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Science Advisory
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# AN SAB REPORT: REVIEW OF DRINKING WATER RESEARCH PROGRAM

## REVIEW BY THE DRINKING WATER COMMITTEE OF THE DRINKING WATER RESEARCH PROGRAM AT THE HEALTH EFFECTS RESEARCH LABORATORY (HERL)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

October 30, 1992

OFFICE OF
THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

EPA-SAB-DWC-93-001

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Subject: Review of the Drinking Water Research Program at ORL's Health Effects Research Laboratory

Dear Mr. Reilly:

The Drinking Water Committee (DWC) of the Science Advisory Board (SAB) met on December 17-19, 1991 in Research Triangle Park, North Carolina to review the scope and direction of the Agency's drinking water health research program of the Health Effects Research Laboratory (HERL) of the Office of Research and Development (ORD). The Committee received overview briefings and resource related presentations from laboratory managers, and presentations on specific research initiatives from researchers.

In general, the Committee found that research was being conducted on appropriate issues and in a sound manner. The laboratory is to be commended for fostering cooperation among scientists from different divisions. Nevertheless, the Committee expressed concern over the fragmentation of the program, dwindling research funds, and the need for focussed leadership. The appointment of the Associate Laboratory Director for Water appears to be a way that research can be coordinated. However, the Committee recognizes the lack of a direct line of supervision to the division and absence of direct control of the resources. Thus, the success of this approach can only be determined with time.

We are concerned that in recent years there has been increased fragmentation of the drinking water program in the Agency. Now, not only are ORD's efforts spread over many different sub-groups, the Program Office has been split within the Office of Water with the "health" people in a different sub-group

from the "treatment" people. Research support takes place within several organizational elements in both Cincinnati and Research Triangle Park. Clearly, this fragmentation has the potential of generating poor communication, and worse, the inability of the Program Office to obtain the information it needs to perform its function.

Broadly speaking there are two issues in the disinfection/disinfectant by-product area that need to be addressed epidemiologically. The first is to provide a clear cut confirmation that chlorinated water increases the probability of cancer. The second is identifying any adverse health effects (not only cancer) that might be associated with alternative methods of disinfection. A chlorine/ chloramine study should be of highest priority as a means of finally settling the issue of whether chlorinated water should be considered carcinogenic. Studies to assess health endpoints of other disinfectants should also have a high priority, but must start with a 10 year outlook. A few ecological studies should be conducted over the next 2-3 years with plans to follow up with more analytical studies of disease types that may be surfaced by the ecological studies.

There appear to be clear cut objectives within HERL for developing research programs in specific areas of environmental health (toxicology). In large part the reorganization of the Laboratory has contributed substantially to that goal. The Committee views this as a genuine success.

There is less evidence that the laboratory is capable of addressing environmental problems in a holistic way. It seems that the research program is oriented too much around individual chemicals and too little by process. In drinking water the real issue is not whether dichloroacetic acid is carcinogenic, teratogenic or neurotoxic. It is whether chlorination is a safe practice of disinfecting drinking water. If it is not a safe process, are there alternatives that are safer? If the laboratory does not take charge of this overall issue, it will continue to have its research agenda defined by the Program Office. This will boil down to data needs listed on a chemical by chemical basis.

The EPA is planning to propose drinking water regulations for various disinfectants and disinfection by-products (DBP's) in June, 1993. Among the DBPs proposed for regulation are chlorate and bromate. Chlorate is introduced to drinking water through the use of chlorine, especially liquid hypochlorite, and chlorine dioxide. Bromate is a by-product of ozonating waters containing bromide. Chlorate and bromate may have significant health effects at the occurrence levels

found in drinking water. The use of liquid hypochlorite is expected to increase dramatically as a result of the Groundwater Disinfection Rule. HERL staff presentations to the SAB Drinking Water Committee on December 17-18, 1991 did not appear to give a sufficiently high priority to health effects research related to chlorate and bromate. We recommend that HERL give a high priority to health effects research related to chlorate and bromate.

Finally, the Committee recommends that HERL more effectively use its existing resources and leverage other resources to address key research needs in drinking water microbiology and health. The Committee suggests that this can be done by putting greater emphasis on drinking water microbiology health effects research activities within existing HERL divisions, by creating stronger and more effective linkages with other EPA labs that have resources and expertise in this area, and by utilizing extramural resources as needed.

We appreciate the opportunity to review this important research program. We look forward to your written response to the advice contained in the attached report.

Sincerely,

Raymond C. Loehr

Dr. Raymond C. Loehr, Chair
Executive Committee
Science Advisory Board

Verne R. Ray

Dr. Verne Ray, Chair
Drinking Water Committee
Science Advisory Board

# ABSTRACT

On December 17-19, 1991, the Drinking Water Committee (DWC) of EPA's Science Advisory Board (SAB) met in Research Triangle Park, North Carolina to review the scope and direction of the Agency's drinking water health research program of the Health Effects Research Laboratory (HERL) of the Office of Research and Development (ORD). The Committee received overview briefings and resource related presentations from laboratory managers, and presentations on specific research initiatives from researchers.

In general, the Committee found that research was being conducted on appropriate issues and in a sound manner. The laboratory is to be commended for providing cooperation among scientists from different divisions. Nevertheless, the Committee expressed concern over the fragmentation of the program, the dwindling research funds, and the need for focussed leadership.

The Committee recommends that HERL effectively use its existing resources and leverage others to address key research needs in drinking water microbiology and health. The Committee suggests that this can be done by putting greater emphasis on drinking water microbiology health effects research activities within existing HERL divisions, by creating stronger and more effective linkages with other EPA labs that have resources and expertise in this area, and by creating and utilizing extramural resources as needed.



Key Words: drinking water; research; toxicology; microbiology

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# 1.0 EXECUTIVE SUMMARY

On December 17-19, 1991, the Drinking Water Committee (DWC) met in Research Triangle Park, North Carolina to review the scope and direction of the Agency's drinking water health research program at the Health Effects Research Laboratory (HERL) of the Office of Research and Development (ORD). The Committee received overview briefings and attended a research poster session organized by the HERL researchers. The review focussed on the five divisions of the laboratory - Genetic Toxicology Division, Environmental Toxicology Division, Developmental Toxicology Division, Human Studies Division, and Neurotoxicology Division. The Committee also addressed needs and priorities for drinking water research.

