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U.S. Environmental Protection Agency
Emergency & Remedial Response Div.
26 Federal Plaza - Room 747
New York, NY 10376

RE: COMMENTS ON THE GREAT LAKES INITIATIVE

Dear Mr. Tomchuk:

Enclosed is a copy of comments submitted by the General Electric Company (GE) on the U.S. Environmental Protection Agencies (EPA's) Great Lakes Water Quality Initiative (GLI). The following is a listing of the main points made:

1) The carcinogenic potential utilized for PCBs is based on outdated information;

2) The utilization of an acceptable daily exposure level (ADE) based on non-carcinogenic effect for PCBs relies on poorly controlled animal studies;

3) Fish consumption rates are overestimated;

4) Bioaccumulation factors utilized are based on overly simplistic assumptions; and

5) The use of Toxic Equivalency Factors (TFFs) for PCBs based on the toxicity of dioxins is not justified given current scientific information.

Many of these issues are identical to issues we raised to you in our comments on your Phase I Hudson River RRI/FS report. However, these comments are the result of additional analysis and information and need to be considered during the Hudson River RRI/FS.

Let me know if you have any question with the comments. Please place a copy of this letter and the attached comments into the Hudson River RRI/FS administrative record.

Yours truly,

John G. Haggard
Engineering Project Manager

Enclosure
cc: William McCabe, EPA
Mariana Stefanidis, EPA (EERD-PSB)

bcc: J. Claussen w/o Enclosure
K. Longo w/o Enclosure
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COMMENTS OF

GENERAL ELECTRIC COMPANY TO THE

DRINKING WATER COMMITTEE OF THE

SCIENCE ADVISORY BOARD

ON THE PROPOSED

GREAT LAKES WATER QUALITY INITIATIVE

HUMAN HEALTH-BASED WATER QUALITY CRITERIA

April 10, 1992

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I. INTRODUCTION

General Electric has been following the development of the Great Lakes Water Quality Initiative ("GLI") and, in particular, the GLI's development of water quality standards ("WQS") that will become applicable to waters within the Great Lakes Basin after the GLI Guidance is promulgated and adopted by the eight Great Lakes states. General Electric has numerous plants within the Great Lakes Basin that discharge wastewater either directly to rivers or lakes within the basin or which discharge to municipal wastewater treatment plants that in turn discharge to waters within the basin. Given that the GLI water quality standards will be used to derive discharge-specific, water quality-based effluent standards, General Electric has a substantial interest in seeing that the water quality standards adopted by the GLI are based on sound science policy and are adequately protective of waters in the Great Lakes Basin.

Having reviewed in detail the methodology used by the GLI to derive the proposed water quality standards, General Electric strongly believes that the GLI has relied on invalid and/or unsupported scientific theories, and has used several overly conservative assumptions. These actions have lead directly to development of water quality standards (WQS) that are much more stringent than reasonably necessary to protect human health, aquatic life and wildlife, and will lead to the development of water quality-based effluent limitations that are technologically or economically unachievable.

Between February 18th and 20th, 1992, the SAB's Great Lakes Water Quality Subcommittee of the Ecological Processes and Effects Committee met in Chicago to review the methodology underlying the GLI's proposed water quality standards. Prior to the meeting, GE submitted extensive comments to the Subcommittee regarding many aspects of the proposed GLI water quality standards, including the derivation of water quality standards based on risk to human health. At the February 18th Subcommittee meeting, it was announced that the Subcommittee would not address in detail the GLI's proposed human health-based water quality standards, and that the human health-based standards would be reviewed at a subsequent meeting to be held by SAB's Drinking Water Committee.

On March 27, 1992, the Drinking Water Subcommittee announced that it would meet on April 13th and 14th to review the scientific underpinnings of the GLI's methodology for establishing human health-based water quality standards and that it would accept public comments through the date of the meeting. The following comments provide GE's views on the extent to which the GLI has departed from good scientific methods and risk assessment theory in developing the proposed human health-based water quality standards. In order to illustrate GE's concerns, GE has used the derivation of water quality standards for PCBs as examples of the GLI's methodological errors. The following issues are addressed in these comments:

1. In the case of many of the compounds for which the GLI has established human health-based water quality standards based on carcinogenicity, GE believes that the GLI has improperly analyzed animal feeding studies, has given undue credence to studies which are demonstrably invalid, and has refused to discount the results of early studies when subsequent, better performed, studies have called into question the results of the earlier studies. The GLI has also erred in several instances by using the derived cancer potency factor for one chemical or mixture as the cancer potency factor for related but chemically different compounds. Further, the GLI has consistently ignored pharmokinetic, clinical and epidemiological studies that cast serious doubt on whether a chemical suspected to cause cancer in animals actually causes cancer in other animal species or in humans. Moreover, the GLI has used a species scaling factor to convert cancer potency factors derived from animal studies to a human equivalent that does not reflect the current EPA position.

As an example, the GLI's risk assessment for PCBs is flawed in at least four respects:

(a) It improperly relies on a rat feeding study involving oral exposure of rats to Aroclor 1260 which has recently been reevaluated. Had the reevaluated results been used, the cancer potency factor for 60% chlorinated PCBs would have been significantly lower.

(b) The GLI has assumed, contrary to virtually all credible data, that lesser-chlorinated PCBs have the same cancer-causing potential as Aroclor 1260,

the most highly chlorinated PCB mixture tested for cancer potency. In fact, there is virtually no data indicating that the lesser chlorinated PCBs are carcinogenic to rats. Moreover, there is little evidence that the lesser chlorinated PCBs have any adverse health effects in humans.

(c) The GLI has wholly disregarded a mass of data indicating that PCBs are not human carcinogens and have few, if any, adverse health effects in humans.

(d) In converting the rat study dose response data into comparable doses for humans, the GLI uses a scaling factor based on ratios of skin area, rather than body weight. The former approach has been questioned, and EPA has recently endorsed the use of a scaling factor based on body weight ratios. This correction in itself would lead to a significant decrease in the human cancer potency factor.

2. The GLI's methodology for determining human health-based acceptable daily exposure levels (ADEs) based on non-cancer effects suffers from some of the same problems discussed above. As an example, the GLI's "Tier 2" assessment of the non-cancer toxicity of PCBs relies on a demonstrably deficient study (Barsotti and Van Miller, 1984) and then applies a safety factor of 1000 to derive an ADE that is so low as to be beyond reason (10 pg/l).

3. The GLI has used flawed assumptions to convert cancer potency factors and acceptable daily exposure levels into human health-based water quality standards. Among other things, the GLI has:

(a) overestimated fish consumption on a regional basis by ignoring subpopulations of fish consumers, assuming that all consumed fish live in impacted waterways, using the mean rather than the median fish consumption rate among anglers, and failing to adequately support the GLI's assumption regarding the percentage of sport-caught versus commercially-caught fish making up the typical angler's diet;

(b) ignored cooking and cleaning loss of pollutants in fish;

(c) overestimated drinking water consumption by at least 40%;

(d) estimated recreational exposure to water by ingestion using extremely conservative assumptions (i.e., swimming in polluted water every day during the summer);

(e) assumed an exposure duration (70 years) which is unsupported by residential surveys and is inconsistent with EPA's risk assessment methodology (i.e., assuming 30 years as the upper bound of the time people live in the same residence); and

(f) calculated bioaccumulation factors using simplistic assumptions regarding the sources of pollutants that bioaccumulate in fish, erring in its assumptions regarding the average lipid concentration in Great Lakes fish, and assuming the same BAF for classes of compounds (such as PCBs) even though substantial evidence indicates that different PCB congeners bioaccumulate at different rates.

4. The GLI proposes to use Toxic Equivalency Factors ("TEFs"), based on the toxicity of dioxin, to determine effluent standards for mixtures of certain structurally related chemicals. Although the GLI has wisely decided not to use TEFs to establish human health-based effluent standards for PCBs, GE nevertheless feels that the TEF approach, at present, has no place in establishing effluent limitations for any chemicals, under any circumstances. As described below, the scientific uncertainties surrounding the TEF approach are simply too many, and of too great significance, to render the TEF approach of any value at this time. Those uncertainties include:

(a) the unproven assumption that TEFs for individual chemicals can be added together to determine the toxicity of a mixture as a whole;

(b) the questionable value of using short term laboratory tests involving either acute toxicity or enzyme induction in laboratory animals or cell cultures to predict carcinogenicity or other long-term chronic effects; and

(c) the general failure of the data to meet the prerequisites to using TEFs to predict the relative toxicity of compounds that are structurally similar to dioxin, namely: (1) evidence of parallel dose-response curves for various congeners; (2) the existence of identical organotropic manifestations for all congeners; and (3) evidence of parallel dose-response curves for various toxicological endpoints for given congeners.

II. COMMENTS

A. THE GLI'S RISK ASSESSMENT METHODOLOGY FOR CARCINOGENS

In establishing a human-health based WQS for PCBs based on carcinogenicity, GE believes that the GLI has improperly analyzed animal feeding studies. The GLI has given undue credence to studies which are demonstrably invalid. Moreover, it has failed to discount the results of earlier studies when subsequent, better performed, studies have called into question the results of the earlier studies. The GLI has also relied on test results using one sex of a species when the other sex has wholly failed to show the same carcinogenic response. The GLI has further erred by using the derived cancer potency factor for one chemical as the cancer potency factor for related, but chemically different, compounds. Finally, the GLI consistently ignores pharmokinetic, clinical and epidemiological studies that cast serious doubt that a chemical suspected to cause cancer in animals actually causes cancer in other animal species or in humans.

As an example of the types of errors the GLI has made, we discuss below the GLI's analysis of the carcinogenicity of PCBs[1]. As the following comments will detail, the GLI has made at least four errors in deriving a human health-based water quality standard for PCBs based on cancer risk assessment:

First, the GLI proposes to establish a cancer potency factor for all of the 209 PCB congeners based on the results of a study using one commercial PCB mixture, Aroclor 1260, that contains only the more highly chlorinated PCBs. The more highly chlorinated PCBs are probably the only PCBs to have any potential for causing cancer at all.

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[1] PCBs are a class of compounds consisting of biphenyls chlorinated to varying degrees. The Aroclors are characterized by four digit numbers. The first two digits indicate that the mixture contains biphenyls (12); the last two digits give the weight percent of chlorine in the mixture (e.g., Aroclor 1242 contains biphenyls with approximately 42% chlorine).

Second, to establish that cancer potency factor, the GLI relies on the results of a single study (Norback and Weltman 1985) using female rats of one species; the GLI wholly ignores the fact that male rats of the same species showed no statistically significant cancer response and that another species of rats showed a much lower cancer response. Simply using all of the rat data for Aroclor 1260 to calculate a cancer potency factor results in more than a three-fold decrease in the estimated potency factor for that compound.

Third, the GLI ignores the fact that the original tissue slides used in the Norback and Weltman study have been recently reevaluated by a panel of expert toxicologists using the most current National Toxicological Program guidance. The result of that review is that the cancer potency factor calculated by Norback and Weltman has been substantially reduced.

Fourth, the GLI ignores animal studies, clinical studies, and epidemiological studies showing that even the more chlorinated PCBs cannot possibly have a cancer risk anywhere as high as that calculated by the GLI. GE realizes that toxicologists must be careful in relying on the results of negative epidemiological studies. However, when several excellent epidemiological studies have been performed using large numbers of workers heavily exposed to PCBs over a long period of time, and the results of those studies have been negative, GE submits that such results must be factored in to the conversion of an animal cancer potency factor to a human cancer potency factor.

1. Overview of PCB Cancer Risk Assessment

The GLI's perception of the risks posed by PCBs is undoubtedly influenced by out-of-date information that has been read by some scientists as indicating that PCBs, as a class, are highly toxic. These include the 1968 "Yusho" human poisoning incident in Japan, which produced chloracne and other symptoms, and the 1975 finding by Dr. Renate Kimbrough of the Center for Disease Control that high dosage feeding with Aroclor 1260, a mixture containing highly chlorinated PCBs, caused liver cancer in rats.

Since EPA's initial regulation of PCBs in 1979, substantial additional information about PCBs has been developed. In particular, recent scientific studies have shown that:

- The adverse health effects observed in the "Yusho" incident are not attributable to PCBs.

