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Proceedings of the Workshop on Cause-Effect Linkages, March 28-30, 1989, Westin Hotel, Chicago, Illinois, U.S.A

Council of Great Lakes Research Managers

International Joint Commission. Great Lakes Regional Office

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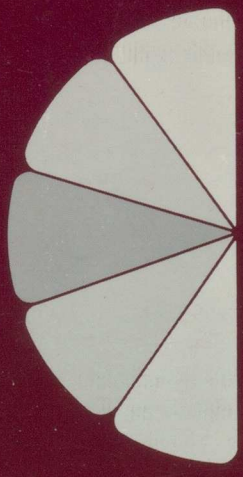

Proceedings of the Workshop on Cause - Effect Linkages

International Joint Commission

Council of Great Lakes Research Managers

Proceedings of the Workshop on Cause-Effect Linkages

Edited by

Michael Gilbertson
International Joint Commission
Windsor, Ontario

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DISCLAIMER

This report to the Chairpersons of the Science Advisory Board and the International Joint Commission was carried out as part of the activities of the Council of Great Lakes Research Managers. While the Commission supported this work, the specific conclusions and recommendations do not necessarily represent the views of the International Joint Commission, the Science Advisory Board or its committees.

If you want to insist on strict proof in the empirical sciences, you will never benefit from experience, and never learn from it how wrong you are.

Sir Karl Popper, 1934

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PREAMBLE AND ACKNOWLEDGEMENTS

On March 28-30, 1989, the International Joint Commission, through the Council of Great Lakes Research Managers, hosted a workshop in Chicago at the Westin Hotel. The workshop was held to explore the ways in which observed effects in populations of fish and wildlife as well as humans could be linked to causes. The causes of particular interest were exposures to persistent toxic substances in the Great Lakes. The workshop participants included not only research scientists and managers but also resource managers and regulatory officials. Appendix A contains the rationale for the Workshop on Cause-Effect Linkages and a brief description of the methodology, derived from epidemiology, that was used as a framework for developing the seven case histories. The Council of Great Lakes Research Managers appointed a Steering Committee to plan and oversee the preparation of the workshop (see Appendix B). A list of participants is contained in Appendix C.

These brief proceedings are published to make the information available to the general public and in particular, for use at the Biennial Meeting of the International Joint Commission to be held in Hamilton, Ontario, on October 11-14, 1989. The full proceedings will be published in the *Journal of Toxicology and Environmental Health* in 1990.

The Council of Great Lakes Research Managers wishes particularly to thank Dr. Renate Kimbrough of the United States Environmental Protection Agency for chairing the workshop and Dr. Bert Liston of National Health and Welfare Canada for delivering the introductory address. Ms. Myrna Reid of the staff of the Great Lakes Regional Office of the International Joint Commission deserves special mention for her logistical skill in implementing the decisions of the Steering Committee.

David Egar, Canadian Co-Chair Jon Stanley, United States Co-Chair

Council of Great Lakes Research Managers

1.0 INTRODUCTION

1.1 Welcome

Renate A. Kimbrough
Office of the Administrator, U.S. EPA, Washington, DC

It is a pleasure being here and I am looking forward to chairing this conference. I have always been interested in methods of investigating human disease. In investigating diseases in animals, a similar methodology may be useful. Some of the assumptions that were made in medicine were later proven wrong and illustrate how difficult it can be to determine cause-effect relationships. The one example I like, is the assumption in the 19th Century that malaria was caused by swamps. We now know that mosquitoes breed in swamps and can carry the malaria organism which is transmitted by the mosquito when it bites a human. Although somehow associated with malaria, swamps certainly did not by themselves cause the disease. So sometimes things are more complicated then they appear at first.

In that spirit I would like to outline some of the rules in epidemiology that evolved from these early studies (Figure 1).

FIGURE 1. Validity of the Association (Sir Karl Popper)*

- Consistency
- Strength of the association
- Specificity of the association
- Time sequence
- Coherence
- Biological plausibility

These rules are:

- **the consistency of the observations**; repeated observations under different circumstances should be consistent;

- **the strength of the association;** a more intense exposure should result in a more severe effect. In other words, there should be a dose/response relationship;

- **specificity of the association**; the disease should be well defined and a recognizable entity. In other words, it should not be claimed that all sorts of illnesses, from headaches to cancer to ingrown toenails, are all caused by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), for instance;

- **time sequence**; in investigating a poisoning episode, all of the people should have been exposed and the exposure should have occurred before the illness occurs; then

- **coherence with other information;** if in one study a particular observation is made and in another study, totally different results or negative findings are obtained, then it must be determined whether the initial observation was a spurious association.

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* Susser, M. The logics of Sir Karl Popper and the practice of epidemiology. *American Journal of Epidemiology*, Volume 124, pages 711-718, 1986.

Thus, all of the factors in Figure 1 should be critically evaluated. The most important factor is the biological plausibility. Could the change that was observed have been caused by the suspected agent? Is the association that was made biologically plausible?

FIGURE 2. Causation of Disease

- Multi-factorial
- Nutrition
- Quality of life
- Aging
- Migration
- Genetic make-up
- Behavior
- Intercurrent infections
- Environmental impacts

For some acute diseases and for many chronic diseases, we cannot identify the cause (Figure 2). Such illnesses are at times referred to as being "essential," which is another term for not knowing. Chronic diseases often have multi-factorial causes. A good example is hardening of the arteries or arteriosclerosis. For arteriosclerosis, genetic makeup is important. Nutrition plays a role; smoking; lifestyle; whether "we take care of ourselves." For other chronic diseases, intercurrent virus infections or other infections can play a role. Finally, aging is something that happens to all of us and some of the changes that all of us experience over time are simply due to aging. There may be environmental impacts on the development of disease. For instance, migration from one county to another may also affect disease such as the incidence of cancer. For instance, the Japanese women in Japan have a much lower incidence of breast cancer than Japanese women who have migrated to this country. This becomes even more evident in their offspring. All of such factors need to be examined when an unknown disease is investigated.

The only other thing that I would like to mention is that we have a questionnaire that we received with our program and we are asked later on to fill out this questionnaire and see whether we were convinced by the presentations as to causation. I am not so sure that by simply listening to presentations it will be possible to make such a judgement because, as I mentioned earlier, it is a very complicated process and one would have to examine the information that is presented here in detail to come to any sort of a conclusion.

1.2 Introductory Remarks

Dr. A.J. (Bert) Liston, Assistant Deputy Minister
Health Protection Branch, National Health and Welfare
Ottawa, Ontario

I am pleased to have been invited here to Chicago by the Council of Great Lakes Research Managers to address this Workshop on Cause-Effect Linkages between environmental contaminants and population-based disease outcomes. It is a pleasure to provide you with the challenge of environmental research and regulation for the 1990s from the perspective of the Department of National Health and Welfare.

Let me focus first on the Great Lakes themselves. Visitors to Canada are truly in awe when they first see the size of our freshwater oceans. Twenty per cent of the globe's entire lake water is one connected waterway, nearly 26,000 cubic kilometres of fresh water. And from this water, two out of every three Canadians draw their drinking water. Many of the nearly one million Canadians who purchase sport fishing licenses in the Province of Ontario are consumers of nearly 40 species of Great Lakes fish. In addition, this fertile basin grows large amounts of food for consumption by its residents. Its crops are sustained by rainwater largely from lake evaporation. Residents of the basin breathe the air transported into the basin and moved throughout the basin. The quality of this air is directly affected by evaporative losses of volatile contaminants in the lake waters. In short, our Great Lakes have the potential to exert influence on nearly every component of our basic needs for clean water, clean food and clean air.

Since the publication of Rachel Carson's book, *Silent Spring* in 1962, there has been a rapidly growing interest in environmental quality and protection. In Canada, there is a growing interest in the impact of environmental pollution on human health. Surveys of the Canadian public have repeatedly demonstrated that the environment is first and foremost, a human health issue. Concern for the impacts on health of chemicals in air, water, soil and food has grown since 1982 from 53% of the population believing that pollution affects their health to 78% in 1986. By 1987, 89% of Canadians believed that human health in Canada had already been affected by existing pollution and 93% believed that a variety of unknown environmental hazards were probably causing serious health damage.

I believe Canadians have a right to expect a healthy and wholesome environment. However, there are now studies in the literature that indicate possible associations between human disease and exposure to environmental organochlorines such as PCB, and metals such as lead. These associations are not proven, but they cannot be ignored.

I wish to present to you some thoughts on the protection of human health from environmental pollutants. I will then elaborate on the Department of National Health and Welfare's research and evaluation plans for the Great Lakes basin that address what I perceive as the needs for assessment of health impacts associated with basin pollutants.

Firstly, I believe we need to adopt the principle of "Environmentally Sustainable Development." Healthy economies and healthy environments can co-exist. Embracing this principle means that we provide for economic and technological development in ways that will not compromise society's ability to meet essential needs for future generations. It means minimizing the adverse impacts on the quality of air, water and other natural elements so as to sustain the ecosystem's overall integrity. It means restricting the use of our renewable resources in ways compatible with the limits of regeneration and regrowth. In many areas, we have made a start. For example, the development of cleaner waste incineration technology, the recycling of metal, paper and glass products, reductions in the use of aerosol products containing CFCs, the elimination of lead additives from gasoline, and reductions in many effluent discharges are important beginnings.

