mortality data for analysis (due to the short period of time that has lapsed since some of the incidents occurred and the relatively small number of workers exposed)
- Exposure levels
- Human health effects from use of defoliants in Vietnam have not been systematically documented.

1.4.3 Acute Toxicity

Conclusions

- For both 2,4-D and 2,4,5-T, the single oral dose lethal to 50 percent of exposed animals (the oral LD_{50}) is between 350-800 mg, based on published data, almost all of which was published 20-30 years ago.
- The cause of death from lethal doses of 2,4-D or 2,4,5-T to animals is unknown; both compounds produce several non-specific effects, such as mild weight loss.
- 2,4-D produces neurotoxicity in humans and animals.

- The LD_{50} values for TCDD are extremely low (between 1-300 ug/kg) and vary widely among different species.

- A long latency period, of about 3 weeks, occurs between TCDD administration to test animals and death, and the cause of death is usually not known.

- The in vivo characteristics of TCDD intoxication suggest toxicity on a cellular level, although TCDD toxicity has not been demonstrated in cultured cells.

- Thymic atrophy (without a corresponding loss in immune function) and severe weight loss have been observed in many species after TCDD exposure.

- Weight loss does not result from decreased food consumption, disturbances in absorption of nutrients from the gastrointestinal tract, or a stress reaction mediated by endocrine glands.

- TCDD produces hepatotoxicity only in some species.

- The oral LD_{50}s for monuron and diuron in animals are about 1,000 mg/kg; both produce neurotoxicity; death usually occurs 1 day after exposure, from respiratory or cardiac failure.

- The oral LD_{50}s for picloram and dalapon in animals are between 2,000-8,000 mg/kg; death occurs within hours of a lethal dose of dalapon.

- The oral LD_{50} for diquat in animals is between 30 and 200 mg/kg; doses in this range produce severe gastrointestinal lesions and death within 2 weeks; doses 4-5 times higher produce neurotoxicity and death within several hours.

- Values ranging from 200 to 3,000 mg/kg have been reported for the oral LD_{50} for cacodylic acid in rodents.

Gaps in Information

The following information has not been reported or is not adequate in published literature:

- Effects of acute exposure to 2,4,5-T in humans

- LD_{50} values for 2,4,5-T samples with less than 0.1 ppm TCDD

- Verification of the LD_{50} values for 2,4-D that were published 20-30 years ago

- LD_{50} values for cacodylic acid, published in a refereed journal, with descriptions of details on sample purity, methods used, and patterns of toxicity that could be compared to those of inorganic arsenic poisoning

- The causes of death and target organs for picloram and dalapon

- Information on the acute toxicity of tandex.

1.4.4 Subacute and Chronic Toxicities

Conclusions

- 2,4-D and 2,4,5-T are not cumulative toxicants.

- Subacute toxicity of both compounds resemble their acute toxicities, except that subacute doses of 2,4-D do not produce myotonia, but cause bleeding of the gums in dogs.

- TCDD is a limited cumulative toxicant; cumulative effects of doses administered within a month of each other have been observed, but not for doses administered beyond about one month.

- The subacute effects of TCDD that are not observed after acute doses are porphyria and depletion of blood cells; iron deficiency protects TCDD-treated animals from the porphyrinogenic effects.

- Chronic doses of diquat cause cataracts in two species tested (dog and rat).

Gaps in Information

- The subacute effects of cacodylic acid, monuron, diuron, bromacil, and tandex have not been described thoroughly or at all.

1.4.5 Reproductive Toxicity

Conclusions

- No human reproductive effects have been verified to date from male or female exposure to 2,4-D, 2,4,5-T, or TCDD.

- In the two experiments that involved exposure of males only to phenoxy acids prior to conception, no evidence of reproductive effects was observed; (combinatinons of 2,4-D, 2,4,5-T, and TCDD were administered in one study and of 2,4,5-T with an unknown level of TCDD contamination in another study).

- After 2,4-D is administered to pregnant animals, decreased fetal growth rates have occurred.

- After 2,4,5-T (with less than 0.1 ppm TCDD) is administered to pregnant animals, decreased fetal growth rates have occurred and at higher doses in mice, cleft palate is produced; these effects are observed in the absence of maternal toxicity, this teratogenic effect of 2,4,5-T has not been observed in the rat, hamster, monkey, or rabbit.

- After TCDD is administered to pregnant mice, cleft palate and renal abnormalities is fetuses have occurred.

- Synergistic effects may occur in mice when the level of TCDD added to 2,4,5-T exceeds 5 ppm; this effect pertains to the incidence of cleft palate.

- Diquat, dalapon, and diuron produce adverse effects on development only when they are administered at doses that cause maternal toxicity.

- Bromacil and picloram have not produced effects on development at any doses tested.

Gaps in Information

The following types of studies have not been conducted and published to date:

- The effects of human male exposure during a limited time prior to conception on reproductive outcome of the resultant pregnancy, for documented exposure to 2,4-D, 2,4,5-T, and/or TCDD

- The effect of exposure of males of mammalian animal species to any single herbicide or dioxin, alone, on reproductive performance.

1.4.6 Mutagenicity

Conclusions

- 2,4-D and 2,4,5-T produce weak mutagenic effects.

- TCDD has shown mutagenic effects in bacteria and yeast systems, which have not been confirmed yet in mammalian in vivo tests.

- Cacodylic acid, bromacil, and monuron have not produced mutagenic effects in in vitro tests.

- Diquat and diuron have produced mutagenic effects in vitro, which have not been confirmed yet in vivo.

Gaps in Information

The following gaps in information remain:

- The in vivo mammalian mutagenic effects of TCDD, diquat, and diuron
- The mutagenic potential of dalapon, picloram, and tandex in any system.

1.4.7 Carcinogenicity

Conclusions

- Evidence from human studies suggest that exposure to phenoxy acids, with concomitant exposure to many other pesticides and to TCDD, may lead to an increased risk of soft-tissue sarcoma; the etiologic role specifically of phenoxy acids has not been elucidated.
- Mortality studies of groups of human workers exposed to TCDD has not revealed an increased carcinogenic risk in these people, although the numbers of deaths in these groups have been exceedingly small to date.
- Animal studies have not produced any evidence that 2,4-D, 2,4,5-T, cacodylic acid or picloram are carcinogenic.
- TCDD appears to act secondarily or indirectly in enhancing the carcinogenicity of other components (usually unidentified) in animal studies.
- Carcinogenic effects of monuron have been observed in animals; further studies of the carcinogenicity of this compound are being conducted.

Gaps in Information

Information on the carcinogenic potential of diquat, diuron, dalapon, bromacil, picloram, and tandex and on only 2,4-D, 2,4,5-T, or TCDD, without concomitant exposure to trichlorphenol or other herbicides in humans is missing.

1.5 RECOMMENDATIONS

This section presents recommendations for further study drawn from the review of the literature addressed in this report.

- Dalapon and bromacil are compounds that were used in small amounts in Vietnam and have not been shown to pose a significant risk; no further studies are recommended on these compounds.

- Picloram also has a low order of toxicity. The carcinogenic potential of monuron is currently under investigation. Monuron was not used extensively in Vietnam and, other than the carcinogenic potential, has a low order of toxicity. No additional studies are recommended for these compounds.

- Diquat has a moderate toxicity and has been well studied. The only study recommended on this compound is in vivo mammalian mutagenicity testing, in light of positive effects observed in in vitro tests. This compound does not produce effects that would be likely to place humans at high risk after exposure.

- The information on cacodylic acid is conflicting and not adequately documented. Its toxicity and metabolism in relationship to the extent of biotransformation to inorganic arsenic after absorption and the toxicological impact of this metabolism should be investigated.

- No information on the toxicology of tandex was found. Low usage of this compound in Vietnam, however, does not make it a likely target of concern.

