CRITICAL REVIEW OF A PROPOSED UNIFORM GREAT LAKES FISH ADVISORY PROTOCOL

(A Science Report to the Council of Great Lakes Governors)

Prepared by
Michigan Environmental Science Board-Council of Great Lakes Governors
Special Fish Advisory Science Panel

MICHIGAN ENVIRONMENTAL SCIENCE BOARD
LEWIS CASS BUILDING
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Michigan Environmental Science Board
Lewis Cass Building
P.O. Box 30026
Lansing, Michigan 48909
517-373-4960

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PREFACE

Michigan Environmental Science Board-Council of Great Lakes Governors
Special Fish Advisory Science Panel

The Michigan Environmental Science Board (MESB) was created by Governor John Engler by Executive Order 1992-19 on August 6, 1992. The MESB is charged with advising the Governor, the Natural Resources Commission, the Michigan Department of Natural Resources and other state agencies, as directed by the Governor, on matters affecting the protection and management of Michigan's environment and natural resources. The MESB consists of nine individuals and an executive director, appointed by the Governor, who have expertise in one or more of the following areas: engineering, ecological sciences, economics, chemistry, physics, biological sciences, human medicine, statistics, risk assessment, geology and other disciplines as necessary. Upon the request of the Governor to review a particular issue, a panel, consisting of MESB members with relevant expertise, is convened to evaluate and provide recommendations on the issue. The MESB is neither a state policy body nor an advocate for or against any particular environmental or public health concern.

On June 27, 1994, the MESB was charged by Governor Engler, as chair of the Council of Great Lakes Governors, to coordinate and lead a regional review of a September 1993 proposed uniform Great Lakes fish consumption advisory document. On October 28, 1994, a Special Fish Advisory Panel composed of two MESB members and eight additional guest scientists with expertise in Great Lakes contaminants, toxicology, risk assessment, human health, and risk communications was convened to conduct the investigation.

Dr. Lawrence J. Fischer
MESB Chairperson
Michigan State University

Dr. P. Michael Bolger
Guest Panel Scientist
U.S. Food and Drug Administration

Dr. Gary P. Carlson
Guest Panel Scientist
Purdue University

Dr. Joseph L. Jacobson
Guest Panel Scientist
Wayne State University

Dr. Barbara A. Knuth
Guest Panel Scientist
Cornell University

Dr. Martha J. Radike
Guest Panel Scientist
University of Cincinnati Medical Center

Dr. Mark A. Roberts
Guest Panel Scientist
Medical College of Wisconsin

Dr. Peter T. Thomas
Guest Panel Scientist
IIT Research Institute

Dr. Kendall B. Wallace
Guest Panel Scientist
University of Minnesota

Mr. Keith G. Harrison
MESB Executive Director
State of Michigan

Critical Review of a Proposed Uniform Great Lakes Fish Advisory Protocol

MAJOR FINDINGS AND RECOMMENDATIONS

The Great Lakes Toxic Substance Control Agreement was signed by the Governors of the Great Lakes states of Illinois, Indiana, Michigan, Minnesota, New York, Ohio, Pennsylvania and Wisconsin on May 21, 1986. Due to extreme variability and often conflicting fish consumption advice existing among the Great Lakes states, a Great Lakes Sport Fish Consumption Advisory Task Force (Task Force), consisting of representatives from public health, environmental or natural resources agencies from each state, was created and charged with the development of a uniform sport fish consumption advisory. During the next several years, the Task Force reviewed various advisories, laws and public health policies that existed among the Great Lakes states, and evaluated the available scientific and regulatory literature on risk assessment and Great Lakes fish toxicology. As a result of its review, the Task Force developed a draft protocol for a regional public health fish advisory. A draft document entitled, *Protocol for a Uniform Great Lakes Sports Fish Consumption Advisory* (Protocol), was presented to the Council of Great Lakes Governors in September 1993.

On June 27, 1994, the Michigan Environmental Science Board (MESB) was charged by Governor Engler, as chair of the Council of Great Lakes Governors, to coordinate and lead a regional review of the September 1993 proposed Protocol. On October 28, 1994, a Special Fish Advisory Panel (Panel), composed of two MESB members and eight additional guest scientists with expertise in Great Lakes contaminants, toxicology, risk assessment, human health and risk communication, was convened to begin the investigation. The investigation consisted of the accumulation and evaluation of peer-reviewed and some nonpeer-reviewed literature and data on the subject. In addition, verbal and written testimony from public health experts, state and federal regulatory agencies, environmental organizations and concerned citizens were considered. Major findings and recommendations of the Panel are summarized below.

♦ The Task Force was thorough in its collection and review of the available scientific literature relating to the development of a Health Protection Value (HPV) and the Protocol; however, it did not summarize and critically review all the relevant scientific literature or make judgments of scientific quality or assign weights to the individual studies used to reach a consensus. Consequently, the Panel recommends that the Task Force use a weight-of-evidence process (qualitative or quantitative) that includes a critical review within the Protocol of the relevant studies (strengths and weaknesses). This is required for adequate scientific justification of the HPV.

♦ The Task Force-developed HPV of 0.05 µg PCB/kg/day is a consensus-determined, composite, risk assessment value based on suspected risk to human health. It was selected to reflect all existing data rather than being purposefully based on a single critical animal or human study or a single adverse health outcome endpoint. Given the manner in which the development of the value was described, the Panel

concludes that the process may not be reproducible and, therefore, capable of accommodating future changes in environmental contamination and/or advances in scientific knowledge.

♦ The Panel also believes that it may be difficult for the Task Force to readily change the HPV chemical contaminant of concern. Such a change may be necessary due to a change in the PCB levels in Great Lakes sport fish and/or the finding of a new environmental contaminant of greater concern. Because of this deficiency, the Panel recommends that the Protocol should delineate a formal procedure to be used for evaluation of a change in the major contaminant of concern. At a minimum, a written set of criteria for changing the major contaminant of concern should be developed and a procedure for determination of a new or modified HPV should be described.

♦ Despite the HPV's inherent limitations, including its uncertainty, the studies reviewed by the Panel support the use of an HPV of 0.05 µg/kg/day for women of child-bearing age. The HPV, if selected based on the higher vulnerability of the fetus to the neurobehavioral effects of PCBs, would presumably also be protective of the potential effects of PCBs in other segments of the human population.

♦ Laboratory animal studies suggest that cancer is another health outcome resulting from PCB exposure. Studies of highly exposed humans show no evidence of PCB-induced cancer. The Panel concludes that the methodology used to calculate human risk from animal data is uncertain and states further that it may result in an unreasonably high risk when applied to PCBs. Consequently, the use of adverse health outcomes other than cancer by the Task Force as a focus for development of an HPV for PCBs represents a reasonable approach.

♦ The levels of total PCBs in Great Lakes fish are decreasing. In spite of the uncertainties and accompanying interpretations of the scientific literature, no conclusive evidence exists that exposure to these compounds via fish consumption induces significant immune dysfunction in humans. The risk to the human immune system from environmental exposure to these xenobiotics is probably quite low and is likely declining. Consequently, the Panel concludes that limiting the dose of PCBs from sport fish to less than 0.05 µg/kg/day should be protective of humans from an immunotoxicologic point of view.

♦ It seems clear from published scientific research that the fetal animal and the human fetus are most vulnerable to the effects of PCBs. The Panel agrees with the conclusion expressed in the Protocol that the selected HPV of 0.05 µg/kg/day is probably protective of normal fetal development in pregnant women consuming fish containing PCBs. It is reasonable to assume from a review of the same literature that an adequate margin of safety resides in that number, which means that it is overly protective for other segments of the population. For this reason, the Panel recommends that, in addition to an HPV for women of childbearing age, there should be a second value used to construct fish consumption advice for the less susceptible portion of the population. This would result in separate fish consumption advice being

provided to two segments of the population.

♦ The absence of a prescribed, basin-wide monitoring plan for sport-caught fish is a major weakness of the Protocol. Consequently, the Panel recommends that the Task Force develop a uniform monitoring program to be used in conjunction with the implementation of a uniform advisory procedure by the member states. Such a program would detail the sampling schedules and standardized analytical methods for PCB residue analyses and be used to make adjustments to the advisory categories and reassignment of fish among categories. In addition, the Panel recommends that objective criteria be developed by the Task Force to evaluate highly contaminated localized areas referred to as "hot-spots" in the Protocol.

♦ The Protocol calls for the assignment of fish species to consumption categories to be based on regression analysis of contaminant residue concentration as a function of fish length. In addition to calling for the development and maintenance of a large and current data base of residue monitoring analyses for all species in each of the Great Lakes, concern was expressed by the Panel regarding the Protocol's use of a nonweighted method of regression analysis and the assumptions used to quantify data for residue analysis that register below the level of detection. The Panel recommends that a more statistically rigorous and objective method of data analysis be used in conjunction with a weighted method of regression analysis in the Protocol. In addition, a description and justification should be provided for the rationale used in making arbitrary assignments of values to samples containing low and unquantifiable levels of contaminants.

♦ In terms of risk communication, the Panel recommends that all communication materials intended for public distribution be pretested with the members of the audiences who are targeted to receive the information. Specific aspects of the communication strategy examined in the pretest should include: (1) proposed graphics (e.g., tables, figures), (2) comparison of the previous advisory methodologies and associated recommendations with the proposed methods and recommendations provided in the Protocol, (3) explanation of the reasons for the change in advisory methodologies, and (4) a proposed content, examined for clarity and ease of understanding by each potential target audience. In addition, the Panel recommends that the recently published USEPA document, *Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories, Volume 4: Risk Communication*, be consulted by the Task Force during the development and implementation of the communication strategy for the Protocol.

The advisory should include descriptions of health effects/risks, benefits, and advice for each audience of concern. If all health endpoints for all segments of the population are covered by the advisory recommendations, that should be stated. The advisory should state if it is intended for use with a particular subset of the population; e.g., women of childbearing age. Particularly if two HPVs are used, as recommended by the Panel, the advisory narrative should reflect which health endpoints have been considered for each segment of the population.

♦ The Protocol's discussion of potential risks associated with chemical contaminants in fish is weak. The Panel recommends that a better description of the chemicals of concern and their health effects be provided. This should include a clear description of the adverse health effects associated with these contaminants. Specifically, noncancer endpoints merit more discussion in the advisory, particularly since the Protocol appears to put emphasis on these health effects and their importance in children and women of childbearing age.

♦ The Protocol currently does not address a comparison between sport- and commercially-caught fish. Anglers may raise questions about the relationship of the sport fish consumption recommendations relative to safety associated with consumption of fish available on the commercial market. Consequently, the Panel recommends that the Protocol include a brief comparison of the risks and benefits of consumption of Great Lakes sport-caught fish to commercially available fish.

♦ The Protocol currently does not address the relative risk of consuming fish versus other foods. The Panel is concerned that this lack of information could lead the uninformed public into believing, inappropriately, that there exists a greater human health concern from fish consumption than can be justifiably based on current scientific data. The Panel recommends that the Task Force consider a brief discussion in the Protocol on the relative risks of consuming fish versus other foods.

♦ The Protocol does not present the information necessary for the public to consider both the benefits and the risks from eating fish. The advisory is derived from only using data related to the harmful effects from chemical contaminants that may be found in fish. There is an abundance of evidence in the scientific literature to document human and animal health benefits of fish consumption. Based on a review of the scientific information from human studies, the Panel submits that the benefits associated with fish consumption by adults may outweigh the risks associated with chemical contaminants in fish caught in the Great Lakes. However, the risk/benefit extrapolation is different for the human fetus, which may be more sensitive than adults to adverse effects from contaminants in fish. The Panel recommends that more consideration be given in the Protocol to the proven benefits of fish consumption. Such a description of the health benefits would improve the Protocol's ability to achieve objectives associated with enabling fish consumers to make their own, informed decision about fish consumption.

CRITICAL REVIEW OF A PROPOSED

GREAT LAKES FISH ADVISORY PROTOCOL

(A Science Report to the Council of Great Lakes Governors)

INTRODUCTION

Council of Great Lakes Governors' Charge

The Michigan Environmental Science Board (MESB) was created by Governor John Engler by Executive Order 1992-19 on August 6, 1992. The MESB is charged with advising the Governor, the Natural Resources Commission, the Michigan Department of Natural Resources and other state agencies, as directed by the Governor, on matters affecting the protection and management of Michigan's environment and natural resources. The MESB consists of nine individuals and an executive director, appointed by the Governor, who have expertise in one or more of the following areas: engineering, ecological sciences, economics, chemistry, physics, biological sciences, human medicine, statistics, risk assessment, geology and other disciplines as necessary. Upon the request of the Governor to review a particular issue, a panel is convened to evaluate and provide recommendations on the issue.