## 1.1 General Findings

a) Research Program - In general, the Committee found that research was being conducted on appropriate issues and in a sound manner. The laboratory is to be commended for providing cooperation among scientists from different divisions. This may not only provide better science, but it also allows for conservation of resources - both animals and dollars. This approach should be encouraged, however, it should be recognized that optimal study designs may be such that they cannot be integrated to cover questions which are different.

We found that there appear to be clear cut objectives within HERL for developing research programs in specific areas of environmental health (toxicology). In large part, the reorganization of the Laboratory has contributed substantially to that goal. The Committee views this as a genuine success, however, there is less evidence that the laboratory is capable of addressing environmental problems in a holistic way. It is apparent that the research program is oriented too much around individual chemicals and too little by process. In drinking water the real issue is not whether dichloroacetic acid is carcinogenic, teratogenic or neurotoxic. It is whether chlorination is a safe practice of disinfecting drinking water. If it is not a safe process, are there alternatives that are safer? If the laboratory does not take charge of this overall issue, it will continue to have its research agenda defined by the program office.

b) Organizational Fragmentation - Originally, all components of drinking water were in one organizational entity. Although each sub-group was small in those days, communication, and thus cooperation was excellent. In recent years, however, there has been an acceleration in the fragmentation of the drinking water program in the Agency. Now, not only are ORD's efforts carried out in many different sub-groups, the Program Office has been split within the Office of Water with the "health" people in a different sub-group from the "treatment" people. Research support takes place within several organizational elements in both Cincinnati and Research Triangle Park. Clearly, this fragmentation has the potential of generating poor communication, and worse, the inability of the Program Office to obtain the information it needs to perform its function.

c) Resources - The Committee is concerned about the dwindling funds being made available to HERL for drinking water research. These funds are woefully inadequate to meet the research needs. The HERL leadership is challenged to meet the needs of the drinking water program through integration of these projects with those of other programs. The Committee is concerned about the stability of such arrangements and recommends that drinking water funding in HERL be carefully examined to determine if additional funding can be forthcoming to address the concerns, especially those currently unmet and mentioned throughout the report, many of which (e.g., microbiology research, ozone disinfection, combined use of disinfectants, epidemiology) would require substantial amounts of money and people.

The Committee recommends that HERL play a key and proactive role in addressing these research needs, despite its institutional and organization constraints. This must be done because no other entity within EPA or in another Federal agency will address these issues. Therefore, the we recommend that HERL more effectively use its existing resources and leverage other resources to address key research needs in drinking water microbiology and health. This can be done by putting greater emphasis on drinking water microbiology health effects research activities within existing HERL divisions, by creating stronger and more effective linkages with other EPA labs that have resources

and expertise in this area, and and utilizing extramural resources as needed.

### 1.2 Response to the Charge

Specific questions addressed to the Committee in its charge are answered in the text of this report. Brief responses are as follows:

a) Is the HERL program targeted to the most important scientific and programmatic needs given the level of resources available?

1) Does the Committee agree with HERL's current priority areas? - The Agency needs to implement a planning process that prioritizes health research on the magnitude of risks, the size of the impacted population and the need to rectify competing risks. Also, the health program in drinking water must focus on microbiological as well as chemical risks.

2) Does the Committee agree with the objectives of the research in each priority area? - The Office of Research and Development should take a more active role in identifying critical areas of research and health problems associated with drinking water. A large part of this responsibility should fall on the Health Effects Research Lab, but it clearly must be coordinated with other programs in ORD that deal with water treatment and distribution or are responsible for assessing health risks.

3) Are the research approaches within each priority area appropriate? - The approaches within the priority areas selected are sound and generally state of the art. The Laboratory Director and Division Directors are to be complemented for the level of science applied and the process of staff development.

b) Is the Water Health Research Program adequate to address drinking water public health needs? - No, however, this is largely because it is resource limited and needs to address areas such as alternate

disinfectants and disinfectant by-products with a priority research program.

# 2.0 INTRODUCTION

## 2.1 Background

On December 17-19, 1991, the Drinking Water Committee (DWC) met to review the scope and direction of the drinking water health research program of the Health Effects Research Laboratory (HERL) of the Office of Research and Development (ORD). This research program is being conducted in support of the Office of Water (OW). The Committee met for three days at EPA's Environmental Research Center in Research Triangle Park, North Carolina.

On the first day, the Committee received extensive briefings on the program with specific overviews of the major components of HERL. The Committee was also briefed on resource allocations and constraints. At the close of the first day, the Agency hosted a Poster Session in the conference room adjacent to the meeting room. The Poster Session contained specific presentations of ongoing research within the program and offered the opportunity for one-on-one discussion between Committee members and HERL researchers. The Poster Session was extremely successful and represents a unique and welcome departure from the usual mode of endless research presentations during the formal meeting.

On the second day, the Committee received additional briefings on specific areas of research, and a final presentation on unmet research needs. On the last day, the Committee conducted an open writing session to draft its report.

Prior to the meeting, the Committee was provided with a number of documents to support discussions held at the public meeting. These documents included:

a) "The Role of Health Research in Support of EPA's Regulatory Programs", USEPA, Office of Research and Development, EPA/600/9-90/034, June 1990.

b) "Strategy for Environmental Health Research at EPA", USEPA, Office of Research and Development, EPA/600/9-90/053, December 1990.

c) "Health research at the U.S. Environmental Protection Agency", Ken Sexton and Larry Reiter, Environ. Sci. Tech. 23(8):917-924. August 1989.

d) A bibliography of recent drinking water publications from HERL.

The Committee also received various handouts and materials during the course of the three day public meeting.

### 2.2 Charge to the Committee

The purpose of this review is for EPA to obtain specific advice from the DWC on the scope and direction of the drinking water health research program of the Office of Research and Development (ORD). Specific questions are:

a) Is the program appropriately targeted on the most important science and programmatic needs given the level of resources available?

   1) Does the Committee agree with HERL's current priority areas?

   2) Does the Committee agree with the objectives of the research in each priority area?

   3) Are the research approaches within each priority area appropriate?

b) Is the program adequate to address drinking water public health needs.

