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

SAB-EHC-88-005

October 23, 1987

OFFICE OF
THE ADMINISTRATOR

Honorable Lee M. Thomas
Administrator
U. S. Environmental Protection Agency
401 M Street, S. W.
Washington, D. C. 20460

Dear Mr. Thomas:

The Drinking Water Subcommittee of the Science Advisory Board's Environmental Health Committee has completed its review of the Office of Research and Development's Health Effects Research Laboratory's Drinking Water Disinfection and Disinfection By-Products Research Program, and is pleased to transmit its report to you. The Subcommittee reviewed this program at a public meeting at the laboratory in Cincinnati, Ohio on June 4-5.

This review is especially timely in view of the growing recognition among scientists, engineers, governmental officials and water supply providers of the public health risks associated with the continuing incidence of waterborne disease, and the increasing need to investigate the public health implications of the use of alternative disinfection techniques and their by-products.

In general, the Subcommittee concludes that current research efforts are well focused in that they appropriately address a number of scientific issues that currently confront the Office of Drinking Water. The caliber of the research personnel and the quality of the individual research projects is generally high. Each researcher appeared to be quite enthusiastic about his/her own research efforts and supportive of each other's projects. The current research efforts presented by EPA staff to the Subcommittee focused almost exclusively in the area of chlorination and the by-products resulting from this treatment process. This is understandable in view of the complexity of the problem, as well as the widespread current usage of chlorine for disinfection.

The Subcommittee's major recommendation is that more attention should be devoted to the potential toxicity problems that could arise from alternatives and/or adjuncts to chlorination such as chloramination, and the use of ozone, chlorine dioxide and other disinfectant processes. In view of the number of treatment systems that are turning to the use of alternative treatment approaches, it is necessary to expand the research focus to determine which treatment methods protect public health most effectively, and to compare the relative effectiveness and risks associated with each treatment technology.

Considerable effort is spent in gathering data to fill in specific gaps in the data base. While this, in itself, is not unproductive, the Office of Drinking Water and the Office of Exploratory Research should more forcefully encourage long-range planning and management as, for example, the initiation of studies on ozone and other disinfectants. At the same time, the investigators need to have the time and resources to develop projects and programs in fundamental research on agents within the framework of the disinfectants program. Specific benefits of this latter approach are: 1) an increase in EPA's capability to identify emerging problems, and 2) providing the scientific staff with opportunities to further develop their skills and gain support for their work in the scientific community. Both of these activities can directly benefit and support EPA's ongoing regulatory activities.

There are definite deficiencies in the development and use in some areas that the Subcommittee believes are important in determining the total toxicological profiles of drinking water disinfectants and their by-products. Notable among these would be neurotoxicology (including the need and feasibility for behavioral studies), cardiovascular toxicology and immunotoxicology. The program is not sufficiently integrated with a readily available battery of tests for neurotoxicity or immunotoxicity. While the Subcommittee recognizes that the personnel and resources that can be assigned to the disinfectants program (and indeed the entire drinking water research program) are finite, such areas need to be addressed. It was somewhat surprising to the Subcommittee that some of this work was not, or could not, be conducted at the Health Effects Research Laboratory (HERL) in Research Triangle Park.

The Science Advisory Board appreciates the opportunity to review this research program. We request that the Agency formally respond to the scientific evaluation and advice presented in the attached report.

Sincerely,

Richard Griesemer

Richard Griesemer, Ph.D.
Chairman
Environmental Health Committee
Science Advisory Board

Norton Nelson

Norton Nelson, Ph.D.
Chairman
Executive Committee
Science Advisory Board

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

SEP 10 1987

OFFICE OF
THE ADMINISTRATOR

Dr. Richard Griesemer
Biology Division
Oak Ridge National Laboratory
P.O. Box Y
Oak Ridge, TN 37831

Dear Dr. Griesemer:

Enclosed is the report of the Drinking Water Subcommittee following its review of the Office of Research and Development's Health Effects Research Laboratory's Disinfection and Disinfection By-Products Research Program. I reported briefly on this review at the meeting of the Environmental Health Committee on August 11, 1987.

I am submitting this report for final approval by the Environmental Health Committee and the Executive Committee.

Sincerely,

Gary Carlson

Gary Carlson
Chairman
Drinking Water Subcommittee

SAB-EHC-88-005

Review of the Office of Research and Development's Health Effects Research Laboratory's Drinking Water Disinfection and Disinfection By-Products Research Program

Report of the Drinking Water Subcommittee

Environmental Health Committee

Science Advisory Board

U.S. Environmental Protection Agency

October 1987

U.S. Environmental Protection Agency

Notice

This report has been written as part of the activities of the Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide a balanced expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by EPA and, hence, its contents do not necessarily represent the views and policies of the EPA, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

U.S. Environmental Protection Agency
Science Advisory Board
Drinking Water Subcommittee

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EXECUTIVE SECRETARY

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* Did not participate in the June 4-5 meeting to review the Health Effects Research Laboratory's Disinfection and Disinfection By-Products Research Program.

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I. Executive Summary

The Drinking Water Subcommittee of the Environmental Health Committee of EPA's Science Advisory Board has completed its evaluation of the Drinking Water Disinfection and Disinfection By-Products health research program. This review is especially timely in view of the growing recognition among scientists, engineers, governmental officials and water supply providers of the public health risks associated with the continuing incidence of waterborne disease, and the increasing need to investigate the public health implications of the use of alternative disinfection techniques and their by-products. Efforts currently taken to reduce waterborne disease should not, in the Subcommittee's view, ignore the potential or actual risks that occur following the application of disinfection techniques.

The current research efforts presented by EPA staff to the Subcommittee focused almost exclusively in the area of chlorination and the by-products resulting from this treatment process. This is understandable in view of the complexity of the problem, as well as the widespread current usage of chlorine for disinfection. The Subcommittee strongly believes, however, that more attention should be devoted to the potential toxicity problems that could arise from alternatives and/or adjuncts to chlorination such as chloramination, and the use of ozone, chlorine dioxide and other disinfectant processes. In view of the number of treatment systems that are turning to the use of alternative treatment approaches, it is necessary to expand the research focus to determine which treatment methods protect public health most effectively, and to compare the relative effectiveness and risks associated with each treatment technology.