- Although Kimbrough's finding regarding Aroclor 1260 has been supported by subsequent studies, other feeding studies have shown that lower chlorinated mixtures do not cause liver cancer. Moreover, the potential of Aroclor 1260 to cause liver cancer has been shown to be less than originally determined. Further, other data from these and other studies suggest that Kimbrough's results are not relevant to human carcinogenicity.

In addition, new scientific information pertaining to the human health effects of PCBs has been discovered. These findings indicate that:

Exposure to PCBs in the environment today does not result in elevated PCB blood levels.

Clinical studies of workers exposed to PCBs show no association between adverse health effects and high levels of exposure.

Epidemiology (mortality) studies of PCB-exposed workers do not indicate that PCB exposure leads to increased mortality, whether based on overall cancer mortality or deaths due to individual cancer types.

The perceived relationship between PCB exposure and chloracne is most likely spurious. Any observed linkage likely arises from contamination of PCBs and from uses of PCBs in conjunction with active agents.

Any suggestion that reproductive or neurodevelopmental effects in humans is related to low-level exposure to PCBs has not been validated.

These findings strongly suggest that human health risks from PCB exposure have been significantly overestimated in current regulations. Thus, EPA should undertake a

thorough re-evaluation of the actual risks posed by PCB exposures, and GLI should not rely on out-of-date information when seeking to establish water quality standards for PCBs.

2. The Basis of the GLI's Cancer Potency Factor for PCBs

The GLI evaluated the cancer risk of PCBs based on D.H Norback and R.H. Weltman (1985), rather than Kimbrough et al. (1975). Norback and Weltman's study involved feeding Aroclor 1260 to 70 male and 70 female Sprague-Dawley rats at 100 ppm for 16 months, followed by a 50 ppm diet for 8 months, then a basal diet for 5 months. Treated females exhibited an incidence of 43/47 hepatocellular carcinomas. Males exhibited an incidence of 2/46 carcinomas. Based on the incidence data for females only, the carcinogenic potency (or cancer slope, q_1^*) was estimated using a linearized multi-stage, low-dose response model, and a species scaling factor based on the ratio of rat to human skin surface area. The potency of all PCBs was estimated to be 7.7 $(mg/kg/day)^{-1}$ (USEPA, 1988).

3. Existing Data Do Not Support the GLI's Cancer Potency Factor For PCBs

The GLI's human health risk assessment which was used to estimate a cancer potency factor for PCBs is flawed in at least four respects:

(a) it improperly relies on a rat feeding study involving oral exposure of rats to Aroclor 1260 which has recently been reevaluated. Had the reevaluated results been used, the cancer potency factor for 60% chlorinated PCBs would have been significantly lower;

(b) the GLI has assumed, contrary to virtually all credible data, that lesser chlorinated PCBs have the same cancer-causing potential as Aroclor 1260, the most highly chlorinated PCB mixture tested for cancer potency. In fact, there is virtually no data indicating that the lesser chlorinated PCBs are carcinogenic. Moreover, there is very little evidence that the lesser chlorinated PCBs have any adverse health effects;

(c) the GLI has wholly disregarded a mass of data indicating that PCBs are not human carcinogens and have few, if any, adverse health effects; and

(d) in converting the rat study dose response data into comparable doses for humans, the GLI used a scaling factor based on ratios of skin area, rather than body weight. The former approach has been questioned, and EPA itself is considering use of a scaling factor based on body weight ratios. This correction in itself would lead to a significant decrease in the human cancer risk.

These issues are addressed below.

a. In Establishing a Cancer Potency Factor for 60% Chlorinated PCBs, as Well as the Other PCBs, the GLI Improperly Relied on the Results of a Study That Has Recently Been Reevaluated

In its assessment of PCB toxicity, the GLI relies heavily on outdated information and assumptions concerning PCB toxicity. As noted above, the GLI's estimate of carcinogenic potency for all PCBs was based on part of a single study: the Norback and Weltman (1985) study of female Sprague-Dawley rats exposed to Aroclor 1260, a 60% chlorinated PCB. As discussed below, GE believes it highly inappropriate for the GLI to base cancer potency estimates for all of the PCBs on the results of a single study of only one PCB. However, just as troublesome is the fact that the GLI has ignored recent scientific data demonstrating that the cancer potency of Aroclor 1260 based on the results of the Norback and Weltman study has been overestimated.

The Norback and Weltman study found that female rats exposed to a commercial mixture of PCBs containing 60 percent chlorine by weight demonstrated the greatest carcinogenic response of any PCB mixture tested. Recently, the liver tissue slides from the Norback and Weltman study and the four other original studies (Kimbrough et al., 1975; Linder et al., 1974; NCI, 1978; and Schaeffer et al., 1984) were screened by a panel of expert pathologists using current guidelines for interpreting liver lesions. (IEHR, 1991). These guidelines were developed by the National Toxicological Program (Maronpot et al., 1986; McConnell et al., 1988) and have been endorsed by EPA. The panel's proceedings

were observed by representatives from EPA, FDA, Experimental-Pathology Laboratories, Inc., the Institute for Evaluating Health Risks, and participants in the original studies.

The reevaluation was performed because the classification scheme for proliferative lesions in the rat liver has changed significantly since the original rat bioassay results for PCBs were published. The current classification scheme for liver neoplasms, developed by the National Toxicology Program (NTP) and endorsed by EPA (1986), employs four diagnostic categories for proliferative lesions of the liver: (1) foci of cellular alteration, (2) hyperplasia, (3) hepatocellular adenoma, and (4) hepatocellular carcinoma. In particular, the current NTP guidelines distinguish between hyperplasia, a nonneoplastic response to degenerative changes in the liver, and adenoma, a benign condition involving clear differentiation of cells from the surrounding tissue (Maronpot et al., 1986; USEPA, 1986a). Several important studies conducted prior to the development of the current classification scheme, including Norback and Weltman (1985) employed such terminology as hepatomas, neoplastic nodules, hyperplastic nodules, and hepatocellular neoplasms to describe certain liver lesions (Kimbrough et al., 1975; Linder et al., 1974; NCI, 1977; Norback and Weltman, 1985; Schaeffer et al., 1984). These pathologic descriptions do not conform to the current classification criteria and terminology, and in some cases, may include both neoplastic and nonneoplastic lesions under the same term. Thus, it was believed that these earlier studies may have significantly over-estimated cancer risk.

As expected, the early studies had indeed over-estimated cancer risk. (A summary of the findings of the IEHR study are set forth in Appendix A.) Although the IEHR (1991) review confirmed that female rats exposed to 60 percent chlorine mixtures developed tumors, the expert panel found that the number of animals with benign or malignant liver tumors was less than originally reported. Using Norback and Weltman (1985), IEHR found that the potency estimate based on female rats decreases from 7.7 to 5.1 $(mg/kg/day)^{-1}$. Using a geometric mean of all positive studies (as advocated by IEHR (1991) for PCBs containing 60 percent chlorine), the potency decreases to 1.9 $(mg/kg/day)^{-1}$. In light of the IEHR review, GE submits that the GLI should use a cancer potency factor of no higher than 1.9 $(mg/kg/day)^{-1}$ for 60% chlorinated PCBs. As discussed below, GE believes that the potency

factor should be reduced still further as the result of performing species scaling on the basis of body weight, rather than surface area.

b. The GLI Has Improperly Applied the Cancer Potency Factor for 60% Chlorinated PCBs to Lesser Chlorinated PCBs

In addition to demonstrating that 60% chlorinated PCB mixtures have a lower carcinogenic potential than assumed by EPA, the IEHR study determined that the Clophen A30 study results (Schaeffer, 1984) (using a PCB mixture containing about 42 percent chlorine) were negative as to the carcinogenicity of this PCB mixture. The panel also confirmed that the study of Aroclor 1254 (a mixture containing 54 percent chlorine) performed by the National Cancer Institute was negative (NCI, 1978). Using the IEHR study results and current risk assessment guidelines, these compounds should not be regarded as carcinogens (OSTP, 1984). Thus, the only positive animal studies cited by EPA are those using PCB mixtures containing 60 percent chlorine and, as discussed above, even in those studies the carcinogenic potency was significantly overestimated.

The basic conclusions of the IEHR review were that different PCB mixtures have significantly different carcinogenic effects and that some mixtures are not carcinogens. Therefore, the appropriate regulation of PCBs requires distinguishing between PCB mixtures. The cancer potency factor used by the GLI is incorrect in light of this new scientific information, and the human health risk assessment performed using this erroneous factor comes to invalid conclusions.

It has been a basic policy of EPA to assume that individual chemicals in a chemical class will differ in their carcinogenic potential. In the OSTP guidelines on chemical carcinogens, it was concluded that "ordinarily, not all chemicals belonging to any class are carcinogenic, nor are all those compounds within a class which exhibit carcinogenicity equally potent." (OSTP, 1985).

EPA has recognized the need to set different standards for different members of chemical classes. For example, EPA's rule on incidental generation of PCBs in manufacturing operations recognizes the difference between very lightly chlorinated PCBs and other PCBs by applying discounting factors of 50 and 5, respectively, for the toxic potential of mono- and di-chlorobiphenyls. Thus, for purposes of determining if a chemical mixture containing incidentally-generated PCBs reaches the regulated level of 50 ppm, the concentration of mono-chlorinated biphenyl is divided by 50, and the concentration of di-chlorinated biphenyl by 5.

Similarly, regulations and health standards for many other chemicals recognize that individual members of chemical families are not equally hazardous. For example, in the PCDD (dioxin) and PCDF (furan) families, which EPA has determined are more toxic than PCBs, only about ten percent of the individual PCDD and PCDF congeners are considered toxic enough to be measured for risk assessment purposes. Other examples of differential regulation within a chemical family include FDA and EPA standards that measure and regulate methyl mercury instead of total mercury and hexavalent chromium instead of total chromium.

Thus, a clear policy and precedent exists for treating different PCBs differently. According to Dr. John Moore, president of IEHR, the panel's clarification of the results of the original studies presents EPA with the opportunity of modernizing PCB cancer risk assessments by (1) developing separate risk assessments for each of the major PCB formulations, and (2) utilizing all the available data when calculating cancer potency for PCB mixtures below 60 percent chlorination[2]. (IEHR, 1991).

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[2] It is, of course, significant that almost all (88 percent) of the PCBs sold in this country by the sole domestic supplier from 1957 to the end of production were mixtures that were below the 60 percent chlorination level.

c. Both Animal and Human Studies Call Into Question the GLI's Assumption that PCBs are Human Carcinogens

Although there is little question that 60% chlorinated PCBs are rat carcinogens, there is little or no information indicating that they are human carcinogens. Rather, both animal and human studies call into question the GLI's assumption that PCBs cause cancer in humans.

(1) Animal Studies

Although the Kimbrough study and subsequent studies have confirmed that 60% chlorinated PCBs are rat carcinogens, other evidence calls into question whether such PCBs are human carcinogens. A review of the PCB animal studies shows that:

> The PCB-exposed rats, including those with liver tumors, lived significantly longer than the controls.
>
> The PCB-exposed rats had significantly fewer cancers of all types, i.e., sum of all cancers, than did the controls.
>
> The liver tumors, although formally classified as cancers, did not metastasize to other organs or invade blood vessels.

In other words, PCB exposure in rats appears to produce non-invasive, non-life-threatening rat liver tumors and indeed may well produce beneficial effects (significant life extension and reduction in number of other cancers relative to the controls). These conclusions seriously call into question the relevance of rat liver tumors to human risk. They provide additional assurance that a declassification of PCB mixtures having less than 60 percent chlorination as animal carcinogens can be made without endangering human health.

EAT YOUR PCBs

(2) Epidemiology Studies

Epidemiology studies also call into question whether the rat studies showing 60% chlorinated PCBs to be carcinogens can be extrapolated to humans. In fact, recent human epidemiology studies do not support the conclusion that exposure to large concentrations of PCBs result in elevated cancer risks in humans. Data from these studies have failed to demonstrate any consistent tumorigenic effects among populations exposed to high concentrations of PCBs.