Secondly, I believe we must accept that health guidelines, standards, maximum tolerable concentrations, etc. are only imprecise measures of what is "safe." They do not ensure absolute health protection. They are regulatory values or yardsticks against which we measure compliance. Unfortunately, they are perceived all too frequently as the maximum limits to which the environment can be polluted. In an ideal world, air, food, water, soil and consumer products would be contaminant-free. This is an unrealistic expectation. Whereas one could measure some complex chemical substances only at concentrations in the parts-per-million range a few years ago, now, due to advances in analytical chemistry, one can measure these same substances in concentrations in the parts-per-quadrillion range. Analytical chemistry has forced us to acknowledge that everything is liable to some degree of contamination -- albeit small.

It is important to realize that there exist many greater health risks than those attributable to environmental pollutants, e.g. from the presence of natural substances in some foods, consumption of alcohol, use of tobacco and from travel. The difference, however, is that the acceptability of such risk is determined through public choice. People can choose whether or not they eat certain foods, consume alcohol, smoke, or how and where they wish to travel. However, exposure to low levels of environmental contaminants in air, food and water is not avoidable. The public has no choice but to live with these exposures and unavoidable risks are less acceptable than voluntary risks. Ultimately, of course, it is the public, not the regulators, who will decide how clean our environment must be.

Thirdly, I believe that we must step up our efforts now to educate our children and inform the public on environmental issues. The public can play a vital role in conserving the environment if it has a better understanding of the complexity of the issues and how they can be resolved. The educational process could and should begin at an early age in schools, but government agencies play a significant role too, in making information available to the public.

Fourthly, regulators must always face the critical question -- "How much information is enough?" I do not believe we will ever have the kind of resources we would like to have to develop a full scientific database on every chemical upon which to conduct our assessments. How much data do we really need before we take a decision and how long can we wait to obtain that data? I suggest that a preventive approach should be taken for all chemicals. Sufficient test data should be provided for any new chemicals so that a judgement can be made as to their acceptability before they are marketed. This is the approach taken for new industrial chemicals under the Canadian Environmental Protection Act. Nor will existing chemicals be ignored. The Canadian Government has just published a list of "priority substances" which will be assessed for their impact on health and the environment over the next five years.

Fifthly, I would like to mention our cleanup record and the prognosis for the Great Lakes basin. Levels of many contaminants have declined dramatically in the Great Lakes basin since the early 1970s. Reproduction rates in fish-eating birds of the Great Lakes have been largely restored. We have succeeded in eliminating the major sources of pollution. We can all be proud of this, but further reduction of pollution will need a different approach. Scientists have indicated that depuration alone will not lower contaminant levels significantly. Less than 1% of the water contained in the lakes flows out the St. Lawrence River. The lakes are essentially a closed system with flushing times that range from several years to more than a century. We must shed forever the notion that dilution will be the solution to pollution. We are going to have to make decisions to carry out expensive remedial programs in the Areas of Concern identified within the basin. It would have been inconceivable five years ago that more than 50% of the PCB entering the upper Great Lakes now comes from atmospheric fallout. The solution to many of the pollution issues of the 1990s will require continental rather than local solutions.

I have already stated my belief that Canadians have a right to expect protection from environmental pollution, especially when it threatens health. Clearly, there is a public expectation that government will take a leadership role in both the assessment of the effects on health and the

development of the means to reduce health impacts. The Prime Minister of Canada announced in October 1988 the government's intention to put 125 million dollars over five years into the Great Lakes Program and an additional sum of money toward the St. Lawrence River Basin Program. I note with considerable satisfaction that the revised Protocol to the 1978 Water Quality Agreement places an increased emphasis on health protection. In Canada, federal responsibility for protection of the health of the general population resides with the Department of National Health and Welfare. The Department recognizes the need to address the emphasis on human health impacts identified in the revised Agreement. These efforts will be concentrated in the following areas:

- human tissue and fluid monitoring to determine concentrations of contaminants in Canadians by age, by sex and by lifestyle;

- monitoring and surveillance appropriate for the assessment of human exposure to contaminants in air, water, soil and food;

- development of toxicological profiles and assessments of potential health exposures and impacts for 300 chemicals found in the Great Lakes basin including their potential for interaction;

- development and application of more sensitive health effects assays, non-traditional indicators of adverse health outcomes and biochemical markers of exposure for human populations;

- utilization of data pertaining to wildlife population effects and concomitant contaminant exposure as an "early warning" signal for human populations;

- population-based studies of individuals exposed to high concentrations of Great Lakes contaminants in water and fish;

- information programs to enable the public to make healthy lifestyle decisions; and

- coordination of program elements with Canadian and U.S. agencies to ensure timely solutions and adequate emphasis on the human health concerns.

This is, in my opinion, an exciting and challenging agenda. It is work that must be done if we are to respond to the increasing public concern about toxic contaminants in the Great Lakes basin.

I extend my very best wishes to each of you for a successful workshop and urge you all to work with me in the push for a cleaner, healthful environment.

1.3 Introductory Methodology

Glen Fox
Canadian Wildlife Service, Ottawa, Ontario

Environmental scientists and managers are faced with determining whether a relationship between environmental factors and observed adverse effects is causal. Epidemiologists have, over the past 200 years, developed a systematic approach to discussing these relationships. The Henle-Koch postulates have been used by public health authorities for over 100 years to evaluate causal relationships involving infectious agents and, more recently, extended to non-infectious agents. In 1964, the Surgeon General's Advisory Committee on Smoking and Health published the following five criteria for objectively evaluating the relationship between a suspect cause and a chronic disease:

a.	**Time Order:**	The necessity that the cause precede the effect in time.
b.	**Strength of Association:**	The degree to which the supposed cause and outcome coincide in their distribution and the size of the effect produced by the presumptive cause.
c.	**Specificity:**	The precision of the association between the presumptive cause and the observed effect.
d.	**Consistency on Replication:**	Has the association been repeatedly observed by different investigations, in different places, circumstances and times?
e.	**Coherence:**	The cause-effect interpretation of the evidence should not seriously conflict with the generally known facts of the natural history and biology of the disease.

These criteria can be used, with little modification, to evaluate associations in relation to diseases in fish and wildlife suspected to be caused by exposures to chemical pollutants. Some populations of fish and wildlife are exposed to the same chemicals as subpopulations of humans. By investigating the incidence of chemically-induced diseases in fish and wildlife, it is proposed that researchers can identify the risks posed by exposures of humans.

From evidence that is discussed using these five criteria, environmental scientists and managers may determine whether a credible case can be made to initiate preventive or remedial action. By applying the null hypothesis, they are forced to consider how much information must be ignored to conclude that a causal relationship does not exist.

2.0 SUMMARIES/ABSTRACTS OF OVERVIEW PAPERS

2.1 Case Studies on Fish

Abstract of Presentation on
Liver Tumors in Brown Bullheads

by
Paul Baumann
U.S. Fish and Wildlife Service, Columbus, Ohio

Populations of certain fish species in certain locations in the Great Lakes basin exhibit a high incidence of tumors. The brown bullhead, which is relatively pollution tolerant, has been used by several researchers to monitor the frequency of liver tumors and to investigate the causes. Polynuclear aromatic hydrocarbons are carcinogenic compounds and are frequently present in waters where bullheads show elevated incidences of liver tumors. The hypothesis is advanced that the incidence of liver tumors in brown bullheads is caused by exposures to high levels of polynuclear aromatic hydrocarbons, particularly from coking operations associated with steel production.

In terms of time order, little is known about the onset of the disease. Though detailed knowledge is available on the dates of the construction of the coking facilities, little is known about the annual production or thus about the likely exposures of fish to polynuclear aromatic hydrocarbons. There is, however, strong time-order information relating to the closure of the coking facilities and the recent decline in the frequency of liver tumors in brown bullheads.

Information on the coincidence of high or low exposures to polynuclear aromatic hydrocarbons and high or low frequency of liver tumors, respectively, supports a causal relationship in terms of strength of association. There are, however, certain locations such as St. Marys River where there is a high tumor frequency and low PAH and other locations such as Presque Ile where there are high PAHs and low tumor frequency. Further research is needed to understand these exceptions perhaps in terms of availability of PAHs, or of the role of alternative etiological agents. The incidence of tumors at reference sites is between 0-2%. However, the incidence in the Cuyahoga River is about 20% and in the Black River up to 60%. Thus, the relative risk in the highly contaminated locations is 10 to 30-fold increase.

In terms of specificity for the causal association of liver tumors and exposure to PAHs, the evidence is not strong. Virtually any compound that is a known carcinogen in mammals is a liver carcinogen in fish. Thus, there is neither specificity in the causes or the effect and this criterion is indeterminate in relation to the hypothesis.

Different investigators working in different locations at different times on different species, including tom cod, bowfin, English sole and rock sole have found consistent relationships between tumor frequency and exposures to polynuclear aromatic hydrocarbons. There are, however, few Great Lakes studies that are adequately designed in terms of numbers of samples, randomization and reliable histopathology. Thus, much more field work is required before the consistency on replication criterion can be satisfied.

The strongest evidence exists in relation to the coherence criterion. The new information, that brown bullheads exposed to polynuclear aromatic hydrocarbons have an increased incidence of liver tumors, coheres with existing knowledge about the carcinogenic properties of these compounds. There are plausible pathways whereby brown bullheads are exposed to polynuclear aromatic hydrocarbons released from coking operations. Wild brown bullheads metabolize benzo-*a*-pyrene to carcinogenic metabolites and aromatic DNA adducts have been found in their livers. There are statistically significant relationships between exposures to PAHs and the incidences of liver tumors.