Specific issues highlighted by the Subcommittee, in view of these general conclusions, include:

o The potential scope of the research program, in terms of the number of compounds that may be present in drinking water as a result of disinfection, and the large number of potential target organs and systems, is appreciated by the investigators as well as the management of the program. The program appears to have made good progress in view of the enormity of the disinfection problem and the limited personnel and funding resources. Current research efforts are also well focused in that they appropriately address a number of scientific issues that currently confront the Office of Drinking Water.

o Identification of disinfectant by-product compounds. It should not be assumed that separation and identification methods can be transferred directly from the study of chlorine by-products to the more polar and labile by-products expected from ozone and chlorine oxide and the more basic, higher molecular weight compounds expected from chloramines. Some fundamental work in these analytical methods will be required, but it is not clear to the Subcommittee that the program has sufficient personnel or advanced instrumentation for these tasks. There is a need to field test analytical methods. Interferences and other analytical difficulties

often make measurement of disinfectant residuals and by-products much more difficult in the field than under controlled laboratory conditions.

o Subacute and subchronic toxicity testing of disinfectant by-products. To date, most of the program's efforts have addressed chlorine and its by-products, with lesser attention devoted to chlorine dioxide and chloramine and none, as yet, to ozone and its by-products. It should re-examine the scientific rationale for using the 10-day test because the more frequent practice is to use 14-day tests for subacute studies. Consideration should also be given to initiating further studies on potential adverse effects identified in these routine studies.

o Developmental and reproductive toxicology. The program currently addresses a most relevant scientific question, that is, the identification of agents that have selective toxicity for the embryo while lacking toxicity for the mother. Researchers in the program have identified at least two agents capable of producing adverse effects in the conceptus at treatment levels lower than those needed to produce acute signs of toxicity in the mothers. Compounds such as these represent a significant developmental hazard, and they merit further study as priority issues.

o There are definite deficiencies in the development and use in some areas that the Subcommittee believes are important in determining the total toxicological profiles of drinking water disinfectants and their by-products. Notable among these would be neurotoxicology (including the need and feasibility for behavioral studies), cardiovascular toxicology and immunotoxicology. The program is not sufficiently integrated with a readily available battery of tests for neurotoxicity or immunotoxicity. While the Subcommittee recognizes that the personnel and resources that can be assigned to the disinfectants program (and indeed the entire drinking water research program) are finite, such areas need to be addressed. It was somewhat surprising to the Subcommittee that some of this work was not, or could not, be conducted at the Health Effects Research Laboratory (HERL) in Research Triangle Park.

o More resources should be provided for epidemiological studies of disinfection systems using both chlorination and other treatment techniques. In this area interactions and joint funding with other organizations, such as the National Cancer Institute, should be continued. Also, further review is needed of the "crash" effort to develop epidemiological and other studies on the possible role of chlorination in relation to cardiovascular disease.

o There is a need to incorporate within research objectives a continuing program for studying mixtures of compounds both in methodology development and testing of water concentrates.

o [redacted] effort is spent in gathering data to fill in specific gaps in [redacted] base. While this, in itself, is not unproductive, the Office of [redacted] Water and the Office of Exploratory Research should more forcefully encourage long-range planning and management as, for example, the initiation of studies on ozone and other disinfectants. At the same time, the investigators need to have the time and resources to develop projects and programs in fundamental research on agents within the framework of the disinfectants program. Specific benefits of this latter approach are: 1) an increase in EPA's capability to identify emerging problems, and 2) providing the scientific staff with opportunities to further develop their skills and gain support for their work in the scientific community. Both of these activities can directly benefit and support EPA's ongoing regulatory activities.

o Related to the foregoing is the difficulty the Subcommittee had in gaining a clear insight into how projects, other than those directly related to data gathering, are initiated and continued. The criteria used in judging the worthiness of individual projects and the mechanisms for their initiation were also not clarified. Equally important is the problem the Subcommittee had in ascertaining how projects are terminated so that new ones may begin. Such endpoints are critical in the distribution of the programs's limited resources.

II. Introduction

A. Drinking Water Disinfection and Disinfection By-Products: An Issue of Public Health Concern

The primary method of disinfection currently used in public drinking water supplies in the United States is chlorination. Through complex chemical interactions the chlorination process can introduce carcinogenic compounds into the drinking water such as the general class of trihalomethane compounds, including chloroform. The health effects resulting from chlorination are only partially known to scientists and public health officials. As part of its regulatory program, EPA's Office of Drinking Water (ODW) is considering alternatives to chlorination such as chloramination, and the use of ozone, chlorine dioxide and other disinfectant processes. To determine which treatment method(s) work most effectively to protect public health, a comparison of their relative effectiveness and the risks associated with each treatment technology needs to be performed.

The detection of synthetic organic chemicals in public water supplies helped motivate the Congress to enact the Safe Drinking Water Act of 1974. Amendments to this Act in 1977 reflected a growing Congressional awareness and concern over the issue of disinfection by-products by mandating EPA to conduct a study of the reaction of chlorine with humic acids to understand the effects of the contaminants that result from such reaction on the public health and on drinking water safety, including carcinogenesis. Subsequent amendments in 1986 specified a time table for EPA to regulate 83 contaminants. By June, 1989, an additional 25 contaminants listed by EPA must be regulated. Some of these latter compounds may also be disinfection by-products.

The re[illegible] disinfection deficiencies viewed by EPA as responsible for outbre[illegible] waterborne disease from 1971-1985, are presented in Table I. [illegible] over health effects associated with disinfection agents and their by-products has centered on chloroform because of the detection of high concentrations in drinking water and the known toxicity of this compound from other routes of exposure. During the past decade, other studies, some funded by the EPA, reported associations betweeen a range of health endpoints (including cancer) and chlorinated water supplies. Over time, this work stimulated interest in examining alternatives to chlorination techniques.

B. Subcommittee Charge and Review Process

At the request of the Deputy Administrator and the Assistant Administrator for the Office of Research and Development (ORD), the Science Advisory Board (SAB) Executive Committee agreed to carry out a scientific review of the component of EPA's research program on Drinking Water Disinfectants and their By-Products conducted by the Health Effects Research Laboratory. The Committee authorized the Drinking Water Subcommittee of the Board's Environmental Health Committee to conduct the review. This action by the Executive Committee is part of a continuing series of SAB research program reviews that is intended to provide independent scientific advice on the objectives, relevance and quality of ongoing research, and to identify any needed modifications to the content and direction of individual research programs. This specific program review was requested by senior EPA managers because of their desire to obtain an expert evaluation of the capability of this program to support the Agency's regulatory information needs.

The Drinking Water Subcommittee addressed four overriding issues in its review. These included:

- Assessment of the scientific adequacy of the conceptual design of the research program, the goals it sets and the needs it fulfills.

- Evaluation of specific objectives of the research program as they support the assessment of risks posed by drinking water disinfectants and their by-products.

- Discussion of cross-cutting scientific issues and integration with other research programs within EPA.

- Formulation of recommendations regarding the program's ability to meet future EPA needs, and flexibility for addressing future issues.

The Subcommittee met in public session on June 4-5, 1987 in the auditorium of EPA's Andrew N. Breidenbach Environmental Research Center, Cincinnati, Ohio. Notice of the meeting was published in the Federal Register on May 15, 1987, Volume 52, No. 94, Page 18447.