### 2.3 Format of this report

This report contains four major Chapters: Chapter 1: Executive Summary; Chapter 2: Introduction; Chapter 3: Review of the HERL Drinking Water Research Program; and Chapter 4: Needs and Priorities for Drinking Water Research.

# 3.0 REVIEW OF THE HERL DRINKING WATER RESEARCH PROGRAM

## 3.1 Genetic Toxicology Division

The professional capability and project orientation of the Genetic Toxicology Division (GTD) are well suited to support the research needs of the Office of Water (OW). The three branches of carcinogenesis and metabolism, mutagenesis and cellular toxicology, and genetic bioassay have ongoing projects that have a relevance to Office of Water needs. Comparative research on the carcinogenesis of haloacids, chlorine, and trihalomethanes (THM's) is underway. The design of the chronic bioassay has included characterization of cell growth kinetics, altered gene expression, preneoplastic and neoplastic lesion markers as well as conventional pathology determinations. This integrated approach provides greater opportunity for mechanistically oriented research than just a pathology assessment. Dichloroacetic acid (DCA), chloral hydrate and trichloroacetic acid (TCA) bioassays were in progress in FY1991. Studies of bromoform, bromodichloromethane, MX, and a disinfectant by-product mixture were scheduled in FY1992. Genotoxicity research on DCA, TCA, MX, chlorine and TCE are underway and projects are proposed for arsenic and haloacetonitriles. An assay for genotoxic halogenated organics using prophage lambda induction in E. coli as a model for identifying a genotoxic basis for carcinogenicity is being evaluated.

Research within the Division is directed towards resolving some of the most difficult regulatory issues within the drinking water program. Hazards identified with the concentrations of disinfectant by-products found in drinking water are almost exclusively concerns over their carcinogenic effects. The central issue is whether the Agency's current methods of assessing carcinogenic risks (i.e., the linearized multistage model) is the appropriate methodology for calculating risks at low doses.

It is clear that the genetic toxicology group has the capability to quickly assess the genotoxic potential of mono and dimethyl arsenite and examine the mechanistic basis for arsenite-induced endoreduplication. We suggest that this effort be given some degree of priority. The advantage of the Office of Water having early information on the genotoxicity of contaminants cannot be over-emphasized.

### 3.2 Environmental Toxicology Division

The Environmental Toxicology Division (ETD) has a very broad mandate with regard to the toxicological endpoints that need to be considered in the evaluation of any chemicals related to drinking water. As with the other divisions, the resources within the divisionmust address the research problems of multiple Agency programs.

The primary branch of this Division focusing on drinking water programs is the Pharmacokinetic Branch. This group has initiated an extensive ongoing program concerned with the toxicity of THM mixtures with appropriate specific emphasis on kidney and liver toxicity. It covers the range of organismal complexity from subcellular components to the whole animal. While well designed as interactive studies, we have some concern that these results may not be relevant to understanding interactions at low levels present in drinking water where exposure is chronic. The comparison of the pharmacokinetic parameters of the individual THM's and haloacetic acids is critical in making decisions about extrapolating from one chemical to another. These data also are critical for the regulation of these chemicals by EPA.

Studies on arsenic speciation and the disposition of parental arsenic forms and methylated derivatives are important in order to address the critical question of saturation of biosynthetic pathways. However, the driving forces for analytic methodology and enzymology need to be accompanied by more fundamental work on whether or not methylation is truly detoxification as assumed by this laboratory. This is related to potential genetic alterations mentioned in Section 3.1 above.

Areas of future work by this Division are very important in judging hazards from drinking water. Evaluation of the effects of chlorination byproducts on immune function is important. However, a higher priority being given to the disinfectants themselves seems warranted by available data. Low levels of both chlorine (Fidler, 1977) and chloramine (Exon et al., 1987) have been reported to have effects on the immune system.

Although not suggested by the Division itself, it would also appear appropriate to involve the Pulmonary Toxicology Branch in studies on drinking water. This Division would seem to be an ideal place to involve EPA in providing an understanding of the roles of both inhalation and dermal exposure on the total dosimetry of volatile organic compounds including the THM's. This issue of

relative exposure is also of concern in the context of indoor air pollution. The Branch has a great deal of experience in making the types of exposure assessments needed to determine the relative source contributions.

### 3.3 Developmental Toxicology Division

The Developmental Toxicology Division (DTD) has produced a well coordinated program to study reproductive and developmental toxicological effects by environmental chemicals. There is a clear appreciation of critical regulatory issues that arise in this very visible and important area of environmental toxicology. This leadership in this group has a well balanced view of the importance of mechanistic work to the risk assessment process and how this must be used in conjunction with more routinely derived data to arrive at a regulatory posture.

In the evolution of HERL's research focus to problems in drinking water a total of five of the available drinking water positions have been allocated to this division. Two of these individuals are to operate at a principal investigator level and three are to be technicians. One principal investigator is to be a reproductive biologist and the other a developmental biologist.

The drinking water program has critical research needs in the developmental toxicology area. Whether these needs are articulated by the program office or simply apparent from prior data, it is clear that these issues will remain on the regulatory agenda for the foreseeable future. Within the context of the disinfectant by-product area, several compounds have been identified that have clear cut reproductive and/or developmental toxicities. From an experimental point of view, these reproductive and/or developmental endpoints appear at lower doses than other toxicological effects. This includes compounds from the halogenated acetic acids and the haloacetonitriles groups. There are members of these groups that are major by-products of chlorination and ozonation that have not yet been adequately tested but which are of concern on a structure activity basis. In addition, there are a number of other major by-products that need to be seriously evaluated for potential reproductive and developmental toxicities. Among these would be chloral hydrate and other halogenated aldehyde by-products. Research to address the dose response characteristics of these effects is well underway to the extent that resources allow. This Division is to be complemented on the way it has picked up on the work that was being done in the health program in water when it was located in Cincinnati. In view of the large number of other chemicals that have

been identified in drinking water that have potential reproductive and developmental toxicities (metals, contaminants of water treatment chemicals, etc.), it is very important that some consideration be given to increasing research in this area. It is clear that resources allocated to this area are not adequate to meet the regulatory agenda in drinking water.

### 3.4 Human Studies Division

The Human Studies Division (HSD) represents a unique capability for assessing the extent to which environmental agents impact human health by direct measurement. Such a capability is essential for maintaining the credibility of environmental regulations that are based on considerations of human health. While the Committee recognizes the limitations inherent in both epidemiological and clinical studies, the highest priority must be given to taking advantage of opportunities presented in the field or the conduct of controlled experiments in humans when they address critical questions and can be conducted ethically.