- The effects of 2,4-D, 2,4,5-T, and TCDD administered in combination have generally not been compared to the individual effects to determine whether the combination produces additive, potentiating, or synergistic effects; an exception is the effect of cleft palate in mice by 2,4,5-T, which was potentiated by doses of TCDD. The effects of combined doses should be investigated.

The major concern of veterans in Vietnam that has not been adequately addressed in published literature to date is the potential for human exposure to TCDD to produce the same health effects with the same potency as those observed in animal studies. The wide variation of responses to TCDD among different species and a lack of understanding of the mechanisms of its toxicity and metabolism have led to this situation. The remaining recommendations address this issue.

- Procedures for evaluating both exposure levels and health effects from occupational exposures and accidents should be established by an international agency. These procedures should be available before another incident occurs, so the most useful types of information can be collected on a timely basis and the same type of data could be obtained from different accidents for purposes of comparison.

  Any protocol should consider the items listed above as <u>Gaps in Information</u> in previous accounts; information on cholesterol levels and other parameters discussed in other recommendatons should be studied.

- The relative importance of the rates and pathways of biotransformation and tissue distribution in various species should be addressed. Studies should be initiated to:

  - Identify the biliary metabolites of TCDD

  - Compare in various species the pathways of TCDD metabolism (based on the types of metabolites formed) and the rates of metabolism with TCDD toxicity in that species, as was done by Gasiewicz and Neal (1979) for the hamster

  - Determine the relative importance of the proportion of TCDD distributed to specific tissues with the toxicity in that tissue. (If disproportionate distribution to specific human tissues occurs, this should become apparent as TCDD levels in autopsy samples become available).

- The potential for the inductive effects of TCDD to alter lipid metabolism and cause depletion of fat stores has not been adequately considered. TCDD produces a long-term elevation of serum cholesterol (in animals and humans), a long-lasting induction of certain enzymes, and a long latency period after exposure and before death occurs, during which time animals become emaciated. The possibility that enzymes that degrade lipid stores are induced and no longer respond to regulatory mechanisms should be investigated.

- The biochemical events that precede chlorance have not been adequately considered and may in time lead to the development of useful therapy.

- Humans have been proposed to be less sensitive than animals to the toxic effects of TCDD (Crow, 1980). Recent experiments by Poland and Glover (1980) demonstrated that the presence of (1) cytosol receptors for TCDD, (2) sensitivity to enzyme induction by TCDD, and (3) sensitivity to the toxic effects of TCDD, including cleft palate and thymic atrophy, all segregated together in certain strains of mice and were all absent in others. If this approach were extended to different animals species and these parameters were shown to correlate in different species, a basis for extrapolating the inductive potential and receptor-binding capacity (which potentially could be measured in vitro in human tissue) to the likelihood of toxic effects in humans may be able to be established.

  By understanding the mechanisms of TCDD toxicity, the degree of correlation of receptor binding, enzyme induction and toxicity, and the role of metabolism in altering toxicity in animals, extrapolations of these parameters to man may become feasible.

Recommendations from Panels of Experts
at Second International Symposium on
Chlorinated Dioxins & Related Compounds

ENVIRONMENTAL CHEMISTRY PANEL

The concensus of the Environmental Chemistry Panel identifies the following key issues in this area of study:

C.F. 1. We need to understand the photodecomposition of PCDDs and PCDFs on particulate matter and/in aerosols.

D.S. 2. We need to understand the bioavailability of PCDDs and PCDFs on particulate matter.

3. How do PCDD and PCDF profiles in soils vary with time?

4. We should make every effort to gather information on PCDFs as well as PCDDs in our experiments.

5. What are the PCDD and PCDF profiles on flyash and related emissions from many different combustion and other sources, and can we use these in conjunction with pattern recognition techniques to identify sources?

6. What is the significance of evaporation of PCDDs and PCDFs from soil and water surfaces into the atmosphere compared to combustion sources?

7. Explain the degradation of PCDDs in the aquatic ecosystem to give a shift in isomer patterns observed in the environment and in biological samples.

8. What are the ambient levels of PCDDs and PCDFs in the environment (soil)?

9. Is uptake the limiting factor in microbial degradation?

D.S. 10. Should PCDD and PCDF surveys be made for the human food chain?

11. What is the relative importance of factors that contribute to emissions for PCDDs and PCDFs; e.g., feed material, temperature, residence time, etc.

C.R. 12. What are the PCDD and PCDF emissions from burning of PCP-treated wood?

L.B. 13. What is the environmental fate of PCDDs and PCDFs that are found in bottom ash of certain municipal waste combustors?

D.S. 14. Pattern recog & multivariant analysis may be prerequisite for interpretation of surveys & relative studies.

ANALYTICAL CHEMISTRY PANEL

A RESUME OF THE DELIBERATIONS OF THE PANEL FOR ANALYTICAL CHEMISTRY; INTERNATIONAL SYMPOSIUM ON CHLORINATED DIOXINS AND RELATED COMPOUNDS, October 25-29, 1981, Arlington, Virginia, USA

The panel, a group of experienced analysts representing agencies from North America and Europe, examined past achievements, the status quo, and future developments.

Progress in the development of analytical methodology for the determination of chlorinated dibenzodioxins (CDDs) and dibenzofurans (CDFs) in products and environmental samples has been extensive and dramatic during the last decade. Thus, the limit of detection for the tetrachlorodibenzo-p-dioxins (T_4CDD) in products has been lowered from one part per million in 1969 to 1 part per billion in 1980. Similarly, the limit of detection for 2,3,7,8-T_4CDD in environmental samples has developed to a part per trillion in 1978 from 50 parts per billion in 1970. Furthermore, the ability to separate a specific isomer in a particular isomer group from all of its isomers and other congeners has advanced from the ability to separate 2,3,7,8-T_4CDD from only two of its isomers in 1974 to an ability to separate all of the 22 T_4CDD isomers in 1978. Likewise, all 10 isomers of H_6CDD have been separated as have the two isomers of H_7CDD.

Such rapid development of highly sensitive methodology suitable for the determination of specific compounds among large numbers of isomers in a series of homologous compounds, as well as a vast number of other related compounds, sets new standards for progress in analytical science. It was achieved by the continuous investment in the finest manpower and equipment, both operating near their optimum potential. Leadership and cooperation by industry, academic, and government agencies were required to accomplish the goal. In no small measure this International Symposium has significantly contributed to this rapid progress by convening viable working groups in which deliberations and free exchange of ideas has taken place. Continua-

Emphasis was given to documenting analytical problems for environmental and commercial sample matrices and the ability of methods of analysis to produce reliable data. There was unanimous agreement that reliability of the method to provide sound data for dioxin residues in various matrices was absolutely necessary. Otherwise, conclusions reached by other disciplines using these data would be in jeopardy if not completely erroneous. It is axiomatic that analytical chemistry serves as the basis on which all our numbers are being generated; for frequently the users of data are inclined to accept without question their reliability when making decisions.

Analysts by nature are individualistic with strong opinions on how to approach an analytical problem. Frequently the end result is a myriad of methods designed to reach the same goal: a procedure capable of generating a number that truly reflects a residue's status in its native or foreign environment. Thus, we are presented with a large variety of methods from which to choose. There are some who feel strongly that an effort to standardize these procedures should be made in one form or another.

It is the concensus of the panel that methodology should not be rigidly standardized. To the contrary, laboratories should be free to develop their own approaches to an analytical requirement. However, it is important that the laboratories attain a high level of analytical proficiency through experience and a quality assurance program. It is also desirable that the laboratories monitor performance via participation in interlaboratory check sample programs. The panel recognizes that the first tentative steps have been taken to develop interlaboratory quality assurance programs, e.g., the dioxin implementation plan, the Canada/U.S. round robin check sample for fish, and the exchange of other samples between various laboratories in Europe, the United States and Canada. However, these efforts should be strengthened and financially supported by all interested parties and agencies.