On June 27, 1994, the MESB was charged by Governor Engler (Engler, 1994), as chair of the Council of Great Lakes Governors, to coordinate and lead a regional review of a September 1993 proposed uniform Great Lakes fish consumption advisory document entitled, *Protocol for a Uniform Great Lakes Sports Fish Consumption Advisory* (hereafter referred to as the "Protocol"; see Appendix 1). On October 28, 1994, a Special Fish Advisory Panel (hereafter referred to as the "Panel"), composed of two MESB members and eight additional guest scientists with expertise in Great Lakes contaminants, toxicology, risk assessment, human health and risk communication, was convened to begin the investigation. The investigation consisted of the accumulation and evaluation of peer-reviewed and some nonpeer-reviewed literature and data on the subject. In addition, verbal and written testimony from public health experts, state and federal regulatory agencies, environmental organizations and concerned citizens were considered at four meetings (Harrison, 1995a; 1995b; 1994a; 1994b). The report was prepared by the Panel members with each individual assigned a specific topic or topics to address. The investigation lasted for 11 months.

The report addresses three directives from the Council of Great Lakes Governors:

1. Evaluate the scientific data and the validity of the various assumptions and uncertainties associated with the proposed fish consumption Protocol,

2. Compare the relative risks which may be associated with Great Lakes sport fish with consumption of other foods, and

3. Prepare and submit a report to the Governors recommending a fish consumption Protocol which would most accurately reflect and inform the public of the risks that may be associated with eating Great Lakes fish.

History of the Great Lakes Fish Advisories and Current Protocol

The Great Lakes Toxic Substance Control Agreement was signed by the Governors of the Great Lakes states of Illinois, Indiana, Michigan, Minnesota, New York, Ohio, Pennsylvania and Wisconsin on May 21, 1986 (CGLG, 1986). Due to the extreme variability and often conflicting fish consumption advice existing among the Great Lakes states, a charge was given to the states to reach an agreement on a common fish advisory for the Great Lakes basin. The 1986 agreement also formally created the Great Lakes Sport Fish Consumption Advisory Task Force (hereafter referred to as the "Task Force") and charged it with the development of the uniform sport fish consumption advisory. Task Force membership includes representatives from each public health, environmental or natural resources agency in the eight states bordering the Great Lakes. Table 1 presents the Task Force membership at the time of development of the Protocol. Additional participants have included the Canadian Province of Ontario, U.S. Environmental Protection Agency (USEPA) and Native American organizations. The Task Force meets once each year to share environmental sampling results, coordinate future sampling programs and review the appropriateness of the placement of fish onto each of the Great Lakes states' advisories.

The development of a uniform sport fish consumption advisory was initiated by the Task Force in 1990 with an extensive evaluation of the similarities and differences among the Great Lakes states' advisory programs (GLSFATF, 1993; Hesse, 1990). In general, the Task Force found that the fish advisory processes differed and cancer risk policies varied among the eight Great Lakes states. Except for Minnesota, which was using quantitative cancer risk estimates, in 1990, all other states were basing their sport fish consumption advisories on the U.S. Food and Drug Administration (USFDA) interstate seafood tolerances. Because the formulas, which states used to incorporate the USFDA tolerances, were different, the advice given for a specific level of contamination varied widely (Anderson, 1995a).

While the sport fish advisories used the USFDA tolerances as a reference, most states' regulatory and other public health advisory programs (such as private drinking water) used USEPA cancer and noncancer risk assessment methodologies which produced very different risk estimates results than the USFDA approach. The various states' public health policies tolerated cancer risks up to one cancer in one million lifetimes and regulatory programs up to one in ten thousand lifetimes (Anderson, 1995a). States assessed noncancer risk by using the USEPA reference dose (RfD) and reference concentration (RfC) process and most relied upon the available RfDs from the USEPA integrated risk information system (IRIS) database (Anderson, 1994a). Further, by 1990, there was growing agreement that the USFDA tolerances for market fish were not adequately protective for anglers who consumed sport fish and thus invalidating the basis for most advisories.

Table 1. Great Lakes Sport Fish Advisory Task Force Membership at the Time of Protocol Development.

Member Name	State Represented	Agency Represented
Lee Liebenstein, CoChair	Wisconsin	Natural Resources
Henry Anderson, CoChair	Wisconsin	Health & Social Sciences
Jim Amrhein	Wisconsin	Natural Resources
Candy Schrank	Wisconsin	Natural Resources
John Hesse	Michigan	Public Health
Harold Humphrey	Michigan	Public Health
Jim Bedford	Michigan	Public Health
Asa Wright	Michigan	Natural Resources
Christine Waggoner	Michigan	Natural Resources
Robert Sills	Michigan	Natural Resources
Tom Long	Illinois	Public Health
Richard Hess	Illinois	Conservation
Tom Hornshaw	Illinois	Environmental Protection
Greg Steele	Indiana	Board of Health
C. Lee Bridges	Indiana	Natural Resources
David Gray	Minnesota	Health
Pamela Shubat	Minnesota	Health
Jack Skrypek	Minnesota	Natural Resources
Dan Helwig	Minnesota	Pollution Control
Kim Mortensen	Ohio	Health
Tracey Shelly	Ohio	Health
Ken Paxton	Ohio	Natural Resources
Roland Jenkins	Ohio	Agriculture
John Estenik	Ohio	Environmental Protection
Robert Frey	Pennsylvania	Environmental Resources
Kandiah Sivarajah	Pennsylvania	Health
Nancy Kim	New York	Health
Tony Grey	New York	Health
Ed Horn	New York	Health
Jim Colquhoun	New York	Environmental Conservation

According to Anderson (1995b), "The Task Force was challenged to develop region-wide unanimity within the milieu of preexisting state law diversity, conflicting public health policies and divergent expert opinions. Resolution required an innovative approach. [The Task Force] ... concluded that a holistic approach to risk characterization, incorporating all aspects of risk, ... was desirable and appropriate for a regional public health advisory. By design, the envisioned process would not directly be linked to regulatory programs, specific RfDs, or cancer risk extrapolations used by such

programs. To avoid confusion ... and to set the Advisory program apart, a new descriptive term, "Health Protection Value" (HPV) was chosen [for the acceptable rate of consumption of the fish contaminant judged to provide the highest risk to human health]."

The Task Force evaluated available scientific literature on toxicologically active compounds identified in Great Lakes sports fish. Polychlorinated biphenyls (PCBs) were found to dominate the typical contaminant pattern seen in fish and were the most commonly found contaminants. The Task Force also examined available human and mammalian toxicological and epidemiological data (occupational, environmental accidents, environmental exposure) on cancer and noncancer health effects of PCBs, and presumably other known contaminants in Great Lakes fish. Based on the above, it was decided that the HPV would be derived using PCBs as the contaminant of highest public health concern. Additional contaminants would be evaluated as needed at a later date by the Task Force.

The HPV is used to place fish onto an advisory that recommends varying degrees of restricted consumption (e.g., unrestricted, 1 meal/week, 1 meal/month, 6 meals/year, do not eat). Analytical data from monitoring fish for PCB content are used to assign fish of a particular species and size to one of the consumption categories. The Protocol also provides preliminary recommendations on how the information regarding restricted consumption is to be presented to the public (i.e., risk communication).

A draft of the Protocol was presented at the 1990 annual meeting of the American Fisheries Society and then further refined by the Task Force over the next three years (Hesse, 1994b). The final draft Protocol (GLSFATF, 1993) was presented to the Council of Great Lakes Governors for review and comment in September 1993 (Liebenstein and Anderson, 1993).

Earlier Reviews of the Uniform Great Lakes Fish Advisory Protocol

Prior to the current review, the Protocol underwent two formal reviews by scientists and interested parties not associated with the Task Force. The first (Round I) took place during the period June - July 1993 after which minor changes were made to the draft document. The second (Round II) was conducted during the period September 1993 - March 1994. In addition, several unsolicited comments were received during the Round II review period. No changes were made to the September 1993 draft of the Protocol by the Task Force as a result of the comments obtained from either the Round II or unsolicited reviewers.

A total of 16 reviewers (Round I - 5, Round II - 5 and unsolicited - 6) commented on the June and September 1993 Protocol drafts. The comments and concerns of the 16 reviewers are summarized in Appendix 2. In general, the dominant criticisms of the Protocol centered on the Task Force's weight-of-evidence process used to derive the HPV and the derived HPV itself. The comments on the weight-of-evidence process ranged from concerns regarding the Task Force's specific use and/or lack of use of

data from certain scientific studies and its sole reliance on PCBs to derive the value (Fischer, 1994; Kamrin, 1994; Van Putten, 1994; Yeomans, 1994; Birnbaum, 1993; GLSFC, 1993; Kimbrough, 1993; Moore, 1993; Paustenbach, 1993) to the inability of the reviewers to clearly discern from the Protocol text how the Task Force obtained the HPV (Fischer, 1994; Kamrin, 1994; Moore, 1993; Paustenbach, 1993). Three reviewers (Sielken, 1994; Steele, 1994; Stoner, 1994) specifically stated their support for the process used by the Task Force.

In terms of the derived HPV, seven reviewers (Adamkus, 1994; Dempsey, 1994; Gorenflo, 1994; Kamrin, 1994; Van Putten, 1994; Yeomans, 1994; Moore, 1993) did not question the value obtained by the Task Force. The remaining nine reviewers specifically referenced their position, with five agreeing (Sielken, 1994; Steele, 1994; Stoner, 1994; Gerken, 1993; Kimbrough, 1993) and four disagreeing (Fischer, 1994; Birnbaum, 1993; GLSFC, 1993; Paustenbach, 1993) with the Task Force's value. Of the four reviewers who disagreed with the value, Fischer (1994) and GLSFC (1993) thought it too restrictive, Birnbaum (1993) thought that it not restrictive enough, and Paustenbach (1993) thought it should be re-evaluated.

Additional comments that appeared more than once included the need for the Task Force to provide special advice regarding fish consumption for women of child-bearing age and children (Dempsey, 1994; Van Putten, 1994; Birnbaum, 1993), the need to consider chemical contaminant mixtures in the development of the HPV (Dempsey, 1994; Van Putten, 1994; Yeomans, 1994; Birnbaum, 1993), and the need to improve the manner in which the final fish advisory would be communicated to target groups (Dempsey, 1994; Fischer, 1994; Kamrin, 1994; Van Putten, 1994). Two reviewers (Sielken, 1994; Steele, 1994) indicated their concurrence with the communication component of the Protocol.

CRITIQUE OF PROTOCOL

The purpose of this section of the report is to evaluate the scientific data, the validity of the assumptions made and to review the uncertainties associated with the Protocol. A critical summary of the scientific literature regarding developmental and immunological outcomes from PCB exposure is presented in Appendix 3.

Review of Scientific Literature

Completeness of Review. During the development of the Protocol, the Task Force considered published and unpublished articles and amassed a comprehensive set of regulatory documents (Protocol, Appendix VI). In addition, it also considered the draft USEPA IRIS documents on Aroclors 1016 and 1254 (USEPA, 1994a; 1994b). The Panel concludes that the Task Force was thorough in its collection and review of the available scientific literature relating to the Protocol.

Weight-of-Evidence Process. The Task Force formulated a "qualitative" weight-of-evidence approach to develop the Protocol and to derive the HPV (Anderson, 1995b). The Task Force reviewed and discussed the available information and through an "expert committee" process of consensus building, reached its conclusions. A "quantitative" weight-of-evidence procedure is a widely accepted and objective method that can be used for estimating risk. However, the Task Force deviated from the procedure because: (1) it used, whenever possible, published reviews of the scientific literature and did not necessarily summarize and critically review all the relevant literature and spend time discussing each study according to Anderson (1995b), (2) it did not make judgments of scientific quality or assign weights to the individual studies used to reach a consensus (Protocol, page 28), and (3) its "qualitative" weight-of-evidence procedure is not clearly described in the Protocol and, therefore, is not readily reproducible. According to the Protocol (page 28), a "quantitative" weight-of-evidence method is currently being developed by a private consultant for possible use by the Task Force. The Panel recommends that the Task Force use a weight-of-evidence process (qualitative or quantitative) that includes a critical review within the Protocol of the relevant studies (strengths and weaknesses). This is required for adequate scientific justification of the HPV.

Selection and Application of the Health Protection Value (HPV)

Characteristics of Value. The HPV of 0.05 µg PCB/kg/day is a consensus-determined, composite value reportedly based on suspected risk to human health. Thus, considering the risk assessment--risk management paradigm (NRC, 1983), the HPV may be classified as a risk assessment value (e.g., includes hazard identification, dose-response relationship and exposure assessment) rather than a risk management instrument (e.g., includes social, political and economic consequences). In this regard the HPV is different from the approach used by the USFDA in its regulation of fish purchased for consumption by the public. The limit of 2.0 ppm of PCBs in commercial

fish, adopted by the USFDA in 1984 (USFDA, 1984) is a risk management value as it includes consideration of economic and other factors. Michigan and certain other Great Lakes states continue to use the USFDA risk management number in constructing sport fish consumption advisories. For most states, use of the HPV of 0.05 µg/kg/day as the basis for advisories will result in the appearance of more fish species in the restricted consumption categories. This result could be interpreted by the public as a logical response to increasing fish contamination or to new information indicating contaminants are more toxic than previously estimated. Neither of these suppositions, however, can be justified based on current information.