Regulatory activities of EPA directly mandate particular treatments (e.g. disinfection) or indirectly force alternate treatment strategies to be employed (e.g. disinfection by-product maximum contaminant levels - MCL's). The ethics of mandating such treatment practices without a thorough evaluation of the major alternatives experimentally for potential human effects before they are introduced to the general population is questionable. While the longer term impacts of disinfection byproducts may not be directly addressed experimentally in humans, epidemiological evaluations of changing incidence of disease in populations should be planned to document the positive or negative impacts of changing such practices. It is clear that these impacts must be weighed along with evaluations of the relative incidence of waterborne infectious disease that may accompany such changes.

Broadly speaking there are two issues in the disinfection/disinfectant by-product area that need to be addressed epidemiologically. The first is to provide a clear cut confirmation that chlorinated water increases the probability of cancer. The second is identifying any adverse health effects (not only cancer) that might be associated with alternative methods of disinfection. These two questions require substantially different approaches.

The recent review of chlorinated drinking water by the International Agency for Research on Cancer (IARC, 1991) concluded that there was insufficient evidence to conclude that chlorinated drinking water is carcinogenic. There were a number

of reasons for this conclusion, but two stand out: 1) the relationship established was an increased incidence of bladder cancer with chlorinated surface water relative to non-chlorinated ground water supplies in the United States; 2) there is only one study that included sufficient controls to establish even this relationship with any certainty (Cantor et al., 1987). Since there are systematic differences in chemical characteristics of ground waters and surface waters in addition to whether they are disinfected, there is a real possibility that the results of this study are confounded by other factors. Secondly, the study was not designed to distinguish between the types of by-products which might be found other than the THM's. There are many non-THM by-products which have been identified which are highly mutagenic and several which have been identified which are at least as carcinogenic as the THM's. The relative proportion of the by-products that are formed depends sharply on other water quality parameters such as pH, bromide concentration and total organic carbon concentration. Therefore, the weak correlations found in previous iterations of this same study are relatively meaningless. Furthermore, the study did not differentiate between potential effects of the residual disinfectant vs. the formation of by-products. This question has very important implications for any modifications of water treatment practice envisioned. It is essential that research (not only epidemiological) be conducted to sort out these relationships. Because of the importance of disinfection of drinking water as a measure to protect public health, it is important that the relative hazards that might be associated with alternatives to chlorine be established before alternative procedures are purposefully or indirectly mandated through regulation.

A comparison of bladder cancer incidence in chlorinated and chloraminated water drawn from the same source is an ideal means of assessing the first question. A preliminary study has already indicated that this is a reasonable hypothesis to pursue, although it was of insufficient sophistication to allow definitive conclusions to be drawn (IARC, 1991). Consequently, there is an excellent justification for the study that was proposed for the New Orleans area. However, it did not appear that the HERL staff describing the proposal were aware of its actual purpose nor did there appear to be an understanding of the power of such a study to resolve basic issues in water disinfection. The advantage of such a study is that it would fairly specifically separate the contribution of by-products of chlorination to the carcinogenic response away from other confounding water-related variables and would provide the strongest possible evidence to confirm or deny the results of previous studies. The by-products formed by the two methods of disinfection are very similar, but the amounts can be very much lower with chloramine (depending upon when the ammonia is added to the system) than with chlorine. There clearly

needs to be a case control study with sufficient statistical power to resolve the problem. The possibility of utilizing biomarkers to document the true relative exposure of populations in these communities should also be explored. If the Agency does not put the resources into a study of sufficient sophistication to resolve this issue, the study should not be performed. There is absolutely nothing to be gained from less than a first class effort. Moreover, the validity of any standards that are developed on disinfection byproducts based on cancer without this research would have to be questioned.

In the course of investigating the relationship between bladder cancer incidence and chlorinated vs. chloraminated supplies, it would be useful to develop a comparison of water borne infectious disease incidence in the same community. Chloramine is a much less effective primary disinfectant than chlorine. There may be a means by which comparative microbiological and carcinogenic risks from water can be directly compared in the same communities.

Studies to determine whether other disinfectants induce adverse health effects must start at a much more primitive level. To the knowledge of the Committee, no studies have been conducted to define disease endpoints that would be the most relevant to study with these alternative methods (i.e. tumor sites or other chronic diseases). Consequently, a limited number of populations utilizing alternative sources of disinfection should be examined in ecological studies to determine if there are any hypotheses that could be profitably pursued in more sophisticated studies. These preliminary studies must, however, obtain some basic water quality data that may systematically modify the types of by-products that are produced (this does not mean a detailed chemical analysis because such a small fraction of the chemicals present can really be identified and fewer quantified). In addition to the disinfectant dose, a detailed description of the treatment processes used in each water system studied should be provided as well as information on pH of the treated water, its total organic carbon content, its chloride and, if possible, bromide concentrations. These studies should only be conducted where there as been a long history for the use of the alternate disinfectant(s) being evaluated and a clear indication that tap water is used for drinking purposes. Even at this modest level of sophistication, some careful thought will have to be given to selecting control populations. If significant relationships are identified, the means for conducting more sophisticated studies should be sought.

The Committee recognizes that the overview of planned activities of the HSD in the drinking water program presented in RTP were very preliminary. This

obviously arises from: 1) the relative lack of expertise and leadership in epidemiology at HERL; and 2) the limited knowledge basewithin the program about the wide variations in the quality of drinking water sources and how these are alteredby differing types of drinking water treatment practices. It is also noted that the Laboratory has specific plans to remedy these deficiencies. Therefore, the Committee would be very disappointed if the criticism presented here is taken to mean that we are discouraging activity in this area, when in fact our intent is just the opposite. This is an area in which large amounts of money can be wasted, but where a large investment is clearly justified if it can yield truly useful information with a high probability of success.