Table 1
Water Supply Deficiencies Responsible
for
Waterborne Outbreaks, 1971-1985

Defficiency		Outbreaks	Reported Illnesses
Surface Water Source:			
Untreated		31	1,647
Disinfection Only, or Inadequate Disinfection		67	23,028
Disinfection With Other Treatment		5	969
Filtration		20	9,852
	Totals	123	35,496
Ground Water Source:			
Untreated		154	11,266
Inadequate Disinfection		90	40,893
Disinfection With Other Treatment		1	22
	Totals	245	52,181
Distribution System:			
Cross-connection		44	8,124
Contamination of Mains/Plunbing		14	3,413
Contamination of Storage		11	6,244
Corrosive Water		10	147
	Totals	79	17,928
	GRAND TOTAL (REPORTED)		105,605
		(ESTIMATED)	300-500,000

Source; G.F. Craun, J. Am. Water Works Assoc., March 1987

The specific focus of the Subcommittee's meeting was the review of "The ORD Health Research Program on Drinking Water Disinfectants and Their By-Products: An Issue Paper Prepared for a SAB Program Review" (May 1, 1987), a document prepared by the Toxicology and Microbiology Division of the Health Effects Research Laboratory in Cincinnati. EPA staff provided supplemental documents to the Subcommittee at its meeting, in addition to oral presentations. Review and discussion of these materials furnished the basis of the Subcommittee's report. Subcommittee members had the opportunity to question ORD scientific staff and research managers, and staff of the Office of Drinking Water, as well as offer their own individual and collective views on the research program.

The Subcommittee enjoyed the full cooperation and support of EPA staff during the course of its review and wishes to express particular appreciation to Dr. Elmer Akin, Director (until July 1987) of the research program on Drinking Water Disinfectants and Their By-Products, and Mr. David Kleffman, ORD Office of Health Research, for their assistance in coordinating the Agency's preparation for this SAB review.

III. Major Elements in HERL's Research Program for Disinfectants and Disinfectant By-Products

A. Identification of Disinfection By-Products

Until recently, research in this area conducted by EPA's Health Effects Research Laboratory has focused almost exclusively on the separation and identification of chlorination by-products. This is an extremely relevant area from a regulatory perspective, but the need to obtain information on by-products of other chemical oxidants/disinfectants is becoming a much higher priority. Current analytical chemistry research has abruptly shifted to the study of ozone by-products, an area where major information gaps exist.

The Subcommittee concurs that work in this area is needed and vital to the Agency's mission, but it cautions that research on chlorine dioxide and chloramines should not be neglected. Moreover, it cannot be assumed that separation and identification methods can be transferred directly from the study of chlorine by-products to the more polar and labile by-products expected from ozone and chlorine dioxide and the more basic, higher molecular weight compounds expected from chloramines. Some fundamental work in these methods will be required, but it is not clear to the Subcommittee that the program has sufficient personnel or advanced instrumentation for these tasks. Even closer working relationships with other EPA and extramural units that are active in this area are essential if EPA is to gain maximum use from its limited research resources. Staff experience in HPLC and HPLC/MS or MS/MS methods could considerably aid this program's efforts as its changes its emphasis from non-polar to polar by-products. An added benefit following the development of an analytical methodology for polar compounds such as ketones, aldehydes, alcohols and acids would be the generation of contaminant data for these chemicals in water supplies. Very little information is available on their occurrence in drinking water because a routine screening methodology with a reasonably sensitive detection limit is not available, and yet these compounds are widely used in industry and have a high potential for contaminating drinking water from past or present use.

the MX compound [redacted] active in an in vitro cytogenetics model but inactive in the in vivo [redacted] nucleus assay. It is also significant that use of a microsomal enzyme preparation (S-9) practically removes the activity observed with TA-100. The program should emphasize the in vitro - in vivo comparisons in order to acquire an early indication of potential hazard even if the Salmonella assay indicates a compound is a potent mutagen.

There is an absence of knowledge on the biological activity of disinfection by-products produced by alternate means of disinfection. A strain of Salmonella typimurium, TA-102, has been derived that is sensitive to oxidative mutagens. If the Salmonella model continues to be used as a primary screen, this strain should be helpful to examine water concentrates for potential mutagens derived from the ozonation process. Also, careful applications of the Ames assay coupled to chromatographic techniques could be useful in following the concentration of water samples to indicate whether activity is associated with a chemical pre-existing in the water sample itself or an artifact of the concentration process.

D. Subacute and Subchronic Toxicity Testing

The assessment of toxicological data for a variety of chemical substances is a critical component of the research program. Subacute and subchronic testing is used primarily to provide scientific support to develop Maximum Contaminant Level Goals (MCLGs) and Maximum Contaminant Levels (MCLs) for noncarcinogenic chemicals, in addition to preparing health advisories for compounds with mutagenic or carcinogenic potential.

These uses necessitate continuous toxicological testing (and associated continuity in resources) to initiate and complete tests to evalute those chemicals whose potential public health impacts require further study, and to establish testing priorities of chemicals on an annual basis. To date, most of the program's efforts have addressed chlorine and its by-products, with lesser attention devoted to chlorine dioxide and chloramine and none, as yet, to ozone and its by-products.

The basic protocols adopted for the subacute and subchronic studies involve 4 and 3 dose levels, respectively, using 10 male and 10 female rats with corresponding controls. Routine body weights, hematology, serum chemistries and urinalysis, along with selective histopathology are monitored. These 14 day subacute studies are necessary to provide evidance of organ toxicity, the nature and development of toxicological effects and dose-response relationships between exposure and effects tested. In addition, these provide the basis for selecting doses for the 90-day studies and ultimately the lifetime studies usually for carcinogenicity or other long-term effects. The Subcommittee recognizes that such studies are time-consuming and place increased demands on the limited resources that must be provided and guaranteed for short and long-term Agency commitments.

The study of the disinfection by-products of ozone, chlorine dioxide and chloramine will require the use of analytical methods that are applicable to polar, high molecular weight and labile by-products, such as HPLC, HPLC/MS or MS/MS methods. Advanced instrumentation and possibly new personnel to support this effort will be needed.

One area that needs to receive more attention is that of analytical methods development. A need that exists regarding the measurement of disinfectant residuals and by-products is that analytical methods be provided that have been field tested. Interferences and other analytical difficulties often make measurement of disinfectant residuals and by-products much more difficult in the field than under controlled laboratory conditions.