Currently, analysts are working at very low levels whose significance on human health is not understood absolutely. At present, agencies in the United States and Canada have issued advisories to jurisdictions consuming

Great Lakes fish which expressed concern about ingestion of fish containing more than 10 (New York State), 20 (Health and Welfare Canada), and 25 (Food and Drug Administration) ppt of 2,3,4,7-TCDD. It is important that available methodology be demonstrated to be capable of determining reliably 2,3,7,8-TCDD at these levels. Another concern directly related to this same situation is the analysts' need for guidance from other disciplines on what level of residue a method would be expected to quantitate in each matrix. In the interest of practicality, this need should no longer be avoided but confronted by all concerned. It is suggested that on recognition of a potential residue problem by an interested party, one of the first prerequisites in planning an adequate response is involvement of the analyst to establish practical quantitation levels.

Primary standards for all individual dioxin congeners and their derivatives are a crucial problem needing immediate attention. They are required for further expansion and validation of present methodology. Common concerns dictate that on an international basis, a cooperative approach be taken and a suitable repository be set up for acquiring and handling these highly toxic compounds and related substances.

Methodology for the determination of dioxins and their derivatives, especially TCDD, is on the leading edge of analytical capabilities, requiring a high degree of analyst expertise to detect and confirm the identity of low ppt levels of some congeners. This presents problems associated with different matrices such as biological, effluents and particulates, waste disposal areas, etc. It has been observed that limits of detection at levels of 0.5 to 10 or 15 ppt may differ widely in their value between samples of the same species, e.g., fish, soil, etc. Thus, there is need of further researching, development and validation of methods, particularly in the areas of waste disposal dumps. incinerators, and commercial products such as fuels for reciprocating engines, power plants, etc.

A serious drawback with present methodology is its complexity and resultant low volume sample output. This has made it difficult to accumulate sufficient data on a matrice's residue status that is statistically

significant. An exception is probably the fish surveys. Research should be directed to developing procedures and techniques that would conceivably maintain accuracy and/or precision with high volume output. Such areas as bioassay, MS/MS techniques, etc., require immediate attention.

Second Draft
10/28/81

ENVIRONMENTAL TOXICOLOGY PANEL

Recent findings of up to 100's of ppt of various isomers of polychlorinated dibenzo-p-dioxins and dibenzo-p-furans in fish in the Great Lakes and some rivers have raised the question of the toxicity of such chemicals. Representative chemicals which are found are the 2,3,7,8-tetrachloro, hexachloro, and octachloro derivatives. The fact that they have been found in fish, birds, and sediment establishes some degree of persistence. The nature of such chemicals leads one to believe they bioconcentrate to some degree. This is supported by the fact that they are detected in fish and not in water. There is little, if any, data on the toxicity of these chemicals to fish or wildlife. Basic data needed for hazard evaluation is almost completely missing aside from data on 2,3,7,8-TCDD. Examples of needed data are water solubility, octanol-water partition coefficient, vapor pressure, sediment partitioning, experimental bioconcentration factors, acute toxicity (with delayed observation) on rats and fish, at a minimum. Depending on the results of this preliminary set of data, some idea of the toxicity to reproduction of some key representative organisms may be needed, especially if monitoring data continue to show concentration of such chemicals to be increasing in the environment. It is recommended that only key tests be done on a limited number of derivatives and a very limited number of organisms on a "need to know" basis and assess the problem after this data becomes available and not to run the entire checklist of test species which could be run. For chemicals which are already present in fish, water, or sediments in minute amounts, a controlled fish reproduction test in situ could be accomplished such as in artifically isolated lagoons of the Great Lakes. Such a test would be a product of the effect of the total load of toxicants which is not accomplished in laboratory tests. This is a field test problem which needs the special attention of fisheries biologists.

A number of predictive models, partition coefficients, and regression equations are available which could be used. However, since the majority of these compounds are likely to have "log P" values in excess of 10^6,

the validation needs to be extended with particular attention to bioaccumulation and the possibility of anomolies with high molecular weight compounds.

The correlating relations are based upon either "log P" or water solubility. With the exception of 2,3,7,8-TCDD, data on these parameters is unavailable. The relative "log P" values of the various groups of homologues should be established to provide a better "log P" base for predictions. Additionally, the isomeric specificity of "log Ps" should be established.

The extent to which dioxins other than 2,3,7,8-TCDD are degraded in vertebrate is not sufficiently understood, albeit analogies can be drawn with the chlorinated furan and polychlorinated biphenyls which suggest that such processes should reflect a high degree of structural specificity. Without an understanding of these patterns, it is difficult to determine with confidence the exposure encountered by an organism simply on the basis of the residues in its tissues. Thus, the bioaccumulation patterns of dioxins should be established for vertebrates.

Because a complex mixture of dioxins and dibenzofurans are known to have entered from a variety of sources, there is a need to monitor the levels and effects in the environment.

There is first a need to investigate the extent of contamination on a geographic basis for a variety of compounds to determine how it relates to potential sources and to identify hotspots where environmental monitoring is needed. In areas where elevated levels are found, there is a need for selection of appropriate biological monitor species both to investigate the incidence of effects among the population and to document the trends in the level of contamination over time.

Because dioxin analyses are so costly, locations for monitoring should be selected taking into account the likely sources that may contaminate the ecosystem.

Some other toxicological problems which come up with all chemicals including the dioxins and related chemicals, are the number of species which need to be tested for representation of various phyla, classes, or families of species. It has been noted that there are similar ranges (several orders of magnitude) in sensitivity, for example, between species of fish as there may be between fish and aquatic invertebrate species. Therefore, a representative of 2-3 species is probably adequate except for evaluation of specific organisms. Some data on surragate species extrapolation exist in the literature.

Another problem is field validation of laboratory data, or vice versa. It can not be expected that they can ever duplicate each other. However, if the data from such experiments come within one order of magnitude, it can be considered to be of limited confirmation and some consolidation, but, also unfortunately, possibly fortuitous. Caution should be exercised. More examples of good laboratory simulation of field tests need to be developed.

From the data presented at this conference, it is evident that certain concentrations of TCDD in soil, sediments and water are related to no-effect levels in animals. We should now be making practical use of this information.

Lorris G. Cockerham
Michael Gilbertson
Don D. Harrison
Eugene E. Kenaga, Chairman
J. Russell Roberts
Charles E. Thalken
Alvin L. Young

The panel considered as its first priority the identification of controversial issues. The first was that of determination of exposure. The assessments of high, medium or low exposure (above background) are all relative terms and vary quite widely in the literature and this makes comparison between studies very difficult.

The skin lesion, chloracne, is an important indicator of exposure to TCDD and other known chloracneigens and is probably the most sensitive indicator of exposure.

As far as human health problems are concerned the aspects of TCDD exposure which the panel has reviewed are teratogenicity, fetotoxicity, cardiovascular disease, neurotoxicity, chromosome aberrations, hepatic porphyria, and carcinogenicity.

Teratogenicity and fetotoxicity are controversial because TCDD is both a fetotoxin and a teratogen in certain laboratory animals. Information indicating that TCDD is fetotoxic or teratogenic in humans is lacking.

The Alsea II study concluded that 2,4,5-T contaminated with TCDD is fetotoxic. (The herbicide was claimed to have been the cause of an increase in spontaneous abortions in the Alsea region of the state of Oregon). This study, however, has been severely criticized on methodological grounds and many remain skeptical about its findings. In addition to this, there is evidence from other studies which challenges the suggestion that TCDD is fetotoxic in humans. There is no evidence that TCDD is a teratogen in humans.