2.1 Case Studies on Fish

Extended Abstract of Presentation on Reproductive Impairment in Lake Michigan Lake Trout

by
Michael Mac and Carol Edsall
U.S. Fish and Wildlife Service, Ann Arbor, Michigan

Lake trout in various parts of the Great Lakes are not self-sustaining and there is little evidence that restocked lake trout are producing viable, year-old young. Research has been undertaken since 1975 to investigate reproductive impairment of wild or feral stocks under controlled conditions and to test the hypothesis that the increased incidence of embryonic and fry mortality has been caused by organochlorine chemicals and specifically, PCB.

Hatchability of eggs of lake trout collected from Saugatuck, Lake Michigan, has improved during the period 1975 through to 1988. Concurrently, the level of PCB has declined. In considering the time order criterion, the year of the onset of the poor hatchability is not known but the onset of the improvement is consistent, in terms of timing, with the reduction in the levels of PCB. A somewhat different pattern was seen for fry survival. Swim-up mortality observed only in Lake Michigan fry was first seen in 1978 and increased through to 1981 decreasing through to 1984. It appeared again in 1985 and 1987. There is, at present, no trend data on a specific contaminant that could account for these findings but retrospective analysis of stored samples for specific isomers may reveal a possible causal compound.

In considering aspects of the strength of association, the 1980 egg-to-fry survival rate was about 2% for Lake Michigan compared with 45% for Lake Superior eggs. Comparable figures for 1987 are improved, with 57% for Lake Michigan *versus* 74% for Lake Superior. Hatchability of eggs from four individual females collected in 1985 was compared with the concentration of 3,3',4,4'-tetrachlorobiphenyl and accounted for 99% of the variability.

The term "hatchability" is not very specific since it describes all the mortality throughout the embryonic stage. The fry mortality, characterized by swim-up mortality syndrome, appears to be a somewhat more specific response. This syndrome has been described by other workers researching the effects of organochlorine compounds and specifically, DDT. The Lake Michigan fry mortality occurs at a specific time in development and is associated with 900 temperature units. This corresponds to the 850 - 950 temperature units found by other researchers working on the effects of DDT on lake trout from Lake George in the 1950s. In addition, the description of the behavioral changes associated with mortality of Lake Michigan fry swim-up are similar to those described by other researchers. There is, however, a difference between the Lake Michigan swim-up syndrome and the DDT poisoning. In DDT poisoning, the swim bladder was over-inflated so the fish could not escape the water surface. In lake trout from Lake Michigan, there was no inflation of the swim bladder.

In considering evidence concerning consistency on replication, swim-up mortality syndrome has been seen in another species from another location. In 1983, eggs of steelhead from Lake Ontario showed a 65% swim-up mortality of fry with characteristics that were similar to those observed for lake trout poisoned with DDT. Similar swim-up mortality of fry was observed with chinook salmon collected for the purposes of propagation from the Manistee River, 200 miles north of Saugatuck. In 1979, fry survival was slightly reduced from 99% in previous years to 98% but the first signs of swim-up mortality were observed in the bottom of hatchery raceways. By 1981, 20% of the fry were being lost. Chinook salmon were sharing the same forage base in Lake Michigan as the lake trout and showed this same syndrome at different locations at the same time.

The findings of increased embryonic mortality and fry mortality associated with exposures of Lake Michigan lake trout to organochlorine chemicals coheres with existing biological theory and

information on other salmonids from other locations. There is a need for further research on the specific mechanistic aspects of toxicity and for information on the sources of the suspected compounds, particularly PCB, to the Lake Michigan environment. There is a close statistical coherence between the incidence of embryonic mortality and the concentration of 3,3',4,4'-tetrachlorobiphenyl.

2.2 Case Studies on Birds

Abstract of Presentation on Bald Eagles in the Great Lakes Basin

by
Theo Colborn, Washington, DC

The use of DDT and dieldrin caused the continent-wide decline of populations of bald eagles. DDT caused eggshell thinning and reduced productivity and dieldrin caused mortality of adult birds. The population of shoreline nesting bald eagles in the Great Lakes basin has not recovered despite the cessation of use of DDT and dieldrin. The hypothesis has been advanced that continuing reproductive impairment and mortality is the result of continuing high levels of these organochlorine compounds in the Great Lakes basin.

In considering evidence in relation to time order, the populations in the 1940s had recovered, under protection from the human depredations of the 1900s caused by egg collecting, shooting and habitat destruction. However, following the introduction of DDT and dieldrin in the mid-1940s and mid-1950s, respectively, populations declined throughout the contiguous United States and eastern Canada. The bald eagle populations in the Great Lakes basin showed similar declines. By the mid-1950s, the Lake Ontario population was extirpated. The dates, however, for the declines in Lake Michigan and Lake Huron are not precisely known but almost all the U.S. population was extirpated by the early 1970s. Population declines in Lakes Superior and Nipigon and most of Ontario province were documented in the early 1970s. A small, relic population of about six pairs remained on the north shore of Lake Erie through the 1970s and early 1980s. The continent-wide declines in levels of DDT and dieldrin beginning in the mid-1970s led to the rapid improvement in reproductive success and increases in the population of bald eagles. Despite declines in the concentrations and diversity of organochlorine chemicals in the Great Lakes basin starting in the mid-1970s, bald eagles have not successfully re-established territories close to most of the Great Lakes shoreline.

In populations of bald eagles that breed normally, greater than 50% of the pairs of birds produce fledged young. However, in the Great Lakes basin a disproportionate number of pairs that occupy territories produce no fledged young. Comparison of the number of fledged young per successful territory with the number per occupied territory provides a useful index of stress. In considering continent-wide evidence, the index of stress was highest in Lake Michigan (11.5) and Lake Nipigon (10.5) during the 1960s and early 1970, intermediate in Lake Superior (3.9) between late 1900 to mid-1980s and lowest in Kodiak, Alaska (1.61) through the 1960s. This rank order is consistent with the relative levels of contamination during those periods and provides evidence for the hypothesis in relation to the strength of association criterion. In addition, statistical analysis of eggshell thinning and productivity has shown a strong dose-response correlation with organochlorine chemicals and particularly, DDE.

In considering the specificity criterion, though the evidence indicates that DDE was primarily responsible for both eggshell thinning and reduced productivity on a continent-wide basis, a case can be made that PCBs and possibly dioxins and furans contributed to embryonic mortality in the Great Lakes basin. The loss of bald eagle productivity is associated with a suite of clinical symptoms in addition to eggshell thinning, including embryonic and hatchling mortality, failure of eggs to hatch, failure of established mature pairs to nest, adult sterility and excessive loss of young birds. Development of biochemical markers associated with this suite of symptoms might improve specificity.

There is extensive evidence to support the hypothesis in relation to the consistency on replication criterion. Populations of bald eagles in the various parts of North America that have been exposed to organochlorine chemicals and particularly, DDE, have declined. In

contrast, those not exposed such as the Saskatchewan and Alaska populations have shown continuing high productivity. The declines coincided with the introduction of DDT and recoveries followed the banning of DDT. The failure of the bald eagle populations in the Great Lakes basin to respond to the declining use of DDT reflects the continuing high levels of this compound in foodwebs and possibly the presence of other organochlorine compounds. Finally, there is corroborative evidence from studies of the congeneric species, the white-tailed sea eagle in Europe, that PCB, in addition to DDE, had reduced productivity.

The new fact, that the levels of organochlorine chemicals in the Great Lakes remain too high for successful re-establishment of bald eagle populations, coheres with existing biological theory and the known effects of these compounds on avian reproduction. Sources and pathways of these compounds are well established. Further research is needed on biological mechanisms and development of biomarkers, and further statistical analysis is required to evaluate the role of compounds other than DDE in the continuing failure to re-establish populations of bald eagles in many parts of the Great Lakes basin. It is suggested that congener-specific determinations should be explored before PCBs are ruled out as a causal agent.

2.2 Case Studies on Birds

Abstract of Presentation on Chick-Edema Disease in Colonial Fish-Eating Birds

by
Michael Gilbertson, International Joint Commission, Windsor, Ontario
Tim Kubiak, U.S. Fish and Wildlife Service, East Lansing, Michigan
James Ludwig, Ecological Research Services, Bay City, Michigan
Glen Fox, Canadian Wildlife Service, Hull, Quebec

Several species of colonial, fish-eating birds nesting in the Great Lakes basin, including herring gulls, common terns and double-crested cormorants, have exhibited chronic impairment of reproduction. In addition to eggshell thinning caused by high levels of DDT and metabolites, the reproductive impairment is characterized by high embryonic and chick mortality, growth retardation and developmental abnormalities. The hypothesis has been advanced that colonial, fish-eating birds are exposed to chick-edema active compounds that have caused outbreaks of chick-edema disease-like effects at the embryonic life stage.

Detailed evidence has been collected from the following three groups of studies on:

- herring gulls in the lower Great Lakes during the early 1970s;
- Forster's terns in Green Bay, Wisconsin in 1983; and
- double-crested cormorants and Caspian terns in various locations in the upper Great Lakes from 1986 onwards.