B. Concentration for Toxicity Testing

One important activity in this area consisted of an extramural evaluation of several preconcentration procedures, especially adsorption methods. The study concluded that all of the methods tested have limitations, particularly in the recovery of very polar compounds. The researchers have also compared low pH XAD-8 extraction with total lyophilization in order to determine if the observed mutagenicity of low pH XAD extracts observed in an earlier study was an artifact. These represent important and complex efforts that are relevant to regulatory decision making and should be continued. They will become increasingly important as the program begins to focus on polar by-products from ozonation and other oxidation/disinfection processes. Additional in-house expertise is needed on concentration methods for toxicity testing of polar, higher molecular weight and more labile by-products such as those expected from the use of ozone, chlorine dioxide and chloramines.

C. Mutagenicity

Mutagenicity models have been a major feature of HERL's approach to identify potentially hazardous substances resulting from water disinfection, primarily with chlorine. The Ames Salmonella assay has been useful in measuring the mutagenic activity of water concentrates, isolation of active components in a mixture and directing attention to specific chemical structures for additional study. However, it is quite clear that the Salmonella assay does not respond well to several classes of chemicals, among which are certain chlorinated aliphatic and chlorinated aromatic compounds. The Subcommittee advises the program to utilize a mammalian cell gene mutation assay to augment the Salmonella model and thereby achieve a greater sensitivity for compounds derived from the chlorination disinfection process.

The results presented at the review on compounds derived from a chlorinated humic acid sample, especially the MX furanone, can serve to illustrate a principle of mutagenicity testing. That is the need to examine multiple endpoints both in vitro and in vivo to acquire perspective on potential hazard and/or risk determinations. It is significant that

The Subcommittee has several specific concerns with this part of the program. First, it questions the usefulness of the 10-day test. While it recognizes that this protocol was established to coincide with the 10-day health advisories, the more traditional subacute study involves 14-day testing. EPA should re-examine its scientific rationale for the 10-day test.

Second, the program is not adequately integrated with a readily available battery of testing for neurotoxicity or immunotoxicity, contrary to what was indicated. For example, the 10-day testing of chloropicrin suggested immunotoxicity based on histopathology of the thymus, and testing of dichloroacetic acid indicated neurotoxicity, but these have not been fully studied. While HERL conducts or contracts out some of these studies, it appears as if both of these functions are part of the activities in Research Triangle Park. The Subcommittee could not identify efforts to readily incorporate the necessary integration of immunotoxicity or neurotoxicity testing. Such integration is necessary not only from a scientific standpoint but also in wisely utilizing resources. It should not be difficult to achieve such integration. For example, the EPA neurotoxicology group at HERL in Research Triangle Park had been active in the design and validation of relatively simple neurological/behavioral tests which have been adopted under the Toxic Substances Control Act.

As more rapid and efficient batteries of tests develop, (either in vitro or in vivo) the program should begin to incorporate them into research protocols. Some flexibility and opportunity to phase in studies should be provided. This includes, for example, the possibility of using biochemical mechanisms of action, or SAR, and the study of chemicals other than chlorine, such as chloramine and chlorine dioxide, ozone and their by-products. However, until it can be demonstrated that in vivo testing using animals can be replaced by equal or better indicators of toxicity, this phase of the program's activities should be maintained.

The Subcommittee is also concerned that there may not be adequate opportunity to pursue additional studies on potential adverse effects identified in those primarily extramural studies.

E. Developmental and Reproductive Toxicology

Substances to which large and diverse groups of individuals are exposed by a variety of routes and intensities are priority areas for research. Coupled with this is the fact that the in utero conceptus is uniquely vulnerable to some test compounds and, since part of the population will be women of childbearing potential in which embryogenesis is completed before the woman is aware of the fact that she is pregnant, it is essential to have and continue major research efforts aimed at detecting agents that are selectively toxic to embryos but essentially nontoxic to the mother.

The existing research in developmental and reproductive toxicology addresses several of the most relevant issues regarding developmental toxicity. The Chernoff test identifies agents that have selective toxicity for the embryo. It does not discriminate the pattern of effects produced by specific agents, but this is acceptable because the pattern of effects is not highly meaningful information for early tests. In its expanded version, which is now an abbreviated Segment II, the study also provides an approximation of the No-Observed-Effect-Level (NOEL), at least for the rat, by the route of treatment used. Again, though not essential for a screening-type test, this is useful information. Finally, the protocol yields an approximation, or an impression, of the dose-response curve in a definitive study. In short, the program is currently addressing the most relevant scientific question, that is, the identification of agents that may be present in drinking water and have selective toxicity for the embryo. Pursuing this kind of inquiry, researchers can hope to avoid repetition of a thalidomide type problem.

Researchers in the program have identified at least two agents capable of producing adverse effects in the conceptus at treatment levels lower than those needed to produce acute signs of toxicity in mothers. Compounds such as these represent a significant developmental hazard. If results of this magnitude were seen for other types of toxicity, e.g. an Ames test, they would precipitate a series of concerns regarding both mutagenesis and carcinogenesis, and would elevate the compound for more detailed testing. Senior managers in the laboratory and within EPA need to more aggressively investigate the implications of these findings that detect chemicals that are a significant potential hazard for the conceptus.

While the program has a reasonable focus in the area of developmental toxicology, the Subcommittee believes that an additional emphasis should be placed on reproductive effects. This is true for both males and females.

F. Determination of Biochemical Mechanisms of Toxicity

A major responsibility of EPA is to evaluate the health effects of the chlorinated disinfection by-products in finished drinking water. A much more difficult scientific problem is determining the biochemical mechanisms by which these many chlorinated products exert their various toxic reactions. As yet, little is known of the target organ toxicity, reproductive and developmental effects, or the carcinogenicity of the varied halogenated compounds found in chlorinated drinking water.

As a portion of a long range study of possible biochemical mechanisms of toxic action, EPA researchers have investigated the nucleophilic capture of glutathione (GSH) in vitro (pH range of 6-8) by chloropropanone (MCP), 1,1-dichloropropanone (1,1-DCP) and 1,3 dichloropropanone (1,3-DCP). As expected, the reactions are base-catalyzed and presumably involve bimolecular displacement of chloride from the haloketones by the glutathionyl anion. The order of reactivity over the narrow pH range is: 1,1-DCP > MCP > 1,3-DCP. The physical-organic chemistry of these displacements appears to have been studied carefully and with insight.

At pH 8 or higher, reactions of the halopropanones may involve alpha-elimination and capture of glutathione rather than direct displacement.

What is not yet clear, however, is the biochemical relevance of the above experiments, the propriety of the glutathione model and the direction of future research in the above area. Can the SAR results obtained be predictive or are they merely descriptive? It would presently appear useful to establish the rates of disappearance, displacement, hydrolysis and capture of certain halogenated organics that are suspected to be highly toxic and are difficult to remove from water. There are, however, far too many chlorination products in drinking water whose rate constants for disappearance should be determined. If there is sufficient financial support, conjugate addition of glutathione to alpha, beta- unsaturated compounds, nucleophilic displacement by, and addition of, ammonia and amine systems, and detoxification of certain products of ozonolysis of drinking water should be modelled in vitro.