In connection with carcinogenicity, the panel reviewed 4 Swedish scientific papers on the carcinogenicity of the phenoxy acids and the chlorophenols. These studies report a positive association between exposure to phenoxy acids and chlorophenols and soft tissue sarcomas and lymphomas but not colon cancer. These findings must be replicated in other areas and by different methods before a cause effect relationship between phenoxy acids and soft tissue sarcomas or lymphomas can be concluded.

Four cases of soft tissue sarcoma have also been observed in two epidemiological studies of workers exposed to 2,4,5-trichlorophenol (and in one case to 2,4,5-T also) at Dow Chemical and Monsanto. In all these cases, the men were exposed to high concentrations of TCDD and in every case there was diagnosed, or suspected, chloracne.

A study is being conducted in New Zealand comparing occupational exposures between soft tissue sarcoma cases and patients with other forms of cancer identified from the National Cancer Registry. A preliminary analysis utilizing occupational data in the Cancer Registry relating to the time of registration does not reveal any occupational differences between the two groups.

A cohort of herbicide applicators in Finland exposed to phenoxy herbicides for at least two weeks between 1955 and 1971 have been monitored since 1972. The incidence of tumours in this group is no higher than would be expected. Thus far there have been 20 cancer deaths (4 less than would be expected) in this group but no cases of soft tissue sarcoma have been observed.

ANIMAL TOXICOLOGY PANEL

I. Toxicology is the science of adverse (toxic) reactions. Animal toxicology centers on responses, usually, but not restricted to vertebrates. In large part our information base is derived from studies on rodents and monkeys. Specific attention is directed toward the polyhalogenated aromatics, especially dibenzodioxins, dibenzofurans and azoxybenzenes.

(a) The wealth of data available suggests that there are several target systems sensitive to these several diverse compounds. These include epithelial structures (especially skin), liver, thymus and the fetus. Alterations in other systems seem less consistent.

(b) Critical evaluation of physiology has been less well described, and as a result, more conflicting data results. Particularly important is that potential reversibility of any one or several targets is not known. Is the thymus less readily reversible?

(c) Absorption, distribution, matabolism and excretion data show very different responses in different species, but suggest TCDD is poorly metabolized.

(d) The conclusion from these studies point to similarity of effects on diverse species, that for TCDD, metabolism may not be requisite for actions, but regardless, similar target systems must be sensitive.

II. The problems that confront analysis of action and effect of the polyhalogenated dibenzodioxins and dibenzofurans.

(a) In large part the data covering injury to the animal is descriptive. Furthermore, there is no consistent analysis of the effect of an agent on structure or function. The [illegible] especially for analysis of visceral

modification, that PBBs, PBCs, and TCDD result in similar acute and chronic morphological changes in [illegible] Without a detailed comparison this seems an unwarranted conclusion.

1. Studies on mechanism of action must differentiate degenerative from restorative changes, must separate responses that are proliferative (e.g., skin) from those that are degenerative (e.g., liver and thymus). ✓

2. More critical analysis of death and its associated phenomena are necessary, and these data used to attempt to define what is happening in the whole organism. ✓

3. More critical analysis of in vivo and in vitro metabolic changes are required and it may not be appropriate to extrapolate from liver to skin. ✓

III. Are there key observations that can be used to further pinpoint areas to be examined? Yes.

(a) The cutaneous response to TCDD is a proliferative one, the thickness of the epithelium increases and hyperkeratosis is prominent. Questions to be asked concern where TCDD is sequestered in the skin. Should Poland be correct, the nucleus probably should be defined by autoradiography. Furthermore, it should be determined whether this represents increased cellular proliferation, or increased cellular [illegible]. Analysis of the rate of gene product formation, [illegible] should be undertaken. ✓

(1) The suggestion that subaceous glands undergo metaplastic transformation is anecdotal. A critical study of the hairless mouse or rabbit may reveal that follicular plugging underlies these changes. ✓

(b) A critical temporal quantitation of hepatocellular response to TCDD is required. This should be accompanied by a [illegible] analysis of cellular modification. It may be possible to separate these aspects of TCDD intoxication which modify phenotype from the more destructive aspects of the same agent by comparing resistant and susceptible species. The perverse and cellular localization of TCDD in these targets should be sought. Poland's hypothesis could be tested directly by seeking gene product identification.

(c) Although hemorrhagic phenomena and vascular changes have been eluded to, actual analysis of the clotting function and vascular permeability have not been assayed. It is not clear whether or not vascular integrity is maintained. The "chick adema" could be caused by decreased oncotic pressure or by reduced regulation of vascular permeability.

(d) The carcinogenic potential of TCDD is not defined. Conflicting evidence of metabolic/promotor function in skin is described. That TCDD results in liver neoplasms, and acts as a promotor with the Peraeno two-step system does not provide definitive evidence of the separation of functions. A major problem that confronts us all is the limited understanding of the biology of neoplasia in general and of cancer in particular.

(e) Specific cytochemical [illegible] following TCDD (and other halogenated hydrocarbons) is necessary. Are there potentially modified membrane [illegible] following an agent that potentially can intercolate in membranes as well as nucleic acid?

(f) The extra decreased weight appears only in lethally intoxicated rats. What relationship does this have to the ultimate demise of the animal? ✓

(g) The striking thymic change is not a property of TCDD alone, but follows other toxins and may be independent of the endocrine axis. What is unique in these cell ✓ populations?

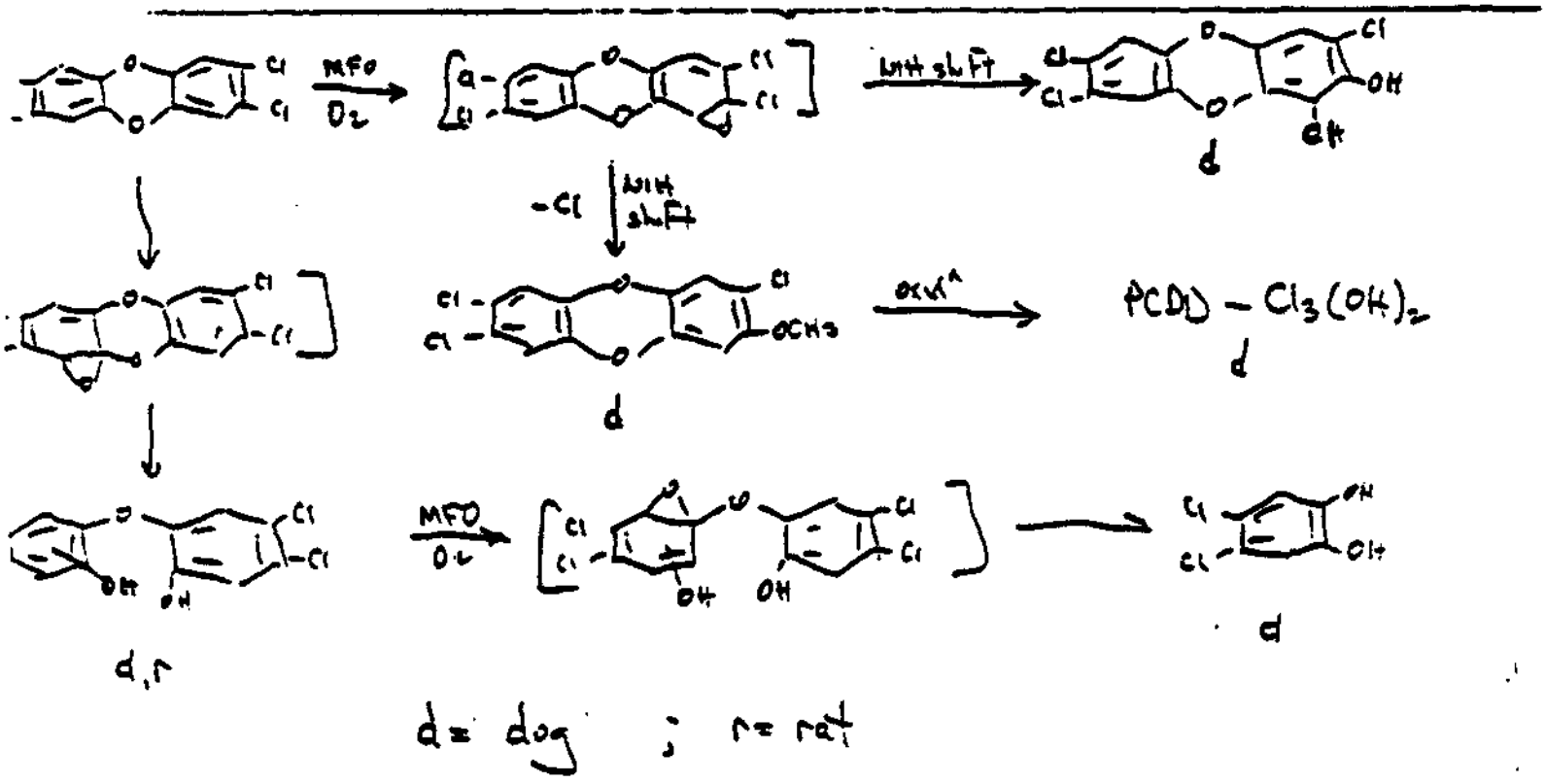
IV. A position: A critical functional analysis of this animal response is necessary, attempting to separate the several acute and chronic processes. To the toxicology is needed good pathology and more extensive pathology