It has proved difficult to establish not only the onset of the disease in the various species at various locations but also the period in which chick-edema active compounds were released. Anecdotal evidence suggested that serious egg mortality in Lake Ontario herring gulls first occurred in 1966, though the signs of chick-edema disease were not looked for until 1974. Only indirect evidence is available on the date of the release of the presumed causal agent, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, but highest levels may have occurred in the early to mid-1960s. More reliable data shows that the onset of the improvement of reproduction of Lake Ontario herring gulls coincided with the declines in organochlorine compounds and particularly 2,3,7,8-TCDD and PCB. Similarly, information on the onset of the disease and exposures in the Forster's tern and double-crested cormorants is uncertain but bird banders did not observe deformities until the 1970s which corresponds with the onset of high levels of PCB.

Chick-edema disease in embryos and chicks of wild birds is difficult to diagnose because there is no specific lesion, but rather there is a suite of lesions. In addition to the elevated incidence of embryonic and chick mortality, growth retardation and developmental abnormalities including bill deformities, club feet, missing eyes and defective feathering, there is also subcutaneous, pericardial and peritoneal edema, liver enlargement, liver necrosis and porphyria. A variety of chick-edema active compounds including non-ortho substituted PCBs and dibenzo-*p*-dioxins and furans substituted at the lateral positions, produce chick-edema disease. The active compounds have specific conformational requirements.

In considering evidence on the strength of association, the embryos and chicks of herring gulls from Lake Ontario and Forster's terns from Green Bay had a significant increase in the incidence of the lesions compared to reference colonies. Similarly, the incidence of bill abnormalities was significantly elevated in Great Lakes colonies of double-crested cormorants, particularly for Green Bay, Wisconsin. There was a significant dose-response relationship between the incidence of embryonic mortality in cormorant eggs and the presence of chick-edema active compounds expressed in 2,3,7,8-TCDD equivalents.

There is a high degree of consistency on replication. The disease has been found in a variety of species in a variety of locations, by different observers using different study designs. Outbreaks of the disease have occurred at different times and seem only to be related to exposures of developing embryos to high levels of chick-edema active compounds.

The new facts, that embryos and chicks of colonial, fish-eating birds can exhibit chick-edema disease when exposed to chick-edema active compounds, cohere with existing biological theory, experience and experimentation. There are plausible routes of exposure and sources of these compounds to the Great Lakes and statistically significant dose-response relationships have been demonstrated.

2.3 Case Studies on Turtles and Mammals

Abstract of Presentation on Hatchability and Deformities in Populations of Snapping Turtles

by
Christine Bishop and John Carey, National Water Research Institute, Burlington, Ontario
Ron Brooks, Department of Zoology, University of Guelph, Guelph, Ontario

Snapping turtles from the Great Lakes and the Hudson River contain surprisingly high levels of PCBs. A 1986 study was undertaken to investigate whether snapping turtle eggs contained PCBs and whether these compounds might have effects on embryo viability and development. Eggs were collected from five sites including a reference site at Algonquin Park, Lake Ontario sites at Lynde Creek, Cranberry Marsh, Cootes Paradise and a Lake Erie site at Big Creek Marsh on Long Point. Eggs were collected for artificial incubation at 28°C and for chemical analysis. Dead embryos and hatching turtles were observed for deformities.

The types of abnormalities found included enlarged unresorbed yolk sacs, missing claws and eyes, and deformed carapaces, tails, fore and hind limbs, and crania, including deformed nostrils and upper jaws, and deformed lower jaws. Some embryos and hatchling turtles were dwarfs. Hamilton Harbour had the highest proportion of unhatched eggs. Cranberry Marsh had the highest incidence of deformities. Artificial incubation of eggs from Algonquin Park has consistently given excellent hatchability and the lowest incidence of deformities.

Since the onset of the reduced hatchability and of the incidence of deformities are not known, it is not possible to make a definitive statement in relation to when snapping turtles near the Great Lakes became exposed to organochlorine chemicals. Thus, evidence relating to the criterion of time-order is indeterminate.

The number of deformed and dead embryos in snapping turtle eggs from Lake Ontario was significantly higher than in eggs from Lake Erie or Algonquin Park. Regression analysis of the incidence of deformities *versus* the organochlorine content of the eggs showed that, though there was a significant correlation with various organochlorine compounds, there was no single compound that consistently explained the variation. In addition, anomalous results were obtained from the Lake Erie location since high residue levels were accompanied by good development of the eggs. Thus, at present, the evidence is indeterminate in relation to the strength of association criterion.

In the absence of studies on the specific effects of chemicals on turtle reproduction, inferences about specific causes must be drawn from studies on other animals. In studies of birds and mammals, PCBs and various chlorinated dibenzodioxins and furans have been shown to be embryotoxic and teratogenic and to cause a wasting syndrome. However, other compounds such as hexachlorobenzene and handling of eggs during incubation, may also cause some of the symptoms. There is not a high degree of specificity and thus, this criterion is indeterminate.

The most common types of deformities, such as tail and limb deformity, occurred consistently between years, within and among populations. The incidence of large unresorbed yolk sacs occurred only at Cranberry Marsh and occurred in two of the three years of study. In addition, highly contaminated populations of organisms such as birds, mammals, fish and amphibians exhibit high incidences of a variety of similar developmental defects. Thus, there seems to be a high degree of consistency.

The presence of high levels of organochlorine chemicals in turtle eggs is associated with embryonic mortality and developmental defects and cohere with existing theory. The exact mechanism of action has not yet been defined but the case makes biological common sense. The statistical analysis indicates a significant relationship between elevated levels of organochlorine contaminants and embryonic mortality and developmental abnormalities. The results from the Lake Erie samples were anomalous and further biological studies and residue analysis are required.

2.3 Case Studies on Turtles and Mammals

Abstract of Presentation on Reproductive Impairment in Mink and Otters

by
Christopher Wren
BAR Environmental, Nicholas Beaver Park, Guelph, Ontario

Extensive laboratory toxicology experiments, following outbreaks of reproductive failure in commercial ranching utilizing Great Lakes fish as feed, showed that mink are particularly susceptible to organochlorine chemicals, especially PCBs and dioxins. The levels of these compounds in some wild mink populations are higher than levels associated with reproductive dysfunction and mortality in laboratory specimens.

The hypothesis is advanced that, because wild mink are exposed to these compounds through consumption of Great Lakes fish, they should exhibit reproductive dysfunction and population declines. Similarly, another piscivorous mammal, the otter, is highly exposed and should show the same effects.

Evidence is presented from harvest data on the population status of mink and otters in certain locations around the Great Lakes. There are several factors that limit the value of harvest data as a surrogate of population status, including pelt price, demand, trapper effort and experience, and habitat quantity and quality. Data on the mink harvest in Ohio are reported on a county basis. Comparison of trapping returns between 1982 and 1987 on mink taken from more highly contaminated counties bordering Lake Erie were consistently lower (380 animals per year) than those from counties removed from Lake Erie (850 animals per year) suggesting an effect of chemicals on the status of mink populations. Evidence was also presented on the harvest data for otters taken from four New York State counties adjacent to Lake Ontario and the St. Lawrence River. Residues in otters from these locations were higher than in other parts of New York State. The harvest data from these four counties between 1959 and 1988 show that between 1960 and early 1970, the number remained stable but have since increased. Comparison of the data for the harvest from these four counties in relation to the overall increasing harvest for New York State indicates that there has been a recent increase in the contribution to 40%. The time order for this improvement in these four counties is consistent with improved water quality in Lake Ontario during the past 15 years. Further research is needed to investigate the time-order aspect of any implied effect on mink and otter populations.

Data relating to strength of association is at present weak and needs to be further analyzed. The specificity of the effects of the chemicals on mink reproduction and mortality is well established from toxicological experiments but there is poor resolution of the information on effects using harvest data. There is a variety of organochlorine compounds including PCBs and various dibenzodioxins and furans that have these effects on mink. These compounds seem, however, to have specific conformational requirements to be toxic. In terms of consistency of association, there are few data on which to make comparisons but there is a trend towards populations of mink and otters in areas adjoining the lower lakes being depressed compared with contiguous locations removed from the lakes.

The strongest case for a causal relationship comes from consideration of the coherence criterion. Some wild populations of mink are sufficiently contaminated such that toxicological effects would be expected based on laboratory toxicology and this would be consistent with the known biology of the species. Much more research and data analysis is required before the factual and statistical aspects can be discussed.

Similar conclusions can be drawn for each of the criteria in relation to otters. In conclusion, before a causal link can be drawn between the status of mink and otter populations and exposure to organochlorine chemicals from the Great Lakes, a large amount of research and data analysis must be undertaken.

2.3 Case Studies on Human Health

Abstract of Presentation on Implications of Eating Great Lakes Fish

by
Wayland Swain
ELI Eco Logic Inc., Ann Arbor, Michigan

Organochlorine compounds bioaccumulate efficiently in large salmonids that form a large part of the Great Lakes sport fishery. Certain groups of people utilize this resource extensively, while others are highly dependent on these fish as a source of protein. Several studies have demonstrated that organochlorine compounds in fish consumed by humans resulted in elevated levels of these chemicals.

The hypothesis has been advanced that the consumption of these sportfish by anglers and their families poses risks to human health. Particular risks may accrue to the developing fetus in fish-consuming mothers and to the newborn offspring dependent on contaminated breast milk. Of particular concern are exposures to high levels of polychlorinated biphenyls, since the deleterious effects of these compounds on humans have been studied following outbreaks of accidental poisoning of humans in Japan in 1968 (Yusho) and Taiwan in 1978-1979 (Yucheng). Infants born following these accidental maternal poisonings were subjected to *in utero* exposures and displayed a characteristic set of symptoms termed "fetal PCB syndrome." In addition to various clinical entities, e.g. hyperpigmentation, there was growth retardation, premature birth, poor psychomotor development and altered behavior.