The epidemiological studies that were discussed at our December 1991 review were directed at important problems surrounding alternative forms of drinking water disinfection. However, there was a certain naivety displayed which suggests that these efforts be much more critically reviewed before they are taken forward. For example, we see no justification for conducting an ozonation study in France. Although ozonation has been practiced extensively in France for many years, much of their water treatment practice has chlorine added after ozone. Secondly, the French drink very small amounts of tap water. Third, there are other differences of water quality and treatment practice that must be considered before an adequate study could be performed. Finally, there is no reason to suppose that bladder cancer is an appropriate endpoint to be focus on in ozonated supplies.

The HSD could also play a crucial role in addressing questions concerning non-cancer endpoints that have previously been identified in animal experiments. Such studies involving controlled exposures in normal human subjects under defined conditions could be done using oral exposures similar to the Division's previous studies on air pollutants. Possible areas of investigation would include, for example, evaluating the immunotoxic effects of chlorine dioxide and the susceptibility of human erythrocytes to the oxidizing effects of chlorate. The validation of species differences or similarities would go a long way in filling data gaps that presently exist in criteria documents and contribute to the development of maximum contaminant level goals (MCLG's) and MCL's on a firmer scientific basis.

### 3.5 Neurotoxicology Division

The research program of the Neurotoxicology Division (NTD) represents a well organized effort in this critical area of environmental toxicology. It is a program with broad capabilities in behavioral toxicology, neuropathology and

neurophysiology. It is a large division, comprising 70 of the 225 government employees and supported by some 30 contract technicians.

There is no doubt that there are chemicals in drinking water which are of concern from a neurotoxicological point of view. Among these are aluminum and dichloroacetic acid, a by-product of chlorination. Research on the neurotoxicology of aluminum is clearly of primary regulatory concern. The research proposed appeared to be on target, but some different populations might be examined where aluminum has been more clearly implicated in diseases other than Alzheimer's (e.g. dialysis dementia). It is not as clear that neurotoxicological research on dichloroacetic acid will make significant contributions to the regulatory agenda in drinking water. Information provided by the laboratory at the review with dichloroacetic acid did not provide any indication that neurotoxicity is a critical endpoint for this chemical considering its clearcut carcinogenic and reproductive effects. In point of fact, much better information is already available on this compound in the open scientific literature.

While the NTD is a well organized research division, the presentations by this division did not reflect a understanding of basic health problems in drinking water nor the type of regulatory effort in which the Office of Water is involved. Nevertheless, a total of five drinking water positions were proposed at the time of our review for this Division, two principal investigators and three technicians. The proposal to support an in vitro neurotoxicologist (and presumably one or more of the technicians) on the drinking water budget does not seem to fit the regulatory needs of the Office of Water. Considering the size of the base program, and the apparently limited basis for research in this area in the drinking water program that was provided it would seem that work in this Division is of a lower priority than that going on in other divisions.

### 3.6 Infrastructure and Resources

The laboratory is to be commended for providing cooperation among scientists from different divisions. This may not only provide better science, but it also allows for conservation of resources - both animals and dollars. This approach should be encouraged, however, it should be recognized that optimal study designs may be such that they cannot be integrated to cover questions which are different. For example, the studies on high doses of DCA may be appropriate for addressing the carcinogenicity question but are much too high to determine whether subtle

behavioral and neurotoxicity effects might occur at the low concentrations seen in drinking water.

The Committee is concerned about the dwindling funds being made available to HERL for drinking water research. These funds are woefully inadequate to meet the research needs. The HERL leadership is challenged to meet the needs of the drinking water program through integration of these projects with those of other programs. The Committee is concerned about the stability of such arrangements and recommends that drinking water funding in HERL be carefully examined to determine if additional funding can be forthcoming to address the concerns, especially those currently unmet and mentioned throughout the report, many of which (e.g., microbiology research, ozone disinfection, combined use of disinfectants, epidemiology) could or would require substantial amounts of money and people.

The appointment of the Associate Laboratory Director for Water appears to be a way that research can be coordinated. However, the Committee recognizes the lack of a direct line of supervision to the division and absence of direct control of the resources. Thus, the success of this approach can only be determined with time.

### 3.7 Relationship to Other Organizational Components within EPA

Originally, all components of drinking water were in one organizational entity. Although each sub-group was small in those days, communication, and thus cooperation was excellent. An example of this cooperation was the rapid and successful completion of the 1969 Drinking Water Survey. Even when USEPA was first founded in 1970, the drinking water part of what is now in the Office of Water and the Office of Research and Development was in the same organizational component. Because of this, the flow of information in both directions was rapid and both groups understood the overall mission, and moved in the same direction.

The fragmentation of the drinking water program in the Agency has accelerated in recent years. Now, not only are ORD's efforts carried out in many different sub-groups, the Program Office has been split within the Office of Water with the "health" people in a different sub-group from the "treatment" people. The occurrence studies are conducted by the Technical Support Division (TSD) in Cincinnati, part of the Office of Water. In ORD the microbiology component of HERL that was in Cincinnati is now housed in the Environmental Monitoring

Systems Laboratory (EMSL). The Drinking Water Research Division still has four Branches, however, one for the control of inorganic contaminants, one for the control of organic contaminants, one for the control of microbiological contaminants, and one for systems and field evaluations. The drinking water health effects studies are scattered throughout five Divisions of HERL at RTP, NC. Thus, the answer to the four questions that the Office of Water poses when preparing any regulation would be answered as follows:

a) Question 1 (Does the contaminant or process cause a health effect?) - answered by HERL - RTP;
b) Question 2 (Does the contaminant or process adversely affect water across the nation or is it simply a local problem?) - answered by TSD - Cincinnati;
c) Question 3 (Can the contaminant be measured quickly and reproducibly?) - answered by EMSL - Cincinnati; and
d) Question 4 (Can the contaminant be removed or process be modified to minimize health risks?) - answered by DWRD - Cincinnati.

Clearly, this fragmentation has the potential of generating poor communication, and worse, the inability of the Program Office to obtain the information it needs to perform its function. As the drinking water program has become more organizationally scattered, the involvement of the personnel with the waterworks industry has declined. Thus, scientists and engineers are working on drinking water problems without being "steeped in the lore" of the water supply industry. Working in a vacuum is always dangerous. This has also impeded the understanding of priorities and thus, progress.