A plea: Since the goal is still to assay for human hazard, both critical monitoring of human health and TCDD levels must be combined with detailed intravitam and post mortem pathological changes. These analyses must be carried out carefully and extensively. Do not let an experiment of nature go unheeded! ✓

A. Metabolism of Dioxins and Related Compounds

Comparative Properties	PCDDs	PCDFs	PCBs	PCNs
1. Rate of metabolism decreases with increasing chlorine substitution	+ (some data)	+	++ (considerable data)	+
2. Hydroxylation site specificity	2,3,7,8	2,3,7,8	p>o>m	- (no data)
3. Phenolic (or diol) compounds are the major metabolites and have been characterized	+	+	++	+
4. Binding to macromolecules observed	+	-	++	-
5. Biohydroxylation catalyzed by mono-oxygenases	+	+	++	+
6. Metabolites are generally less toxic than their hydrocarbon precursors and the process (metabolism) results in detoxication	+	-	+	-

2,3,7,8-TCDD Metabolism (Poiger et al.)



d = dog ; r = rat

2,3,7,8-TCDD metabolite (≤) 10^0 less toxic than 2,3,7,8-TCDD (limited LD_{50} experiments in guinea pigs).

RECOMMENDATIONS FOR FUTURE WORK

1. Further characterization of all the 2,3,7,8-TCDD metabolites. ✓
2. Comparative metabolic studies in diverse animal species. ✓
3. Toxicity testing of 2,3,7,8-TCDD metabolites (presumably using synthetic compounds). ✓
4. Additional metabolic studies on other relevant PCDDs and related compounds. ✓
5. Do the metabolites bind to the receptor (and are some toxic)? (Test the bile metabolites in the binding assay) ✓
6. Is TCDD-protein covalent binding important in toxicity? ✓

B. PHARMACOKINETICS

Comparative Properties	PCDDs	PCDFs	PCBs	PCNs
1. Highly dependent on species	+	+	++	-
2. Regulation of residues by the size of the fat reservoirs	-	-	+	-
3. Marked effect of structure on fat retention (e.g., ortho substitution - PCBs)	-	-	+	-
4. Increasing chlorine content of the halohydrocarbons results in increased long-term retention in adipose tissue except for highly chlorinated compounds > Cl_7.	-	-	+	-
5. Readily metabolized congeners are rapidly removed from tissues	+(?)	+	++	+

\- very little data
\+ some data
++ considerable data

RECOMMENDATIONS

It is clear that the pharmacokinetics of dioxins and related compounds is dependent on numerous factors (lipophilicity, molecular volume, shape, etc.) and is species dependent. Appropriate mathematical models should be developed to explain the myriad of results.

C. BIOCHEMISTRY AND MECHANISM OF ACTION

Comparative Properties	PCDDs	PCDFs	PCBs	PCNs
1. Marked effect of structure on activity (most active chemicals are isosteric with 2,3,7,8-TCDD)	++	+	++	-
2. Correlation of AHH induction with toxicity	++	+	+	-
3. Correlation of avidity of receptor binding and toxicity	++	+	+	-
4. Segregation of activity with Ah locus	++	+	+	-

DIOXINS AND RELATED COMPOUNDS -- UNRESOLVED PROBLEMS

1. Confirmation that binding to the receptor is required for the biologic and toxic effects.
2. Determination of the structural factors which facilitate the ligand-receptor binding.
3. The mechanism of the interaction between the ligand-receptor and DNA and the related controls.
4. Is the induction of P-450$_c$ responsible for any of the toxic responses?
5. There is a need for the development of more *in vitro* assays.
6. Several anomalies must be resolved or explained, e.g.:
   (a) Why is the guinea pig more susceptible to TCDD toxicity than the hamster even though their receptor levels are comparable?
   (b) Is there any evidence that ligand-receptor interactions are different in tissues of different species (e.g., hamster, rat, guinea pig)?

ATTACHMENT F

POSSIBLE FORM OF AN AGENDA

Mechanism of Action

a. Investigate cytosol receptor model and the link between complex formation and enzyme induction as initial steps leading to manifest toxicity.

b. Determine patterns of biotransformation, distribution, and excretion of 2,3,7,8-TCDD in various species, including humans.

Toxicities of Concern

a. Determine a finite set of adverse health effects which would most likely be associated with exposure to AO.

b. Study the toxicities of concern in a range of animal models, obtaining dose-response relationships and interspecies variation data.

Exposure

a. Estimate maximum exposures likely in Vietnam.

b. Investigate adsorption of toxicants via various routes of exposure.

c. Investigate degradation of toxicants under Vietnam-like conditions.

d. Compare possible Vietnam exposure with those

resulting from environmental levels found in the U.S.

Chemcal Analysis

a. Develop reliable qualitative and quantitative methods of analysis for various samples, including human tissue. (See report of the Fat Biopsy Subcommittee.)

b. If appropriate, gather information on 2,3,7,8-TCDD levels in Vietnam veterans for comparison with levels in the U.S. population.

Human Studies

a. Evaluate the adequacy of ongoing or completed studies in assessing toxicities associated with exposures.

b. Examine the time interval between exposure and manifestation of toxicity, relating this to severity and persistence.

c. Develop rational measures of exposure on a group or individual basis.

Laboratory Toxicology

a. Investigate the effect of dosing regimen on toxicity; e.g., compare response to 7 daily doses per week vs. 1 7-fold dose per week.

NOTE: In any final agenda there would be a narrative link between (a) the final goal ("Resolution of the alleged connection between exposure to AO in Vietnam and adverse health effects") and (b) each of the elements of the agenda. This link is needed in order to justify the inclusion of any given element.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date March 13, 1984

From Director
Center for Environmental Health

Subject Agent Orange Working Group

To Dr. Miriam Davis
Program Analyst
Office of the Deputy Assistant Secretary
for Health (Health Planning and Evaluation), OASH
Room 740-G HHH Bldg.

This is in response to Dr. Brandt's views on the structure of the Agent Orange Working Group (AOWG) and the Science Panel establishing a research agenda.

I believe that the AOWG should concentrate its efforts on the Agent Orange issue as it relates to veterans. This obviously will need input, particularly on human health studies and dioxin exposure in the occupational setting as well as the nonoccupational environmental setting. The research agenda prepared by the subcommittee of AOWG was in my opinion far too broad and inclusive. It would seem to me that it is appropriate for each agency to establish its own research agenda on the dioxin question. All of these could then be reviewed by a subcommittee of the Science Panel for two purposes: (1) To select those issues that have implications for the Agent Orange veterans question and to request being kept informed and (2) to identify where there may be gaps in the research agenda of the various agencies in relation to this question and to make recommendations for filling those gaps.