These accidental exposures to high doses of PCB were different from the long-term, repeated exposures to lower levels of PCB characteristic of people who consumed Great Lakes sportfish. Fetal PCB syndrome has not been seen in any of the three epidemiological or exposure studies undertaken on offspring of mothers who ate Great Lakes sportfish. But subtle deficits which were reported were based on rigorous testing with sensitive methodologies, the use of stringent statistical analysis, and extensive control of confounding variables, e.g. smoking, alcohol consumption, medications, and the like.

In one study, initiated in 1980, infants of paired mothers from western Michigan were weighed and measured, and administered psychomotor and behavioral tests soon after birth, at seven months and at four years. During hospital admission for delivery, mothers were administered a questionnaire concerning various socio-economic and lifestyle aspects, including questions on the history of their consumption of fish from Lake Michigan. The results of the study showed that those mothers who ate about one pound of fish per month gave birth about a week early to babies that weighed less (200 - 250 g) and had a smaller head circumference (0.3 - 0.7 cm). The infants had lessened psychomotor development. These changes were correlated with the amount of PCB in the mother's blood and in umbilical cord blood. Subsequent testing into early childhood showed that these children did not catch up with their peers in terms of growth or mental abilities.

In a second study, in Wisconsin, infants of fish-eating mothers had a higher frequency of infectious illnesses in the first four months of life. This finding was correlated with increasing *in utero* exposure to PCB.

In terms of time order, little can be said about the onset of the effects found in the studies or about when PCB exposures in mothers eating fish from Lake Michigan increased. Thus, the evidence in relation to this epidemiological criterion is indeterminate.

The evidence indicates that consumption of Lake Michigan fish prior to pregnancy leads to higher PCB exposures. These exposures *in utero* are associated with decreased gestational age, head circumference and birth weight, and poor psychomotor development. Furthermore, these measures are significantly correlated statistically with levels of PCB in umbilical cord blood yielding a dose/response relationship. Thus, in relation to the criterion of the strength of association, the evidence supports the causal hypothesis.

Accidental maternal ingestion of acutely toxic dosages of PCB resulted in not only *in utero* exposure of the developing fetus, but also in the onset of a disease entity named "fetal PCB syndrome." In the outbreak of Yusho and Yucheng, infants born to these mothers exhibited characteristic "Coca Cola" coloring, tended to be born prematurely, and they were of diminished size in relation to their gestational age (small for date). Infants also exhibited disturbances in neuromuscular organization and impaired intelligence. Repeated observations of this phenomenon among exposed infants have demonstrated that the specificity of association criterion is satisfied. Although PCB is specifically involved in fetal PCB syndrome, it is uncertain which specific congener or combination of congeners is responsible for this disease entity. Initial studies had implicated dibenzofuran contamination of PCB compounds, but based on recent findings, these data are subject to scientific doubt.

Unfortunately, though exposures in the Great Lakes basin may have been occurring for the past 20 years, there is only a single, reliable epidemiological study which has been undertaken involving mothers and their infants. Thus, no opportunity exists to examine internal consistency on replication. However, the results are consistent with the findings of other health researchers dealing with the outbreaks of PCB poisoning in Japan (1968) and Taiwan (1978-1979).

The new facts, that ingestion of PCB-contaminated fish leads to *in utero* exposure and to prematurity, growth retardation and psychomotor and developmental impairment are consistent with existing biological theory and with experimental findings. Transplacental mechanisms of exposure and biological mechanisms of causation have been proposed. Further, both statistically significant gradients and biological dose/response relationships have been documented.

3.0 WRAP UP

Ian Nisbet, Lincoln, Massachusetts

Our abilities to link causes with effects depends on the levels at which we try to pose the questions of causality and on the levels at which we try to answer them. We can illustrate the complexity of these levels of inquiry with reference to reproductive impairment in the bald eagle. At the simplest level, we can reconstruct the histories of the status of the bald eagle populations and of their exposures to organochlorine compounds. These histories provide several different lines of evidence for correlation between exposure and effects. On a temporal basis, population crashes and eggshell thinning followed the increase in organochlorine levels. On a geographic basis, we know that: i) the most abrupt declines occurred in the most polluted areas; ii) within the Great Lakes basin there were gradients of severity of the effects that coincided with gradients of exposures to organochlorine pollutants, and iii) bald eagles just a few miles inland were unaffected. We find extremely close correlations between productivity, eggshell thickness and organochlorine chemicals for 200 pairs of bald eagles from throughout the North American continent statistically analyzed on an individual basis. The recovery of the bald eagle populations in much of North America followed the improvement in reproductive productivity that followed declines in levels of DDE, dieldrin and PCBs. These same general trends have been found in a wide variety of fish-eating bird species, not only in the Great Lakes area but also in the rest of North America and in other species in Europe. Similar -- though less detailed -- evidence is available for several other groups of animals. Anyone who does not accept the proposition that this body of evidence reflects underlying cause-and-effect relationships can only belong to a lunatic fringe.

At the next level of causal analysis, however, the issues are more complicated and difficult. Population status is affected by several components, including production of young, survival of young to sexual maturity, recruitment, emigration, immigration and adult mortality. In bald eagles the change in population size seems to be quite closely coupled with adult survival but less clearly so with reproductive success. Reconstruction of the history of declines in osprey, bald eagles and peregrine falcons indicates that adult mortality was probably at least as important as reproductive impairment.

At the next level, we can try to look at cause-and-effect pathways within the reproductive impairment. Organochlorine compounds can affect fertilization, male and female behavior, eggshell thinning, eggshell structure, and the structure and functioning of the developing embryos leading to hatching failure. Similarly organochlorine chemicals can impair post-hatching growth, development and behavior affecting chick survival, and there is strong evidence for impairment of parental care. Conventional wisdom holds that eggshell thinning was the most important effect; however, using multi-variate analysis it seems that while both eggshell thinning and productivity are correlated on a nest-by-nest basis with DDE, they are not correlated with each other. Thus, the mechanism of the effect of DDE on productivity of bald eagles was not by eggshell thinning but by some other mechanism. Eggshell thinning was a parallel symptom. Probably, this whole field of ecological effects of toxic chemicals, including the case studies presented at this workshop, is full of parallel symptoms and we don't know what the full causal chain is for any species in the wild.

At another level, we may want to elucidate the physiological mechanisms by which the chemical causes the effect. For example, embryonic death associated with the extended chick-edema syndrome was characterized by a whole series of different functional effects including edema, structural malformations, AHH induction, porphyria and elevated Vitamin A metabolism. Which ones of those are the primary links in the causal chain and which are just parallel symptoms?

At the final level we may want to ask what is the biochemical mechanism of action. Dioxins, dibenzofurans and non-ortho PCBs bind to the Ah receptor and switch on the gene at the

Ah locus. But these compounds also bind to other receptors and thus, there is neither certainty about the primary biochemical link that leads to embryonic mortality nor which are the parallel symptoms.

Thus, we can draw conclusions about cause-and-effect relationships at the ecosystem level of organization but we don't know the exact mechanism at any level from the molecular to the population level.

Further complexity is added by the presence of many different organochlorine compounds including DDT, DDE, dieldrin, heptachlor, heptachlor epoxide, 209 different PCBs, 75 different dioxins and 135 different dibenzofurans. Residues of these compounds are often intercorrelated and attempts to use multi-variate analysis to separate out the effects have been either inconclusive or, at best, marginally suggestive.

Knowledge about mechanisms is needed not only because scientists like to find answers to complex and interesting problems, but also to support remedial actions and to undertake differential remediation. For fish and wildlife species, in contrast to humans, correlations are frequently not sufficient for appropriate remedial actions to be undertaken. Controls have been placed on the compounds that caused the major effects: DDT, aldrin, dieldrin, heptachlor, chlordane and PCBs. Residual effects may be occurring as a result of continuing releases of these compounds from a variety of sources, inputs may be occurring from the atmosphere and releases from contaminated sediments and dumps. We have only recently learned about the discharges of dioxins from paper mills. Many compounds in environmental samples have not yet been identified and any one of them might be significant. Thus we need to keep monitoring and studying to find out the next residual problem which needs remediation.

The fish and wildlife studies have generally been of an investigational type, in that some anomaly was found and studies were begun to investigate the reasons. In contrast, the human health research was undertaken as a cohort study in which fish eaters were identified and the effects were observed as the study progressed. The one human study that has been undertaken yielded positive results, suggesting that PCBs (and/or co-occurring contaminants) may be affecting human reproduction at exposure levels near to the average for the entire population of the United States and Canada. This study urgently needs replication and it is a disgrace that no agency has attempted to do so since the initial findings were published in 1984.

4.0 REPORTS OF PANEL MODERATORS

4.1 Report of Panel on Case Studies on Fish
Panel Moderator: Mary Henry

As with any good science, I think we have become acutely aware that we don't know as much as we would like to know and the questions seem to outweigh the answers. The case studies show that we have much less information on fish than birds, but a few very clear needs emerge from the two fish studies that have been presented and some of the discussions that have ensued. They center on the following five different areas:

- improvements in experimental design;
- knowledge of life histories of organisms;
- information for managers that may be different from information required by researchers;
- money; and
- communication.