The Subcommittee recognizes the difficulties of designing meaningful in vitro experiments for determining the biochemical mechanisms of toxicity of different levels of drinking water quality. As with other projects, the Subcommittee believes that research for determining the in vitro mechanisms of toxicity of chlorinated water need independent peer review.

G. Evaluation of the Effects of Chlorine on Atherogenic Potential of Chlorinated Drinking Water

Research on the atherogenic potential of chlorinated water incorporates both animal and human trials as well as some epidemiological studies. Studies with pigeons demonstrated that serum cholesterol levels became elevated when birds were exposed to chlorinated drinking water. This initiated further investigations with monkeys and human volunteers. Currently, there are epidemiological evaluations of chlorinated and nonchlorinated water supplies, but these investigations are linked to hard and soft waters.

The Subcommittee has concerns regarding the design of studies and the future direction of this component of the program. The Subcommittee endorses the research review that is to take place in the fall. This review is urgently needed. Its objectives should include: 1) impartially examine the entire program, 2) critically review progress to date, and 3) help focus on crucial design issues as well as help the program determine the critical research necessary to strengthen or verify the evidence of an effect of chlorine in water on atherosclerosis. The necessity to develop this research in the manner that most quickly

clarifies the health hazards of chlorine in drinking water is of great importance because of the high percentage (approximately 33%) of the extramural budget ($843K) that is devoted to this research effort. There is the strong potential for the investigators to become lost in the rather complex and voluminous biochemical issues that can be followed up in this type of investigation, as opposed to identifying those critical experiments that will prove or disprove the issue before the Agency. This is especially true since there is really no basic hypothesis advanced for such an effort. The investigators also must guard against overstating results, especially in light of the experimental designs used (i.e., internal controls).

Another concern to the Subcommittee was the lack of reference in the presentations to the current status of heart disease in this country in relationship to the work being undertaken and some of the newly recognized, though still highly controversial, issues that could influence both the approach and the interpretation of the data currently generated. For example, mortality for cardiovascular disease has decreased in the United States by 34% and ischemic heart disease by 42% since 1968[1]. How this information is factored into the relevance of the current or expected findings from either epidemiological or human trials is unclear. For example, how much variability of risk factors or how much of the disease might be explained by chlorination of drinking water?

Also not addressed in any of the discussions was the Agency's view of those individuals at high risk to cholesterol (familial hypercholesterolemia). It may be that this sensitive part of the population is at higher risk from consumption of chlorinated drinking water than the majority of the population, if the evidence thus far presented is substantiated.

Several specific comments related to research projects are described below:

1. Epidemiological Studies

While understanding the rationale of selecting hard and soft water communities, the current design falls somewhat below the optimum because intermediate hardness was not included and most likely represents the drinking water of a large segment of the population.

Although the very preliminary data look especially interesting for women in the cohort, a possible confounding factor may be due to dietary changes that are effective at reducing total cholesterol by only 6.9%. Its value will be decreased, if a number of factors have not been controlled (i.e., diet, smoking history, exercise, and familial hypercholesteroliemia.) This

[1]The National Center for Health Statistics, Vital Statistics Report, Final Mortality Statistics, 1982.

last factor [redacted] important, and EPA should consider the next type of study [redacted] this effort. Appropriately designed retrospective studies [redacted] quickly address some of these issues and may be sensitive enough to detect reasonably large effects.

2. Human Trials

While it is understandable to use individuals as internal controls in order to convince the skeptics of the effect of diet and chlorine on cholesterol and HDL, the effect of diet alone over long periods must be ascertained. Without a nonchlorine-exposed control, this question cannot be adequately answered. The population selected for study is not typical of the U.S. population.

In the figure presented on "total cholesterol by the study period," the Subcommittee is concerned that the baseline value decreased so dramatically although, from the information provided, it appears that individuals had been placed on the high cholesterol diet upon entering the hospital. This is important because, if this value had been higher, the subsequent study values would most likely have not been significant. An approach to resolve this issue would be to evaluate to baseline twice before initiation of chlorine exposure.

3. Primate Trials

In this component of the program it would also be useful to have a set of animals that receive only the high cholesterol diet. The Subcommittee has a concern over the highly complex schedule of the protocol. The verification of the study by an independent laboratory is useful, and perhaps this work could include a control group that did not receive chlorine in the drinking water. The future direction of research in this phase should be carefully considered as to the detail required in plaque formation to serve the Agency's need. There was a tendency to overstate results and some lack of awareness of the effect of diabetes on cholesterol and HDL.

All the studies should state the concentrations of chlorine related to potential NOEL or Lowest-Observed-Effect-Levels (LOELs). Obviously, the concentrations eliciting effects in animals are far in excess of the concentrations likely to be experienced by the public. Thus, the need to perform controlled studies in humans at still higher exposure levels is questionable in view of the negative findings to date. A further general question that should be directed to the Office of Drinking Water is to document the number of supplies that are likely to continue using chlorine as a primary disinfectant as regulated THM levels decrease.

A general concern regarding both human and primate trials is the toxicity of the disinfectant itself compared to the by-products produced by these strong oxidants. The disinfectant itself reacts rapidly, especially at the high concentrations used in these studies.

H. Short-Term *In Vivo* Tests for Screening of Toxicants

The concept of utilizing short-term tests for identifying chemicals that have mutagenic or carcinogenic potential is an attractive one both from scientific and economic considerations. However, the major problems in implementing this approach are as follows:

- Not all carcinogens can be detected as genotoxic substances.
- The ability to identify and quantitate the probability of effects are issues that arise due to the intrinsic nature of the assays employed and criteria used to judge a particular response as positive or negative.
- *In vivo* evaluations of *in vitro* positive results depend in some cases on models whose sensitivities are low or require extensive testing with large numbers of animals. There are additional questions of whether the endpoint observed early in a treatment regimen adequately represents a slowly developing disease state produced by chronic administration of a chemical.
- The standard against which short-term tests are finally judged, the rodent bioassay, has serious flaws due to methods of testing and toxicity issues generated by dosage regimens that may not adequately reflect human exposure or potential hazard.