The most celebrated incident in which PCBs became linked to causing cancer in humans is the so-called "Yusho" incident. In 1968, about 1500 persons in Japan became ill after consuming rice oil that was accidentally contaminated with a PCB mixture known as "Kanechlor 400." (Amuno et al., 1984; Kuratsune, 1986). A similar incident, known as "Yucheng," occurred in Taiwan in 1979. Typical symptoms were chloracne, swelling of eyelids and eye discharges, brown pigmentation of the nails and skin, and curling of fingernails and toenails. Signs of the disease were also observed in some offspring of affected mothers. Although the major symptoms disappeared over the next sixteen to twenty years, subsequent studies suggested a possible increase of cancer and adverse developmental and behavioral effects in offspring.

The cause of the incident was extensively studied and the rice oil was found to contain high levels of polychlorinated dibenzofurans ("PCDFs"), a chemical that is 100 to 1,000 times more toxic than PCBs. After finding that workers exposed to much higher levels of PCBs showed minimal adverse health effects, and after performing dose-response studies on the rice oil mixture, Japanese and Taiwanese scientists concluded that PCDFs were the prime causal factor in the Yusho and Yucheng incidents. (Kashimoto et al., 1985)

In 1985, Dr. Kimbrough and Dr. Goyer of the National Institutes of Health unequivocally concluded that:

> The scientific community assumes now that most of the effects observed in these two outbreaks were caused by the ingestion of the polychlorinated dibenzofurans.

(Kimbrough, et al., 1985). Likewise, the Halogenated Organics Subcommittee of EPA's Science Advisory Board reviewed a PCB health advisory from EPA and concluded that:

> The health effects section [of EPA's advisory] suggests that the short-term human exposure to Yusho poisoning is representative of polychlorinated biphenyl toxicosis. Recent studies indicate that the major etiologic agents in Yusho were polychlorinated dibenzofurans rather than polychlorinated biphenyls. . . . Thus, a discussion of the human health effects of polychlorinated biphenyls should not use 'Yusho' as an example. Industrial exposure data more accurately reflect human health effects.

(Doull, et al. 1986).

Significantly, this scientific re-interpretation of the Yusho and Yucheng incidents is consistent with data from animal studies that show a relatively low level of acute toxicity, e.g., LD_{50}s ranging from about 1 to 11 g/kg-body-weight in rats, depending on the Aroclor mixture. Moreover, this explanation is consistent with the numerous studies discussed below that show no significant adverse health effects in workers who had been exposed to average levels of PCBs higher than the Yusho patients were.

Subtracting Yusho from the universe of epidemiological studies leaves nine other referenced studies, five of which (Brown and Jones, 1981; Gustavsson et al., 1986; Davidoff and Knupp, 1979; Brown, 1987; and Zack and Musch, 1979) reported no causal connection between PCB exposure and cancer. EPA has interpreted the other four studies (Bahn et al., 1976, 1977; Bertazzi et al., 1987, Sinks et al., 1990; and Liss, 1990 (see Appendix C)) to suggest that exposure to PCBs causes cancer. This interpretation is not consistent with good science as further discussed below.

Bahn et al., (1976; 1977) evaluated the incidence of tumors occurring in a New Jersey petrochemical facility where Aroclor 1254 had been used from 1949 to 1957. A significantly increased incidence of malignant melanomas was observed among research and development workers (2 of 31) and refinery personnel (1 of 41). In an update of that same study, NIOSH (1977b as cited in ATSDR, 1989) observed eight cancers in the total study population (5.7 expected). Three of these tumors were melanomas and two were pancreatic cancers. The incidence of these tumor types was reported to be significantly above calculated expectations, although no data were presented (ATSDR, 1989). The results of this study were further confounded by the small cohort size and the fact that the workers in this facility were exposed to numerous other chemicals (Bahn et al., 1977; Lawrence, 1977).

Bertazzi et al., (1987) conducted a retrospective cancer mortality study of 544 male and 1,556 female workers who had been employed for at least one week in the manufacture of PCB-impregnated capacitors in an Italian plant between 1946 and 1978. Mortality was examined for that cohort from 1946 to 1982 and was compared to both national and local mortality rates. Mortality due to all cancers (14 observed vs. 5.5 national and 7.6 local) and due to cancer of the gastrointestinal tract (6 observed vs. 1.7 national and 2.2 local) was significantly increased among male workers. Death rates from hematologic neoplasms and from lung cancer were also elevated, but not significantly. Overall mortality was significantly increased above local rates (34 observed vs. 16.5 local) in the female population. Total cancer deaths (12 observed vs. 5.3 local) and mortality from hematologic neoplasms (4 observed vs. 1.1 local) were also significantly elevated over local rates in the female population.

The results of the Bertazzi et al. (1987) study are limited by the small number of cancer cases observed and the limited latency period (ATSDR, 1989; Kimbrough, 1987). A major problem in the study design was the one week minimum period of employment required for inclusion in the study and the inclusion in the cohort of workers who had no PCB exposure. This makes it difficult to assume that excess cancer cases are attributable to PCB exposure rather than to other factors. This study also did not show a dose-response relationship or any direct relationship between latency and the disease. Moreover, the results of this very

small study are dissimilar from the results of much larger and statistically more valid studies of similar worker populations in the United States.

Liss (1989 [unpublished]) (See Appendix C) conducted a retrospective cohort mortality and cancer incidence study of 1,073 workers employed between 1960 and 1976 at a transformer manufacturing plant (Ferranti-Packard Ltd.) in Ontario. Cohorts were defined in this study by exposure intensity and frequency to characterize those who had worked, and those who had never worked, in a job considered to be "exposed." Among females, there were few deaths; one each occurred due to cancer of the lung and of the breast in the "ever exposed" group, and one death from lung cancer occurred in the "nonexposed" group. Overall mortality among males was less than expected when compared to the population of Ontario. Mortality due to all malignant neoplasms was elevated, but not significantly so, in "ever exposed" workers. This elevation was due primarily to statistically significant increases in deaths from cancer of the brain and nervous system (4 observed vs. 0.8 expected) and prostate (5 observed vs. 1.2 expected). The brain cancer incidence rate among "ever exposed" males was significantly elevated over the expected rate (4 observed vs. 0.9 expected) and the prostate cancer incidence rate was elevated, but not significantly so.

A separate analysis of 159 men who had ever worked in the "highest exposure" jobs indicated that deaths from all malignancies were fewer than expected, and no deaths due to cancer of the brain or prostate was observed. In this "highest exposure" group, no significant increase in cancer incidence rates were observed. Among male workers not known to have been exposed, deaths from malignant neoplasms were less than expected, and deaths due to cancer of the gallbladder or bile ducts were significantly elevated (2 observed vs. 0.11 expected).

From these results, the author concluded that, because no brain or prostate cancers were observed in the "highest exposure" group, the relationship of these excesses to PCB exposure is not confirmed. In addition, no liver, biliary tract or gall bladder cancers were observed among workers in exposed jobs, nor were deaths or incident cases from tumors of the lymphatic and hematopoietic tissue significantly elevated above expected rates.

Sinks et al. (1991) conducted a retrospective cohort mortality analysis of 3,588 workers who were employed for at least one day at an electric capacitor manufacturing plant between 1957 and 1977. Aroclor 1242 was used in this plant through 1970, and Aroclor 1016 was used from 1970 to 1977. Mortality from all causes and from all cancers was less than expected. A significant increase in mortality rate was observed for skin cancer (8 observed vs. 2 expected) and death rates from brain and nervous system cancers were non-significantly elevated over expected rates. No excess deaths were observed from cancers of the rectum or lung, liver biliary and gall bladder, or from hematopoietic malignancies. Based on a cumulative dose estimate, which incorporated information on job station history, limited PCB environmental sampling data, and serologic data, the authors were not able to establish a clear relationship between latency or duration of employment and risk for malignant melanoma. Sinks et al. (1991) point out that the skin cancer excesses are not consistent with those of similar studies. Though an excess of malignant melanomas was reported by Bahn et al. (1976; 1977), as discussed above, there were a number of problems with that particular study which confound the results. The authors also point out that mortality may not be the best index of risk for malignant melanoma, as survival can be affected by differences in health care quality. In addition, other limitations include the lack of evaluation of exposures to other chemicals, (e.g., metals and solvents), the relatively short latency period, the small number of deaths within the cohort, and possible misclassification of brain cancer cases.

By contrast, the largest study of PCB exposed workers involved a cohort of 6,292 persons employed for at least three months during the period 1946-1976 at the GE Hudson Falls and Ft. Edward facilities (Taylor, 1988) (See Appendix D). This study showed no increase in cancer mortality or in overall mortality compared to national averages. Neither deaths due to malignant melanoma, lymphopoietic cancers or the combination of liver, gallbladder and biliary cancers were significantly elevated, and brain cancers were well below the expected value. PCB exposure was shown to be negatively associated with cancer mortality (all types combined) and lung cancer (the only cancer outcomes with numbers of cases sufficient to permit a regression analysis). In other words, as PCB exposure increased, the numbers of overall cancer deaths and lung cancer deaths decreased. This study was initiated

when Dr. Taylor, an employee of NIOSH, was assigned to the New York State Department of Health (NYSDOH) and involved collaboration with other scientists at NYSDOH. Unfortunately, EPA has failed even to consider the largest and most relevant epidemiological report in existence.

Thus, none of the cancer incidence and mortality studies demonstrate a cause-effect relationship between PCB exposure and cancer. Not only do the individual studies fail to show causation, but the weight of the evidence from the studies taken collectively fails to establish any such relationship.

The scientific convention applied in weight-of-the-evidence evaluation of epidemiological studies requires (a) the observation of a specific cancer endpoint, and (b) the meeting of other criteria (strength of association, dose-response relationship, temporally correct association, specificity of the association, and biological plausibility) before a causal relationship between an agent such as PCBs and cancer can be inferred (Hill, 1965; Mausan and Kremer, 1985; OSTP, 1985; Kelsey et al., 1986; IARC, 1987). In the PCB studies, small increases in a wide variety of cancer endpoints were seen in different populations with no common thread, and many studied populations showed no increases at all. The discrepancies can be explained in innumerable ways, including exposures to other chemicals, population life styles, and even chance. Thus, little evidence exists that PCBs are human carcinogens, and the weight of the evidence fails to establish a definitive causal relationship between exposure to PCBs, even in high concentrations, and the incidence of cancer in humans.[3]

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[3] EPA has analyzed data that demonstrates that its methodology of calculating PCB cancer risk is incorrect. In EPA's Phase 1 RI/FS Report on the Hudson River Superfund Site, EPA concludes that if the EPA cancer slope factor is applied to the maximum allowed OSHA PCB exposure limit in the workplace, an estimated cancer risk of 3.4 in an exposed population of 10 would exist. (USEPA, 1991c). Since the literature contains numerous epidemiological studies of capacitor worker cohorts having significant long-term high exposures to 42 percent and 54 percent chlorinated PCBs in the workplace, and no virulent cancer epidemic such as would have been predicted by the current EPA approach has been discovered, this is a further demonstration that EPA's treatment of all PCBs as probable human carcinogens is unsupported by empirical evidence and good science.

GE's analysis of the epidemiological data is consistent with that of Chase, Doull, Friess, Rodricks and Safe (1989) (See Appendix F), who concluded:

> There is insufficient evidence to show a causal relationship between PCB exposure and the subsequent development of any form of cancer. In light of the long-term and widespread usage of PCBs in the workplace and, in some cases, the extensive exposures of workers, it is likely that evidence of carcinogenicity in humans would have been observed in the various epidemiological studies discussed above if PCBs were in fact potent carcinogens.

d. Exposure to PCBs at Elevated Levels Has Not Been Related to Increased Incidence of Any Disease

It is also significant that clinical studies of PCB-exposed workers do not indicate that non-cancer adverse health effects are associated with high PCB exposures.