With regard to experimental design, the case studies showed the importance of the relationship between laboratory and field studies. Both kinds of studies are needed and they are required for different reasons at various points in the sequence of the investigations. Secondly, the idea of formulating a null hypothesis that can be tested is probably a better strategy than setting out to prove a point. It is also a critical underpinning of good experimental design. Thirdly we need to select field sites very carefully. Sites should be selected that span a variety of degrees of contamination and include control sites so that cause-effect relationships can be elucidated. Consideration should be given to the effect of sampling on the population of organisms being studied.

More needs to be known about the life histories of the fish species under investigation. For instance, information is needed on fish movement and location of exposure and on recolonization. In several seriously polluted locations only the most hardy species and individuals remain. Consideration should be given to the value of invertebrates as organisms affected by pollution as well as vertebrates.

Researchers need to know the kinds of information required by managers to make regulatory decisions on whether to control the release of persistent toxic pollutants into the Great Lakes. Perhaps we do not need to identify all the chemicals responsible for a given biological effect, or completely understand the biochemical mechanisms, before taking action.

Resources are required for capital expenditures to undertake congener-specific analysis. In addition, changes are needed in funding so that long-term research can be conducted. These arrangements are needed because many biological processes and certain disease states take a long time. For instance, some economically important fish species, such as lake trout, require six to seven years to come to maturity. Cancer in some indigenous fish species may require seven years for expression. If sufficient resources and long-term commitments cannot be made, then managers may have to rely on information derived from surrogate species, such as medaka, that have short life cycles but are of no economic importance.

The quality of the cause-effect linkages has been enhanced by the similarity of findings in the many different taxa that have been considered. It is essential that scientists working on organisms from different taxa meet on a regular basis to communicate their findings and thereby find commonalities and differences.

4.2 Report of Panel on Case Studies of Birds

Panel Moderator: Michael Fry

The case studies on birds represent the best wildlife data available and are remarkably good. Though there are many kinds of chemical residues and we do not understand all that is happening, we have better knowledge for wildlife than for humans. Fortunately, for the general population we do not have the human health problems that are evident in wildlife. Regulations have maintained relatively low levels of contamination in the human food chain. Otherwise it might be much easier to perform studies on human health.

My comments on research needs are listed by the following levels of biological organization: molecular aspects, individual animals, population effects and research on ecosystems.

At the molecular level, we need to explain the mechanism of action of the toxic chemicals. We have identified specific toxins and mixtures of toxins in the wild birds. However, the specific abnormalities found are different from abnormalities seen in rats, mice and chickens. Egg injection studies are required to look at the specific abnormalities obtained from specific congeners. We need to determine the activities of specific PCB congeners and establish the relationship to dioxin equivalents in some manner that is acceptable to government agencies. Budget constraints have meant that several approved studies on this topic have been unfunded.

In terms of individuals species, we have good data on gulls and cormorants. It would, however, be useful to obtain information, from egg injection studies, of the species-specific abnormalities and syndromes caused by specific compounds. We need to link the information from wildlife studies to the risks to humans from exposure to Great Lakes chemicals.

Long-term studies of bird populations have yielded information essential to making the cause-effect linkages. In other organisms such as fish and turtles, the absence of such data raises questions as to when the observed syndrome began. Canadians have been archiving samples and have been able to go back and look for previously undetected compounds. There is a need for the United States to evaluate their requirements in specimen banking, both in relation to wildlife specimens as well as blood samples from epidemiological studies. We need to analyze and integrate data from studies of many different populations of a species. For instance, information on the status of different bald eagle populations has provided an assessment of the respective roles of declining levels of DDT *versus* continuing exposures to PCBs and dioxins.

At the ecosystem level we need information on the different rates at which specific congeners biomagnify from sediments to invertebrates, fish, birds and humans. To undertake this kind of work is extremely expensive. However, some of the screening work to find the highly contaminated samples may be undertaken relatively cheaply using enzyme bioassays such as EROD or AHH.

Finally, toxic waste sites with specific emissions need to be cleaned up.

4.3 Report of the Panel on Case Studies on Turtles, Minks and Otters

Panel Moderator: Robert Ringer

After listening to the people at this conference, I recall 1972 when we presented a paper at a conference on PCBs and the summary-conclusion by the chairperson was that PCBs were chemicals for which we would have no further concern. I certainly heard today of the continued concern about the PCBs as an environmental chemical.

The turtle studies are just beginning and I think this area of research is wide open. I am pleased to see this gap in our data being filled. The snapping turtle is an interesting species but I don't know whether it's a surrogate species. Snapping turtles produce a large clutch of eggs so that one can do residue studies and still have sufficient eggs to study hatchability and offspring survival and follow embryonic development for a teratogenic affect and embryo mortality. The symptoms were similar to those of birds and follow somewhat that which we have seen in the mammals. One particular research need is to undertake congener specific toxicology studies so that we can identify which compounds are causing what effect.

With the mink studies we have a carnivore, a top-of-the-foodchain species. The reported studies indicate multiple gaps in the database and despite many years of study in the laboratory, there are difficulties in extrapolating data from the laboratory to the field. One possible approach would be to use telemetry on feral mink so that we can follow these mink in their habitat, locate their dens, study behavior and reproduction, and even take blood samples. With biopsies, we can do congener-specific studies. Site selection would be very important in these studies, particularly in picking out an area that is not contaminated.

Within the laboratory we need to expand our studies on congener-specific effects on the mink. Though several studies have been done, this is inadequate to determine what the coplanar compounds are doing and to correlate this with enzyme induction or with immunology and to interpret this in relation to offspring survival. We need congener-specific studies in this mammal in relation to placental and mammary transfer. We have already completed this for mixtures but not on a congener-specific basis.

We could look at the otter in the wild just as I suggested we look at the wild mink using telemetry. There are certainly pitfalls when we look at trapping data, which we need to collect on a county-by-county or township-by-township basis if we are to understand population status. The annual trapping of otters along the shores of the various Great Lakes may supply samples for residue analysis that can be correlated with population status.

4.4 Report of Panel on the Case Studies on Human Health

Panel Moderator: Katherine Davies

I should like to make six comments which fall into the categories of research and policy needs for human and environmental health:

Firstly, we need to develop new methodologies to look at complex problems of linking long-term, low-level chemical exposures and human health. We need new "hard" science methodologies in the specific areas of toxicology and epidemiology. Neither of these scientific disciplines was originally developed to answer the sorts of complex environmental questions that we're asking them to answer today. Toxicology was developed as the study of drugs on the human body, and epidemiology as the study of communicable diseases in human populations. But we're using these same scientific tools to answer questions that they were never intended to answer, so I think we need to develop new methodologies for assessing environmental exposures and human health.

In that regard, the new techniques of molecular or biochemical epidemiology are a very promising development and one that I think is bringing together the two disciplines of toxicology and epidemiology in a very exciting way. On the hard science side, we need to look at using and developing more sensitive health indicators. Traditionally, we've looked at counting dead bodies and maybe a few birth defects. These are relatively gross health indicators so we need to develop measures to determine the incidence of more subtle health outcomes. In connection with this, we also need to develop methodologies to study behavioral problems in a much more systematic way.

My second point is that scientists need to communicate more with each other and to promote many more interdisciplinary and multi-disciplinary studies. We need to link the human health data with wildlife data bearing in mind that the human health data is very sparse at present. But we also need to link the researchers through meetings such as the one that we've had here during the past couple of days. By linking data and people, research will address an ecosystem approach in the Great Lakes basin. We will see ourselves as human beings who are a part of the ecosystem; see ourselves as open biological systems that are affected by the environment in profound ways. We need to develop new methodologies to research multi-cause, multi-effect problems, including synergism and antagonism.

Other areas that require careful development concern interpretation of data and risk communication. Over the last 10 years we've seen an incredible improvement in analytical methodologies. We've seen minimum detection levels fall by many orders of magnitude. We're good at developing analytical methodologies and measuring changes in the environment, but what we have not yet developed is the ability to interpret this data. What good is the measurement of change in the environment down to a part-per-quadrillion if we don't know what that means? For example, what does 20 parts-per-million of PCBs in breast milk mean or what does one-part-per-quadrillion of dioxins mean? The public wants to know and I think we are failing them if we cannot interpret the reams of data that we now have in ways that they can understand. In addition, our interpretation should be meaningful in terms of public policy and decision-making in both Canada and the United States.

Related to this is the question of perceived risk *versus* actual risk. In Canada, a recent survey showed that nine out of ten Canadians think that their health has already been affected by environmental pollutants. That's a very profound statistic. It's profound not so much because of what it may mean about actual health risk but what it says about perceived risk, and we need to interpret data and look at the differences between perceived risk and actual risk in ways that the public can understand.

We need a new paradigm for cause and effect because we are never going to prove cause and effect conclusively. We need to consider new frames of reference for science to deal with these problems rather than relying on the traditional frameworks. It may be that the rigor of the rules of scientific evidence needs to be modified in matters of public policy and public decision-making. The rules necessarily apply in laboratory situations but we may need to formally acknowledge that the rules for public policy and decision-making need to be less rigorous.

Lastly, but most importantly, despite incomplete information, we must still make decisions; advise people what to do; pass laws; and implement programs and policies. How much evidence and of what type is needed to make these kind of decisions? We can learn from the public health paradigm of preventive health care. The environmental community in the Great Lakes basin could take a leaf out of the public health's book and begin to practice some preventive health care for the Great Lakes basin in terms of the environment such as cleanup of existing contaminated sites and prevention of new sources. I feel strongly that we should view ourselves as human beings who are part of the ecosystem and recognize the prevention of future problems.