However, the tests suggested as a Tier I approach, the Ames assay and an *in vitro* cytogenetics model, are among those recommended for screening consideration. As knowledge and experience accumulates, it would be prudent to utilize short-term test models that have a sensitivity and specificity spectrum appropriate for the chemical class being examined. This raises important issues when testing mixtures. The Tier II assays that give additional perspective on *in vitro* genotoxic positives include the micronucleus test and *in vivo* metaphase analysis utilizing mouse or rat bone marrow cells. The DNA damage assay using unscheduled DNA synthesis (UDS) in rat hepatocytes has given a poor performance even with hepatocellular carcinogens. It may be more productive to quantify the number of cells in S phase in adult rodent livers as a function of time and dose than to attempt a UDS assay. The sister-chromatid exchange assay is a more sensitive indicator of potential *in vivo* genetic effects, but interpretation of its results represents a large challenge. Cell transformation assays are becoming more useful, especially when joined to the newer methods of DNA analysis, e.g. DNA fingerprinting and hybridization techniques. These techniques should be part of an exploratory toxicology program at the laboratory.

Other *in vivo* assays in a Tier II configuration, such as mouse skin painting, are useful in determining carcinogenic potential of compounds especially those where exposure patterns are best modeled by skin painting. Both the rat liver altered enzyme and mouse lung adenoma models have mechanistic and relevance problems that can be confounding for hazard evaluation purposes.

The utility of the matrix process could be quite substantive in assisting decisions on compound selection for further testing and hazard evaluation. However, the entry portal for compounds, the two mutagenicity models, may be too narrow to adequately identify subtances of concern.

Short-term and in vitro arrays for other types of toxicity should also be examined for how they may aid evaluation of the large number and mixtures generated by these processes.

I. Carcinogenicity

The carcinogenesis studies in progress focus on dichloroacetic acid (DCA) and trichloroacetic acid (TCA). Previous studies have shown that chronic administrations of either DCA or TCA are associated with an increased incidence of hepatic tumors in male mice. Thus, by definition, these two chemicals are formally designated as hepatocarcinogens. Ongoing studies extend this work by testing whether these two chemicals demonstrate a dose-response relationship for their carcinogenic activity in the male mouse liver. The studies are also broadened by studying their activity in female mice, including another species, the rat, and testing a related chemical, monochloroacetic acid. Other studies will be performed to determine the genotoxicity of these chemicals. These studies will test the induction of unscheduled DNA synthesis in hepatocytes, mutagenesis in mammalian cells, and nuclear abnormalities in cells that come into contact with chlorinated drinking water. Additional studies will test for other evidence of carcinogenic activity using assays of cell transformation in vitro, and will assay for initiation and promotion activity using the rat liver focus bioassay and the neonatal mouse liver system.

The topic considered most extensively in the presentation for this part of the program was the issue of peroxisomal proliferation. Studies were reported that described the extent of peroxisomal proliferation induced by DCA and TCA in mouse and rat liver. Other studies reported that prior initiation of hepatocarcinogenesis with ethylnitrosourea (2.5 ug/g b.w.) at 15 days of age did not increase tumor incidence. Studies of enzyme induction by TCA and DCA showed only small incremental increases of tumor incidence with further increases in peroxisome proliferation. Other studies reported that induction of palmitoyl CoA oxidase activity was notably lower in rats than mice and that there was particular sensitivity for the C57Bl strain of mice. In contrast to the mouse, TCA and DCA did not induce palmitoyl CoA oxidase activity in green monkey or rat cells.

This component of the HERL-Cincinnati program is responsible for evaluating of the carcinogenicity of substances present in drinking water. The choice of TCA and DCA for carcinogenicity tests is well founded. Both chemicals have been detected in drinking water, and initial studies have successfully demonstrated carcinogenicity in the livers of male mice. Would these studies have been pursued with the same priority if this categorical program did not exist? In general, however, this is a very favorable component of the program.

The presentations and written documents did not discuss the process used by this program to select chemicals for evaluation or to establish the order of priority for their testing. This question is important because the choice of one chemical for testing may preclude the testing

of another, more relevant and more hazardous chemical. Also the interrelationships of this program, the Office of Drinking Water, and other Federal resources such as the National Toxicology Program, should be considered in describing how the choices and priorities for carcinogenicity testing are determined.

The choice to focus much of the attention and financial resources of this group narrowly on the peroxisomal proliferating potential of TCA and DCA as a possible mechanism for their carcinogenic activity certainly seems premature. Before this line of investigation is vigorously pursued, it would be valuable to establish that TCA and DCA have carcinogenic activity in rats. The isolated observation of apparent carcinogenicity exclusively in the mouse liver will allow the significance of this observation to remain in doubt. Both TCA and DCA are strong organic acids, and both have great potential to exert toxic effects in the mouse liver following oral administration. Such toxicity could cause an accelerated growth rate in surviving hepatocytes, and this proliferation, coupled with the genetic instability of the mouse, could cause an increased rate of "spontaneous" transformation. It could also be argued that mechanisms of carcinogenicity of peroxisome proliferators will continue to be studied by other laboratories that originated these observations. These laboratories are likely to be far better equipped to pursue this topic. Conversely, it is less likely that independent investigators will pursue the questions of the role of toxicity in producing hepatocarcinomas in mice. This might be a better choice for investigations by EPA.

Aside from the issue of the choice of areas of study, the design of the experiment deserves comment. The work presented was an interesting collection of what seemed to be original observations. The studies, however, did not seem to have a clear focus and the individual investigations did not appear to have a strong line of continuity. What has been proven by these experiments? Are further unfocused investigations of this type appropriate at this time?

In summary, this program component performs some studies that are appropriate and probably of high priority (long-term carcinogenesis studies). The short-term studies on peroxisome proliferation are probably of lesser value. More long-term studies or the proposed assays of genotoxicity are preferable. The larger issues about selection of chemicals for study, the interactions between HERL and ODW, and connections to other Federal units performing carcinogenicity testing, were not considered in sufficient detail.

J. Exposure Assessment

The component of the program that addresses exposure assessment focuses to varying degrees on a number of generic regulatory problems but also have specific applicability to drinking water disinfectants and their by-products. The staff presented five issues: 1) macromolecular alkylation of physiologic

substances to hemoglobin (as an index of combined human exposures to genotoxicants), accumulation of selected chlorinated organic compounds in fish fat and muscle (as an indicator of daily dose from one part of the food supply); 3) examination of one class of chlorination byproducts, the haloacetonitriles, for the ability to cause DNA strand breaks (as an indication of chronic injuries relatable to short-term exposures); 4) a search for improvements in low-dose extrapolation techniques by elucidating pursuit of the underlying bases of cancer causation by trichloroethylene and isomers of dichloroethane in laboratory animals (to examine the weight of evidence that cancers observed in laboratory mice may be more likely due to promotional events related to secondary mechanisms invoked only via high concentrations of hepatic metabolities, hence possibly altering the approach to estimating possible risks to human health); and 5) the biological reactions postulated in the newly proposed Moolgavkar-knudson multi-stage model.

The individual experimentation described is thoughtfully conceptualized and carried out with appropriate technical rigor. In each case, there is a clear understanding of the background information from which an hypothesis is proposed, the hypothesis is clearly articulated, and the results interpreted in a balanced fashion.