(1) Generally

The most extensive long-term exposure of humans to PCBs has occurred in capacitor plants; 17 capacitor plants used PCBs in the United States. Many employees in these plants had daily PCB skin contact for years and inhaled PCBs (primarily Aroclor 1242 or 1016) at levels in the 100 to 1000 $\mu g/m^3$ range.[4]

In capacitor plants, the most frequent PCB-related health effect observed was transient skin rashes that affected a small percentage of exposed employees. In contrast to

[4] In the United States, notable studies include (1) Westinghouse Capacitor Workers et al. NIOSH (1981), updated by G. Steele, ISBH, and NIOSH (1990); (2) Utility Transformer Service Employees, by A.B. Smith, et al. NIOSH (1981); (3) Government Service Administration Transformer Service Employees, by E. Emmett, al., Jones Hopkins Univ. (1985-88); (4) Penn Central Transformer Service Employees, by Chase, Wash. Occup. Health Associates (1983); (5) Sangamo Capacitor workers, by D.H. Robinson, South Carolina State Department of Health and Environmental Control (1978); and (6) GE Capacitor Workers, by I. Selikoff, A. Fischbein, et al., Mt Sinai Hospital (1976-79).

chloracne, this condition responded to simple topical treatment and employee reassignment to other work areas. The medical records of these worker populations have shown no obvious incidence of systemic disease attributable to PCBs.

Medical surveillance by GE of the group of 174 heavily exposed capacitor workers has consisted of multiple examinations over the last fifteen years. (Lawton, 1985). The length-of-service of this group averages over 20 years and ranges from 1 to 40 years. PCB blood tests of 174 heavily exposed GE capacitor workers have indicated a mean serum level of about 500 ppb. Ten percent of the individuals' analyses were above 1000 ppb. By comparison, mean serum PCB background levels for people exposed to environmental background levels in the United States range from 2 to 24 ppb, with a mean of approximately 6 ppb. The only clinical parameter found to be statistically correlated with serum PCB level is that of serum triglycerides. The interpretation of this correlation is confounded by the fact that PCBs distribute equally among all lipid pools in the body, including those in the blood; hence, for any given PCB body burden, the serum PCB level must vary directly with the level of serum lipids. Thus, increased serum PCB levels are probably the result, not the cause, of increased serum lipids. (Brown, 1984).

Medical examinations of these workers have not revealed serious health problems related to PCB exposure. The pulmonary function tests of the non-smokers in this heavily exposed population were in the normal range.

A number of other worker clinical studies have been carried out in this country and abroad. (Ouw, et al. 1976; Maroni, et al. 1981(a); Maroni, et al. 1981(b); Hasegawa, et al. 1972; Kitamura, et al. 1973; Karppanen, 1973). Observations of high PCB blood levels, some dermal conditions, and isolated cases of chloracne have been reported in the industrial hygiene literature of Japan, Finland, Australia and Italy. Although the reported biochemical examinations identify scattered individual abnormalities in serum enzymes, the various liver function tests were generally considered normal. The Italian chloracne cases were observed in men who had worked where the air levels of Aroclor 1254 were 5200 to 6800 ppb (i.e., 10 to 14 times the U.S. permissible exposure level). The Finnish capacitor workers were also found

to be in good health, despite PCB concentrations in their blood approximately 50 times greater than that of a control group. The researchers were unable to detect any biological effect caused by PCBs in these workers.

The findings from these studies were summarized by A.B. Smith, M.D., of NIOSH, as follows:

> None of the published occupational or epidemiological studies (including ours) have shown that occupational exposures to PCBs is associated with any adverse health outcome . . . except for the occurrence of chloracne.

(Smith, et al. 1982). Notably, chloracne was not observed by the NIOSH researchers. The relationship of PCB exposure to occurrence of chloracne is discussed below.

(2) Chloracne

The first incident relating chloracne to PCB exposure was reported in 1936 (Jones and Alden, 1936). After performing skin patch tests with suspect chemicals, including PCBs, on PCB-exposed workers, the authors concluded that the cause was an impurity in the benzene used to make the biphenyl, and that "the chlorinated biphenyl can absolutely be absolved as the irritating agent."

The second episode involving PCBs and chloracne occurred in 1950 and 1951, when 14 people were exposed to PCB vapors (reported at 100 $\mu g/m^3$) from a leaky heat exchanger, and seven of the 14 developed chloracne (Meigs et al., 1954). A third episode was noted in the early 1960s, when 13 of 16 people exposed to vapors from an oven in which PCB-plasticized enamels were being baked were similarly affected (Birmingham, 1964). Other occurrences of chloracne have involved PCB usage abroad, where data on conditions of use or contaminant concentrations do not permit reliable conclusions to be drawn about the cause of the health effect.

In light of the circumstances surrounding these isolated PCB incidents, i.e., impurities in the materials and the heating of PCBs under oxidative conditions, it seems reasonable to attribute the chloracne to contamination by polychlorinated dibenzofurans (PCDFs). As demonstrated by the Yusho/Yucheng incidents and confirmed in the laboratory, PCDFs can be formed by partial oxidation of PCBs at elevated temperatures. PCDFs also occur in varying concentrations in commercial PCB mixtures with higher concentrations in Japanese and European products than in Aroclors. As pointed out by NIOSH (1977), "[c]hloracne has frequently been associated with processes where the PCBs were heated."

Perhaps most revealing, however, is the fact that in the three largest and most recent studies of capacitor manufacturing and transformer repair workers, not one case of chloracne was identified (Smith et al., 1982; Lawton et al., 1985; Emmett et al., 1988). This result is particularly significant because the mean PCB serum levels in one of the studies were two orders of magnitude greater than national population mean levels, and because one of the researchers, Dr. E. Emmett of Johns Hopkins University, was a dermatologist and made a special search for signs of chloracne.

In short, much like the initial hypotheses that surrounded the Yusho incident, subsequent study has shown that any relationship between PCB exposure and chloracne is likely spurious. No reliable study has shown that, absent confounding factors, PCB exposure causes chloracne.

(3) Reproductive and Developmental Outcome

One of the early studies to evaluate the impact of PCBs on reproductive outcome was conducted by Taylor et al. (1984), who reported a slight decrease in mean birth weight and gestational age of 51 infants born to women with a history of high exposure to Aroclors 1254, 1242, and/or 1016. As with many epidemiological studies, the inability to control a variety of confounding factors compromised the study. According to ATSDR (1989), "the results of this study are considered suggestive but inconclusive because the effects were small and confounding factors such as smoking and alcohol consumption, prenatal care,

underlying medical conditions, maternal weight, and previous history of low birth weight were not considered."

In a recent article (see Appendix G), Harold Humphrey, Ph.D., Michigan Dept. of Public Health, discusses the evidence associating environmental contaminants and reproductive outcomes. He summarizes a series of studies carried out by Fein, Jacobson and himself as follows:

> In a Michigan study of 242 children born of mothers who ate sport-caught Lake Michigan Fish and 71 comparison children, investigators used maternal fish consumption and maternal serum and cord blood PCB levels to estimate exposure. They found an association between maternal fish consumption and smaller birth size and an association between cord blood PCB levels and depressed Brazelton scales and poorer visual recognition memory at seven months of age. Like the Bayley scales used in North Carolina, the Brazelton scales represent an indication of poorer cognitive performance that could possibly be related to learning. When the Michigan children were evaluated again at age four, researchers found that deficits in body size (weight gain) persisted and indicators of poorer cognitive performance (McCarthy verbal and quantitative performance scales) continued to be present and associated with *in utero* exposure as measured by cord blood PCB levels.

In the same publication (see Appendix G), Nigel Paneth, MD, MPH of Michigan State University, points out numerous shortcomings in the Fein, Jacobson, and Humphrey studies, including:

- The difficulty of assessing exposure through interviews of mothers regarding fish consumption, especially individual fish species.

- Selection of controls. All mothers with intermediate levels of fish consumption were eliminated from the study. The control sample was restricted to one-third the size of the exposed group, placing "enormous weight on the 71 women chosen (as controls) to represent the entire universe of unexposed mothers." A random, rather than a matched

> sample, of controls was chosen. This decision may have introduced major confounding factors, since a variety of socioeconomic and other maternal characteristics greatly influence such outcomes as birth weight and cognitive function. For example, powerful factors such as increased consumption of alcohol, caffeine and cold medicines, and lower maternal weight were reported for the exposed mothers relative to the controls. This introduces a strong bias toward adverse reproductive/developmental outcomes in the exposed group that may be impossible to correct.

Paneth also points out that fish consumption did not predict PCB exposure based on maternal serum levels. Therefore, if any relationships of fish consumption to adverse outcomes are real, they must be associated with factors other than PCBs. Obvious chemicals for consideration are pesticides, heavy metals, and chlorinated dibenzofurans and dioxins. (Unfortunately, these chemicals were not evaluated as part of the study.) This possibility was also recognized by Jacobson, who noted "since behavioral deficits are unrelated to cord blood level, it is possible that toxins other than PCBs found in these same contaminated fish are responsible." (Jacobson, et al., 1985a).

In a review of the Fein et al. (1984) and Jacobson et al. (1983, 1984) studies, IEHR (1991) (see Appendix J) concluded that the findings are difficult to evaluate because: (1) exposure in the population was not well defined; (2) dose response relationships were not well established; (3) other potentially confounding factors, such as exposure to heavy metals, were not considered; and (4) the mothers' lifestyle, well-being, and genetic make-up were not considered. IEHR concluded that while these findings need to be studied further, it appears that if PCBs make any contribution to the factors affecting birth weight, growth, and development, their contribution is likely to be minor.

Rogan et al. (1986a) reported the results of a prospective study of 912 children born between 1978 and 1982. In that study, cord blood PCB levels and maternal milk PCB levels were studied. Maternal milk PCB levels were measured periodically for the duration of lactation. A modified version of the BNBAS (Jacobson et al., 1984b) was administered to all

neonates within 31 days of birth. Multiple regression analysis was used to assess the relationships between birth weight, head circumference, and the BNBAS scores to PCB and DDE levels in maternal milk. Although the authors analyzed for PCBs in cord and maternal serum, only milk fat PCB levels were used in the statistical analyses. Parameters used as covariates in the BNBAS analysis included mother's age, education, occupation, smoking history, alcohol consumption, and level of fish consumption during pregnancy, as well as the infant's race, sex, birth weight, age at which the BNBAS was administered, and number of hours since the infant was last fed.

In contrast to Jacobson et al., Rogan et al. (1986b) found no association between levels of PCB and birth weight or head circumference. The only significant findings for the BNBAS were for tonicity and reflex cluster scores. Within the tonicity cluster, higher PCB levels were found to correlate with reduced muscle tone and activity, but only at the highest PCB levels. Within the reflex cluster, both PCBs and DDE were associated with hyporeflexia. The PCB effect was observed only at the highest PCB levels, whereas the effect of DDE increased as dose increased. The authors concluded that although they observed hypotonicity and hyporeflexia associated with PCBs, "there remains the possibility that even the measured amount of PCBs or DDE is a surrogate for some other agent." (Rogan et al.,1986b).

In a follow-up study, Gladen et al. (1988) assessed mental and psychomotor development in 858 children from the earlier Rogan et al. (1986a, 1986b) studies. In this study, the Bailey Scales of Infant Development were applied at age 6 and 12 months. Again, an estimate of the mother's body burden of PCBs and DDE at birth (i.e., breast milk levels expressed as levels in milk fat at the time of birth) was used as a measure of exposure of the neonates prior to birth. Neither postnatal PCB or DDE exposure were found to be related to either the Mental Development Index (MDI) or the Psychomotor Development Index (PDI) scores. For prenatal exposure, these authors reported decreasing PDI scores with increasing maternal milk fat PCB levels and increasing MDI scores with increased maternal milk fat DDE levels. Correlation coefficients for both effects were statistically significant ($p < 0.05$). When discussing their findings, Gladen, et al. (1988) noted that their observed association between the Bailey Scales of Infant Development and exposures to PCB and DDE "is an observation

rather than an experimental finding and is seen for the first time at these exposure levels; it is, of course, possible that it is related to some factor that we did not measure, or to residual uncontrolled confounding."