In contrast to other commonly employed regulatory values (e.g., RfDs), the HPV is purposefully not based on a single critical animal or human study or a single adverse health outcome endpoint (Protocol, page 28). Rather, the HPV was selected to reflect all the data that exist (Anderson, 1995b). According to the Task Force, one advantage of using the HPV over other already available regulatory values for fish consumption advice is that "[It] *... would provide greater stability and be less likely to need to change precipitously should federal science policy or individual cancer potency factors be revised, or new RfDs adopted by the USEPA*" (Protocol, pages 27 - 28). The Panel suggests caution with the development and use of such a value, however, since the same factors that help to provide stability to the HPV may also help to insulate it from being readily modified to reflect changing conditions in environmental contamination and advances in scientific knowledge.

Consideration of Adverse Health Outcomes from PCBs. According to the Protocol (page 28), "*... toxicologic and epidemiologic studies of adverse reproductive and neuro-developmental endpoints were given greater evaluation time and therefore consideration in the HPV selected than other toxicologic endpoints*." Consistent with this statement, the justification of the HPV (Protocol, pages 27 - 46) appears to have depended heavily on the Minnesota Model (Shubat, 1990), which was based on reproductive and developmental outcomes. The Minnesota Model used selected data from the epidemiological research of Jacobson *et al*. (1989; 1985; 1984) and Jacobson, Jacobson and Humphrey (1990a; 1990b) using fish-eating and nonfish-eating individuals living in selected locations in Michigan. Evidence that these studies were given considerable attention by the Task Force includes a lengthy discussion of them in the Protocol (pages 40 - 45). However, the Task Force reiterated at the end of the discussion that the studies implicating developmental deficits in the children of PCB-exposed mothers "... *should not be given or assumed to have more weight than any other of the reports reviewed*" (Protocol, page 46). The diverse nature of the verbal testimony presented to the Panel and written justification of the HPV did not permit the Panel to fully discern the degree to which results of human epidemiological studies were involved with the selection of the HPV.

A review of the two primary human epidemiology studies (Rogan *et al.*, 1986 and Jacobson *et al*., 1984) considered by the Task Force in its selection of the HPV is provided in Appendix 3 (Developmental Outcomes) of this report. It is authored by Panel member, Dr. Joseph Jacobson. In addition to comparing the results obtained

from both investigations, an analysis of the strengths and limitations of each is presented. In both investigations, the developing fetus was reported to be markedly more vulnerable to low-level environmental PCB exposure than the newborn child or adult. Results from studies in laboratory animals support this view (Lilienthal and Winneke, 1991). The Panel concludes that the studies reviewed support the use of the HPV of 0.05 µg/kg/day for women of childbearing age. This HPV, if selected based on the higher vulnerability of the fetus to the neurobehavioral effects of PCBs, would presumably also be protective of the potential effects of PCBs in other segments of the human population. Whether the HPV is "overly protective" for less susceptible segments of the population (e.g., adults except females of child-bearing age) will be considered elsewhere in this report.

As a result of testimony presented to the Panel by Task Force representatives (Anderson, 1995b; 1994b; Hesse, 1994b), an apparent shift in the primary health outcome involved in the HPV selection occurred during the development of the Protocol. Verbal discussion focused on the results of studies in Rhesus monkeys by Tryphonas *et al.* (1991a; 1991b; 1989) that reported the effects of PCBs on the immune system. This also appeared to coincide with the release of a RfD for Aroclor 1254 by the USEPA (1994b), which was also based on these monkey studies. Appendix 3 presents a focused literature review, conducted by Dr. Peter Thomas of the Panel, of the immunological outcomes from PCB exposure. As part of this review, the Tryphonas *et al*. (1991a; 1991b; 1989) Rhesus monkey studies are discussed. The Panel agrees that while the Tryphonas *et al*. (1991a; 1991b; 1989) studies have serious weaknesses, the evidence does indicate a modest effect. However, the biological significance of the results should be interpreted with caution for the following reasons: (1) many measures of immunity were largely unaffected, (2) no objective measure of host defense could be made (a limitation of primate studies), (3) only female animals were investigated as this was originally designed as a reproduction study, and (4) the background and origin of the study animals were not clearly defined and, therefore, effects of unknown previous investigations on the animals cannot be discounted.

The Panel concludes from a consideration of the immunological consequences of PCB exposure that the HPV of 0.05 µg/kg/ day of PCB intake via fish consumption should be protective of humans from an immunotoxicologic point of view. This statement is made with knowledge of the dose-related effects of PCBs in laboratory animals and from the fact that there is insufficient evidence currently existing to suggest that exposure to these compounds induces clinically important immune dysfunction in humans.

Laboratory animal studies suggest that cancer is another health outcome resulting from PCB exposure. Studies of highly exposed humans show no evidence of PCB-induced cancer. However, the risk of human cancer can be estimated by quantitative cancer risk assessment methodology using data obtained from laboratory animals. This procedure, using the USEPA default criteria, is known to result in a risk management value showing an unreasonably high human cancer risk from PCBs (Sielken, Bretzloff and Stevenson, 1995; Goodman, 1994). While cancer has been the focus of risk assessment for PCBs in the past, recent focus is on other health outcomes (e.g.,

neurobehavioral and immunological). This switch to noncancer outcomes has reduced the dependence on a cancer risk assessment methodology and is consistent with a lack of epidemiological evidence for PCB-induced human cancer (Swanson, Ratcliffe and Fischer, 1995). Nevertheless, cancer risks must be considered from a comparative viewpoint and the Task Force indicated (Protocol, page 28) that the HPV eventually selected must result in risks no higher than 1×10^{-4} (1 cancer case in every 10 thousand individuals exposed to the HPV. This value represents the highest risk usually found acceptable in the regulation of contaminants by governmental agencies (USEPA, 1986).

The Task Force calculated the cancer risk (USEPA methodology) associated with human exposure to the HPV of 0.05 µg/kg/day. The risks were three to four cancer cases in every ten thousand individuals exposed to the HPV. The Protocol (page 49) explains that "*Although these estimated cancer risks are slightly above the 1 X 10^{-4} cancer risk, the upper end of the normally acceptable range for regulatory programs, the uncertainties in these cancer risk estimates specific for fish residues were recognized in the Task Force evaluation and in the selection of the HPV.*" The Panel agrees that the methodology used to calculate human risk from animal data is uncertain and states further that it may result in an unreasonably high risk when applied to PCBs. The selection of an acceptable level of risk (e.g., 1 in 10 thousand) is not a scientific issue. Rather, it is a policy issue and should be handled as such. The cancer risk from PCB exposure via fish consumption is probably orders of magnitude lower than that predicted by assuming intake of 0.05 µg/kg/day and calculations using current USEPA-approved default risk assessment methodology. Consequently, the use of noncancer endpoints by the Task Force as a focus for development of an HPV for PCBs represents a reasonable approach.

Risk Management Decisions. A problem encountered by the Panel with the HPV selection involved the exactitude of the number itself. The single number of 0.05 µg/kg/day suggests that it accurately delineates the boundary between safe and harmful intake of PCBs via fish consumption. This is not the case, as there is much uncertainty in the number and more than likely an appropriate degree of "error on the safe side."

The Panel submits that, given the uncertainty involved in the estimates of exposure and toxicity, a value twice the HPV or perhaps even one-half the HPV could have been selected and still fit the outcome of the subjective analysis of the large and diverse volume of published data used by the Task Force. While it is unclear whether such differences in the HPV would have an impact on health protection, information presented to the Panel (Hesse 1994a; Protocol, Appendix V) suggests that such differences could have large effects on the assignment of various species and sizes of fish to restricted consumption categories. This being the case, a small change in the HPV will provide a large change in the consumption advice given to consumers of Great Lakes fish. The Panel believes that sport fish consumption advice should be developed using health risk assessment and a consideration of other factors such as health benefits, and economic and other relevant social factors. This procedure would be

consistent with the risk assessment--risk management paradigm advocated by the National Research Council (NRC, 1983).

It seems clear from published scientific research that the fetal animal and the human fetus are most vulnerable to the effects of PCBs. The Panel agrees, as previously mentioned in this report, with the conclusion expressed in the Protocol that the selected HPV of 0.05 µg/kg/day is probably protective of normal fetal development in pregnant women consuming fish containing PCBs. It is reasonable to assume from a review of the scientific literature that an adequate margin of safety resides in that number, which means that it is overly protective for other segments of the population. For this reason, the Panel recommends that, in addition to an HPV for women of childbearing age, there should be a second value used to construct fish consumption advice for the less susceptible portion of the population. Having stated this, the Panel recognizes the current lack of quantitative data addressing the difference in sensitivity to effects of PCBs between the fetus and adult and, therefore, the difficulty in calculating an quantitative estimate. Nevertheless, the Panel believes that less restrictive fish consumption advice should be determined by those involved in risk assessment/management.

Chemical Contaminant Selection and Changes. The presentations (Anderson 1994b; Hesse, 1994b) made to the Panel, more so than the Protocol, clarified the rationale for the selection of PCBs as the chemical contaminant of concern for sport fish consumption. Based on the information presented, the Panel believes that it would be difficult for the Task Force to readily change the chemical contaminant of concern. Such a change may be necessary because of decrease in the PCB levels in Great Lakes sport fish and/or the possibility of finding a new environmental contaminant of concern.

While the segment of the Protocol dealing with selection of the major contaminant of concern is vague, additional information presented to the Panel (Anderson, 1994b; Hesse, 1994b) indicated that the Task Force members would continue to meet periodically to review the advisory process. The meetings would be used to review new quantitative and qualitative information on chemical contaminants identified in Great Lakes fish. The Task Force would base its advice each year on a composite of the information accumulated on a three-year rolling cycle to reduce unneeded changes in advice due to sampling and analytical consistency problems.

It was clear to the Panel that changes in the major chemical of concern were not to be conducted using an objective, predetermined approach. Presently, each state constructs consumption advice based on regional differences in chemical contaminants in fish. For example, Michigan advisories are usually based on PCB exposure but in some lake regions mercury or dioxins have been used as the chemical of concern. It is not known whether this would continue to be the case if the Protocol was adopted for use. Because of this deficiency, the Panel recommends that the Protocol should delineate a formal procedure to be used for evaluation of a change in the major contaminant of concern. At a minimum, a written set of criteria for changing the major

contaminant of concern should be developed and a procedure for determination of a new or modified HPV should be described. The Panel was assured that immediate steps would be taken in cases of sudden and severe problems such as those that might be associated with chemical spills or other large discharges.

Sensitivity Analysis/Justification of HPV

The Protocol section entitled, *Sensitivity Analysis* presents an effort to justify the validity of the HPV. The title of the section is misleading because a sensitivity analysis is by definition a quantitative assessment of the degree of dependence of an outcome measurement on the variables used to derive the measurement. Instead the Protocol (page 46) states that "*A major Task Force consideration in the decision to develop a new protocol was whether a significant public health risk remained for those* [persons] *... following the existing advisories and whether that residual risk was sufficient to warrant more restrictive advice.*" It appears to the Panel from reading the Protocol (pages 46 - 49) and from correspondence from Clark (1994a; 1994b) that the Task Force concluded that (1) an unacceptable risk existed using current advisory methodologies and (2) the selected HPV would address this risk by providing a needed, more restrictive approach to fish consumption.

The Panel believes that the analysis described in the Protocol does not allow for a meaningful judgment of the degree of "public health gain" resulting from use of the proposed HPV. This is because the measures of risk from PCBs (e.g., cancer risk) that can be used to estimate a benefit from use of the proposed HPV are highly uncertain values as is the HPV itself. Comparing uncertain risk values to the uncertain HPV does not allow a meaningful measure of public health gain (or loss). Rather, the sensitivity analysis described in the Protocol is an exercise that allows a comparison to see how alike or different the HPV is to other uncertain regulatory values. At best, results of the analysis performed by the Task Force are useful as a "reality check" for determining whether the HPV is likely to provide an unacceptably large change in the regulatory climate surrounding exposure to PCBs.

Assignment of Consumption Categories

Total Dietary Intake. According to the Protocol, fish are assigned to the various consumption categories according to best estimates of the dietary intake of PCBs via fish that will not exceed the predetermined HPV. Assumptions inherent to these dietary estimates are:

1. A PCB intake reduction factor of 50% for all fish species provided that the recommendations for preparing and cooking the fish are followed, and

2. A uniform meal size of 227 g "raw" fish/70 kg body weight.

Regarding the first assumption, it is not clear from the Protocol how the value of "50%" was selected. Consequently, the Panel recommends that this issue be clarified in the

Protocol. In terms of the second assumption, the USEPA (1994a) recommends using an average meal size estimate of 227 g/70 kg body weight. It is suggested (Protocol, page 8) that a 227 g meal is an "*overestimate ...*[and] *... provides an additional margin of safety*" to the HPV. The Panel agrees that a 227 g meal probably is an overestimate and suggests that the Task Force continue to research the literature for a values which are more reflective of actual meal sizes for individual segments of the population (e.g., women of child-bearing age, pregnant women, adult men, etc.). This information could be used as a basis to more accurately assign fish to the consumption categories.