The selection by investigators of either research areas or individual studies within areas was not discussed; hence, no comment can be made about the relative technical merits of research undertaken or proposed. The Subcommittee notes that no reference was made to the consideration of the role of research activities in reducing uncertainties in the Agency's evaluation of the consequences on human health of any or all of the chlorination by-products (or other group of substances to which the generic research could be of relative value). For example, what are the relative advantages of using adducts to hemoglobin compared to other forms of delimiters of systemic exposure? Were the documented gains substantial in relation to other options? With limited resources, such a structured analysis is not only desirable but essential.

Selecting research priorities requires an understanding of priorities of the regulatory program that is the client for the research. When initiating a new area of regulatory activity, it may be sufficient to ask researchers to focus on numerous fronts simultaneously; however, as a regulatory area matures, topics of high relevance should surface and represent opportunities to guide future research endeavors. It is clear that communication between the research and regulatory staffs is open and continuous; but the level at which priorities are assigned appears to be less than systematic to achieve achieve a full harmonization between the two entities. For example, while both agree that disinfection by-products are of paramount importance, agreement is unclear that the indirect mechanisms of cancer (such as those suggested for trichloroethylene and dichloroethylenes via trichloroacetic acid and dichloroacetic acid, respectively) are of value to articulated policy objectives. Similarly, while scientific interest is commendably high for a more advanced low-dose extrapolation model than the presently used linearized multi-stage model, it is unclear whether such activity is of major interest

to the [redacted] Drinking Water which will be faced inexorably with the selection [redacted] of a model incapable of being validated at low doses. As a first [redacted]ation of the issue of priorities, the method of measuring tissue dose to classes of agents (e.g., genotoxicants) is of experimental value particularly for epidemiologic studies; however, there is little indication of how such a method would be used effectively to regulate substances.

Although the presentation was necessarily brief, two important omissions include: the absence of experimentation to reduce uncertainties on extrapolating toxicity data from laboratory animals to humans; and the absence of a significant effort to elucidate the collective toxicity of mixtures of substances in tap water. The first is important because it addresses the question of the appropriateness of assuming that rodent responses are in fact indicative of those in humans. In vitro technology with human cell lines provides the tools by which to enhance the certainty either of possible human injury from substances in the environment or of the lack of relevance for humans of a laboratory observation. The second recognizes the complexity of chemical exposures in tap water, and can be addressed experimentally in ways that lead to supportable conclusions regarding safe exposures and health risks.

Several research directions include: the examination of the toxicity of mixtures; the application of in vitro methods to bridge the gap in extrapolating test results from experimental animals to humans; the elucidation of the relative contributions of exposures and injuries by alternative routes of exposure; the role of organ repair processes and reserve capacity for estimating the potential for chronic toxicity; and evaluating the pathways of pathology that are particularly critical to the manifestation of clinical disease.

K. Epidemiology

The epidemiology program at the EPA-HERL in Cincinnati is modest in size, meaning number of staff and budget. It was quite active before 1981 when it was essentially discontinued, and then resumed in 1983 with fewer resources than in the pre-1981 period.

The program was last reviewed by an external advisory panel in December 1983. At that time, additional epidemiological research was recommended to determine the associations between water quality and cancer and cardiovascular diseases.

The program does not perform in-house epidemiological investigations; however, it does fund such external studies and the small staff interacts substantially in the design and interpretation of the results of these investigations. It cooperates with other governmental organizations in the development of these and related studies and in their joint funding. These have included the National Center for Health Statistics and the National Cancer Institute (NCI).

Previously in the late 1970's, small-budget "ecological" studies supported by [redacted] group provided preliminary evidence of relationships of some cancers with chlorination. In the 1980's the small number of funded case control and other epidemiological studies provide continuing evidence of such relationships, especially with colon and bladder cancer. These studies support the animal and in-vitro evidence of the effects of chlorination by-products.

The Subcommittee's specific conclusions and recommendations on the epidemiological component of this program include:

o This small epidemiology group has interacted extensively with, and is respected by, outside scientists in these efforts, and has effectively utilized limited resources.

o The group has initiated research important for the Agency's regulatory activities in the area of controlling disinfection by-products, a major thrust of the Office of Drinking Water.

o Funds have not been provided for epidemiological studies of disinfection systems other than chlorination and chloramination. The rapid momentum towards the use of ozone in particular, as well as other possible disinfection processes, supports the need to expand the modest epidemiological studies into these areas.

o Interactions and joint funding of epidemiological studies with other organizations, such as NCI, should be continued. The ongoing discussions with the National Center for Health Statistics to supplement their NHANES III survey to include environmental factors should consider the feasibility of using this important resource to include data relative to disinfection by-products. Also, relevant international organizations should be contacted, since ozone, in particular, is widely used in Europe.

o The "crash" effort to develop epidemiological and other studies on the possible role of chlorination in relation to cardiovascular disease appears to have been somewhat hasty and needs further review.

The Subcommittee's overall conclusion is that, in spite of a small budget and few personnel, the epidemiology program has been effective in the field of disinfection by-products in helping to define possible human health effects in all areas except those on reproductive capacity and in utero development which also merit evaluation. It has been hampered by the diminution of the overall role of epidemiology within EPA. The research is highly relevant to the regulatory activites of EPA. Although it is often difficult to find conclusive epidemiological evidence in the non-occupational communities exposed to anthropogenic chemicals, the national costs for modifying treatment, and the regulations on disinfection being planned by the EPA warrant further epidemiological studies that would help elucidate the effects of different disinfection systems on human health. The small epidemiology group at HERL is knowledgeable, effective, and capable of undertaking this research, provided that it receives the necessary resources and support.

IV. Major Program Recommendations

In general, the Subcommittee concludes that current research efforts are well focused in that they appropriately address a number of scientific issues that currently confront the Office of Drinking Water. The caliber of the research personnel and the quality of the individual research projects is generally high. This group, including a number of relatively young researchers, is professional. Each researcher appeared to be quite enthusiastic about his/her own research efforts and supportive of each other's projects.

Parts of this program to study drinking water disinfectants and their by-products are relatively new. The number of compounds that may be present in drinking water as a result of chlorine disinfection, and the large number of potential target organs and systems, is appreciated by the investigators as well as the management of the program. The program appears to have made progress in view of the enormity of the problem and the limited degree of staffing and funding, and lack of long-range (greater than two to three years) planning and implementation.