## 3.8 Strengths and Weaknesses of the Overall Research Program Direction and Priorities

### 3.8.1 Comments on Some of HERL's Current Priority Areas

a) Pharmacokinetics of THM's - Clearly appropriate

b) Pharmacokinetics of haloacids - Clearly appropriate

c) Immunotoxicology of disinfectant by-products - There is very little rationale for pursuing immunotoxicological effects of THM's. On the other hand, there are data which suggest that further research into

the immunotoxicological effects of the disinfectants themselves might be profitably undertaken. (Note papers: Fidler et al. 1977, 1982).

d) Carcinogenicity of haloacids and THM's - Haloacid work is clearly appropriate. The nature of the hypothesis being tested and the priority for THM work proposed was not as clear. EPA Staff did not mention work that is ongoing at the Chemical Industry Institute of Toxicology (CIIT) on chloroform. They should be aware of this.

e) Reproductive hazards of haloacids - Clearly there is a solid basis for doing the proposed work. Hopefully this work will be followed by mechanistic work which will clarify the risk these compounds present to human populations drinking chlorinated and ozonated water.

f) Neurotoxicity of dichloroacetate - It is not clear that the direction proposed will add substantially to knowledge already available in the literature. All indications are that neurotoxicity will not be the primary driver for regulation of this compound, it would seem that this project must be considered of a lower priority. A more directed investigation of DCA and related compounds might be justified.

g) Human studies - A chlorine/chloramine study should be of highest priority as a means of finally settling the issue of whether chlorinated water should be considered carcinogenic. Studies to assess health endpoints of other disinfectants should also have a high priority, but must start with a 10 year outlook. A few ecological studies should be conducted over the next 2-3 years with plans to follow up with more analytical studies of disease types that may be surfaced by the ecological studies.

h) Chlorate and Bromate - The critical need for information on these two compounds has evidently escaped HERL's attention or they have mistakenly assigned them a low priority. There may be reason to increase the priority for work on chlorate, in particular, because of recent documentation of its occurrence as a contaminant of hypochlorite solutions. This might be most efficaciously accomplished by some relatively straight-forward subchronic studies followed by the development of a study in human volunteers. After all, it is a major contaminant of a direct additive whose use is being mandated by the

Agency. Bromate is primarily a problem in ozonated water and its established carcinogenic properties may well limit the use of this disinfectant in supplies having trace quantities of bromide in their source waters. It is essential that the mechanism and dose-response characteristics of this compound be understood at low doses. Using the Agency's current cancer risk assessment guidelines, it is among the most potent carcinogens produced as a disinfectant by-product. On the other hand, there may be a basis for arguing that this compound does not behave linearly with dose. However, this argument must be supported by appropriate research. These two chemicals also point out the general need to understand the toxicology of oxidants in general. It would appear that oxidants will always play a role in drinking water treatment and there is a real need to consider their toxicities in quantitative and mechanistic terms (e.g. add chlorite, potassium permanganate, hypochlorite and the various chloramines to this list).

### 3.8.2 Research Objectives

There appear to be clear cut objectives within HERL for developing research programs in specific areas of environmental health (toxicology). In large part the reorganization of the Laboratory has contributed substantially to that goal. The Committee views this as a genuine success.

There is less evidence that the laboratory is capable of addressing environmental problems in a holistic way. It seems that the research program is oriented too much around individual chemicals and too little by process. In drinking water the real issue is not whether dichloroacetic acid is carcinogenic, teratogenic or neurotoxic. It is whether chlorination is a safe practice of disinfecting drinking water. If it is not a safe process, are there alternatives that are safer? If the laboratory does not take charge of this overall issue, it will continue to have its research agenda defined by the program office. This will boil down to data needs listed on a chemical by chemical basis.

There is a basis for an integrated program that is being developed within the laboratory through the Associate Laboratory Director positions that has the potential for addressing this problem. The question is how much authority do positions outside of line management have in the distribution of resources and the evaluation of a research division's performance for their program. If there is real authority vested in these positions, it may provide the kind of focus that is needed

within the drinking water area. Then the program can become efficient in addressing the larger questions. Integrated management of such problems may well provide a basis for obtaining the resources that are really needed to address questions of the complexity that is unfolding in this area.

### 3.8.3 Microbiology

There are capabilities in place at HERL, particularly in the immunotoxicology group within the Environmental Toxicology Division and within the Human Studies Division, that can be utilized to at least partially address problems with infectious disease. In addition, the laboratory plans to add an infectious disease epidemiologist to the program. These efforts require more attention than some of the marginal activities proposed for research within the same program.

In terms of chemically-induced disease, the history of HSD has been with inhalation exposures and the lung as a target organ. There is no a priori reason why this same expertise cannot be brought to bear on problems that are critically important to the Agency's regulatory program in drinking water. It is noted that only two positions from the drinking water program have been assigned to this division, one of which is to be a infectious disease epidemiologist. In view of where the regulatory issues are in the drinking water, we believe that efforts in this division should receive more priority than seems indicated by these limited resources.

As previously stated in the DWC's review of EPA's drinking water microbiology research program there are crucial and pressing scientific research needs that must be addressed in order for EPA to implement existing regulations (e.g., the Surface Water Treatment Rule) and to progress in formulating new regulations (e.g., the Groundwater Disinfection Rule). The Committee recommends that HERL play a key and proactive role in addressing these research needs, despite its institutional and organization constraints. This must be done because no other entity within EPA or in another Federal agency will address these issues. Therefore, the DWC recommends that HERL effectively use its existing resources and leverage others to address key research needs in drinking water microbiology and health. This can be done by putting greater emphasis on drinking water microbiology health effects research activities within existing HERL divisions, by creating stronger and more effective linkages with other EPA labs that have resources and expertise in this area, and by creating and utilizing extramural resources as needed.