5.0 CONCLUDING REMARKS

by

Workshop Chairperson, Renate A. Kimbrough, U.S. EPA, Washington, DC

This session, on human health implications, has been a very interesting session for me and I think we have learned a lot from the entire workshop, which has produced a great deal of discussion and a number of recommendations. One aspect that has not been mentioned is the very important role that the International Joint Commission could play in pulling this all together. First, it could help the two governments consolidate their funding. Second, it would harmonize the studies that are being undertaken in the two countries -- not only on fish, birds and turtles but also on fish-eating human populations. For instance, there is a need to compare protocols for the studies and to undertake interlaboratory quality control for chemical analysis of blood specimens.

Another area in which the International Joint Commission could aid the two countries' efforts could be in specimen banking. I'm a great believer in specimen banks. For instance, after the 1976 accident at the chlorophenol plant in Seveso, Italy, many specimens were collected and banked. We are now able to measure the exposure of the Seveso population to the chlorinated dibenzodioxins by analyzing these specimens. Similarly, the International Joint Commission could help in the development of protocols for the collection and preparation of samples for specimen banks, so that the results of analyses that are undertaken in the two countries can be compared.

In the presentations, it was mentioned repeatedly that something should be done about the sources of pollutants; we should clean up the sediments and the chemical dump sites. I sensed a frustration that there has been so much delay and that nothing has been done. In the same vein, improvements were mentioned but there is a growing awareness of the significance of the air from outside the Great Lakes basin as a source of pollutant deposition into the lakes.

This suggests to me a growing need to better define the problems and to set priorities. I understand from conversations in the hall that the Council of Great Lakes Research Managers will host a workshop on priorities in the Fall and that this will be followed by a report that will provide some of the needed information. Again, if we could then jointly address these problems, we would probably make better progress in getting the communities around the Great Lakes to collaborate in studies undertaken by the two governments.

Finally, I should like to thank the audience for its patience and cooperation. I would also like to thank the speakers who have made some very excellent presentations. As a newcomer to the "area" of turtles, otters and birds, I found the presentations very informative. I thank the moderators who have done an excellent job and we should all thank the organizing committee who have made this meeting possible. I hope that we will have another meeting in the near future. Thank you very much.

Reply by Jon Stanley:

We've left out thanking one very important individual in this whole process: that is Dr. Kimbrough who has very ably led us in the two days. We have done lots of hard work but she kept everybody on schedule. The talks were interesting but I think she deserves a great deal of credit for keeping us focused on the problem at hand.

6.0 RESULTS OF QUESTIONNAIRE BALLOT

During the planning of the workshop, the Steering Committee decided that there was a need to measure whether the participants believed that a cause-and-effect linkage had been made. The Steering Committee designed a ballot (see Figure 3) that was contained in the program and was distributed to participants during registration. The ballot comprised a brief name of the paper and a scoring system ranging from "causality believed" through "don't know," to "causality disbelieved." There was extensive discussion, before the ballots were completed and after the wrap-up session, about what exact questions or hypotheses were being noted on. The following clarifications of the various hypotheses were put forward.

SESSION 1: CASE STUDIES ON FISH

- Liver tumors in brown bullheads were caused by exposures to polynuclear aromatic hydrocarbons.

- Reproductive impairment in Lake Michigan lake trout was caused by 3,3',4,4'-tetrachlorobiphenyl causing embryonic mortality and 2,3,3',4,4'-pentachlorobiphenyl causing fry mortality.

SESSION 2: CASE STUDIES ON BIRDS

- The decline in the Great Lakes population of bald eagles was caused by exposures to organochlorine compounds and particularly DDE and PCB.

- Outbreaks of chick-edema disease in colonial fish-eating birds were caused by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in Lake Ontario and by two pentachlorobiphenyls in Green Bay.

SESSION 3: CASE STUDIES ON TURTLES AND MAMMALS

- Embryonic mortality and deformities in snapping turtle eggs sampled from areas close to Lake Ontario were caused by PCBs.

- Declines in populations of mink and otters from around Great Lakes shorelines were caused by exposures to organochlorine chemicals.

SESSION 4: CASE STUDY ON HUMAN HEALTH

- Decreases in head circumference, birth weight, gestational age and in psychomotor and cognitive behavior in infants of mothers that ate fish from Lake Michigan were caused by exposures to PCBs.

Based on this clarification of the hypotheses on the ballot, the following results were obtained (Figure 4) based on a return of 59 ballots out of 76 issued:

- More than 90% of the respondents believed that there was a causal relationship between exposures of brown bullheads to PAHs and the increased incidence of liver cancers. Only about 40% believed that there was a causal relationship between embryonic mortality and fry mortality and exposures to specific PCBs. About 8% believed that there was no relationship.

CAUSE-EFFECT BALLOT

HOW WOULD YOU RANK THE DEGREE OF BELIEF YOU HAVE FOR THE CAUSAL RELATIONSHIP?	CAUSALITY BELIEVED			DON'T KNOW			CAUSALITY DISBELIEVED			C O M M E N T S
	8	7	6	5	4	3	2	1	0	
SESSION 1: CASE STUDIES ON FISH										
• Liver Tumors in Brown Bullheads	□	□	□	□	□	□	□	□	□	
• Reproductive Impairment in Lake Michigan Lake Trout	□	□	□	□	□	□	□	□	□	
SESSION 2: CASE STUDIES ON BIRDS										
• Bald Eagles in the Great Lakes Basin	□	□	□	□	□	□	□	□	□	
• Chick-Edema Disease in Colonial Fish-Eating Birds	□	□	□	□	□	□	□	□	□	
SESSION 3: CASE STUDIES ON TURTLES AND MAMMALS										
• Hatchability and Deformities in Populations of Snapping Turtles	□	□	□	□	□	□	□	□	□	
• Reproductive Impairment in Mink and Otters	□	□	□	□	□	□	□	□	□	
SESSION 4: CASE STUDIES ON HUMAN HEALTH										
• Implications of Eating Great Lakes Fish	□	□	□	□	□	□	□	□	□	

FIGURE 3. Cause-Effect Ballot

- Over 60% accepted the causal relationship between the status of the bald eagle in the Great Lakes basin and exposures to organochlorine compounds and particularly DDE and PCB. Again, about 8% believed that these phenomena were unrelated.

- More than 80% believed the evidence for a causal relationship between the outbreaks of chick-edema disease and exposures to 2,3,7,8-TCDD and specific PCBs.

- There is an encouragingly believable story developing, despite the newness of the research, on the causal relationship between PCB levels and deformities in snapping turtles.

- The voting was almost evenly split on the mink and otter evidence with 4% disbelieving any relationship.

- Finally, more than 70% believed that, in the western Michigan epidemiological study, the cause of the observed anomalies was *in utero* exposures to PCBs. There was, however, about 5% who disbelieved such a relationship.

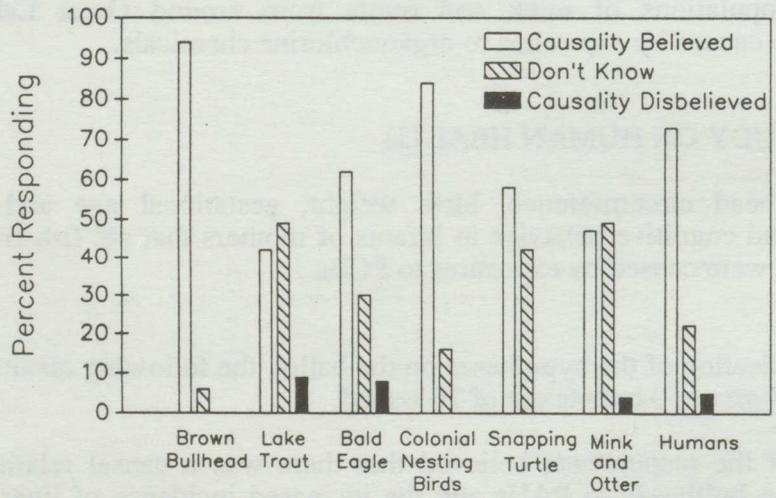

FIGURE 4. Results of Cause-Effects Ballot

7.0 CONCLUSIONS AND RECOMMENDATIONS OF THE WORKSHOP PARTICIPANTS

7.1 Design, Organization and Funding of Research

- The workshop concluded that the five criteria (time order, strength of association, specificity, consistency on replication and coherence) which had been developed by epidemiologists for inferring causality, constitute a reliable framework in which to discuss suspected outbreaks of chemically-induced diseases in fish and wildlife in the Great Lakes Basin Ecosystem as well as in humans. However, the various case studies presented at the workshop show that insufficient research has been carried out to effectively investigate actual outbreaks of diseases suspected to have been caused by chemicals. Much of the past research on contaminants has focused on the concentrations of substances in various components of the environment and on experimentation on the fate and effects of substances. This approach remains important but more field research, beginning with observation of species showing biological effects, is required.

  It is thus recommended that some of the research on chemicals in the Great Lakes be reoriented to interpretation of the causes of outbreaks of diseases suspected to be induced by chemicals. There is a need to design disease-related research so that laboratory experimentation and analytical chemistry are reoriented to investigate affected wild populations in the field. Research managers should keep the epidemiological criteria in mind when designing this kind of research program.

- No one researcher, agency or country has the requisite skills to solve all of the toxicological riddles posed by chemically-induced diseases or epidemics occurring in the Great Lakes basin.