I agree with Dr. Brandt's recommendations for structuring the various panels of the AOWG, specifically, the Science Panel. However, I doubt that an outside advisory group can be part of the Science Panel. It is my understanding of the charter that only Federal Government officials can participate as members of the group. Certainly, there would be nothing wrong with having an advisory group chaired by a member of the Science Panel and reporting to the Science Panel, but those outside scientists not being appointed as members of the Science Panel.

Vernon N. Houk, M.D.

Congress of the United States
OFFICE OF TECHNOLOGY ASSESSMENT
WASHINGTON, D.C. 20510

JOHN H. GIBBONS
DIRECTOR

March 21, 1984

Dr. Miriam Davis
Agent Orange Working Group
Room 740G
Hubert Humphrey Building
200 Independence Avenune, NW
Washington, DC

Dear Miriam:

Hellen Gelband and I have discussed the suggestion that the AOWG form a subcommittee to draw up a research agenda. We are against the idea. We think that it is entirely appropriate for the AOWG, in its review and oversight functions, to make comments about needed information. Likewise, it is appropriate for it to make comments that research efforts look like they are dupplicative. Importantly, however, AOWG has no funding authority, and we think research agendas should be set by the agencies that grant the money and which will assemble the necessary experts to decide on the wise expenditure of funds. Certainly we would oppose AOWG being inserted into a decision loop about what research to fund and what not to fund. That would slow up a system that ~~need not be slowed up~~ is already slow.

Sincerely,

Mike

Michael Gough

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date March 1, 1984

From Carl Keller, Chair Pro Tem, Science Panel, AOWG

Subject Science Panel Meeting

To Dr. Edward N. Brandt, Jr., Chair Pro Tem,
Cabinet Council Agent Orange Work Group

I am attaching for your information a copy of the minutes of the January 26, 1984 Science Panel meeting and an announcement for the next meeting scheduled for March 15.

I would also like to comment on the Research Agenda Report. I agree with the thrust of the Report, i.e., that a research agenda is both feasible and desirable. I do think, however, that a research agenda should be organized around the essential questions which need to be answered in order to accomplish the type of risk assessment which is needed. These almost certainly involve estimates of exposure and the identification of measurable adverse health outcomes with the intervening steps of degradation, absorption, elimination, sequencing of toxic responses, etc. I certainly agree that it is essential that the narrative link between individual research projects and the basic questions need to be developed.

3/12/84

Marian —

As requested

Carl

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Washington DC 20201

FEB 23 1984

NOTE TO DR. BRANDT

Through: Dr. Crooks BLC/for

Subject: AOWG Research Agenda--COMMENTS

The report of the Agent Orange Working Group (AOWG) Subcommittee on Research Agenda that I have been asked to review is not a research agenda per se; it is a statement of mission for the Subcommittee. The report contains a rationale for three recommendations which are to be carried out through the science panel. The recommendations are as follows:

1) assemble one-page technical descriptions of current Federal research projects related to the mission of AOWG;

2) serve as an exchange point for information on AO-related research at State, Federal, and international levels;

3) develop a research agenda that provides descriptive guidance rather than prescriptive detail.

My feeling is that recommendation 3), the development of a research agenda--however descriptive or prescriptive--is a superfluous task for this high level group. The development of a research agenda is an endeavor that is best accomplished at the program level, if the purpose is to assist researchers in the field. Surely, a prospective or established researcher in the field would not rely on an AOWG agenda; rather, to carve out a research niche, they would survey the existing literature to determine for themselves what research needs to be done, or they would seek mild guidance from a program officer at the agency sponsoring the grant.

If the research agenda is intended for the policymaker or if it is designed to inform the public, then it should be in terms far more broad and simple than those envisoned by the Subcommittee.

The greatest utility of the Subcommittee's report is contained in recommendations 1) and 2), the assembling of technical descriptions of current Federal projects, and the exchanging and transferring of technical information. I would like to suggest that the scope of the research that is described and exchanged should be expanded to include dioxin in addition to Agent Orange, since Agent Orange is no longer available. If it is feasible, 2,4,5-T and 2,4-D should also be included.

TRACER 81228

The one-page technical descriptions of Federal research projects would be very handy for scientists in the field. I assume that by "Federal" research, it is meant grants and contracts through the Federal Government, as well as research conducted in Federal laboratories. Others--such as the States and industry--who sponsor research should be encouraged to contribute.

Most importantly, it might be very valuable to publish an annual report of "Synthesis and Commentary" based on the one-page technical descriptions. Such an annual report might be very useful to the research community, both to scientists in the area as well as in other areas. The annual report may even provide a better vehicle for "oversight" of research than that provided by a formal research agenda. It should also be comprehensible to the educated layman and policymaker, perhaps through a nontechnical executive summary.

If appropriate, I will be happy to compile and consolidate the comments you will be receiving from AOWG members on the Subcommittee on Research Agenda report.

Miriam

Miriam Davis, Ph.D.

Department of Labor

Occupational Safety and Health Administration
Washington, D.C. 20210

Reply to the Attention of:

MAR 15 1984

MEMORANDUM FOR: EDWARD N. BRANDT, JR., M.D.
Acting Chairman
Cabinet Council Agent Orange Working Group

FROM: STEPHEN J. MALLINGER
Deputy Director
Directorate of Technical Support

SUBJECT: Agent Orange Research Agenda Comments

This is in response to your January 23, 1984, memo requesting comments on the Research Agenda developed by a Subcommittee. I have reviewed the material you forwarded to me and believe it addresses all the major areas. However, I do have other concerns about a formalized Research Agenda for Federal agencies. First, if the agenda or the analysis of studies to develop the agenda went into considerable depth in reviewing current literature, the work burden could become tremendous. Assuming that the product will look similar to what was sent with your memo, this type of agenda appears adequate. Secondly, is the question of what the AOWG believes is the purpose of the agenda? While the Department of Labor and OSHA have an interest in the health effects resulting from occupational exposures to dioxins and furans, the agency does not have near the interest that other members of the group have (such as EPA). Because of this diversity of interests mainly stemming from different mandates for different agencies, a formalized agenda will have very little utility or impact on this agency's research priorities. In addition, some of the studies we sponser are funded because of other factors. One of these factors is cost. Some studies allow that for some additional money added to the original study much more information can be obtained. Another factor is timing. Some facilities are only available during limited times and work must be scheduled as their time permits.

In summary, while a formalized Research Agenda may provide some guidance to States and universities as to where work needs to be done and provide additional information to the public on the status of current knowledge, it should not be used to direct Federal agencies or their activities. If you have any questions concerning these comments, please call me.

cc: William Plowden

AOWG, Ex Sec has

DEPARTMENT OF THE ARMY
WALTER REED ARMY INSTITUTE OF RESEARCH
WALTER REED ARMY MEDICAL CENTER
WASHINGTON, D.C. 20307

IN REPLY REFER TO:

SGRD-UWH-S

19 March 1984

SUBJECT: AOWG Research Agenda Memorandum, 23 January 1984

Edward N. Brandt, Jr., M.D.
Chair Pro Tempore
Assistant Secretary for Health
Department of Health and Human Services
Room 716-G, HHH Building
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Dr. Brandt:

Reference your letter of 23 January 1984, I believe AOWG sponsorship of a research agenda would be useful if it provides "descriptive guidance" to address the three questions posed by the subcommittee: 1) Where are we?; 2) Where do we want to be?; and 3) How do we get there from here? However, I'm not certain how to successfully answer these questions. For example, can we agree to limit the scope of the agenda to only Agent Orange? Dioxin? Herbicides? All chemicals used in RVN? Similarly, what is our target population? Is it only RVN vets (and their families) or does it include occupational exposures, and even Vietnamese nationals? In short, a clear statement of the AOWG mission and scope would be essential to a meaningful Agenda.