### 3.8.3.1 Drinking Water Microbiology and Health Effects Research in Division of Clinical Studies

a) Human studies. The DWC recommends that the Division of Clinical Studies implement as a research priority the development of dose-response data in humans for previously identified, important waterborne pathogens that are being regulated or are targeted for regulation. Specifically, the Clinical Studies Unit should conduct quantitative, human dose-response studies on hepatitis A virus (HAV), Norwalk virus (and other Norwalk-like GI viruses), and Cryptosporidium parvum. These studies are needed to provide the Office of Water with dose-response data that are essential to the risk assessment process. HAV studies could be done using live, attenuated vaccine strains now being developed, Norwalk studies using the National Institutes of Health (NIH) human safety-tested inoculum, and Cryptosporidium studies by developing a safety-tested inoculum obtained from calves or other animals. These studies could be followed by human dose-response studies for other waterborne microbes of importance.

b) Epidemiology. According to the information presented to the DWC, the epidemiology unit of HERL identified infectious disease epidemiology of drinking water as a priority research area. The Committee recommends that HERL aggressively pursue the revitalization and stabilization of the program, as stated (extramural advisory group, acquisition of branch chief and staff, protection and increase of funding, and development of extramural and cooperative activities). However, the DWC believes that current drinking water infectious disease epidemiology research objectives and tasks be critically reviewed in order to identify priority research needs and then create a focussed program to pursue them. This approach is recommended because the Committee concludes that epidemiology program lacks focus, expertise, and scientific validity and capability in this particular area, based on the information presented.

The waterborne disease outbreak surveillance, reporting and investigation program needs to be revitalized and made effective. Linkages in this area must be re-established with appropriate entities in the Centers for Disease Control and State agencies.

The efforts to develop infectious disease epidemiology studies must be critically re-evaluated and should be re-directed to integrate effectively with proposed studies by other interested parties, such as the American Water Works Association Research Foundation (AWWARF) and the Canadian study team. Specifically, the GI illness component of the proposed "French Ozone Study" should be reconsidered because we conclude that there are clear deficiencies in terms of stated objectives, sources of exposure, study population, sources of data, analytical methods and the relevance of such data to U.S. populations and U.S. water supplies.

#### 3.8.3.2 Drinking Water Microbiology and Health Effects Research in Division of Environmental Toxicology

From the review of the immunotoxicology program in the Environmental Toxicology Division, the Committee concludes there are pressing, currently unmet research needs that could be addressed through this program. Studies on the role of immunocompetence in the infectivity (including infectious dose), pathogenesis and clinical course of important waterborne infectious diseases could be done. Specifically, studies comparing the infectivity, quantitative dose-response relationships and virulence of waterborne pathogens in immunocompetent and immunocompromised animal models are critical needs for the health risk assessment of some important waterborne pathogens. These agents include *Cryptosporidium*, non-tubercular mycobacteria and many opportunistic bacterial pathogens.

### 3.8.4 Ozonation

Apparently, studies of ozonation and other disinfection by-products are being pursued only as a complex mixture question. The major effort seems to be genetic bioassays of one type or the other to identify genotoxic compounds. While this is a very important area to pursue, one has to wonder about whether it can be profitably addressed with the resources available to the research program at this time. Considerable effort has been expended in this area in the past that resulted in the identification of a large number of compounds that are active in Salmonella. The followup on these data to determine whether they pose real carcinogenic hazards remains to be determined. This approach also neglects the fact that chemical identification of by-products has been a much more efficient means for identifying by-products of regulatory importance (e.g., the THM's, haloacids, haloacetonitriles, bromate, chlorate). Most of these compounds were

"non-mutagenic" or so weakly mutagenic so that they certainly would not have been detected by bioassay-directed fractionation. Some of the blind spots in these assessments are being addressed with new bioassay techniques. However, there are major problems with the question of how representative the samples are of the source water. For example, are the important ozonated by-products recovered by the same methodology used for chlorination by-products? Considering the limited resources available to the research program and a relatively large list of chlorination by-products that are clearly genotoxic, a focus on characterizing the carcinogenic risks from these compounds that have already been classified as genotoxinswould be a better strategy in determining the relative risk of these compounds to human health. There are certain by-products of other disinfection processes (e.g. aldehyde byproducts of ozonation) that can also be predicted to be problems without resorting to an inadequate screening program. A few years ago, the Committee reviewed the Drinking Water research effort in Cincinnati. At that time the concern was expressed that the health researchers had not taken the lead in studies on ozone by-products. This is still the case. The Committee was gratified to see that some work is ongoing in this area. Specifically, research on the genotoxic properties of the chlorinated acids has been undertaken to clarify the mechanisms by which they may be acting. The work with MX was also very interesting, but it needs to be taken to an in vivo system for evaluation as quickly as possible. As the data for this compound stands, it cannot be viewed as a serious risk.

### 3.8.5 Chemical by Chemical Approach

We believe that the chemical by chemical approach to identifying research needs has to be abandoned in favor of a broader license for HERL to operate. The regulatory agenda should not be a formula for failure on the part of the laboratory. For example, the thought that one will regulate chlorination byproducts to the point that they may mandate ozonation without dealing with ozonation by-products seems to be irresponsible. This is clearly a much more important and pervasive problem of the chemical safety of drinking water than concerns about hazardous waste sites and contamination of source waters (by orders of magnitude). Despite the clear reasons to be concerned about chlorination by-products, the hazard does not seem to be of a magnitude that delay in regulation by 10 years would have much impact on the public health. To regulate now (except perhaps to mandate removal of precursor) would simply introduce even larger uncertainties about the safety of drinking water.

The HERL needs to be brought into the process of problem identification in this and other areas in the drinking water field. If research needs are only identified through the research committee process as a demand for data by the program office against inadequate resources, frustration by both the program office and the HERL will be the only outcome. Resources are so inadequate in this program that the only way that reasonable progress can be made is by a coordinated effort at the laboratory level.

# 4.0 NEEDS AND PRIORITIES FOR DRINKING WATER RESEARCH

## 4.1 Identification of Research Needs and Priorities

In a regulatory agency such as EPA, there is little doubt that research will be driven by the regulatory agenda. It is clear that the mandate placed upon the Agency in the Drinking Water area is much larger than can be responded to by the limited resources assigned for research in this critical area in environmental health. The Agency clearly has not developed a means of prioritizing research needs and rectifying the regulatory program to the ability to provide meaningful data that can be used in the risk assessment process. The Agency continues to force (or is itself forced to through legal action) regulatory actions even though the science suggests that regulation could lead to actions that can potentially endanger the public health. Given this set of circumstances, the regulatory agenda should be coupled to the research agenda rather than the other way round. Until realism of this sort is injected into the process, then frustrations between program offices and research programs within the Agency will continue.

The Agency continues to approach problems on a chemical by chemical basis. It appears that a program office is apparently rewarded based on the number of regulations it gets through the process rather than the number of environmental problems it solves. Therefore, research needs tend to be expressed on a chemical by chemical basis. This almost guarantees that a research program, particularly a health research program, has little stake in the real problems facing a program office.