  It is recommended that research managers build genuine interdisciplinary teams that physically work together with a project leader on a well formulated problem involving actual disease outbreaks or epidemics.

- Much of the funding for research on field effects and actual diseases has been piecemeal and inconsistent from year to year. Additional, long-term funding is required to investigate the actual effects of chemicals on populations of organisms, including humans, exposed to Great Lakes chemicals. While long-term funding is difficult to obtain, there are examples (PLUARG, IFYGL*) in which several agencies have made formal agreements to undertake large-scale, long-term studies on the Great Lakes. Also, researchers have successfully looked to alternative sources of funding, such as local or private organizations; these approaches should be continued and encouraged.

  It is recommended that funding agencies make long-term, financial commitments to investigate the spatial and temporal variation in disease outbreaks and epidemics, and the etiologic agent(s) involved. Research institutions should work together to develop proposals for long-term funding.

- There is a priority requirement for the research scientists involved in cause-effect linkages to meet and communicate their findings on a regular basis and to coordinate interagency and interdisciplinary research on effects.

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* Pollution from Land Use Activities Reference Group
International Field Year on the Great Lakes.

It is recommended that the International Joint Commission convene a committee on the reproductive effects of persistent toxic substances on Great Lakes biota. The International Association for Great Lakes Research is encouraged to organize annual sessions concerned with the actual effects of toxic substances on populations of fish, wildlife and humans.

7.2 <u>Research Findings and Implications</u>

° Despite shortcomings in the way in which research is designed, organized and funded to investigate actual outbreaks of disease in populations of fish and wildlife, there are strong indications of a variety of diseases in some Great Lakes fish and wildlife populations that are causally linked to the presence of persistent toxic substances, specifically to DDT and metabolites, dieldrin, PCBs and polychlorinated dibenzo-*p*-dioxins. Examples of these disease outbreaks include:

- embryo and fry mortality in some Lake Michigan lake trout;
- embryonic mortality and deformities in snapping turtles in some areas of Lake Ontario;
- embryonic mortality and deformities in herring gulls, Caspian and Forster's terns and double-crested cormorants;
- declines in mink and otter populations in wetlands close to the Great Lakes;
- reproductive impairment and adult mortality in bald eagles; and
- excess rate of liver tumors in certain populations of brown bullheads, related to exposure to polynuclear aromatic hydrocarbons.

° Persistent toxic substances are the most important and serious problem facing the administration of the Great Lakes.

° Preliminary studies of a human population in western Michigan have shown that mothers who ate a pound or more of Lake Michigan fish per month produced children who weighed about 5% less at birth and had discernible (7%) neuro-behavioral abnormalities. These effects have been associated with the presence of PCBs in the ingested fish, but the significance of these observations is uncertain.

° These preliminary findings are consistent with the findings of reproductive anomalies in Great Lakes fish and wildlife populations and indicate the need to focus on other risks to human health besides cancer. There is a need to develop more sensitive health indicators, including behavioral anomalies.

It is recommended that the perinatal findings of the Michigan fish-eater study be verified by followup at four and eight years of age and that other studies of fish-consumers be conducted in the Great Lakes basin.

It is recommended that this study in which positive findings were made, should be replicated on another population that has been highly contaminated with organochlorine chemicals as a result of eating certain Great Lakes fish.

° Though there is strong evidence linking teratogenic chemicals in the Great Lakes with developmental anomalies of structure and function in fish and wildlife, much of the mechanistic (placental transfer, physiological and biochemical) aspects of the teratogenic action and the implications for human reproduction are poorly understood.

It is recommended that research be undertaken on biomarkers, receptor sites and other biochemical aspects of mechanisms of teratogenesis to give a more complete scientific explanation of the observed teratogenesis and to assess the scale of the risks to human reproduction.

- The objective of all epidemiological research is to interpret the causes and control of disease outbreaks. Interpretation of the outbreaks of teratogenesis and reproductive anomalies in Great Lakes organisms requires a knowledge of both the toxicity of and exposure to each teratogenic agent. Analytical techniques for determining isomer/congener-specific compounds have only recently been developed and are still expensive, but they are essential for the research and monitoring required to interpret the epidemics and epizootics. Some of the analytical costs can be reduced by screening samples, by using enzyme bioassay techniques.

It is recommended that future monitoring and research on PCBs, dioxins and furans place more emphasis on an isomer/congener specific basis to understand the levels, fates and effects of suspected causal agents in the outbreaks of chemically-induced diseases in the Great Lakes basin.

- The causal agent of a disease may be identified many years after the initial observations of effects were made. It is essential to have tissue samples stored from the time of the initial observations to verify the presence of the suspected chemical agent in samples taken at the time of the disease outbreak. There have been several proposals for specimen banking by various U.S. agencies in past years, but no centralized system exists for Great Lakes specimens from U.S. programs.

It is recommended that provision be made for the storage of sufficient materials and tissue samples from outbreaks of chemically-induced diseases for demonstration of the presence of the suspect chemicals by retrospective analysis. The current development of a proposal, by the Great Lakes National Program Office of the U.S. EPA, for a system of tissue banking of Great Lakes specimens is commended. Similarly, samples of human tissues should be placed in long-term storage for retrospective analysis of chemical residues.

7.3 Control of Sources and Remedial Actions

- There is a priority requirement to eliminate sources of teratogenic and carcinogenic chemicals to the Great Lakes and to prevent the continued contamination of Great Lakes food chains with substances already in the environment. Substantial progress has been achieved in controlling direct discharges of these chemicals; however, releases from landfill sites and combined sewer overflows still continue. In addition, releases from contaminated river and harbor sediments persist. The continuing presence of unacceptably high levels of persistent toxic substances in the Great Lakes ecosystem remains a continuing concern for fisheries and wildlife managers and for health authorities.

It is recommended that research continue to be undertaken to determine feasible methods for the remediation of contaminated sediments through removal or detoxification.

APPENDICES

A. Rationale for Workshop

B. Workshop Steering Committee Members

C. List of Participants

APPENDIX A

Rationale for Workshop on Cause-Effect Linkages

Issue

The presence of persistent toxic substances in the Great Lakes has posed not only serious dangers to fish, wildlife and people, but also complex technical problems for researchers and regulatory administrators. One of the recurrent themes during the past few years has been how to relate observations of disease in organisms in the Great Lakes basin to the presence of persistent toxic chemicals suspected to have caused the diseases. In addition, there has been a concern about how to interpret the extensive databases derived from determinations of the concentrations of chemicals in the Great Lakes environment. Because fish bioaccumulate many persistent toxic substances, particular concern is being focused on populations of people that eat or have eaten large quantities of Great Lakes fish. Attempts to synthesize information on this topic have lamely concluded that the relationship was only "circumstantial" or not "formally demonstrated." The question is now being asked, "How do you prove causality?"

Development of Criteria for Inferring Causality

This is a questions that has been posed by medical and veterinary science for a long time. The first set of formalized propositions to relate certain diseases to specific (microbial) agents was made about 1860 by Robert Koch and became known as Koch's postulates. In the early 1950s, the U.S. Surgeon General set up an advisory panel to investigate the possible relationship between smoking and health. Similarly, an investigation was launched to inquire into the causes of lung cancer in uranium miners. One of the outcomes of these investigations was the formulation of the following five criteria for inferring causality:

i. **Time Order** - the exposure must come before the manifestation of the disease.

ii. **Strength of association** - there must be a statistically significant increase in the incidence of the disease in exposed populations compared to unexposed populations.

iii. **Specificity** - are the signs and symptoms only manifested with exposure to the suspected agent and is the agent linked only to specific signs and symptoms?

iv. **Consistency** - do similarly conducted studies in different times and places yield similar relationships?

v. **Coherence** - does the supposed relationship make biological sense and conform to existing knowledge?

These criteria have been extensively used in epidemiology to discuss the linkage between human diseases and suspected causes. However, there are few examples where it has been used to infer causality in relation to disease in fish and wildlife populations.

Proposal for a Workshop

The Council of Great Lakes Research Managers recognizes this is an important topic in relation to the successful implementation of the Protocol to the Great Lakes Water Quality Agreement. The Council, therefore, proposes to hold a workshop to explore the use of these criteria in relation to outbreaks of diseases in biota in the Great Lakes basin suspected to have been caused by chemicals.

There are several objectives for the workshop:

- First, it is a forum in which to critically examine case histories or examples of research where the cause of a disease has been related to chemicals in the environment.

- The second objective is to examine five criteria and to decide whether they are an adequate framework for relating effects to causes in relation to the above examples and case histories.

- The third objective is to determine whether this framework can be used to design future research on outbreaks of disease suspected to be caused by chemicals.

- Finally, the workshop will examine the limitations of the research for policy decisions for the control of toxic chemicals in the Great Lakes.

Background papers will be prepared, under contract, on the following case histories:

A. FISH	- Tumors in black bullheads
	- Reproductive impairment in Lake Michigan lake trout or Chinook salmon
B. FISH-EATING BIRDS	- Eggshell thinning in bald eagles
	- Chick-edema disease in herring gulls
C. FISH-EATING MAMMALS	- Reproductive impairment in mink
D. HUMAN HEALTH	- Reproductive outcomes for eaters of Great Lakes fish

Participants

The workshop is designed to bring together scientists from a variety of disciplines with managers responsible for research and control of toxic substances. The workshop will thus be a forum to focus first on the technical aspects and the limitations of the evidence and second, to explore the management implications for decision-making in the face of uncertainty. The workshop should include active participation of public interest groups.

APPENDIX B

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