Gladen and Rogan (1991) recently reported the results of a follow-up study to the Rogan et al. (1986a, 1986b, 1988) cohort. These investigators administered the McCarthy Scales of Children's Abilities at 3, 4, and 5 years of age. In addition, report card grades for at least one school year were evaluated for each child. Exposure measurements were identical to those of Rogan et al. (1986a, 1986b, 1988). Gladen et al. (1991) found no association between transplacental PCB exposure and McCarthy scores. For postnatal exposure, there was an insignificant decrease in verbal and memory scores in the mid-exposure group, but not in the high exposure groups in 3-year-old children. No relationships were observed in the same children at 4 and 5 years of age. The authors concluded that "in these data the association of prenatal PCB exposure with delayed development, seen previously up to 2 years of age in these children, does not persist. We were unable to confirm an association between prenatal PCB exposure and scores on the McCarthy Memory and Verbal Scales at 4 years of age."

Upon review of the Gladen, et al. (1988) study, Cole (1991) (see Appendix E) commented that:

> The association reported between PCBs and PDI is almost certainly attributable to chance, bias or to residual confounding.... More importantly, the study provides as much or more evidence in refutation of a causal interpretation of this association as it does in favor. This contracausal evidence appears in the paper's Table II which shows PDIs at 6 and 12 months according to 'Transplacental' PCB exposure divided into 8 levels. The lowest exposure category (0.0–0.9 ppm PCB) has a PDI score (at 6 months) of 118.0 while the highest (4.0+ ppm PCB) has a score of 110.9. However, the PCB-PDI association is, in fact, found only if these two extreme exposure groups are compared with one another. When one looks within the data there is no suggestion of a continuous (or dose-response) relationship. Indeed, excluding the two extreme exposure groups (both of which include relatively small numbers of children) leaves a pattern that suggests that

higher PCBs are associated with a higher PDI. For example, children in exposure levels 2 and 3 (1.0--1.4 and 1.5--1.9 ppm PCB) have a PDI score of 115.0 (N=461) while those in exposure levels 6 and 7 (3.0--3.4 and 3.5--3.9 ppm PCB) have a PDI score of 116.4 (N=52). The information at age 12 months also suggests that any overall association derives primarily from findings in extreme categories.

Despite the statistical significance of the PCB-PDI findings, chance remains a highly credible explanation. For one reason, if 8 independent evaluations of non-existent associations are made, there is a 50% chance that one statistically significant finding will emerge. In this study there is only one independent finding regarding PCBs. For another reason, we do not know how many comparisons were actually made. The METHODS section of the paper clearly indicates that observations were made at 9 different ages. (It is not clear whether PDI and MDI were assessed at each age.) Why were findings at 6 and 12 months the only ones presented?

Bias is a substantial possibility as an explanation of these results. Examiners were aware of the children's nursing status and, no doubt, of many other aspects of each child (i.e., in effect, socio-economic status). There could easily be a tendency to score low those children who appeared poorer (of course, such children would tend to have higher PCB levels (and vice-versa)). In this regard it is important to keep in mind that a slight, almost trivial, bias of this sort could produce the weak and inconsistent association that was reported.

Finally, both residual confounding by factors studied (e.g., education) and complete confounding by those not studied (e.g., income) could produce the weak result seen. While good efforts were made to control confounding for some factors, such efforts are always imperfect. Uncontrolled factors, of course, could have enormous effects.

In conclusion, this study provides some evidence that PCBs and PDI at ages 6 months and 12 months are not inversely related and may even be directly related. The weak inverse association reported can not be interpreted in casual terms.

Thus, while several epidemiological studies have investigated the potential relationship between PCB exposure and adverse reproductive and neurodevelopmental effects,

the results of these studies are generally inconclusive (ATSDR, 1989; Kimbrough, 1987; IEHR, 1991 (Appendix J); Paneth, 1991 (Appendix E)). Although maternal milk PCB levels and cord serum PCB levels may be markers of exposure, it is possible that the observed effects may result from confounding factors such as exposure to other environmental chemicals, which are not measured, rather than from exposure to PCBs that are now measured routinely.

In summary, GE believes that these findings indicate that PCBs are not related to non-cancer adverse health effects. They call into question, therefore, the need to promulgate stringent water quality criteria for PCBs based on alleged human health impact.

e. Environmental Exposure to PCBs Does Not Lead to Elevated Blood Levels of PCBs

Not only is there no statistically significant data from epidemiologic studies indicating that PCBs are human carcinogens or cause other adverse health effects, it is also significant that elevated levels of PCBs resulting from environmental exposure have not been found in humans in recent comprehensive studies.

The Center for Disease Control has conducted a study of PCB blood levels of persons thought to have the highest risk of exposure to PCBs at 12 waste sites where PCBs had been disposed. (Stehr-Green, et al., 1988). Site contamination levels ranged from 3,436 to 330,000 ppm on-site to 3 to 133,000 ppm off-site. Persons who were chosen for inclusion in the study reported participating in activities involving one or more contamination pathways (e.g., swimming in contaminated waters, eating contaminated fish, and direct contact with contaminated soils).

The blood-level screening study resulted in a finding that:

> [I]n 10 of the 12 site-specific investigations conducted under this protocol, no excess proportion of potentially exposed persons was found to have serum PCB levels greater than 20 ppb attributable to nonoccupational exposures from the sites in spite of high PCB

levels in soil or leachate on the sites. As a result, we concluded that there was no need for further studies.

Moreover, in the two settings where elevated blood levels were found, one was thought to be attributable to "historical prevalence of occupational exposures," and the other (in New Bedford, Massachusetts) was believed to be a result of substantial consumption of PCB-contaminated fish. As a result of the latter finding, the Center for Disease Control embarked on a broad population survey of PCB blood levels in New Bedford. (Miller, et al. 1991). That study found that levels in 1985-86 were within national population background levels.

In addition, the Agency for Toxic Substances and Disease Registry surveyed a population of residents of Paoli, Pennsylvania, who lived in a neighborhood where PCB levels in residential soil ranged from 1 to 6,400 ppm. (ATSDR, 1987). The study found that "[t]he geometric mean and distribution of serum PCB concentrations in this group did not differ from the means and distribution of a large sample of persons from across the United States having no known environmental exposure." Accordingly, the report concluded that "the population near the site in Paoli did not show exposure different from other U.S. populations having no known unusual source of exposure." (See Appendix H.)

These findings -- that exposure to PCBs in the environment do not result in elevated blood levels -- strongly indicate that the public health risks of PCBs are much lower than originally assumed.

4. Recommendations for Developing an Appropriate Cancer Potency Factor for PCBs

As discussed above, GE believes that EPA's estimates of the cancer potency of highly chlorinated PCBs are based on outdated and technically incorrect information. Moreover, recent studies have concluded that PCB mixtures having less than 60% chlorination are not carcinogenic. Therefore, the GLI should not use the Norback and Weltman-based

cancer potency factor in setting water quality criteria and EPA should re-evaluate its overall approach toward the regulation of the lesser chlorinated PCBs.

The approach that GE believes GLI and EPA should adopt is to regulate PCBs according to their degree of chlorination, rather than as a group. On the basis of the recent scientific studies described above, and in particular the IEHR study, GE submits that a clear and sufficient scientific basis is now available to warrant regulation of PCBs by their degree of chlorination ("closest Aroclor" approach). To accomplish this, GE believes both a short-term and long-term plan is needed.

For the short term, IEHR's reevaluation of the results of earlier rodent studies allows EPA and GLI to treat the risk assessment of Aroclors 1260, 1254 and 1242 differently. With respect to Aroclor 1260, EPA should utilize a cancer potency of either 5.1 or 1.9 $(mg/kg/day)^{-1}$. As discussed above, using only EPA's preferred study, Norback and Weltman (1985), as re-read by IEHR (1991), the cancer potency of Aroclor 1260 decreases from 7.7 to 5.1 $(mg/kg/day)^{-1}$. Therefore, it is clear that no basis now exists for EPA to continue to use a cancer potency factor of 7.7 $(mg/kg/day)^{-1}$.

GE further believes that the most precise estimate of cancer potency for Aroclor 1260 can be derived using all of the experimental rat data. Using a geometric average of all positive studies, as advocated by IEHR (1991), the potency of Aroclor 1260 decreases to 1.9 $(mg/kg/day)^{-1}$. GE believes this approach is justified because there is simply no logical basis to continue EPA's current practice of only using the results obtained in female Sprague-Dawley rats. It should be noted that three separate strains of rats have been used in the relevant studies and that the similarity of response of each strain is apparent when one compares female Sherman rats, male Wistar rats, and female Sprague-Dawley rats. Male Sprague-Dawley rats, while developing the same type of liver tumors, did so at a lower incidence. To assume that this reduced response reflects a genetic tendency of male rats not to develop tumors is not supported by the data. The greatest incidence of liver tumors (91.2%) was observed in male Wistar rats. The results in male Wistar rats also do not support continuing the practice of censoring the male Sprague-Dawley results from the calculation of a cancer slope factor.

Employing the geometric mean of the cancer potency factors of the four rat study groups -- female Sherman, male Wistar, male Sprague-Dawley, and female Sprague-Dawley -- would reflect a less arbitrary use of all existing data. There is ample precedent for this approach in a number of EPA decisions. The geometric mean, using the re-evaluation results, would yield a cancer potency factor for Aroclor 1260 of approximately 1.9 $(mg/kg/day)^{-1}$.

As discussed above, there is no evidence that lesser chlorinated PCBs are carcinogenic. Accordingly, the best estimate for the carcinogenic risks from intake of water and/or fish contaminated with these compounds is zero. A highly conservative alternative assumption to this zero estimate can be made by interpreting the negative bioassays to produce non-zero estimates of potency. Using this approach, cancer potencies of 0.2 $(mg/kg/day)^{-1}$ for Aroclor 1242 and 0.4 $(mg/kg/day)^{-1}$ for Aroclor 1254 can be derived. GE believes that, at a minimum, the GLI should use these reduced potencies as a basis for establishing water quality standards for these compounds until sufficient data on non-carcinogenic endpoints is available and has been assessed for estimating risk. While GE does not subscribe to utilizing this data, i.e., negative studies, to define cancer potency factors, it would clearly be protective of human health and the environment.

5. The GLI Has Used an Unsupportable Species Scaling Factor to Convert the Potency Factor Derived From Animal Studies to an Equivalent Human Potency Factor.

To determine a cancer potency factor from a rodent study, a toxicologically equivalent human dose must be estimated by scaling the rodent bioassay results to humans. EPA policy has been to extrapolate from rats to humans on the basis of relative skin surface area (which is equivalent to the ratio of animal body weight to human body weight to the 2/3 power, referred to herein as "$aw/hw^{2/3}$") (USEPA, 1986b). This policy is based on a study (Freireich et al. 1966) that did not consider carcinogenicity as the endpoint of concern and, therefore, is inapplicable to extrapolating from rats to humans when deriving cancer potencies.

Moreover, recent reviews of interspecies scaling factors indicate that all measures of dose, except dose rate per unit of body weight, tend to overestimate risk. (Mordenti, 1986; Brown et al., 1988; Crump et al., 1989). Consistent with these studies, the FDA and Center for Disease Control have been performing species scaling (FDA, 1986; Bayard, 1988) based on the ratio of animal to human body weight. GE, therefore, would propose that the GLI perform scaling by the ratio of animal body weight to human body weight to the first power.

In the alternative, GE suggests that the GLI perform species scaling consistent with EPA's recent compromise agreement with the FDA whereby EPA will use a scaling factor based on the ratio of animal to human body weights, to the 3/4 power. (USEPA, 1991b). With respect to the agreement, EPA (1991b) stated that,

> It is not merely a compromise; it is as well supported by the empirical data on carcinogenic potencies in animals and humans as the methods it would replace. More importantly, it has an explicit rationale (the concept of species-independent 'physiologic time') that may be derived from principles of interspecific allometric variation in anatomy, physiology, and pharmacokinetics.

The Norback and Weltman-based cancer slope factor of 7.7 $(mg/kg-day)^{-1}$ was estimated by the GLI using the previous EPA (1986b) surface area scaling method of $aw/hw^{2/3}$. Using the "reread" tumor incidence reported by IEHR (1991) for the female rats in the Norback and Weltman (1985) bioassay, and the previous EPA surface area scaling method ($aw/hw^{2/3}$), results in a cancer slope factor of 5.1 $(mg/kg-day)^{-1}$. Using the most recent EPA position concerning body weight scaling ($aw/hw^{3/4}$), results in a cancer slope factor of 3.3 $(mg/kg-day)^{-1}$. Substitution of the FDA-supported body weight scaling factor to this calculation yields a cancer slope factor of 0.9 $(mg/kg-day)^{-1}$.