Fish Sample Preparation for PCB Analysis. The Protocol (page 10) recommends a skin-on, belly flap-on fillet as the standard fish sample preparation for residue analysis. Exceptions to this standard practice are provided, based on what is perceived to be the most common practiced method of fish preparation for individual species (Protocol, Appendix III). Modifying the sample preparation to most accurately reflect the actual practice of meal preparation for each species is prudent. However, it warrants notation that the error in extrapolating to consumed dose from residue analyses varies with the different methods of sample preparation.

Residue Sampling. Critical to the assignment of individual species to consumption categories are the results of analysis of PCBs in the flesh of each species. Contaminant residue analysis is also the determining factor for periodic reassignment of fish among consumption categories. Accordingly, it is essential to both establish and enforce a statistically sound and technically precise methodology for deriving contaminant residue values for all species of fish and bodies of water within the jurisdiction of the Protocol. Included in this should be a periodic sampling schedule by which the database is maintained current. Imprecisions in the contaminant residue database may overshadow any attempts to perfect the hazard assessment and extrapolation processes. The absence of a prescribed, basin-wide monitoring plan is a major weakness of the Protocol. Consequently, the Panel recommends that the Task Force develop a uniform monitoring program to be used in conjunction with the implementation of a uniform advisory procedure by the member states. Such a program would need to detail the sampling schedules and standardized analytical methods for PCB residue analyses. The Task Force would need to strongly encourage compliance by all member states.

Assignment of Fish Species. According to Appendix V of the Protocol, assignment of fish species to consumption categories will be based on regression analyses of residue concentration as a function of fish length. Accordingly, it is essential that a large and current database of residue monitoring analyses be maintained for all species in each of the Great Lakes. The criteria referenced in the Protocol for fit of the regression analysis are an $R^2 \geq 0.6$ and an "acceptable level of significance." It is not clear, however, how the value of "0.6" was determined or how the Task Force would establish an "acceptable level of significance." The Panel recommends that a more statistically rigorous and objective method of data analysis should appear in the Protocol.

The Protocol implies the use of a nonweighted method of regression analysis. The

Panel recommends that it would be more appropriate to weight the analysis because: (1) confidence in the residue analysis would be greater for the more contaminated samples and (2) the weighting of the data would reflect the size distribution for that particular species and no data should be included for samples below the legal size limit.

The Panel also has concerns regarding quantifying the data for residue analyses that register below the level of detection (LOD). First, it is noted that different analytical laboratories may have different LODs. Accordingly, the management of the monitoring data may not be consistent throughout the Great Lakes basin. Furthermore, the Protocol suggests that if all analyses are below LOD (Protocol, page 66, example "a"), an average value of 1/2 the LOD will be assigned to all data points for that data set. This seems inappropriately conservative. A value of zero should be assumed in this case. Only when near half the samples register greater than or equal to the LOD analyses should the "nondetects" be assigned a value greater than zero. As currently proposed, samples below the LOD will be arbitrarily assigned to the "*...consumption category...one group less restrictive than the category defined by the detectable values*" (Protocol, page 66, example "b"). Assignment of value in this case should be based on weighted regression analyses, if possible, giving the larger fish greater weight. Assignment of the random nondetect analyses, as in example "c" (Protocol, page 66) values of 1/2 LOD seems appropriate. Regardless, the Task Force needs to describe and justify in the Protocol the rationale it uses in making arbitrary assignments of values to nondetect samples and the quantitative methods of data analysis that it proposes to use.

According to the Protocol (page 67), adjustments to the advisory categories and reassignment of fish between categories will be based on consensus weight-of-evidence judgments by the Task Force following annual reviews of the available data. The monitoring data will be an important factor in determining adjustments in advisory categories and reassignment of fish species among categories. Therefore, it is critical that a uniform and rigorous basin-wide sampling program be instituted as part of the Protocol.

Finally, identification of highly contaminated localized areas ("hot-spots"), which are to be excluded from lake-wide advisories, will also be determined by consensus judgment of the Task Force. In its current version, the Protocol does not specify the criteria or methods by which Task Force decisions would be made in this area. The Panel recommends that objective criteria be developed by the Task Force to evaluate such areas.

Risk Communication

It is important to remember when considering the risk communication aspects of the Protocol that the Task Force was not proposing a "final" risk communication program. Indeed, Liebenstein and Anderson (1993) in their September 10, 1993, letter transmitting the Protocol to the Council of Great Lakes Governors noted that "*...further work will be required to develop a thorough communication strategy before release to*

the general public."

The Panel recommends that any communication materials intended for public distribution be pretested with the members of the audiences who are targeted to receive the information. The use of focus groups may be an effective and low-cost method of conducting such pretests. Specific aspects of the Protocol communication strategy examined in the pretest should include: (1) proposed graphics (e.g., tables, figures), (2) comparison of the previous advisory methodologies and associated recommendations with the methods and recommendations based on the Protocol, (3) explanation of the reasons for the change from past approaches, and (4) a proposed content, examined for clarity and ease of understanding by each potential target audience.

The USEPA (1995) recently published a guidance document on health advisory risk communication. That document, *Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories, Volume 4: Risk Communication*, should be consulted by the Task Force during the development and implementation of the communication strategy for the Protocol.

Explaining Advisory Changes. The shift to an HPV as the basis for advisories may result in changes in the listing of species on the advisory, as well as the specific fish consumption maximum frequencies recommended in the health advisories. Without explaining why those changes have occurred, the public will draw its own conclusions (e.g., contaminant levels have changed, scientific knowledge about the toxic effects of PCBs has changed, government agencies are not credible information sources, etc.). It is imperative that the Protocol's advisory risk communication effort explicitly address how the new recommendations differ from the old, and why. This will be a critical element of the risk communication pretesting efforts.

Targeted Populations. Care should be given to explicitly identifying the target audiences for the health advisory. The USEPA (1995) risk communication guidance document may be of help; it includes several lists of potential target audiences and suggestions regarding what types of communication strategies may best reach different types of audiences.

The advice contained within the Protocol should be relevant and meaningful to the intended target audiences, thus the critical importance of pretesting proposed materials with those audiences. Care must be taken to include descriptions of health effects/risks, benefits, and advice for each audience of concern. For example, the Protocol section on *Contaminants in Fish* (page 16) states: "*The meal advice in this advisory is intended to protect children from these potential developmental problems.*" This statement may cause adults to wonder how the advisory pertains to them. If all health endpoints for all segments of the population are covered by the advisory recommendations, that should be stated. The advisory should state if it is intended to protect only children or adults or the developing fetus. Particularly if two HPVs are used, as recommended by the Panel, the advisory narrative should reflect which health

endpoints have been considered for each segment of the population. If the intent of the more conservative HPV (for women of child-bearing age) is to protect the developing fetus, that should be stated explicitly. Similarly, males and female adults not of childbearing age should be informed about the health effects pertinent to them. Thus the advisory should include recommendations (and the reasons underlying them) for each general population segment. The health advisory should avoid, however, including so many different sets of fish consumption advice as to be incomprehensible to the reader. For example, rather than listing explicit consumption advice for those with heart problems, those with a family history of cancer, etc., the advisory may include a narrative section about "other factors to consider when deciding how much fish to eat" (see section on Risk/Benefit Considerations).

An example below illustrates how one state (GDNR, 1994) proposed communicating about whom the advisory is designed to protect. In this example, both children and adults are the targets of the fish consumption advice:

"*PCBs can cause infant development problems in children whose mothers were exposed to PCBs before becoming pregnant. This consumption advice is intended to protect children from developmental problems. ... Some forms of PCBs also cause cancer in laboratory animals and may cause cancer in humans, but these guidelines are designed to prevent this from happening.*"

Risk/Benefit Considerations. The Protocol could be improved with increased description of the health benefits of fish consumption (see section on Relative Risks and Health Benefits of Fish Consumption), particularly for those target audiences for whom the type of health benefits available through fish consumption may be particularly important. Such a description would improve the Protocol's ability to achieve objectives associated with enabling fish consumers to make their own, informed decision about fish consumption. The following example is loosely based on the USEPA (1995) risk communication guidance document:

"*You may be concerned about comparing the risks and benefits of eating fish. Consider your own lifestyle and health background. For instance, if you have high cholesterol, you may be wise to eat fish as often as once a week. For you, the benefits of eating fish may be more important than the cancer risks. But if you are also feeding your children fish, you might be concerned about the possible health risks that they may face from exposure to environmental contaminants. For your children, you can choose fish low in contaminants, and give them fish to eat from a variety of sources.*"

Developers of the communication materials should specifically consider including explicit recommendations to prospective or current nursing mothers. This discussion should include a clear explanation of the health and other (e.g., psychological, emotional) benefits to mother and child associated with breast-feeding, versus the potential health risks associated with potential infant exposure to the contaminants of concern through breast milk. Pretesting this information will be critical to ensuring the recommendations minimize the level of perhaps unnecessary anxiety created.

The Protocol discussion of potential risks associated with chemical contaminants in fish is weak. Greater description of the chemicals of concern and their health effects is needed. This should include a clear description of the adverse health effects associated with these contaminants. Specifically, noncancer endpoints merit more discussion in the advisory, particularly since the Protocol appears to put emphasis on these health effects and their importance in children and women of childbearing age.

Complexity and Clarity of Presentation. The recommended pretesting of any advisory communication materials will help ensure that the presentation is of the appropriate complexity for the intended target audiences. Suggestions for specific language changes within the Protocol are presented below:

(1) page 16 (paragraph 1): The wording "*Fish are 'nutritious'...*" should be simplified to: "*Fish are good for you ...*"; page 6 (paragraph 2) of the Protocol uses the simplified wording.

(2) page 16 (paragraph 1, 3rd sentence): It should also be noted in this paragraph that the contaminants can harm the fetus if the mother eats them, either while pregnant or before pregnancy.

(3) page 16 (section entitled *Health Benefits*): This section should be expanded so it is clear what types of people may want to weigh more heavily the health benefits (e.g., those with susceptibility to heart disease).

(4) page 16 (section entitled *Contaminants in Fish*):

(a) (paragraph 2) - The meaning of the sentence "*Although this advisory is primarily based on effects other than cancer...*" is not clear, since other effects have not been described (as previously noted under Risk/Benefit Considerations, this report).

(b) (paragraph 2) - It is unclear by the wording "*At worst, ... it is estimated that approximately one additional cancer case may develop...*" among what group this one additional cancer will appear. For instance, is this among people who follow the advisory, or people who do not follow the advisory? Also, there is no comparison provided between people who do and do not follow the advisory. If such statements are included, their intent must be clear.

(5) page 17 (section entitled *How to Use this Advisory*):

(a) (paragraph 3) - This paragraph would benefit from a bold subheading suggesting special advice for women of child-bearing age and children in terms of meal spacing.

(b) (paragraph 4) - This paragraph would benefit from a bold subheading suggesting advice for women beyond their childbearing years and men.

(c) (paragraph 5) - This paragraph would benefit from additional explanation regarding how the reader should interpret the assumptions underlying the

health advice. For example, if a smaller fishmeal is eaten (less than 1/2 lb), presumably fish can be eaten more frequently than suggested in the tables.

(6) page 18 (section entitled *Cleaning and Cooking Your Fish*):

(a) (paragraph 2) - The following sentence should be added to the end of the paragraph: "*Throw away any liquid you used to cook the fish, including frying oil.*"

(b) (disclaimer at bottom of page) - There is no indication what will happen if the reader does not follow the cleaning and cooking directions. As noted, the reader should be provided with enough information to understand the implications if that individual does not fit with the major assumptions underlying the health advice. Assumptions and the consequences of their invalidity should be expressed.

(7) pages 20 - 24 (*Meal Advisory Tables*):

(a) Some audiences may not be familiar with the "<" and ">" mathematical symbols. The words "*less than*" and "*more than*" should be substituted. Ideally, this could be examined during a pretest of health advisory communication materials.

(b) If the spacing of meals is an important issue for health protection, consideration should be given to including separate columns for women of childbearing age (one meal per month) versus women beyond childbearing years and men (12 meals per year). This approach should be pretested with different target audiences.

(c) If spacing meals is important, an asterisk and footnote for each table should be included regarding how to interpret/apply the "*One Meal a Week (52 meals/year)*" column heading and then pretest this with different target audiences.

Relationship to Commercial Fish Consumption. The Protocol currently does not contain any comparison between Great Lakes sport- and commercially-caught fish. Anglers may raise questions about the relationship of the sport fish consumption recommendations relative to safety associated with consumption of fish available on the Great Lakes' commercial market. Consequently, the Panel recommends that the Protocol include a brief comparison of the risks and benefits of consumption of Great Lakes sport-caught fish to commercially available fish.