The research efforts described to the Subcommittee have focused almost exclusively in the area of chlorination and the by-products resulting from this treatment process. This is understandable in view of the complexity of the problem as mentioned above, as well as the widespread current usage of chlorine for disinfection. The Subcommittee strongly believes, however, that more attention should be paid to ozonation, and other disinfectants because of the number of water supply systems that are turning to this alternative process and the distinct likelihood that more treatment systems will utilize ozonation in the future. While the analytical group is presently studying the results of ozonation using a humic acid prototype, it is not clear what will trigger a more aggressive investigation of the toxicological problems that may be associated with this disinfection method. It is imperative that this group be on the forefront of this research. It may well require critical thinking to establish new methods to assess toxicity and less dependence on simply assessing mutagenicity. Such an effort may require additional support in terms of personnel and money.

Considerable effort is spent in gathering data to fill in specific gaps in the data base. While this activity is not unproductive, more effort must be spent in long-range planning as, for example, the initiation of studies on ozone and other disinfectants. At the same time, the investigators need to have the time and resources to develop their own projects and programs in fundamental research on these agents within the framework of the disinfectants program. This is essential if the program is to avoid becoming simply service oriented and not progressive in exploiting opportunities in the fundamental science of toxicology.

The Subcommittee is also concerned over possible conflicts between direct program related investigations and data gathering exercises versus investigations more exploratory and longer term in nature, e.g. methods development or fundamental mechanisms. Greater emphasis for the latter type of research is important for two reasons: 1) it will increase EPA's capability to identify emerging problems, and 2) it will provide the scientific staff with opportunities to further develop their skills and gain support for their work in the scientific community. Some of these concepts that have been discussed but not studied to any great extent, such as studying the toxicological interaction of compounds as mixtures, portend great difficulty but should not be impeded. In addition, these activities can directly benefit and support EPA's regulatory mission.

Related to the above is the difficulty the Subcommittee had in gaining a clear insight into how projects, other than those directly related to data gathering, are initiated. The criteria used in judging the worthiness of individual projects and the mechanisms for their initiation were also not clarified. Equally important is the problem the Subcommittee had in ascertaining how projects are terminated so that new ones may begin. Such endpoints are critical in the distribution of the program's limited resources.

There are definite deficiencies in some of the areas that the Subcommittee believes are important in determining the total toxicological profiles of the drinking water disinfectants and their by-products. This includes, for example, the compounds that may have effects on the nervous system that would go undetected unless carefully examined. This would include possible effects on behavior. Although studies are ongoing for evaluating the relationship between chlorination and atherosclerosis, other cardiovascular effects are not being considered. These chemicals might also have effects on the immune system, the presence and possible importance of which would go largely undetected.

While it is fairly obvious that the personnel and resources that can be assigned to the disinfectants program (and indeed the entire drinking water program) is finite, such areas need to be addressed. The Subcommittee believes that some of this work could be conducted at the EPA Health Effects Research Laboratory in Research Triangle Park, even though the Subcommittee appreciates that the distribution of effort among EPA laboratories is primarily along media lines. While it is encouraging to note that a few of the research groups, e.g. reproductive and developmental effects and carcinogenesis, appear to have contact with similar research groups in RTP, there is room for much more interaction within EPA and also with various units of the National Institutes of Health.

In considering working relationships within EPA, the Subcommittee concludes that stronger ties involving coordinated planning should be established for issues involving water treatment technology and monitoring. This should especially be encouraged within HERL. The former certainly impacts on the program with regard to what may be removed prior to chlorination,

and the latter as to verification of what is in the drinking water from many communities in comparison to what is found with the model chlorination systems employing humic acid. The program also needs to be better attuned to the engineering aspects as to how chemicals are used in the entire water treatment process. For example, chlorine is being rapidly replaced by other oxidizing agents such as ozone, chlorine dioxide and potassium permangenate for chemical oxidation (as opposed to disinfection). This will definitely influence the types of compounds that are appearing and will appear in the finished water.

It was quite clear from the extended discussions that the Office of Drinking Water and Office of Research and Development spend considerable effort planning the types of short-term projects undertaken and the direction of the research through the Water Research Committee's Disinfectant By-products Workgroup, and informal discussions. The Subcommittee recommends that, in addition, the drinking water disinfectants program should undergo a through and continuous review of ongoing research as well as future projects to insure that the long-term as well as the short-term needs of the Agency are met. This could be conducted by competent external scientists. Its purpose would not be to impede the activities of the program, prescribe what should be done or usurp the duties of the Agency, but to serve as a guide to the overall operation and direction of the program. This could be done in a colleageal and non-adversary manner and provide expert guidance and opinions on the worth of individual projects. This mechanism may be more satisfactory than simply relying on ad hoc advisory panels that exist and have proven to be periodically useful.

Finally, and related to some of the other points outlined above, the Subcommittee is apprehensive that the program and the individual scientists, in particular, may become entrapped in a data gathering mode. This is reflected in the great dependence on outside contractors for much of the work. The individuals within the unit need to be acutely aware of the keys which trigger additional research in the various areas of the program. Their input into when and how to follow up interesting and important findings from "routine" subchronic and mutagenicity studies, and from short-term reproductive toxicity tests, is essential. Moreover, they need to share in the knowledge of how their data are used in the Agency's decision making processes.

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

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October 23, 1987

OFFICE OF
THE ADMINISTRATOR

Honorable Lee M. Thomas
Administrator
U. S. Environmental Protection Agency
401 M Street, S. W.
Washington, D. C. 20460

Dear Mr. Thomas:

The Drinking Water Subcommittee of the Science Advisory Board's Environmental Health Committee has completed its review of the Office of Research and Development's Health Effects Research Laboratory's Drinking Water Disinfection and Disinfection By-Products Research Program, and is pleased to transmit its report to you. The Subcommittee reviewed this program at a public meeting at the laboratory in Cincinnati, Ohio on June 4-5.

This review is especially timely in view of the growing recognition among scientists, engineers, governmental officials and water supply providers of the public health risks associated with the continuing incidence of waterborne disease, and the increasing need to investigate the public health implications of the use of alternative disinfection techniques and their by-products.

In general, the Subcommittee concludes that current research efforts are well focused in that they appropriately address a number of scientific issues that currently confront the Office of Drinking Water. The caliber of the research personnel and the quality of the individual research projects is generally high. Each researcher appeared to be quite enthusiastic about his/her own research efforts and supportive of each other's projects. The current research efforts presented by EPA staff to the Subcommittee focused almost exclusively in the area of chlorination and the by-products resulting from this treatment process. This is understandable in view of the complexity of the problem, as well as the widespread current usage of chlorine for disinfection.

The Subcommittee's major recommendation is that more attention should be devoted to the potential toxicity problems that could arise from alternatives and/or adjuncts to chlorination such as chloramination, and the use of ozone, chlorine dioxide and other disinfectant processes. In view of the number of treatment systems that are turning to the use of alternative treatment approaches, it is necessary to expand the research focus to determine which treatment methods protect public health most effectively, and to compare the relative effectiveness and risks associated with each treatment technology.