The following table sets forth the potency factors for various PCBs using the different scaling factors:

PCB Type	Source of Potency Factor	Scaling Method	Scaled Potency Factor
Aroclor 1260	Norback & Weltman	EPA 1986b $aw/hw^{2/3}$	7.7
Aroclor 1260	Norback & Weltman re-read	EPA 1986b $aw/hw^{2/3}$	5.1
Aroclor 1260	Norback & Weltman re-read	EPA 1991b $aw/hw^{3/4}$	3.3
Aroclor 1260	Norback & Weltman re-read	FDA	0.87
Aroclor 1260 Clophen A60	All positive studies re-read	EPA 1986b aw/hw2/3	1.9
Aroclor 1260 Clophen A60	All positive studies re-read	EPA 1991b $aw/hw^{3/4}$	1.2
Aroclor 1260 Clophen A60	All positive studies re-read	FDA	0.33
Aroclor 1242 Clophen A30	Schaeffer re-read	EPA 1986b $aw/hw^{2/3}$	0.2
Aroclor 1254	NCI re-read	EPA 1986b $aw/hw^{2/3}$	0.3
Aroclor 1254	NCI re-read	EPA 1991b $aw/hw^{3/4}$	0.19

B. THE GLI'S DERIVATION OF ACCEPTABLE DAILY EXPOSURE LEVELS THROUGH NON-CANCER RISK ASSESSMENT

The GLI's methodology for determining human health-based WQS based on non-cancer effects suffers from some of the same problems discussed above. Specifically, GE believes that the GLI has improperly analyzed animal studies, has given undue credence to studies which are demonstrably invalid, and has refused to discount the results of earlier studies when subsequent, better performed, studies have called into question the results of the earlier studies. Moreover, in converting NOAELs and LOAELs derived in animal studies to human health standards, EPA has applied "safety factors" that are substantially over-protective.

1. Derivation of an Acceptable Daily Exposure Level for PCBs

As an example, the GLI's "Tier 2" assessment of the non-cancer toxicity of PCBs relies on a demonstrably deficient study (Barsotti and Van Miller, 1984) and then applies a safety factor of 1000 to derive a water quality standard that is so low as to be beyond reason (10 pg/l). The Barsotti and Van Miller study, in which female Rhesus monkeys were fed Aroclor 1016, found a statistically significant reduction of birthweight in offspring of the monkeys fed Aroclor 1016, as compared to control animals. However, for several very good reasons, this study was rejected for use by EPA in establishing a drinking water standard for PCBs.

Moreover, even though the study is demonstrably deficient, the GLI nonetheless applied a safety factor of 1000 in converting the Barsotti NOAEL to an "Acceptable Daily Exposure" (ADE) for humans. This was done in accordance with the GLI's newly developed policy of determining water quality standards for chemicals for which an adequate toxicological database does not exist and, on top of that, using extremely conservative safety factors to derive a human health ADE.

A detailed discussion of the GLI's derivation of the human health, non-cancer water quality standard for PCBs serves well to illustrate the deficiencies in the GLI's methodology. Although the human non-cancer value was calculated based on the NOAEL derived from the Barsotti and Van Miller (1984) study, the GLI cited three additional primate studies to support its use of Barsotti and Van Miller (1984). No studies in other laboratory animals were cited by the GLI, although numerous chronic studies exist on the noncarcinogenic effects of PCBs in mice, rats, minks, and guinea pigs. The four primate studies cited by the GLI are discussed below, and their deficiencies are noted.

a. Barsotti and Van Miller Study

The GLI discussion of the Barsotti and Van Miller (1984) study of rhesus monkeys exposed to Aroclor 1016 was an accurate, but brief, summary of the methods and findings reported by the authors. However, several methodological problems have come to light which should be considered by the GLI. The GLI indicated that Barsotti (1980) and Barsotti and Van Miller (1984) fed rhesus monkeys diets containing 0, 0.25, or 1.0 ppm Aroclor 1016. According to Barsotti (1980), however, animals were actually fed diets containing either 0, 0.025, 0.25, or 1.0 ppm Aroclor 1016, which correlates to daily doses of approximately 0, 0.0007. 0.007, or 0.03 mg/kg-day. Barsotti and Van Miller (1984) did not discuss the 0.025 ppm group, but Barsotti (1980) indicated that this dose group was eliminated from the study due to a contamination problem.

As noted by the GLI, mean birth weights in the high dose group were significantly lower than in the controls. However, as discussed below, the observed differences in birth weights could be the result of, or largely influenced by, non-treatment related factors such as genetic differences, pre-pregnancy maternal birth weight, length of gestation, maternal age, and sex of the offspring.

First, Barsotti and Van Miller (1984) reported that all animals were feral and that the control animals were purchased in 1973, whereas the experimental animals were purchased in 1977. Because the control animals had been in captivity longer than the experimental animals, it is possible that pre-pregnancy maternal weights were greater in the control animals due to the extended time on a controlled diet in conjunction with limited exercise. Therefore, it is plausible that differences in maternal weights may have influenced infant birth weights. Given the different dates of purchase, it is also possible that significant differences in genetic makeup existed between the two groups of monkeys. Barsotti (1980) reported that feral animals were captured in India, but did not describe the area from which the animals were captured. Animals obtained from different geographic areas may be of different strains or of different genetic makeup; these variations could have affected the birth weight of offspring. Finally, because control animals and experimental animals were purchased four

years apart, the control animals were likely, on average, to be older than the experimental animals. Neither Barsotti (1980) nor Barsotti and Van Miller (1984) reported maternal age or individual maternal body weights.

Second, although birth weights of animals in the high dose group and the control group differed statistically, both groups appear to be within the range of historical measurements. In a study of physical growth in rhesus monkeys, Van Wagenen and Catchpole (1956) reported a mean birth weight of 465±70 g for females and 490±60 g for males. These data suggest that normal birth weights, for both sexes, range from about 395 g to 550 g. The birth weights of infants in the Barsotti and Van Miller study (1984) appear to have ranged from about 393 g to 576 g. On the low end of birth weights, it appears that nearly all animals were probably within the normal range. On the high end, however, it appears that control animals in the Barsotti and Van Miller (1984) study may have been moderately heavier than normal. Therefore, the difference between the 1.0 ppm group and controls may be the result of control animals that were not truly representative of experimental animals with respect to birth weights. In addition, although there may have been a statistically significant difference between the high dose group and the control animals, there appears to be no significant difference between the high dose group and historical controls.

Third, Barsotti and Van Miller (1984) and Barsotti (1980) provided only limited information on other potential cofactors. Neither study reported maternal ages or individual birth weights or sex of individual offspring. In addition, although the authors noted that all animals carried their infants to term, the length of gestation was not reported. As a result of this lack of data, the effects of possible differences in the maternal age, prepregnancy maternal weight, sex of offspring, and length of gestation cannot be evaluated. Each of these factors could significantly affect birth weights.

Fourth, Barsotti and Van Miller (1984) did not discuss the apparent polybrominated biphenyl (PBB) contamination of monkey chow, which was reported previously by Barsotti (1980). During analysis of subcutaneous tissues, PBBs were detected in animals from the 0.025 ppm group. Barsotti (1980) concluded that "the 0.025 ppm Aroclor 1016

group received PBB diets for an undetermined time due to a mix up at the pelleting site." Although Barsotti (1980) did not report PBB feed analyses for the other dose groups, the possibility exists that other feeds were also contaminated.

Finally, in addition to the PBB contamination of the monkey chow, a review of the gas chromatograms suggests that other highly chlorinated compounds were present which were tentatively identified by Barsotti and Van Miller (1984) as PCBs, but which probably were not. The presence of these compounds in samples analyzed as part of the study demonstrates another contamination problem that further weakens the validity of the study in linking PCB exposure to effects in monkeys.

In summary, a number of methodological problems with the Barsotti and Van Miller (1984) study should be further evaluated by the GLI, and important questions answered before this study should be considered for use in establishing regulatory criteria. These questions include:

Did pre-pregnancy maternal body weights influence birth weights?

Did maternal age influence birth weights?

Did PBB contamination of feed confound the results?

Did the ratio of male/female infants impact the results?

Could length of gestation have affected the outcome?

b. Other Studies

Barsotti et al. (1976)

The Barsotti et al. (1976) study originally consisted of 12 female and 6 male controls, 9 females fed a diet containing 2.5 ppm Aroclor 1248, and 9 female and 4 male monkeys fed a diet containing 5.0 ppm Aroclor 1248. In the breeding study portion of the experiment, 8 surviving females from each dose group were allowed to breed with control males. All dosed females developed severe toxic effects after two months including acne, alopecia, and swollen eyelids (Barsotti et al., 1976). Although the authors reported decreased birth weights in the combined dose groups, for an agent to be classified as a developmental toxicant, it must produce adverse effects on the conceptus at exposure levels that do not induce severe toxicity in the mother (e.g., substantial reduction in weight gain, persistent emesis, hypo- or hyperactivity, and convulsions). Adverse effects on development under these conditions may be secondary to the stress on the maternal system (Manson and Kang, 1986) . Thus, the interpretation of this study is, at best, equivocal with respect to developmental toxicity. Additional information on the design of this study has been reported by Barsotti (1980).

Allen et al. (1980)

Allen et al. (1980) reported a statistically significant difference in birth weights between the 5.0 ppm group and controls, but not between the 2.5 ppm group and controls. Similar to the earlier discussion of the Barsotti and Van Miller (1984) study, the mean birth weights in the 2.5 ppm group (480±83 g) and the 5.0 ppm group (440±55 g) are clearly within the normal range of about 395 g to 550 g for rhesus monkeys reported by Van Wagenen and Catchpole (1956). Furthermore, as discussed previously, the female monkeys receiving the PCB doses in this study were observed to have severe adverse effects from the exposure (Barsotti et al., 1976); therefore, it cannot be determined as to whether or not the effects observed in infants were the direct result of dosing or due to maternal toxicity.

Bowman et al. (1978)

Bowman et al. (1978) studied behavioral effects in the three surviving infants from the 2.5 ppm dose group previously described by Barsotti (1980) and Allen and Barsotti (1976). These investigators selected four of the twelve control animals used by Barsotti (1980) and Allen and Barsotti (1976) as the control animals for this study. The limited number of experimental animals in this study raises questions about the significance of the findings.

Upon critical examination of the chronic PCB developmental and reproductive studies conducted on rhesus monkeys (Allen and Barsotti, 1976; Allen et al., 1980; Barsotti, 1980; Barsotti and Van Miller, 1984; Bowman et al., 1978), there appears to be sufficient evidence to suggest that factors other than PCB treatment may be associated with the observed effects, particularly with respect to studies of Aroclor 1016. It should be noted that nearly every study on reproductive or developmental effects from chronic exposure to PCB mixtures cited by the GLI was conducted at the same laboratory (Biotron Laboratory, University of Wisconsin-Madison) by the same core group of researchers. It is conceivable that the problems regarding PBB contamination and limited characterization of control animals in the Barsotti (1980) and Barsotti and Van Miller (1984) Aroclor 1016 studies may have also occurred in the Aroclor 1248 studies conducted by Allen et al. (1980), Allen and Barsotti (1976), and Bowman et al. (1978).

In order to calculate an Acceptable Daily Exposure (ADE), the GLI divided the NOAEL from the Barsotti and Van Miller (1984) study (0.008 mg/kg-day) by a 1000-fold safety factor composed of one factor of 10 for intraspecies variability, a second factor of 10 for interspecies variability, and a third factor of 10 for subchronic exposure duration.