Meal-spacing Advice for Health Protection. All advice included in the health advisory should be examined in terms of its importance or necessity to achieve desired levels of health protection. For example, if it is not critical for health reasons that fishmeals be spaced out evenly over a one-year period, that advice should be deleted. Such recommendations tend to increase the burden on the individual who seeks to follow the health advice, and should be deleted if they are not important to achieving the health protection goals targeted. However, if the spacing of meals is an important behavior, the explanation within the Protocol (page 16, paragraphs 3 and 4) should be retained as is, because it is clear and direct. A footnote or addition to the consumption table may be necessary to better convey the meal-spacing advice.

RELATIVE RISKS AND HEALTH BENEFITS OF FISH CONSUMPTION

The purpose of this portion of the report is to briefly discuss the relative risks associated with the consumption of Great Lakes fish and other foods and to evaluate the health benefits of eating fish.

Putting Risks into Perspective

Great Lakes fish have been shown to contain varying levels of persistent toxic substances (including PCBs), which may pose a risk to human health if consumed in large enough quantities and/or over a long enough period of time. The Task Force chose to focus the Protocol (page 2) on PCBs because it was "*...the chemical contaminant most frequently encountered in Great Lakes fish which necessitates guidance.*" Considerable uncertainty exists, however, in estimating human harm from consumption of PCB-contaminated Great Lakes fish. For instance, the risk associated with consumption of PCBs has been given a carcinogen category of B-2 by the USEPA (1990), meaning that it is considered a probable human carcinogen (i.e., sufficient evidence for animal carcinogenicity but insufficient evidence for human carcinogenicity). In addition, factors used as the basis to calculate the levels of risk for human cancer and for developmental, behavioral and reproductive harm are based on a series of assumptions regarding, for instance, similar response to PCB exposure between humans and other animals, occurrence of similar mixtures of PCBs in both environmental and experimental fish, amount of fish consumed, frequency of fish consumption, number of years of fish consumption, etc. Alteration to any one of these assumptions can influence the calculation of the final risk value.

Except for data suggesting harm to human fetuses as a result of maternal consumption of PCBs (Jacobson and Jacobson, In press; Jacobson, Jacobson and Humphrey, 1990a; Jacobson *et al.*, 1992), the Panel is unaware of any data on documentable human abnormalities, illnesses or occurrences of cancer or deaths that can be attributed to the consumption of Great Lakes sport fish at current or past PCB contaminant levels found in the environment. This is not to suggest, however, that the risk of harm is not present or that such data will not exist in the future, but rather to indicate that to date, little direct evidence exists documenting such harm.

Occurrence of Food Contamination

Contrasting the suspected risk of harm from eating PCB-contaminated Great Lakes fish to the better documented and projected harm to humans from the consumption of biologically contaminated foods provides a ready contrast and helps to put the risk of consumption of Great Lakes sport fish into perspective. According to Young (1989), "*... the most urgent threat* [to human health] *that is taking lives in this country every year comes from the familiar, well-known microorganisms that contaminate poultry, eggs, dairy products, and meat.*" According to Baird-Parker (1994), there is an increased incidence of food-borne illness reports. This is due to several factors including,

increased reporting and data collection, new agricultural practices, changes in eating habits, identification of new pathogens, and changing population sensitivities. Marshall (1988) cites statistics that suggest when a consumer buys a steak, there is a one in 20 chance that it is contaminated with *Salmonella*. For pork, the chances are one in eight, and for poultry, one in three.

Estimates of Food-borne Deaths, Illnesses and Cancer

Each year, about 30,000 cases of salmonellosis are reported in the U.S. Because many milder cases are not diagnosed or reported, the actual number of infections may be 20 to 100 times greater (Mahon, 1995). In terms of all food-borne illnesses, the Council for Agricultural Science and Technology (CAST, 1994) task force has estimated that 6.5 million to 33 million cases of food-borne illness occur annually, with death resulting in as many as 9,000 cases (DHHS, 1990). The most common food-borne illnesses are the infections caused by the bacteria *Salmonella* and *Campylobacter*, and by the Norwalk family of viruses (DHHS, 1990).

Short of death, long-term complications of food-borne illnesses can also occur. Archer and Kvenberg (1985) have estimated that chronic illnesses are likely to occur in two to three percent of cases of food-borne infection. According to CAST (1994), chronic complications sometimes are a function of infection, not illness, and can occur even if the immune system successfully fights off the illness. In such cases, activation of the immune system facilitates the chronic condition. Complication of food-borne illness can include arthritis, kidney damage, blood poisoning, heart disease, pancreatic infection, pneumonia and neurological damage. In addition, congenital impairments associated with a maternal toxoplasmosis infection can be passed on to the fetus and result in mental retardation, blindness and/or hearing loss (Roberts and Frenkel, 1990). Generally, the elderly, infants and those with impaired immune systems are more likely to have the most severe illness.

The risk of cancer due to consumption of biologically contaminated nonfish food sources is not as documentable. However, besides containing a wide variety of natural cancer-causing chemicals (Scheuplein, 1992; Ames, Magaw and Gold, 1987; Weisburger, Barnes and Czerniak, 1986; Ames, 1983), major protein-rich foods such as ground beef, beefsteak, pork chops, eggs, fried chicken, ham, roast beef and bacon, if cooked well-done, are known to contain bacterial mutagens (Falk *et al.*, 1988; Felton *et al.*, 1983; Sugimura, 1979). As one example, the consumption of such foods, according to Felton *et al.* (1983), can result in ingested mutagenic and carcinogenic components. Scheuplein (1992) has estimated that the risk of death from cancer from dietary exposure to carcinogens occurring in traditional foods (meats, poultry, fruits, vegetables and grains) to be 7.61×10^{-2}. Mortality estimates are unavailable for cancer resulting from consumption of biologically contaminated foods.

Based on the above example, the Panel concludes that the risk of harm to human health resulting from the consumption of biologically-contaminated nonfish and cooked foods could be much greater in terms of occurrence and documentable acute and

chronic ailments and death than is the risk of harm currently suspected to occur from eating PCB-contaminated Great Lakes sports fish at current environmental contamination levels. The Protocol currently does not address the relative risk of consuming fish versus other foods. The Panel is concerned that this lack of information could lead the uninformed public to believing, inappropriately, that there exists a greater human health concern from fish consumption then can be justifiably based on current scientific data. The Panel recommends that the Task Force consider a brief discussion in the Protocol on the relative risks of consuming fish versus other foods.

Health Benefits of Fish Consumption

There is an abundance of evidence in the scientific literature to document the health benefits of fish consumption. A search of published information in the medical literature since 1990 by the Panel produced over 40 publications (see Appendix 4) derived from human studies of the effects of omega-3 fatty acids, fish oils or fish consumption on various physiological or biochemical parameters. The conclusions from these studies emphasized observed beneficial effects to the human cardiovascular system with no adverse effects from fish-derived products or fish consumption (Simon, 1994; Burr, 1992). Ingestion of the omega-3 fatty acids (docosahexanoic acid and eicosapentaenoic acid) found in fish oils produce a variety of antiatherogenic changes (Bagdade *et al*., 1990) as well as a reduction of mildly elevated blood pressure (Vandongen *et al*., 1993), reduction of serum triglycerides (Fumeron *et al*., 1991) and cholesterol (Mori *et al.*, 1994), and an enhancement of the therapeutic action of antihypertensive drugs (Howe *et al*., 1994; Singer *et al*., 1990). Fish consumption also has been shown to have beneficial effects on smokers and nonsmokers suffering from lung disease (Shahar *et al.*, 1994; Sharp *et al.*, 1994).

Fish-eating populations such as the Inuit in North America have much lower incidence of cardiovascular disease when compared to the general population of the U.S. and this can be correlated with a much higher intake of beneficial components in fish (Dyerberg, Bang and Stofferson, 1975). The lower but increasing incidence of cardiovascular disease in the Inuit over the last 30 years may be due to changes to a more western diet and a higher incidence of rheumatic heart disease possibly attributed to an increasing rate of infectious disease (Davidson, Bulkow and Gellin, 1993). It is important to note that the U.S. diet is relatively deficient in omega-3 fatty acids at 0.2 g/day compared to Denmark at 3.0 g/day and the Inuit at 14.0 g/day (Feskens and Kromhout, 1993).

A recent epidemiology study found that increasing fish consumption from one to two servings per week to five or six servings did not substantially reduce the risk of coronary heart disease in men (Ascherio *et al.*, 1995). This result obtained from a study of health professionals across the U.S. may indicate that consumption of larger amounts of fish are not further protective when compared to the more moderate rate of fish consumption typical of the diet of educated health professionals. One interpretation of this result is that high fish consumption is not protective from heart disease (Katan, 1995). However, in light of the large amount of evidence for a positive effect of fish

consumption on human cardiovascular function, the results of the health professional study indicating no further benefit of high fish exposure suggests a maximum effect may be obtained with a moderate rate of fish consumption.

Beneficial effects of fish or fish oil consumption in pregnant women have been observed. A reduction in levels of thromboxanes by administration of fish oils may have a beneficial effect in managing women at risk for preeclampsia (Schiff *et al*., 1993). Animal studies have documented beneficial effects of omega-3 fatty acids in the development of the eye and brain in the fetus (Connor *et al.*, 1991; Simopoulos, 1991; Walker, 1967). Conclusions reached in certain human studies have indicated that pregnant women should be counseled to consume more fish during pregnancy (Nettleton, 1993).

Presently, available results provide an indication that moderate fish consumption can provide the beneficial effects known to result from ingestion of omega-3 fatty acids (Vandongen *et al*., 1993). Undoubtedly, the relatively low level of fish consumption in the general U.S. population is likely to be insufficient to produce the magnitude of beneficial changes that can be gained by consuming higher amounts of fish or fish oils. The indirect benefits, derived from a reduced consumption of saturated fatty acids in red meat and from the direct action of omega-3 fatty acids and possibly other beneficial components of fish, are well documented from human and animal studies. Based on available scientific information from human studies, the Panel submits that the benefits associated with fish consumption by adults may outweigh the risks associated from chemical contaminants in fish caught in the Great Lakes. However, the risk/benefit extrapolation is different for the human fetus, which may be more sensitive than adults to adverse effects from contaminants in fish.

The Protocol does not present the information necessary for the public to consider both the benefits and the risks from eating fish. The advisory is derived from only using data related to the harmful effects from chemical contaminants that may be found in fish. The large number of tables and textual information in the Protocol reflecting the estimated risks from fish consumption overwhelms the few sentences devoted to health benefits. The poor dietary habits of most U.S. citizens reflect a large void in the knowledge base needed for making intelligent decisions regarding nutrition and health. Therefore, sport fish advisories should not assume that anglers and the public have the information needed to make informed decisions regarding benefits and risks attendant with consumption of fish. Assuming the goal of the advisory is to promote changes in behavior consistent with improved public health, the Panel recommends that more consideration be given in the Protocol to the proven benefits of fish consumption.

MAJOR CONCLUSIONS AND RECOMMENDATIONS

The purpose of this section of the report is to summarize the Panel's major conclusions and recommendations, which when addressed as revisions in the Protocol, should better reflect and inform the public of the risks that may be associated with eating Great Lakes fish.

1. The Task Force was thorough in its collection and review of the available scientific literature relating to the development of the HPV and the Protocol; however, it did not summarize and critically review all the relevant scientific literature or make judgments of scientific quality or assign weights to the individual studies used to reach a consensus. Consequently, the Panel recommends that the Task Force use a weight-of-evidence process (qualitative or quantitative) that includes a critical review within the Protocol of the relevant studies (strengths and weaknesses). This is required for adequate scientific justification of the HPV.

2. The Task Force-developed HPV of 0.05 µg PCB/kg/day is a consensus-determined, composite, risk assessment value based on suspected risk to human health. It was selected to reflect all existing data rather than being purposefully based on a single critical animal or human study or a single adverse health outcome endpoint. Given the manner in which the development of the value was described, the Panel concludes that the process may not be reproducible and, therefore, capable of accommodating future changes in environmental contamination and/or advances in scientific knowledge.

3. The Panel also believes that it may be difficult for the Task Force to readily change the HPV chemical contaminant of concern. Such a change may be necessary due to a change in the PCB levels in Great Lakes sport fish and/or the finding of a new environmental contaminant of greater concern. Because of this deficiency, the Panel recommends that the Protocol should delineate a formal procedure to be used for evaluation of a change in the major contaminant of concern. At a minimum, a written set of criteria for changing the major contaminant of concern should be developed and a procedure for determination of a new or modified HPV should be described.

4. Despite the HPV's inherent limitations, including its uncertainty, the studies reviewed by the Panel support the use of an HPV of 0.05 µg/kg/day for women of childbearing age. The HPV, if selected based on the higher vulnerability of the fetus to the neurobehavioral effects of PCBs, would presumably also be protective of the potential effects of PCBs in other segments of the human population.