The HERL has assembled a dedicated group of scientists that are clearly dedicated to improving the Agency's capabilities in the assessment of health risks. However, only a few research needs issued by the Office of Water recognized this concern. Conversely, it is not clear that the HERL is interested in pursuing the

drinking water disinfection issue in a holistic way. Therefore, the Office of Water must continue to provide its research needs on a chemical by chemical basis rather than depending upon the research program to identify the direction that regulation should be going. This mismatch does not appear to be the fault of the principals being reviewed (i.e. HERL and the Office of Water), but represents an institutional flaw that concerns us greatly and which requires serious attention.

### 4.2 Short and Long Term Research Needs Being Met

HERL clearly has picked up on critical research areas in the disinfection by-product area especially in the area of chlorination by-products that are being addressed by the Genetic Toxicology, the Environmental Toxicology and the Developmental Toxicology Divisions. In general these efforts are well directed as far as they go towards the overall problem with drinking water disinfection. There are a number of other areas that are receiving attention such as aluminum neurotoxicity. An effort is underway to address some of the program's difficulties with risk assessments for arsenic, although the committee would disagree somewhat as to whether the direction being taken is the most efficient. Research directed at dioxins, TCDF, PCBs appear of marginal importance to the drinking water program.

### 4.3 Shortfalls in the Research Program

In the drinking water disinfection area, there are no plans to examine the toxicology of alternate disinfectants except for a bioassay program aimed at the genotoxicity of by-products. While this is certainly an appropriate area for research, it is not altogether clear that it is the most efficient way to identify problems. It is clear that much more effort must be directed at chemically identifying disinfection by-products that occur in the highest concentration and obtaining some indication of the toxicological risks they represent. The industry, in collaboration with the program office, has been much more aggressive in this type of activity than HERL. Consequently, the HERL does not seem to be in a position to anticipate research needs or to understand why priorities of the program shift from year to year.

It should be recognized that many of the problems associated with drinking water disinfection revolve around mechanisms of oxidant induced toxicity. Virtually all economically attractive processes currently used or likely to be used in the foreseeable future will involve the introduction of oxidants into the water,

production of oxidants as by-products, and the maintenance of residual oxidant to prevent the outgrowth of microorganisms in the distribution system. Clearly, there is a need for a broad understanding of the factors that modify oxidant toxicology in vivo. Research to develop systematic knowledge in this area will greatly shorten the time required to resolve this particularly complicated issue in environmental toxicology.

Somewhere between the documents distributed to the Committee, e.g. "Strategy to Environmental Health Research at EPA" and the presentations made at the meeting, the area of cardiovascular toxicology became lost. While it is realized that it may not be possible for EPA to have scientists working in each and every area of scientific endeavor, this appears to be a large area of concern. For example, is there really any connection between blood pressure and drinking water? What about the cholesterol question? What is the true relationship between hard water -- soft water and cardiovascular disease? It should be noted that in "The Role of Health Research in Support of EPA's Regulatory Programs" this is emphasized as one of the emerging research needs of the Drinking Water Program.

The EPA is planning to propose drinking water regulations for various Disinfectants and Disinfection By-Products (DBP's) in June, 1993. Among the DBPs proposed for regulation are chlorate and bromate. Chlorate is introduced to drinking water through the use of chlorine, especially liquid hypochlorite, and chlorine dioxide. Bromate is a by-product of ozonating waters containing bromide. Chlorate and bromate may have significant health effects at the occurrence levels found in drinking water. The use of liquid hypochlorite is expected to increase dramatically as a result of the Groundwater Disinfection Rule. HERL staff presentations to the SAB Drinking Water Committee on December 17-18, 1991 did not appear to give a sufficiently high priority to health effects research related to chlorate and bromate. We recommend that HERL give a high priority to health effects research related to chlorate and bromate.

a) Chlorate. Chlorate levels in drinking water may be higher than previously assumed. Health effects information on chlorate is limited. Historically, the water industry has assumed that most chlorate in drinking water was introduced through the use of chlorine dioxide. Since chlorine dioxide use is limited, it was assumed that occurrence was limited. The fact that chlorate is formed in hypochlorite decays means that significant levels may be present as drinking water systems, especially those systems using liquid hypochlorite. The

primary concern is for chlorate formed as stored liquid hypochlorite decays, but chlorate may also be formed in water distribution systems due to the decay of hypochlorite ion. A number of large water systems are considering switching from chlorine gas to liquid hypochlorite, primarily due to safety requirements related to the use of chlorine gas and frequent objections of those living near facilities where the gas is stored. A number of small systems are considering using liquid hypochlorite due to requirements of the Groundwater Disinfection Rule.

b) Bromate. Bromate is a by-product of ozonating waters containing bromide. Health effects information on bromate is limited. Preliminary assessments indicate that bromate may be of significant concern at levels commonly found in ozonated drinking water. Recent findings indicate that bromate may be formed when ozonating waters with low bromide levels. Significant levels of bromate have been found when ozonating waters containing less than 50 μg/L of bromide.

## 4.4 Means to Improve the Process

### 4.4.1 Internal Communications

The Associate Director with HERL must be an expert in problems in drinking water and given sufficient authority in the Laboratory to see that the Research Divisions respond to commitments made to the program office. This individual must also have the authority to transmit the Laboratories priorities back to the program office in a manner that is consistent with the resources that have been allocated. This individual must work with the program office to make it clear to upper management how inadequate resources limit the development of research information that is needed for the assessment of human risk.

### 4.4.2 Research Committee Process

The Committee was impressed with the fact that significant progress has been made in integrating the water research program into the HERL Laboratory in RTP. It was also pleased to see that integration with other programs, such as hazardous waste, etc., was occurring to provide for both efficiency and prevention of duplicative efforts. However, the Committee still (in view of its previous review in Cincinnati) is uncomfortable with the Research Committee process for directing

research. The involvement of laboratory scientists seems to be remote and depend upon the ability and perhaps even interests and understanding of the Associate Laboratory Directory for Water. It is not clear to the Drinking Water Committee whether the clearly defined research efforts presented to the committee get done because of, or in spite of, the research committee process. In light of these concerns, we welcome the changes that have been occurring in the research committee process.

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