In the case of the 10-fold safety factor for exposure duration, the GLI states that "none of these studies were chronic in duration, generally spanning less than 10% of the expected lifespan of about 20 years (Gold et al., 1984)." This is not an accurate comparison. Gold et al. (1984) reported specifically on cancer bioassay protocols, not on protocols for conducting developmental toxicity studies. Clearly, for studies in which carcinogenicity is the

endpoint of interest, an exposure duration similar to the animal's one-half lifetime is desirous. However, for the assessment of reproductive and developmental effects, the critical exposure periods are the period immediately prior to conception and through gestation, as well as the period during lactation, for evaluating postnatal exposures (Johnson, 1989; Paustenbach, 1989). Although a consensus has not been reached as to whether exposures of 1 or 2 years are adequate for the assessment of chronic toxicity in nonrodents, studies are generally conducted for 1 year (Stevens and Gallo, 1989 [in Hayes, 1989]). Female monkeys in the Barsotti (1980) and Barsotti and Van Miller (1984) study were fed a diet containing Aroclor 1016 over a period of 12 months, seven months prior to breeding and throughout gestation. The normal gestational period for rhesus monkeys is about 168 days (Jacobson and Windle, 1960; Van Wagenen, 1958; Van Wagenen et al., 1959). The reasoning presented by the GLI for applying a safety factor for exposure duration is to predict the effects of long-term exposures using dose-response information from short-term exposure studies. In the case of the 1-year exposure regimen used by Barsotti and Van Miller (1984), the exposure duration covered the critical period of interest, i.e., the period when a toxic response would be expected to occur. In the case of human exposure and possible reproductive or developmental effects, gestation is also the exposure period of interest (Amdur et al., 1991). The ratios of gestational length to lifespan for monkeys and humans are about 8 and 4, respectively, indicating that monkeys spend a proportionately greater amount of their lifetime in a single gestational period than do humans. For the purpose of comparing exposure duration in the Barsotti and Van Miller (1984) study to a biologically plausible human exposure scenario, the exposure duration of 1 year in monkeys appears to be more than adequate for extrapolating to humans. A safety factor to account for differences in exposure duration is certainly not necessary.

The traditional 10-fold safety factor for interspecies variation (Klaassen, 1986) may not be necessary due to the physiologic similarities among different primates, such as humans and monkeys (Kimbrough, 1991). Numerous studies of PCBs have indicated that nonhuman primates are more sensitive to the effects of PCBs and dioxins than man (Barsotti, 1980; Kimbrough, 1991). Based on the premise that a 10-fold safety factor was traditionally derived for extrapolation from rats to humans (Paustenbach, 1989) and adjusting that safety factor using a rat to monkey surface area and body weight correction (Klaassen, 1986),

indicates that a 5-fold safety factor may be more appropriate for extrapolating from monkeys to humans.

C. THE GLI's CONVERSION OF CANCER POTENCY FACTORS AND ACCEPTABLE DAILY EXPOSURE LEVELS INTO HUMAN HEALTH-BASED WATER QUALITY STANDARDS

The human health carcinogenic criteria for the Great Lakes and their tributaries were calculated using the following equation:

$$HCV = \frac{RAD \times Wh}{WC + (FC \times BAF)}$$

where,

HCV is the water quality standard (mg/L) which is protective against the chemical's carcinogenic effects;

RAD is the risk-associated dose, that is, the daily dose of chemical (mg/kg-day) that corresponds to an incremental cancer risk equal to 1 in 100,000 (calculated by dividing the cancer potency factor into 0.00001);

Wh is the body weight (kg) of the average adult human;

BAF is the bioaccumulation factor (L water/kg fish) for the chemical;

FC is the amount of fish consumed on a daily basis (kg/day); and

WC is the amount of water consumed on a daily basis (L/day) through drinking water or the incidental ingestion of surface water.

The human health noncarcinogenic criteria for the Great Lakes and their tributaries were calculated using the following equation:

$$\text{HNV (pg/L)} = \frac{\text{ADE x Wh x RSC}}{\text{WC + (FC x BAF)}}$$

where,

HNV is the water quality standard (mg/L) which is protective against the chemical's noncarcinogenic effects;

ADE is the acceptable daily exposure level of a chemical (mg/kg-day);

Wh is the body weight (kg) of the average adult human;

RSC is the relative source contribution factor which expresses that portion of chemical exposure that is attributed to fish and water consumption;

BAF is the bioaccumulation factor (L water/kg fish) for the chemical;

FC is the amount of fish consumed on a daily basis (kg/day); and

WC is the amount of water consumed on a daily basis (L/day) through drinking water or the incidental ingestion of surface water.

GE believes that the GLI has made at least six errors in deriving health-based water quality standards from cancer potency estimates and acceptable daily exposure levels. These are discussed in turn.

1. The GLI Has Used Incorrect Assumptions Regarding Fish Consumption

The primary route of human exposure to many pollutants occurs through the ingestion of fish obtained from waterways containing those compounds (Rifkin and LaKind, 1991). Because of this, the estimation of a representative rate of fish consumption from potentially impacted waterways is important to the derivation of a scientifically-based and health-protective water quality criterion. Most of the estimated rates of fish consumption that

are found in the scientific literature are based either on national surveys or are specific to a particular region of the United States (Puffer et al., 1981; Humphrey, 1978; Javitz, 1980; Rupp et al., 1980). Many of these surveys have either not adequately characterized the types of fish consumed (USEPA, 1989a), or made no distinction between the consumption of commercially-harvested and recreationally-harvested fish (Javitz, 1980; USEPA, 1989a). These factors are important to define in a risk assessment approach to derive a water quality standard, as there may be interspecies differences in potential to bioaccumulate lipophilic chemicals such as TCDD and PCBs (Spacie and Hamelik, 1982; Spigarelli et al., 1982; Lech and Peterson, 1983; Niimi and Oliver, 1983; Rand and Petrocelli, 1985; Gobas et al., 1987). In addition, regional variations in consumption of preferred species, availability of these species, access to productive fisheries, length of fishing season and cultural heritage can greatly influence fish ingestion habits. The EPA has stated that "whenever possible, data on local consumption patterns should be collected or obtained from a current database" (USEPA, 1989a). This is important because regional and local fish consumption patterns may vary significantly. In addition, it is important that subpopulations of fish consumers be considered. It may not always be relevant to select a fish consumption estimate based on the general population of an area.

The GLI Procedure for Deriving Human Health Criteria assumes a mean consumption rate of 15 g/day of regionally caught fish to "estimate the consumption rate of the mean angler population and their families for all sport fish caught" (p. 67). This consumption rate of 15 g/day is based primarily on data from three regional surveys of sport anglers in three Great Lakes states, specifically Michigan (West et al., 1989), Wisconsin (Fiore et al., 1989), and New York (Connelly et al., 1990). Based on a review of these studies, the GLI assumed a "conservative mean total of 24 meals per year of sport-caught and regional commercially-caught fish at 8 ounces per meal or up to 48 meals per year at 4 ounces per meal" (p. 67), which is equivalent to 15 g/day. The value of 24 meals per year apparently was based on an assumption of 42 total fish meals per year consumed by anglers, of which 18 meals per year (43%) are sport-caught and 6 meals are commercially-caught within the region. These values are equivalent to approximately 11 g/day of sport-caught fish and approximately 4 g/day of commercially-caught fish.

While it is appropriate to base the derived consumption rate on studies from the Great Lakes Region, it is likely that 15 g/day overpredicts actual consumption. There are several factors that could contribute to this overprediction, including the following:

1. No allowance for the skewness of fish consumption data;
2. Assumption that all consumed fish are from an impacted waterway;
3. Imprecise estimation of sport-caught versus commercially-caught fish meals.

a. Skewness of Data

The 15 g/day rate selected by the GLI for the derivation of human health criteria is a mean value based on data for the angler populations of the Great Lakes Region. This mean value is heavily weighted by high consumption rates for a relatively small portion of the regional angler population. It is well documented in the scientific literature that fish consumption rates are positively skewed with most anglers eating little or no fish and a few anglers consuming higher quantities, i.e., the number of anglers that eat small amounts of fish greatly exceeds the number of anglers that eat large amounts of fish (Soldat, 1970; Landolt et al., 1985, 1987; West et al., 1989; Meunz and Peterson, 1990; ChemRisk, 1991). Because of the skewness of the consumption rate distributions, the mean consumption rate is not representative of the "typical or average" consumer, but rather represents a much higher percentage of the angler population. This is recognized in the GLI Technical Support Document where it is stated that 15 g/day "represents at least the 95% exposure level for regionally caught fish for the regional population as a whole, i.e., fisherpersons as well as nonfisherpersons." Rupp et al. (1980) estimated that the average rates of freshwater fish consumption by adults in the east north central region of the U.S. (Ohio, Indiana, Illinois, Michigan, Wisconsin) was 2.0 g/day. This is an average rate for the general population of this region and includes non-consumers of freshwater fish as well as consumers. The 90th percentile freshwater fish consumption rates for this region was 6.2 g/day.

The 15 g/day rate selected by the GLI for the derivation of human health criteria is a mean value based on data for the regional angler population. Because the fish consumption rates are positively skewed, i.e., most consumers eat small amounts of fish while a small segment of the population consists of high consumers, a median consumption rate would tend to represent the "typical" angler, as it is a more accurate estimate of central tendency within the angler population. A far better approach would be to incorporate actual fish consumption distributions into a Monte Carlo uncertainty analysis along with distributions of the other factors involved in calculating the human health criteria.

b. Impacted Waterways

Implicit in the GLI fish consumption rate is the assumption that all fish consumed are from impacted waterways. While this assumption may be appropriate if all angler-utilized waterways in a region are subject to discharges of a specific chemical, it is unreasonable when only a percentage of the waterways is impacted. For example, Connelly et al. (1990) reported an average consumption rate of approximately 28 g/day for New York anglers. However, they also reported that the mean number of fish meals eaten from Lake Ontario was 7 (Connelly et al., 1990). If it is assumed that meal size was 1/2 pound (227g), this equates to a consumption rate of 4.4 g/day. Thus, on average, anglers consumed only a fraction of their total fish from a single waterbody, indicating that they were getting their fish from a number of other sources. Many of these sources may be unimpacted by industrial discharges and chemical contamination. Thus, if only a portion of a region is impacted by discharges of the chemical of concern, it is inappropriate to assume that all of the fish consumed will come from that portion.

Another example is presented in a recent survey of Maine anglers which reported consumption from all of Maine's rivers, streams, and brooks, and did not focus solely on consumption from sections of the rivers in which a specific chemical of concern had been detected. Of the 748 favored fishing locations identified by survey respondents, only 27 were located either on impacted river sections, or on tributaries, streams, or brooks connected with

those river sections. Of the 464 respondents who reportedly consumed fish from rivers and streams, only 100 identified one of those impacted locations as one of their five most frequently fished locations. In no case were all of the locations named by individual anglers potentially impacted (ChemRisk, 1991a).

It is likely that the consumption data for Great Lakes regional anglers used to derive the 15 g/day value include consumption of species from non-impacted portions of the Great Lakes, their tributaries, or other non-impacted inland waters. Thus, it is likely that only a fraction of the fish consumed by those anglers came from impacted waters.

c. Sport-Caught Versus Commercially-Caught Fish

While it is appropriate for the GLI to include commercially-caught fish in the estimated fish consumption rate of the angler population, it is unclear how the GLI derives this proportion of the estimated rate. The GLI Technical Support Document indicates that, based on the Michigan (West et al., 1989) and Wisconsin (Fiore et al., 1989) surveys, approximately 43% of the fish meals consumed by the angler populations are sport-caught. This means that, at an assumed rate of 42 total fish meals per year for the angler population, 18 meals per year are sport caught. At 227 g (8 ounces) per meal, this equates to 11 g/day of sport-caught fish. It is unclear from the GLI Technical Support Document how the estimated 4 g/day (i.e., 15 g/day minus 11 g/day) of commercially-caught fish from the region was calculated. It is possible that 4 g/day is an appropriate value, because the GLI document states that "the major amount of regionally caught commercial fish are sold outside of the region and, therefore, generally [are] not available to regional anglers" (p. 67). However, the specific rationale for the 15 g/day figure needs to be clarified, especially in terms of the proportion of this overall consumption rate that is attributed to commercially-caught fish from the region.