5. Laboratory animal studies suggest that cancer is another health outcome resulting from PCB exposure. Studies of highly exposed humans show no evidence of PCB-induced cancer. The Panel concludes that the methodology used to calculate human risk from animal data is uncertain and states further that it may result in an unreasonably high risk when applied to PCBs. Consequently, the use of adverse health outcomes other than cancer by the Task Force as a focus for development of an HPV

for PCBs represents a reasonable approach.

6. The levels of total PCBs in Great Lakes fish are decreasing. In spite of the uncertainties and accompanying interpretations of the scientific literature, no conclusive evidence exists that exposure to these compounds via fish consumption induces significant immune dysfunction in humans. The risk to the human immune system from environmental exposure to these xenobiotics is probably quite low and is likely declining. Consequently, the Panel concludes that limiting the dose of PCBs from sport fish to less than 0.05 µg/kg/day should be protective of humans from an immunotoxicologic point of view.

7. It seems clear from published scientific research that the fetal animal and the human fetus are most vulnerable to the effects of PCBs. The Panel agrees with the conclusion expressed in the Protocol that the selected HPV of 0.05 µg/kg/day is probably protective of normal fetal development in pregnant women consuming fish containing PCBs. It is reasonable to assume from a review of the same literature that an adequate margin of safety resides in that number, which means that it is overly protective for other segments of the population. For this reason, the Panel recommends that, in addition to an HPV for women of childbearing age, there should be a second value used to construct fish consumption advice for the less susceptible portion of the population. This would result in separate fish consumption advice being provided to two different segments of the population.

8. The absence of a prescribed, basin-wide monitoring plan for sport-caught fish is a major weakness of the Protocol. Consequently, the Panel recommends that the Task Force develop a uniform monitoring program to be used in conjunction with the implementation of a uniform advisory procedure by the member states. Such a program would detail the sampling schedules and standardized analytical methods for PCB residue analyses and be used to make adjustments to the advisory categories and reassignment of fish among categories. In addition, the Panel recommends that objective criteria be developed by the Task Force to evaluate highly contaminated localized areas referred to as "hot-spots" in the Protocol.

9. The Protocol calls for the assignment of fish species to consumption categories to be based on regression analysis of contaminant residue concentration as a function of fish length. In addition to calling for the development and maintenance of a large and current data base of residue monitoring analyses for all species in each of the Great Lakes, concern was expressed by the Panel regarding the Protocol's use of a nonweighted method of regression analysis and the assumptions used to quantify data for residue analysis that register below the level of detection. The Panel recommends that a more statistically rigorous and objective method of data analysis be used in conjunction with a weighted method of regression analysis in the Protocol. In addition, a description and justification should be provided for the rationale used in making arbitrary assignments of values to samples containing low and unquantifiable levels of contaminants.

10. In terms of risk communication, the Panel recommends that all communication materials intended for public distribution be pretested with the members of the audiences who are targeted to receive the information. Specific aspects of the communication strategy examined in the pretest should include: (1) proposed graphics (e.g., tables, figures), (2) comparison of the previous advisory methodologies and associated recommendations with the proposed methods and recommendations provided in the Protocol, (3) explanation of the reasons for the change in advisory methodologies, and (4) a proposed content, examined for clarity and ease of understanding by each potential target audience. In addition, the Panel recommends that the recently published USEPA document, *Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories, Volume 4: Risk Communication*, be consulted by the Task Force during the development and implementation of the communication strategy for the Protocol.

The advisory should include descriptions of health effects/risks, benefits, and advice for each audience of concern. If all health endpoints for all segments of the population are covered by the advisory recommendations, that should be stated. The advisory should state if it is intended for use with a particular subset of the population; e.g., women of childbearing age. Particularly if two HPVs are used, as recommended by the Panel, the advisory narrative should reflect which health endpoints have been considered for each segment of the population.

11. The Protocol's discussion of potential risks associated with chemical contaminants in fish is weak. The Panel recommends that a better description of the chemicals of concern and their health effects be provided. This should include a clear description of the adverse health effects associated with these contaminants. Specifically, noncancer endpoints merit more discussion in the advisory, particularly since the Protocol appears to put emphasis on these health effects and their importance in children and women of childbearing age.

12. The Protocol currently does not address a comparison between sport- and commercially-caught fish. Anglers may raise questions about the relationship of the sport fish consumption recommendations relative to safety associated with consumption of fish available on the commercial market. Consequently, the Panel recommends that the Protocol include a brief comparison of the risks and benefits of consumption of Great Lakes sport-caught fish to commercially available fish.

13. The Protocol currently does not address the relative risk of consuming fish versus other foods. The Panel is concerned that this lack of information could lead the uninformed public into believing, inappropriately, that there exists a greater human health concern from fish consumption than can be justifiably based on current scientific data. The Panel recommends that the Task Force consider a brief discussion in the Protocol on the relative risks of consuming fish versus other foods.

14. The Protocol does not present the information necessary for the public to consider both the benefits and the risks from eating fish. The advisory is derived from

only using data related to the harmful effects from chemical contaminants that may be found in fish. There is an abundance of evidence in the scientific literature to document human and animal health benefits of fish consumption. Based on a review of the scientific information from human studies, the Panel submits that the benefits associated with fish consumption by adults may outweigh the risks associated with chemical contaminants in fish caught in the Great Lakes. However, the risk/benefit extrapolation is different for the human fetus, which may be more sensitive than adults to adverse effects from contaminants in fish. The Panel recommends that more consideration be given in the Protocol to the proven benefits of fish consumption. Such a description of the health benefits would improve the Protocol's ability to achieve objectives associated with enabling fish consumers to make their own, informed decision about fish consumption.

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APPENDIX 1

June 27, 1994 Letter from Council of Great Lakes Governors to the Michigan Environmental Science Board

COUNCIL OF GREAT GOVERNORS

June 27, 1994

Dr. Lawrence Fischer, Chair
Michigan Environmental Science Board
Lewis Cass Building, 2nd Floor
320 South Walnut
P.O. Box 30026
Lansing, Michigan 48909

Dear Dr. Fischer:

The Great Lakes Toxic Substance Control Agreement was signed by the Governors of the Great Lakes states on May 21, 1986. Among the charges given to the states was to reach an agreement on a common fish advisory for the Great Lakes basin. A Great Lakes Fish Consumption Advisory Task Force has been working on this issue for several years now, and appears to be close to finalizing a common fish consumption protocol.

Given the significance of a fish advisory to the well being of the citizens and the economies of the Great Lakes states, it is important that any such protocol have its basis in sound and defensible science. Therefore, and on behalf of the Council of Great Lakes Governors, I am requesting that the Michigan Environmental Science Board coordinate and lead a regional review of the proposed Great Lakes Fish Consumption Advisory Protocol and its supporting documents.

Specifically, I would request the Board to arrange for and host a requisite number of meetings of a Panel composed of the most eminent scientists within the Great Lakes states to:

(1) Evaluate the scientific data and the validity of the various assumptions and uncertainties associated with the proposed fish consumption protocol;

(2) Compare the relative risks which may be associated with Great Lakes sport fish with the consumption of other foods; and

(3) Prepare and submit a report to the Governors recommending a fish consumption protocol which most accurately reflect and inform the public of the risks that may be associated with eating Great Lakes fish.

I am directing the Departments of Public Health and Natural Resources and the Office of the Great Lakes to fully cooperate with and support the Panel's investigation. A similar directive has been made by the other Great Lakes Governors to their respective agencies. You are also encouraged to actively seek the assistance from various members which comprise the Great Lakes Fish Consumption Advisory Task Force.

We would appreciate it if your report is completed by November 15, 1994.

Sincerely,

John Engler
Chairman

APPENDIX 2

Summary of Uniform Great Lakes Fish Advisory Protocol Review Comments

APPENDIX 2. Summary of Uniform Great Lakes Fish Advisory Protocol Review Comments.

Prior to the current review by the Michigan Environmental Science Board-Council of Great Lakes Governors' Special Fish Advisory Panel (Panel) of the *Protocol for a Uniform Great Lakes Sports Fish Consumption Advisory* (Protocol), the document had undergone two formal reviews by scientists and interested parties not associated with the Task Force. The first review (Round I) took place during the period June - July 1993 after which minor changes were made to the draft document. The second review (Round II) took place during the period January - March 1994. In addition, several unsolicited comments were received during the Round II review period. No changes were made to the September 1993 draft of the Protocol by the Task Force as a result of the comments obtained from either the Round II or unsolicited reviewers. The purpose of this Appendix is to present a summary of the comments provided regarding the draft Protocols.

A total of 16 reviewers (Round I - 5, Round II - 5 and unsolicited - 6) commented on the Protocol. The comments and concerns of the 16 reviewers are summarized in Tables 1 - 3, respectively). In general, the dominant criticisms of the Protocol centered on the Task Force's weight-of-evidence process used to derive the HPV and the derived HPV itself. The comments on the weight-of-evidence process ranged from concerns regarding the Task Force's specific use and/or lack of use of data from certain scientific studies and its sole reliance on PCBs to derive the value (Fischer, 1994; Kamrin, 1994; Van Putten, 1994; Yeomans, 1994; Birnbaum, 1993; GLSFC, 1993; Kimbrough, 1993; Moore, 1993; Paustenbach, 1993) to the inability of the reviewers to clearly discern from the Protocol text how the Task Force obtained the HPV (Fischer, 1994; Kamrin, 1994; Moore, 1993; Paustenbach, 1993). Three reviewers (Sielken, 1994; Steele, 1994; Stoner, 1994) specifically stated their support for the process used by the Task Force.

In terms of the derived HPV, seven reviewers (Adamkus, 1994; Dempsey, 1994; Gorenflo, 1994; Kamrin, 1994; Van Putten, 1994; Yeomans, 1994; Moore, 1993) did not question the value obtained by the Task Force. The remaining nine reviewers specifically referenced their position with five agreeing (Sielken, 1994; Steele, 1994; Stoner, 1994; Gerken, 1993; Kimbrough, 1993) and four disagreeing (Fischer, 1994; Birnbaum, 1993; GLSFC, 1993; Paustenbach, 1993) with the Task Force's value. Of the four reviewers disagreed with the value, Fischer (1994) and GLSFC (1993) thought it too restrictive, Birnbaum (1993) thought it not restrictive enough and Paustenbach (1993) thought it should be re-evaluated.

Additional comments that appeared more than once included the need for the Task Force to provide special advice regarding fish consumption for women of child-bearing age and children (Dempsey, 1994; Van Putten, 1994; Birnbaum, 1993), the need to consider chemical contaminant mixtures in the development of the HPV (Dempsey, 1994; Van Putten, 1994; Yeomans, 1994; Birnbaum, 1993), and the need to improve the manner in which the final fish advisory would be communicated to target groups (Dempsey, 1994; Fischer, 1994; Kamrin, 1994; Van Putten, 1994). Two reviewers (Sielken, 1994; Steele, 1994) indicated their concurrence with the communication component of the Protocol.

Table 1. Round I Comments to June, 1993 Draft *Protocol for a Uniform Great Lakes Sport Fish Consumption Advisory* (Liebenstein and Anderson, 1993).

Reviewer	Adequacy of HPV[(a)]	Other Comments on the Protocol
Birnbaum, 1993	Disagrees with HPV; should be Lowered	•PCBs do not occur in isolation. There are significant levels of PCDFs and often PCDDs. •Animal and human data suggest that the developing embryo/fetus is at the greatest risk. •Major problem with the HPV is that all anglers are treated as equal. •HPV may be too high given subtle developmental effects observed in humans and Rhesus monkeys. •Assumption made that body burden is due to fish. PCBs are present in many foods.
Gerken, 1993	Agrees with HPV	•Aroclors in fish are not identical to aroclors tested in animals.
Kimbrough, 1993	Agrees with HPV	•Human mortality data in workers are inconsistent and do not show any particular trends. •In human studies sometimes a positive association with PCB exposure was found and sometimes a negative association was found. •Adverse effects reported in Michigan and North Carolina studies are inconsistent and do not agree on the area of the brain affected. •Japan rice oil was also contaminated with naphthalenes and dibenzo-p-dioxins. •Using monkey data for calculations is protective. •The promoting of estrogen-like activity has only been shown in animals. •Persistent chlorinated organic chemicals at low concentrations have not been known to increase the incidence of breast cancer.
Moore, 1993	Neither Agrees nor Disagrees with HPV	•Decision to conceptually adopt a weight of the evidence approach is scientifically sound, however, it is not clear that incorporating all the information into a single composite HPV represents a sound scientific judgment. • Michigan human data are unverified, lack a true dose response, failed to detect body burdens consistent with large quantities of fish consumption and did not control for confounders. North Carolina human data do not corroborate the Michigan study since the endpoints are different and the nonhuman primate data are known to have major shortcomings. •Reason for not using cancer data needs to be stated. •Protocol infers that all studies are equally weighted which indicates that the process was a collation rather than a scientific review. Also, HPV selection appears to have been based more on policy than a true weight-of-evidence evaluation of the studies. •Not clear what the Task Force did.