It is particularly difficult to address the question of where we want to be and how to get there. For example, laymen focus on some vague scientific "proof" as the end product of this research. However, it is doubtful that a link between Agent Orange and the conditions it is alleged to cause will ever be as rigorous as the association scientists have established between smoking and lung cancer, heart disease, etc. Yet science does not deal in certainties, only in the best hypothesis, and thus its conclusions are vulnerable to rejection by those who cannot or will not accept them for other reasons either religious, social, economic, political, etc. Congress has mandated that scientific research be done to see if Agent Orange has caused disease in our veterans but they did not specify the end points that will satisfy their needs as decision makers? And even if they are satisfied, what will satisfy the veteran and the courts? Such specifications are important to meaningful research efforts but may be unavailable. For example, stress on causality would suggest priority be given to actual or relative risk while stress on the magnitude of the problem would emphasize attributable risk.

SGRD-UWH-S
SUBJECT: AOWG Research Agenda Memorandum, 23 January 1984 19 Mar 84

In short, I feel only a very general research agenda, "descriptive" not "prescriptive", is useful under these circumstances.

Sincerely,

Richard A. Hodder

RAH/jp

RICHARD A. HODDER, M.D., M.P.H.
COL, MC
Member, Science Panel
DA/Cabinet Council Agent Orange Working Group (AOWG)

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20500

February 24, 1984

MEMORANDUM FOR EDWARD N. BRANDT, JR.

FROM: ALVIN YOUNG

SUBJECT: AOWG Research Agenda

I am pleased to respond to your request for the preparation of a formal AOWG Research Agenda. The need for a coordinated Research Agenda is especially important at this time if the Government is to resolve the concerns of the Vietnam Veterans in a timely and fiscally responsible way.

In developing the Research Agenda, I believe it is important to review the questions asked by Vietnam veterans exposed to Agent Orange and its associated dioxin, namely:

1. Are they more likely to have children born with birth defects?
2. Are they dying in increased numbers, at earlier ages or from unexpected causes?
3. Are they more likely to develop connective tissue cancer (i.e., soft tissue sarcoma)?
4. Are they more likely to develop other forms of cancer?
5. Do they have residual levels of dioxin in their body tissues, and is it likely that these residues will cause subsequent health problems?
6. Are there other long-term problems peculiar to phenoxy herbicide and/or TCDD exposure?

Obviously, the health concerns of individuals exposed to the herbicides and 2,3,7,8-TCDD are varied. Any approach must encompass studies comparing morbidity, reproduction and mortality patterns between exposed and non-exposed populations. Moreover, for Vietnam veterans, an added dimension is present - if Agent Orange is not the causative agent, other factors associated with the Vietnam War may be responsible. Consequently, the goal of some research efforts must be to determine whether Vietnam veterans as a group are experiencing more or different health problems than their counterparts who did not serve in that part of the world. In such a complex situation, no single study can provide all of the answers. Thus, there is a need for a number of different approaches to examining the health of the Vietnam veteran.

ve prepared a table (Table 1) of the major federal studies t I am aware of. This table of research projects address e concerns noted in the above paragraphs. The identified ojects suggest that AOWG presently has a "reasoned" Research genda. I believe it is only necessary to explore how AOWG can "fine tune" and maximumly use this agenda. The following items are proposed:

1. Is there sufficient duplication between "components" of projects (e.g., mortality) to adequately provide valid conclusions? To address this issue the Science Panel should evaluate mortality, morbidity and reproductive components of the appropriate studies. For example, the VA has a mortality study of 60,000, yet the VA Twin Study and two of CDCs Epidemiologic studies will provide mortality information.

2. Are the procedures used to collect the data comparable between studies thus permiting comparisons of results? Again the Science Panel (or an independent group of scientists) can evaluate this item.

3. Are the populations (cohorts) involved in each study sufficiently defined so as to avoid using the same individual in more than one study. I note with some concern that both NCI and CDC will be using cases from SEER.

4. The scope of the AOWG research effort appears to be centered around the Vietnam veteran. A formal declaration of that scope should be made or is it appropriate for the AOWG to play an extended role and oversee all research on dioxins and phenoxy herbicides in the Federal government? If the latter is the selected option than it will be important to explore the individual research projects of CDC, EPA and DOD

Thank you for the opportunity of assessing the AOWG Research Agenda. I look forward to reviewing the comments of the participating agencies.

The Deputy Administrator
of Veterans Affairs
Washington, D.C. 20420

MARCH 9 - 1984

Edward N. Brandt, Jr., M.D.
Chair Pro Tempore
Agent Orange Working Group
Department of Health and Human Services
Room 716-G, Humphrey Building
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Dr. Brandt:

As decided at the last meeting of the Agent Orange Working Group, the Veterans Administration staff has reviewed the report of the Subcommittee on Research Agenda submitted December 15, 1982. I enclose our comments following this review. Please do not hesitate to let us know if we can contribute further to the development of a Research Agenda.

Sincerely,

EVERETT ALVAREZ, JR.
Deputy Administrator

Enclosure

Comments on Research Agenda

As requested, we have reviewed the Research Agenda prepared for the Agent Orange Working Group in 1982. The considerations raised at that time are still relevant, especially the close relationship between Agent Orange, the phenoxy herbicides, and TCDD as research subjects.

1. Phenoxy herbicide and TCDD roster

One area of investigation has aroused more interest and concern than any other, namely, the long-term effects on humans of exposure to these substances. The problems for investigators have centered on the evaluation of exposure initially and then the maintenance of contact with the exposed people. The first difficulty includes obtaining and evaluating records to estimate exposure, the latter involves retaining and updating rosters with addresses.

Several groups are now compiling information of importance to the continuing evaluation of exposed persons. After the current status of their health is determined, the records may be destroyed or dispersed. Several federal and some state agencies are involved independently in the present evaluations. They include NIOSH, NCI, VA, EPA, CDC, Air Force, New York state officials and the Army Agent Orange Task Force.

It seems reasonable to establish a single repository of records compiled for current projects in order to make them available for future "follow-up" studies. The records would include as a minimum a roster of names, identifiers, addresses, etc. as well as the evaluation of each individual's exposure or control status.

Such a data collection, however, may violate current laws and regulations protecting the privacy of individuals. Furthermore, no single federal agency has the responsibility, authority, and funding for maintaining such a collection. It may be necessary to obtain legislative action to authorize and fund the effort. The AOWG seems the logical origin of a request for a joint facility of this type, a request that includes suggested means for protecting the privacy and rights of the persons included in the roster.

2. Access to information

A closely related area of research difficulty consists of the impediments encountered in seeking information from federal sources about individuals, a present handicap to epidemiological research. The difficulties were created by legislation and regulations designed to protect the privacy and other rights of citizens. This end is, of course, most desirable and the protection should be preserved.

Legislation will be necessary before the protected information is available to federal and other epidemiologists with justifiable research needs. The information they seek includes identifiers, such as social security numbers, current addresses, and vital status.

Measures to protect the individual's rights can be made part of a new law, including penalties for improper dissemination of information by the investigators and prior approval by a recognized authority before release of information to the investigators. The latter provision could even include a judicial review resembling a subpoena duces tecum, if this were believed necessary, before releasing the information.

3. Research Agenda

The "Possible Form of An Agenda," Attachment F to the December 15, 1982, Report of the Subcommittee on Research Agenda, covers the areas that need investigation with respect to the consequences of Agent Orange exposure. The suggested areas are broad and it would be well to emphasize that long-term effects are most likely to appear as some form or forms of malignant neoplasm. This re-enforces the argument for continuing to maintain rosters of persons exposed to phenoxy herbicides, including Agent Orange, or TCDD since the lapse between exposure and tumor-formation can be several decades.

DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institute of
Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, N.C. 27709

Memorandum

Date February 22, 1984

From Chief
Biochemical Applications Section, BRAP

Subject Review of AOWG Agenda

To Director, NIEHS

In regards to the defined question of Agent Orange effects on soldiers in Vietnam, there really isn't a great deal that can be done except to perform careful epidemiological studies focussing on possible changes in rates of cancer and fertility. Additionally, animal models that reflect appropriate exposure conditions should be evaluated and risk analyses made.

I have a number of comments regarding the attachments as they include some misinformation and they do not clearly state some important research areas. These comments are as follows:

1. We really need analytical methods to determine blood levels of TCDD.

2. There is a lack of good dose response data in susceptible vs. resistant species which look at a variety of endpoints such as carcinogenesis, fertility, thymic atrophy, death, and hepatic AHH activity. This information would provide information useful in determining if multiple mechanisms of toxicity exist and coupled with receptor occupancy data would help us evaluate the role of receptor(s) actions in each toxic response. Risk analyses then could more easily be made for each toxic effect. Moreover, the role of a possible endogenous ligand for the TCDD receptor might be critical to understanding mechanism(s) of action of TCDD and related compounds.

3. Discovery of markers of TCDD actions that persist long after the exposures would be quite useful in human monitoring studies. Along these same lines, sensitive indicators of human fertility need to be developed and applied.

4. Animal studies on the possible potentiative actions of chemicals that bind the TCDD receptor(s) need to be undertaken.

5. The VA summary contains some misinformation as itemized below.

   a) 1-7, last line; several species have the receptor

   b) 1-10, top line; the LD_{50} range is 1-5000 µg/kg.

c) 1-12, 2nd conclusion; TCDD is considered to not be a potent DNA damaging agent. Since it is such a potent acute toxin and tumor promotor and is not very DNA reactive (irreversible interactions) we should look elsewhere for mechanism of action.

d) 1-13, 4th conclusion on "carcinogenicity" this statement doesn't make much sense; TCDD is clearly a tumor promotor in the 2-stage model for skin and liver carcinogenesis.

6. Pharmacokinetic studies should focus on relative concentrations of TCDD as a function of (a) exposure (b) organ (c) cell type and (d) receptor binding. This should be done for a series of TCDD analogs and the pharmacokinetic data should be related to toxic responses such as tumor promotion.

7. Studies need to be performed on the possible existence of TCDD receptor in peripheral blood and if present we need to know if receptor properties and number reflect tissue concentrations.

8. Is there a higher incidence of fish cancer in polluted regions?

9. Are there qualitative species differences in metabolism of TCDD that could possibly account for wide species variation? If only quantitative species variations can be found, then metabolism is probably not an important factor in toxic responses.

10. The tables on metabolism of dioxin and related compounds and mechanism of action (comparative properties) are filled with errors.

George W. Lucier

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 24 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Dr. Ed Brandt
Chair, Agent Orange Work Group
Assistant Secretary for Health
Department of Health and
Human Resources
Washington, D.C. 20201

Dear Dr. Brandt:

The December, 1982 report of the Agent Orange Work Group's Research Agenda Subcommittee has been reviewed within the Environmental Protection Agency (EPA).

We are in general agreement with the thrust of the report; namely, it is both feasible and desirable to establish a research agenda designed to address questions associated with the long-term health effects of phenoxy herbicides and their contaminants. It is important, however, to amplify the note stuck in the report where it cautions against using the research agenda as a means of establishing individual agency priorities. Rather, the agenda should serve as a guide for researchers within and outside the government to aid them in determining how they might contribute to the total effort.

We believe that the Science Panel should take the information being gathered on the FY 84 and FY 85 government-sponsored studies and integrate it with what is known about the problem in order to generate a description of where we stand today. This would form the basis upon which the agenda would be built.

The Agency believes that the following areas should be considered for inclusion in such a strategy:

Fate, transport and ultimate bioavailability of 2,4,5-T, 2,4-D and 2,3,7,8-TCDD.
Mechanism of action of these compounds.
Background levels of 2,3,7,8-TCDD in the environment, including humans.
Absorption, distribution, and metabolism of 2,3,7,8-TCDD in various species, including primates.
Destruction methods for 2,3,7,8-TCDD.
Environmental and health effects of Agent Orange and 2,3,7,8-TCDD as might be revealed from examination of previous spray areas.

Development of less expensive analytical methods for the detection of 2,3,7,8-TCDD in the environment and in humans.
Therapeutic treatment for folks exposed to Agent Orange and 2,3,7,8-TCDD.
Effects on male reproduction.

We look forward to working with you further on this important, complex problem.

Sincerely,

John A. Moore, DVM
Assistant Administrator
for Pesticides
and Toxic Substances

[redacted]

[redacted]

TAB C

Attachment C

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date · FEB 28 1984

From Chair Pro Tempore
Agent Orange Working Group

Subject Functions, Operational Activities and Organization of the AOWG

To Members
Agent Orange Working Group

At our first meeting, I promised to write my thoughts about the functions, operational activities and organization of the AOWG. After many discussions and some thought, I would like to offer the following outline for discussion.

FUNCTION

The AOWG is to coordinate the Federal Government's efforts to determine the health effects, if any, of exposure to Agent Orange of Vietnam Veterans. It is not to be prescriptive, but rather to develop the mechanisms to insure that a coordinated, total effort is forthcoming with each department and agency accomplishing a part of the total effort according to its own mission. The functions of the AOWG are limited to Agent Orange and Vietnam Veterans, and will be concerned with dioxin and related chemicals only insofar as that involvement contributes directly to the primary mission.

OPERATIONAL ACTIVITIES

To accomplish its priority mission, the AOWG must be concerned with the following:

- the development of policies;
- the setting of priorities; and
- the guidance of implementation.

Specifically, the AOWG, being concerned with the scientific risk assessment of Agent Orange, has the following principal activities:

o Research

- Defining the scientific needs and seeing that they are met.

- Reviewing of research activities both as to design and results.

- o Resources
  - Definition of resource needs to meet the defined research goals and methods for meeting them.
  - Resources include funding, people and access to necessary information.
- o Accountability
  - Define policies for timely and complete information dissemination.

The above outline should permit the AOWG to achieve its mission and meet its coordination goals.

ORGANIZATION

In view of AOWG's mission and activities, the following organization is proposed:

- o Science Panel

  To include three sub-panels with the following purposes:

  - Research Agenda - This sub-panel will provide an agenda of necessary research to be completed. The agenda will be updated yearly unless there is a scientific accomplishment dictating an earlier review.
  - Research Review - This sub-panel will review all planned research for adequacy of design and conformance with the research agenda. It will (1) give one of four conclusions after review: agree with or without suggestions, agree but with necessary modifications, disagree due to inadequacies of design, or disagree as inconsistent with the mission of AOWG; and (2) comment on likely resource requirements.
  - Advisory Committee - This sub-panel composed primarily of nongovernment scientists, will review the results of ongoing or completed research projects and give their analysis of same.

- o Resources Panel

  This panel will further define the resources necessary to accomplish proposed and ongoing research in concert with the implementing department or agency.

- o Public and Congressional Affairs Panel

  This panel will define the policies to be used in information dissemination to insure that such dissemination is timely, accurate and complete.

To make this organization most effective, it will be necessary to have overlapping membership on the panels and sub-panels. Each agency should be represented on each panel if they choose to be so represented.

SUMMARY

The above descriptions are my thoughts on the AOWG. I look forward to our discussing them and your ideas. I will schedule a discussion for our April meeting, and would like to receive your written response by March 23. Following our development of a concensus, I will implement the decisions.

Edward N. Brandt, Jr., M.D.