(a) HPV = Health Protection Value (0.05 _g PCB/kg/day).

Table 1. Round I Comments to June, 1993 Draft *Protocol for a Uniform Great Lakes Sport Fish Consumption Advisory* (Liebenstein and Anderson, 1993) (continued).

Reviewer	Adequacy of HPV[(a)]	Other Comments on the Protocol
Paustenbach, 1993	Disagrees with HPV; should be Re-evaluated	•Using NTP-recognized classification scheme and body weight to the 3/4 power, the geometric mean cancer potency factor for the four data sets is 1.2 $(mg/kg/day)^{-1}$, not 1.9 as reported by the Task Force. •Recommended the use of 1.2 $(mg/kg/day)^{-1}$ when calculating the cancer risks for humans. •Questioned if each study received the same weight because methodology was unclear. •Recommended that limited weight be given for current EPA RfD for PCBs. •National Wildlife Federation derived RfDs, 0.05 _g/kg/day; (Byrne et al., 1988); 0.2 _g/kg/day (Bruckner et al., 1974); 0.01 _g/kg/day (Allen et al., 1979), need to be looked at cautiously since each has inherent problems. •Faulted Rhesus monkey studies. •Faulted epidemiology studies' inability to differentiate between PCB exposure and exposure to other chlorinated compounds and heavy metals in fish. •Meal size: Protocol indicates that 227 g (0.5 lb)/70 kg man, this value does not agree with published data; range = 6.4 g/day to 37 g/day. •Tables do not report meal size of 227 g/day.

(a) HPV = Health Protection Value (0.05 _g PCB/kg/day).

Table 2. Round II Comments to September, 1993 Draft *Protocol for a Uniform Great Lakes Sport Fish Consumption Advisory* (Liebenstein and Anderson, 1993).

Reviewer	Adequacy of HPV[(a)]	Other Comments on the Protocol
Fischer, 1994	Disagrees with HPV	•Not possible to determine how HPV was calculated. •Weight-of-evidence approach does not address the quality of the scientific information used to establish the HPV. •Equal weight to each study used in the analysis. •Assume HPV was chosen because it was deemed low and in current use in the state of Minnesota. •Appears that the Task Force used to a large measure the Michigan study to calculate/select the HPV. The Michigan study is subject to much scientific controversy. •Large tables of lakes, fish species and fish size for consumption sends a confusing and unrealistic message to the public regarding dangers of Great Lakes fish consumption. •Mode of text and information in tables should reflect the uncertainty in risk assessment. •Questions why the uniform Protocol appears to be treated as a governmental regulatory instrument. •Methyl mercury in fish not considered. •Statement regarding neurobehavioral effects in children is not supportable by current information. •Task Force commended for their re-analysis of Tilson data. •HPV is unrealistically low. •50% reduction when trimming fish a reasonable number.
Kamrin, 1994	Neither Agrees nor Disagrees with HPV	•No way to know which studies were used and which were excluded to determine HPV. •HPV is a risk management number. •Information not presented in a way conducive to risk communication. Goal of risk communication is to inform individuals so that they can make the best choices. •Discussion about mercury is confusing, no information about which fish have mercury contamination is provided. •Distinction between risk levels for older persons, males, pregnant, etc is not clear. •If compliance is really the goal, risks should be greatly exaggerated to convince people to take even limited action. •Statement regarding neurobehavioral effects in children is not supportable by current information. •Difficult to convince people that fish with over 1.89 ppm should not be eaten when the FDA is saying that fish with contamination below 2 ppm can be eaten 365 days a year.

Table 2. Round II Comments to September, 1993 Draft *Protocol for a Uniform Great Lakes Sport Fish Consumption Advisory* (Liebenstein and Anderson, 1993) (continued).

Reviewer	Adequacy of HPV[(a)]	Other Comments on the Protocol
Sielken, 1994	Agrees with HPV	•Following Protocol statements are appropriate: ••Cancer risk from eating contaminated fish cannot be predicted with certainty. ••The background cancer rate is about 1 in 4 people. ••Sport fish consumption may not increase an individual's cancer risk at all. ••By following the advisory, a consumer can minimize his or her cancer risk. ••By following the advisory, at worst, according to the USEPA methods, 1 additional cancer case in 10,000 people eating contaminated fish over their lifetime would be expected.
Steele, 1994	Agrees with HPV	•Accepts weight-of-evidence process and results. •Higher chlorinated congeners are thought to cause cancer in laboratory animals; all commercial PCBs cause reproductive and development effects in animals. Humans - PCBs cross the placenta/enter fetal circulation/mothers' milk. •Human epidemiological data were emphasized by the Task Force - major strength of the approach. •HPV developed by Task Force appears to be protective of public health. •Task Force has taken a major step forward in trying to convey the risks of fish consumption. The approach allows the sport fisherman to weigh the risk and benefits. •The weight-of-evidence approach uses all of the data that are available rather than one single study. The assumptions used in selecting point estimates for variables are reasonable, well described, and supportable. •Eating foods low in unsaturated fats and high in protein is thought to reduce the risk of cardiovascular disease.
Stoner, 1994	Agrees with HPV	•There are clear explanations of the factors considered in arriving at the HPV. Assumptions leading to assigned value of 0.05 _g PCB/kg/day are reasonable. Risk estimations are an imprecise science. •Levels of PCBs are going down which may result in the need to recalculate the HPV every few years. Consideration should be given to other compounds (which are stable over time and have a sufficient data base in terms of human toxicity) to calculate an HPV. •Animal studies - questioned if fish meal plus PCBs was fed to animals, would it lead to similar biological effects. •Human epidemiological data - some studies of fish consumers have high blood PCBs and some have marginal blood PCBs - some other source of PCBs. •Monkey data - major concern - health effects on the developing human fetus. •No epidemiological study has established a link between cancer and humans. From a carcinogenesis standpoint, PCBs in fish may not present a risk to humans.

(a) HPV = Health Protection Value (0.05 _g PCB/kg/day).

Table 3. Unsolicited Comments to September, 1993 *Draft Protocol for a Uniform Great Lakes Sport Fish Consumption Advisory* (Liebenstein and Anderson, 1993).

Reviewer	Adequacy of HPV[(a)]	Other Comments on the Protocol
Adamkus, 1994	Neither Agrees nor Disagrees with the HPV	•Credit given to the Council of Great Lakes Governors for national leadership in this critical area. Ohio has set the pace for implementation of the new Protocol with its recent successful advisory for Lake Erie.
Dempsey, 1994	Neither Agrees nor Disagrees with the HPV	•Special advice for women of child-bearing age and children should be added. •Exclusive emphasis on PCBs is inappropriate; advice for other contaminants should be developed. •Communication - advice on fish consumption has been technical and not clearly targeted to the audience at greatest risk. •Any communication strategy adopted by the states needs to be stressed using the channels through which subsistence anglers, women of child-bearing age, and other sensitive populations are likely to receive health advice and take it seriously.
Gorenflo, 1994	Neither Agrees nor Disagrees with the HPV	•Recommended the formation of a Monitoring Plan Subcommittee of Task Force to establish a monitoring plan for each of the Great Lakes. Subcommittee should be made up of groups that currently monitor fish for contaminants.
Van Putten, 1994	Neither Agrees nor Disagrees with the HPV	•National Wildlife Federation believes that the Protocol is a tremendous step forward. It will provide much greater protection from exposure to some chemicals, notably PCB. It can be improved by incorporating the following suggestions: ••Special advice for women of child-bearing age and children must be incorporated. ••Combinations of pollutants must be addressed; the PCBs, TCDD, DDT/DDE, and mercury. ••Cooking and cleaning assumptions must be more thoroughly documented - 50% reduction is not supported by the data. •Process for finalizing and implementing the Protocol is not clear and should be explained. •Ohio chose to provide less stringent advice to walleye pike fisherman in 1994 than is recommended by the Protocol without scientific justification.

(a) HPV = Health Protection Value (0.05 _g PCB/kg/day).

Table 3. Unsolicited Comments to September, 1993 Draft *Protocol for a Uniform Great Lakes Sport Fish Consumption Advisory* (Liebenstein and Anderson, 1993) (continued).

Reviewer	Adequacy of HPV[(a)]	Other Comments on the Protocol
GLSFC, 1993[(b)]	Disagrees with HPV	•HPV is unreasonable. •The reduction to FDA's action levels of 2.0 ppm down to 0.05 ppm reflects no basis in scientific evidence to substantiate the change. •Use of risk assessment is an inexact science, and is at best highly questionable and sends out conflicting signals. •Peer reviewers selected by the Task Force have severely criticized the methodology, HPV and studies used to develop the Protocol, yet the Task Force has chosen to ignore that information. •No consideration is given to the abundant and compelling body of research available that suggests positive health effects - reproductive and cardiovascular effects from eating fish. •No consideration given to the potential economic impact the new Protocol-based advisories will have on the Great Lakes region.
Yeomans, 1994	Neither Agrees nor Disagrees with the HPV	•Regrettable that the joint advisory effort was not completed and implemented for the 1994 fishing season. •States should be encouraged not to change the scientific standards proposed by the Task Force. •Fish advisories should be consistent throughout the eight states. •Children and women of child-bearing age should be specifically warned of possible reproductive and developmental problems of PCB consumption. •Updates of the advisory should consider multiple contaminants in Great Lakes fish.

(a) HPV = Health Protection Value (0.05 _g PCB/kg/day).
(b) GLSFC = Great Lakes Sport Fishing Council.

APPENDIX 3

Critical Health Outcomes from PCB Exposure

APPENDIX 3. Critical Health Outcomes from PCB Exposure.

The purpose of this appendix is to present a brief overview of the pertinent literature regarding the developmental and immunological outcomes from polychlorinated biphenyl (PCB) exposure. Dr. Joseph Jacobson and Dr. Peter Thomas of the Panel prepared the review on developmental outcomes and immunological outcomes, respectively.

Developmental Outcomes

Two studies, one in North Carolina (Rogan *et al*., 1986) and one in Michigan (Jacobson *et al*., 1984) have examined effects of prenatal PCB exposure on cognitive and behavioral development in infants and children. Although initiated independently at the end of the 1970's, the Michigan and North Carolina studies were similar in research design. Both cohorts of children were recruited during or immediately after gestation and assessed on similar measures longitudinally as newborns, during infancy, and during the preschool period. Both studies collected cord serum and maternal serum and milk samples to assess PCB exposure, and both used multivariate statistical analysis to control for potential confounding influences.

The studies differed in two important respects: (1) the Michigan cohort was selected to over represent the offspring of women who had eaten relatively large quantities of Lake Michigan fish, which during the 1970's were among the most highly contaminated in the U.S. By contrast, the North Carolina cohort was drawn from the general population, and (2) although both studies used the Webb and McCall (1973) method to analyze the biological samples, the values reported are not comparable. In Michigan, total PCB level was determined by summing 10 Webb-McCall peaks. In North Carolina only two peaks were quantified, and total PCBs was estimated by assuming that the two peaks constituted the same proportion of human serum and milk samples as in the laboratory standard (26.4%) (McKinney *et al*., 1984). The Michigan data showed, however, that the two peaks actually represent approximately 40% of the PCBs in human biological samples. The North Carolina estimate also adjusted statistically for recovery loss. The estimation procedures led the North Carolina values to be artificially inflated relative to the Michigan values, and they need to be divided by a factor of at least two to make them comparable to the values reported in the Michigan study and elsewhere (Jensen, 1987; Jacobson and Jacobson, In press). Given the specific environmental exposure of the Michigan cohort and the fact that effects were seen on a broader range of developmental outcomes (e.g., birth size, 4-year memory), there is reason to suspect that the Michigan children may have been more highly exposed.

In both studies, the cord serum PCB levels were generally lower than those typically found in milk and body fat samples, which is not surprising given that PCBs are lipophilic and cord blood is lean. In North Carolina, where 88% of the cord blood samples were below the laboratory's detection limit, prenatal exposure was estimated based on two maternal blood samples and series of breast milk samples obtained from the mother periodically while the infant was being nursed. Since PCBs are in equilibrium in fat deposits throughout the body, maternal blood and milk PCB levels indicate maternal body burden, which determines the level of PCBs transmitted prenatally across placenta. Although maternal blood and milk provide a less direct measure of fetal exposure than cord blood, PCB accumulation is higher and, therefore, easier to detect. In Michigan cord serum PCB level and maternal milk PCB level were used as indicators of prenatal exposure.

Both studies found developmental deficits in relation to prenatal PCB exposure although not always on the same outcome measures. On the Brazelton Neonatal Behavioral Assessment Scale, both found the higher exposed newborns to be less responsive to environmental stimulation (Rogan *et al*., 1986; Jacobson *et al*., 1984). The North Carolina study found depressed tonicity and activity level and a larger number of weak reflexes. The Michigan study found more restricted range of state, poorer autonomic regulation, and weaker reflexes. The Michigan neonatal findings were tentative because the effects were seen in relation to reported maternal consumption of contaminated fish but not in relation to the biological

measures of PCB exposure.

Both studies administered the Bayley Scales, which is the most widely used standardized test of infant development. The North Carolina study found a significant relation between prenatal PCB exposure and poorer gross motor function at six, 12, and 24 months (Rogan and Gladen, 1991; Gladen *et al*., 1988). In Michigan no effects were seen on the Bayley, possibly because it was administered only at five months when the gross motor test focuses on reaching and grasping rather than independent sitting and walking, which become the focus from six months onward. The principal infancy finding in the Michigan study was an association between prenatal PCB exposure and poorer visual recognition memory at seven months on the Fagan Test, which was not administered in North Carolina (Jacobson *et al*., 1985). This finding was recently replicated in a new cohort of infants born to Yu-cheng exposed mothers in Taiwan (Ko *et al*., 1994). Unlike the Bayley, which has poor long-term predictive validity, the Fagan Test predicts childhood cognitive function, probably because it directly assesses fundamental components of information processing skill (McCall and Carriger, 1993; Bornstein and Sigman, 1986).

The infancy findings reported in both Michigan and North Carolina are subtle, and their long-term significance for intellectual function during childhood is not clear. The findings that provide the greatest cause for concern are the poorer performance on the McCarthy Memory and Verbal Scales by the more heavily exposed infants in the Michigan cohort at four years (Jacobson *et al*., 1990). On the Memory Scale, the most highly exposed children were more than twice as likely to perform poorly (more than 1 standard deviation below the mean). No effects were seen on the McCarthy Scales in North Carolina. In Michigan, deficits were also seen on tests of pictorial memory and visual discrimination processing at four years (Jacobson *et al*., 1992).

Many of the children in both studies breast fed for extended periods. The Michigan study obtained serum samples from most of the children at age four years and found that the breast-feeding children received significant postnatal exposures, leading in many cases to four-year serum PCB concentrations almost as high as those of their mothers (Jacobson *et al*., 1989). Nevertheless, there was no evidence in either study of any impairment in cognitive function because of this postnatal exposure; all the observed deficits were seen in relation to prenatal PCB exposure. The greater vulnerability of the fetus was confirmed in an experimental rat study, in which animals were randomly assigned to receive either pre- or post-natal PCB exposure (Lilienthal and Winneke, 1991). Deficits in learning and visual discrimination were seen only in the prenatally exposed animals. Thus, although larger quantities of PCBs are transferred to the infant postnatally via breast-feeding, the data from both Michigan and North Carolina indicate that the infant is markedly more vulnerable when the exposure occurs *in utero*.

The first attempt to use the Michigan and North Carolina data to calculate a reference dose was by Tilson, Jacobson and Rogan (1990). By their calculations, the Michigan data provided the lowest threshold for a neurotoxic effect. Although the Task Force characterized its derivation of the HPV in terms of an imprecise weight-of-evidence approach, the proposed HPV appears to have been derived largely from the Michigan data using a slightly different set of assumptions than Tilson, Jacobson and Rogan (1990). One problem in basing the HPV heavily on the Michigan findings is that, although they have been corroborated by parallel findings in North Carolina and in experiments with laboratory animals, there has been no specific replication on the same outcome measures. Similar impairments have also been seen in Yu-cheng exposed children in Taiwan (Yu *et al*., 1991), but the exposure may not be comparable since it contained more polychlorinated dibenzofurans than PCBs. The decline in the levels of these contaminants in Great Lakes fish since 1980 makes replication of the Michigan findings more difficult, because it is now harder to locate a cohort of infants exposed at sufficiently high levels.

The strengths of the Michigan study include the use of a comprehensive, state-of-the-art cognitive assessment battery and careful assessment and statistical control for a broad range of potential confounding influences. Despite the absence of replication data on other cohorts of similarly exposed children and the uncertainty of the long term implications of the deficits reported to date, the Michigan study provides the clearest evidence for risk to humans from low level environmental PCB exposure and,

therefore, the most relevant available data for calculating an HPV. Unfortunately, however, the Task Force has ignored one of the most important findings from the Michigan and North Carolina studies; namely, that the fetus is markedly more vulnerable than the infant, child, or adult and that the threshold for neurobehavioral risk for the latter is, therefore, presumably significantly higher. While the Michigan data provide a scientifically defensible basis for an HPV to protect against fetal risk, there is no basis for using these data to determine consumption criteria for adult males or women beyond child-bearing age.

Immunological Outcomes

The immune system comprises a complex set of cellular and chemical components that are designed to protect the body against foreign pathogens while not responding adversely to self. The distinction between self and nonself is made by an elaborate recognition system that depends on specific receptor molecules associated with the cell surface of T- and B-lymphocytes. Nonspecific effector mechanisms that amplify the specific T- and B-cell responses are also important in the immune response. These nonspecific features include mononuclear phagocytes, natural killer cells, polymorphonuclear leukocytes, and the complement system. Optimal functioning of the immune system requires that specific cells and cell products interact with each other in a sequential, regulated manner.

Immunotoxicology is the discipline concerned with the study of the deleterious effects of chemical xenobiotics on the immune system. These potential deleterious effects can range from immunosuppression and the associated increased risk of infection and tumor growth to immunoenhancement and the associated risk of developing autoimmune or allergic reactions.

Immunosuppression in humans due to genetic, disease-related, or chemotherapy-induced defects in immunity nearly always results in decreased resistance to infections. The types of organisms to which such patients are susceptible provide clinical evidence for the role of various immune effector mechanisms in different diseases. Similarly, there is a broad base of data demonstrating enhanced tumor development in patients undergoing immunosuppressive drug therapy (Penn, 1985). Thus, increased incidence and severity of infection and increased incidence of cancer are justifiable expectations following exposure to immunotoxic chemicals. There are no data, however, in humans highly exposed to PCBs to document this assertion.

Quality and Regulatory Usefulness of PCB NOAELs and LOAELs. With regard to PCB exposure in the Great Lakes basin, it is clear that potential exists for human exposure due to bioconcentration in the food chain. In addition to the presence of measurable residues in fish and wildlife as well as in humans living in the Great Lakes basin, these compounds have documented immunotoxic effects in laboratory animal studies. The effects range from causing an increased incidence of experimental infection, to specific effects on immune system structure (histopathology) and function. For a comprehensive review of the literature on the immunotoxicity of PCBs and related compounds, see articles by Thomas *et al*. (1988); Murray and Thomas (1992); Luster, Blank and Dean (1987); Newcombe and Esa (1992); and Sharma (1988).

Currently the best source of information concerning the potential immunotoxic effects of these compounds comes from animal studies. The mouse has served as the primary test system for most of the immunotoxicology studies involving PCBs and related compounds. Although differences exist regarding absorption, metabolism and distribution of these compounds, the structure and function of the murine and human immune systems are quite similar; lending strength to any observed effects.

In the vast majority of cases, laboratory animal studies involving these compounds have been conducted under carefully controlled conditions with acute or relatively short-term exposures at concentrations considerably higher than those encountered in the environment. Furthermore, a review of these studies reveals that considerable variation exists in particular isomer or isomers evaluated, animal species used, route, duration and level of exposure, as well as endpoint examined. In almost no case were efforts made to verify actual delivered dose. In studies reporting dose-response experiments, little effort was made to

determine a LOAEL or NOAEL. In some cases, increased susceptibility to an infectious agent and alterations in immune function parameters were reported; in others, only changes in immune function were examined.

A review of the literature also reveals a lack of information concerning the potential immunotoxicity of long term exposure to PCB compounds. The most significant and comprehensive chronic studies to date to examine potential PCB immunotoxicity were those reported by Tryphonas *et al*. (1991a; 1991b; 1989). These investigators studied a group of Rhesus monkeys who received up to 80 _g Aroclor 1254/kg/day in the diet for as long as 4.5 years. Critiques by USEPA of these studies (Smialowicz, 1993a; 1993b; Henningson, 1993; Benson, 1993) concluded that despite some weaknesses, the data suggest potential adverse effects to the immune system from chronic, low level exposure. Based upon IgM antibody titers to sheep red blood cells (SRBC), the Lowest-Observed-Effect-Level (LOEL) can be estimated at 5 _g/kg PCB/day or less.

While all these studies suffered from significant weaknesses, the weight-of-evidence does suggest a modest effect. However, the biological significance of these results should be interpreted with caution for the following reasons: (1) other measures of immunity were largely unaffected, (2) no objective measure of host defense could be made (a limitation of primate studies), (3) only female animals were investigated as this was originally designed as a reproduction study, and (4) the background and origin of the study animals were not clearly defined.

That the SRBC antigen is not appropriate for evaluation of primate immunity in these studies (Paustenbach, 1993) cannot be justified based on current immunologic thinking. The mechanism(s) responsible for generation of an immune response to this antigen are similar to other "clinically relevant" T-cell dependent antigens (e.g., Tetanus toxoid) that could have been used. The differential effects on antibody production to pneumococcal polysaccharide (vs. SRBC) are not surprising and suggests that the B-cell is not a target.

The Panel agrees with comments by Van Putten (1994) and Birnbaum (1993) concerning the issue of mixtures. Potential environmental exposure is rarely limited to the PCBs alone, but includes other polyhalogenated aromatic hydrocarbons such as the polyhalogenated dibenzofurans and dioxins. As part of the USEPA dioxin health reassessment, much attention has recently been paid to reports that tetrachlorodibenzo(p)dioxin (TCDD) alters experimental infection or tumor challenge in laboratory animals. Although there are great differences in experimental design, challenge agent and animal model, the weight- of-evidence suggests that TCDD exposure at low levels impairs host resistance mechanisms. For example, significantly increased mortality was seen in mice treated with a single injection of as little as 100 ng TCDD/kg and challenged with influenza A2/Taiwan virus (House *et al*., 1990). Clark *et al*. (1983) reported that mice were susceptible to *Herpes simplex* type II virus following weekly (x 4) injections of TCDD at dose levels as low as 40 ng/kg. These two studies are significant because the LOEL for TCDD is below the ID50 dose for suppression of the murine antibody forming cell response (0.7 _g/kg).

It is clear that under carefully controlled laboratory conditions, PCBs and related compounds associated with the Great Lakes basin are capable of modulating the immune system of experimental animals at environmentally relevant concentrations. However, problems associated with assessing potential risks to the immune system of humans from environmental exposure include: (1) determining the exposure variables related to a particular compound, (2) identifying the appropriate immunological endpoints for evaluation, and (3) interpreting the data gathered because of these evaluations. Subtle perturbations in immune function following exposure to environmental chemicals may not, in every instance, result in a relevant health effect. Alternatively, subtle changes in certain immune functions could increase the likelihood of adverse immune-related health effects only during the brief period when these effects are present, or may result in minor health changes unlikely to be revealed in an epidemiology study. Current epidemiological evidence, however, concerning some of the more toxic environmental chemicals does not provide support for a strong link between subtle immunological perturbations and adverse clinical changes. It cannot be ruled out, however, that problems associated with studies such as these have

precluded the detection of evidence for this link.

Relative to the Great Lakes, the levels of PCBs entering the food chain through the consumption of contaminated fish are decreasing. In spite of the uncertainties discussed above, no conclusive evidence exists that exposure to these compounds induces significant immune dysfunction in humans. As a result, the risk to the human immune system from environmental exposure to these xenobiotics is probably quite low and is likely declining. Therefore, the Protocol's limitation of the dose of PCBs from sport fish to less than 0.05 _g/kg/day should be protective from an immunotoxicologic point of view.

Epidemiological Considerations of Adult Human Exposure to PCBs. Evaluation of human health effects associated with exposure to PCBs draws on diverse sources of data sets that were developed under very different conditions. Occupationally-derived human exposure data reflect the response of a group of individuals selected based on physical characteristics, training, innate abilities and health status. Exposure in the occupational setting involves multiple exposure routes, usually dermal and respiratory, and set periods of time. In addition, the species of PCBs is often known and measurable in the work place setting. Catastrophic exposures (i.e., environmental accidents) usually involve a more diverse subset of the population than exposures in the occupational setting and may include the dermal and respiratory exposures but often are of higher intensity and of shorter duration. Examples of this group would include the episodes in Japan in 1968 and Taiwan in 1979 (Rogan *et al.*, 1988). Data derived from general populations reflect sampling biases associated with specific study designs, incorporates diverse groups, many exposure routes, and varying durations of exposures. Health outcomes from studies of the general population are generally not as dramatic as those found in the occupational or environmental accident groups and involve outcomes that are far less dramatic in terms of observable health effects.

The published literature provides some indication of the potential human health risk associated with consumption of PCB-contaminated fish but has major gaps. Tilson, Jacobson and Rogan (1990) is an example of peer-reviewed information that can provide a basis for development of NOAELs and LOAELs for human exposure to PCBs as well as give scientific support to current and future advisories. But noncancer endpoint data are needed and must be used to periodically revisit the levels that are set for fish consumption.

APPENDIX 4

Fish Consumption Health Benefits Bibliography

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