In summary, it is likely that the assumed 15 g/day figure for fish consumption is an overprediction of the actual fish consumption rate for the angler population of the Great Lakes Region. This mean consumption rate is based on data for the angler population, including all sport-caught and commercially-caught species from both impacted and non-impacted

waters. It is recommended that the GLI revise this value to reflect median consumption rate, which is a more accurate estimate of central tendency within the angler population than the mean rate. Refinements are also recommended to account for the proportion of consumed fish (both sport-caught and commercially-caught) from non-impacted waters. In addition, clarification is needed relative to the proportion of the overall consumption rate attributed to commercially-caught fish from the region.

2. The GLI Has Ignored Cooking and Cleaning Loss in Deriving Water Quality Standards Based on Fish Consumption

Most people clean and cook fish before they consume it. PCBs in fish will be most highly concentrated in the body lipids. Because there is fat lost during cleaning and cooking, it is likely that some of the PCBs will be removed when the fish are cleaned and cooked so that tissue concentrations in the cooked fish will be lower than those measured in the raw fish.

Chemical losses have been observed in various methods of cooking of whole fish and fish fillets containing PCBs (Zabik et al., 1979, 1982; Puffer and Gossett, 1983; Smith et al., 1973). Zabik et al. (1979) studied the changes in Aroclor 1254 levels in lake trout fillets after cooking by broiling, roasting, baking and microwaving. Broiling reduced the concentrations by an average of 53 percent, while roasting reduced levels by an average of 34 percent. Cooking fillets by microwave reduced levels by an average of 26 percent.

Zabik et al. (1982) found similar reductions in the concentrations of total PCBs in carp fillets cooked by various methods. Total PCB levels, expressed on the basis of the fat content of the fillet, were reduced by 25 percent by deep-frying, 27 percent by poaching, 25 percent by charbroiling, 33 percent by microwaving, and 20 percent by roasting. However, conflicting information presented in the report results in a level of uncertainty in the experimental results that compromises the reliability of the report's findings and conclusions.

Smith et al. (1973) reported that baking of chinook and coho salmon fillets reduced concentrations of Aroclors 1248 and 1254 by 11 to 16 percent. Poaching resulted in 2 to 6 percent reductions of the two Aroclors (Smith et al., 1973).

Puffer and Gossett (1983) reported cooking losses of Aroclors 1254 and 1242 resulting from pan frying of white croaker, a bottom feeding fish from the southern coast of California. In croaker obtained from Santa Monica Bay, 65 percent of the PCBs were lost during pan frying, while 28 percent of the PCBs were lost from the croaker obtained from Orange County. These differences were assumed to be a function of the differences in the initial levels of PCB contamination in the fish obtained from these two areas. Fish taken from Santa Monica Bay contained PCB levels four times greater than fish taken from Orange County.

Other studies (cited in Puffer and Gossett, 1983) have reported greater reductions in PCB levels. However, these studies have compared concentrations in whole raw fish to concentrations in cooked fillets and thus are of little use in estimating cooking loss from the fillet portion alone. However, based on a review of the PCB cooking losses reported in the scientific literature, it is reasonable to conclude that at least 25 percent of the PCBs found in the fish fillet will be lost as a result of cooking. GE therefore believes that cooking loss should be taken into consideration in assessing the risk resulting from consumption of PCBs in fish.

3. The GLI has Used Incorrect Assumptions Regarding Consumption of Drinking Water

The draft the GLI guidance for deriving human health criteria assumes a default estimate of 2 L/day for adult human water consumption. This conservative estimate is not appropriate for deriving human health criteria; a value of 1.2 L/day is more reasonable.

At the present time, the EPA (1989a) uses a value of 2.0 L/day to represent the average adult consumption rate of water. This value is based on the daily ration of water

required by the United States Army. (USEPA, 1989a). While this number may be appropriate for a population that has little access to other beverages, it is likely to overestimate actual water consumption by average adults. In addition, due to their increased physical exertion and exposure to the outdoors, Army personnel are likely to require considerably more water in a day than the average individual.

Results of several studies have indicated that the average adult consumption rate for liquids ranges from 0.4 to 2.2 L/day (Pennington, 1983; NAS, 1983; Cantor et al., 1987; Gillies and Paulin, 1983; USEPA, 1984a; ICRP, 1974). The FDA Total Diet Study (Pennington, 1983) provided estimates, broken down by age and sex, of average daily intakes of a large number of foods and beverages. While the average adult consumes approximately 2 L/day of fluids (1.485 and 2.094 L/day for women and men, respectively), women and men were reported to consume an average of only 0.456 L of water daily. Total water-based beverages (including water alone) consumed were 0.971 and 1.149 L/day for women and men, respectively. The remainder of fluid intake consisted of milk and milk-based drinks and soups; alcoholic beverages including beer, wine, and hard liquor; and carbonated soft drinks. Although alcoholic beverages and carbonated sodas are water-based beverages, it is likely that they are produced and bottled using purified water from non-local sources.

A number of additional studies have investigated the consumption rate of drinking water by adults. The National Academy of Sciences (NAS, 1983) calculated the average consumption rate of liquids to be 1.63 L/day, based on data obtained in nine studies. Cantor et al. (1987), in an investigation of the relationship between drinking water and bladder cancer conducted for the National Cancer Institute, calculated the average water consumption rate to be 1.39 L/day. Gillies and Paulin (1983; cited in USEPA, 1989a) reported a range of 0.26 to 2.80 L/day with a mean intake of 1.256 $\pm$ 0.39 L/day. The EPA (1984a) estimated tap water consumption intake levels by age, using data collected by the Department of Agriculture. The daily intake levels for adults ranged from 1.24 to 1.73 L/day. These levels included soft drinks and alcoholic beverages. The International Commission on Radiological Protection (ICRP, 1974) estimated the range of consumption to be 0.4 to 2.2 L/day for adults.

In 1986, EPA reported that mean water ingestion rates range from 0.3 to 1.2 liters per day (USEPA, 1986b).

It is quite evident that the GLI's estimate of 2 L/day overestimates the water consumption rate for the average individual. As indicated by the Pennington (1983) data, a large percentage of intake includes non-water-based as well as water-based beverages from a remote source. The Pennington data suggest that approximately 60% of the total dietary fluid intake by the average adult consists of water or water-based soups or beverages. If a total fluid consumption rate of 2 L/day is reasonable, it can be assumed that 50%, or 1.2 L/day, is water.

4. The GLI Has Erred in its Assumptions Regarding Recreational Exposure

The GLI Technical Support Document for deriving human health criteria includes an adjustment factor of 0.01 L/day for incidental water exposure for surface waters used only for recreational activities (p. 70). This value is based on the assumption that a swimmer may consume a mouthful (30 ml) of water per swimming event. Also, it is conservatively assumed that there is an average of one swimming event per day during the four month warm weather period from mid-May through mid-September (p. 61). Although this incremental exposure value is generally insignificant in comparison with potential exposure through ingestion of fish, it almost certainly represents an overestimate of typical swimming activity in the Great Lakes region.

5. The GLI Has Used an Incorrect Estimate of Exposure Duration

The GLI Draft Technical Support Document for Human Health Criteria assumes that individuals will consume fish at a constant rate throughout their entire lifetimes. However, a survey reported by Rupp et al. (1980) indicates that the national average consumption rate of freshwater finfish is greatest for those people 18 to 98 years old (1.5 g/day; average range

0.30 — 2.3 g/day) and lowest for those 1 to 11 years old (0.49 g/day; average range 0 — 1.0 g/day). This would suggest that a single consumption rate would not accurately estimate fish consumption for an entire average lifetime. EPA also assumes an exposure duration of 70 years. This may be appropriate if the impacted waterbody is large enough to allow individuals to change their place of residence and still be close enough to the impacted waterbody to be affected by it. However, for smaller waterbodies, this assumption is likely to be inappropriate as individuals are less likely to remain adjacent to smaller waterbodies when they move to a new residence.

The EPA Exposure Factors Handbook (USEPA, 1989b) identifies 9 and 30 years as representative of the average and reasonable upper bound, respectively, of length of time residing in the same house. EPA (1989b) data indicate that only 7 percent of the U.S. population live in the same home for 33 years or more.

6. The GLI's Bioaccumulation/Bioconcentration Factors Are Lacking in Scientific Basis

In aquatic environments, the primary route of potential human exposure to many types of compounds, especially super lipophilic chemicals such as TCDD and PCBs, is through the ingestion of fish tissue (USEPA, 1984a and 1984b). Due to the importance of this pathway, water quality criteria based upon fish ingestion will be more restrictive than those based upon other considerations. The GLI proposes using a bioaccumulation factor (BAF) approach to predict the amount of a water-borne compound a fish will accumulate from its surroundings. As indicated above, the BAF for a specific chemical is combined with the toxicity of the chemical and an estimate of human fish consumption to determine the level of human exposure.

Bioaccumulation factors for the GLI are derived in three possible ways. In order of preference, the first method is to use a BAF based on field studies, the second is to use a bioconcentration factor (BCF) derived from laboratory studies and apply a food chain multiplier (FCM), and the third method is to predict the BAF based on the log K_{ow} and application of an

FCM. The resulting BAF is normalized to a six percent lipid concentration to estimate accumulation in the edible tissue of Great Lakes fish.

It is essential that an appropriate accumulation factor be used in the equation for a water quality criterion (Rifkin and LaKind, 1991). Understanding what constitutes a suitable factor is fundamental to deriving scientifically based water quality standards. The ramifications of choosing incorrect factors are significant and will be discussed below.

a. Measuring Chemical Accumulation in Fish

Historically, scientists have used several approaches to predict the uptake and accumulation of chemicals in fish. Two of the most important approaches used to estimate the tendency of an animal to accumulate environmental contaminants are bioconcentration and bioaccumulation. The method for estimating bioaccumulation factors (BAFs) involves direct measurement in vivo of concentrations of chemicals in fish tissue and in the environment, while calculation of bioconcentration factors (BCFs) involves the prediction of chemical behavior in a biological system based on laboratory experiments and application of physicochemical constants.

The development of a bioconcentration factor (BCF) has been the most common approach used by scientists to predict the concentrations of environmental contaminants in fish tissues. However, the BCF model addresses only the uptake of a compound by fish via the transfer of a dissolved compound across the membranous gill surfaces (USEPA, 1989a). BCFs can be calculated by dividing the concentration of a chemical in the fish tissue by its dissolved concentration in water (USEPA 1989a). Studies conducted in the past few years, however, indicate that this model does not adequately characterize the behavior of lipophilic chemicals like TCDD, PCBs, and other organochlorine compounds. For example, the hydrophobic nature of TCDD, combined with its great affinity for organic carbon, means that the amount of compound sorbed to organic matter far exceeds that dissolved in the aqueous environment (Rifkin and LaKind, 1991). A number of considerations, including the cross-sectional size of sorbed compound, the molecular weight, and solubility are important in limiting the ability of

lipophilic compounds, like TCDD, to penetrate the gills of aquatic organisms (McKim et al., 1985; Gobas et al., 1987; Rifkin and LaKind, 1991). Therefore, in the natural environment, where an insignificant fraction of the compound is dissolved, bioconcentration is not the primary route of uptake, and BCFs are not good predictors of fish tissue levels.

A bioaccumulation factor (BAF) which includes the ingestion route of uptake can be calculated based upon fish uptake from water, food and sediment. The BAF for a given ecosystem, at equilibrium, can be calculated based upon the dissolved water concentration, water column concentration (including suspended sediment, colloidal bound chemicals and dissolved chemicals) or any other system concentration. The numerical value of the BAF may vary greatly depending upon the specific reference concentration chosen. In the abstract, no choice is inherently right or wrong. However, it is essential that a scientifically valid choice be made based on the purpose for which the BAF will used. For example, to determine a sediment quality standard, one must use a BAF based on concentrations of the chemical of concern in sediments, along with a valid model describing fish uptake of the chemical from sediments. To determine a water quality standard, one must use a BAF based on concentrations of the chemical of concern in water, along with a valid model describing fish uptake of the chemical from water. In any case, the model must be a field-demonstrated distribution model which can describe the relationship between ambient concentrations of the chemical of concern and concentrations of the chemical in fish tissue. In the absence of a validated model, a calculated BAF has little use for the purpose of regulation.

b. Use of a BAF to Establish a Water Quality Standard for PCBs

In the case of PCBs, GE is aware of no validated model which can predict concentrations of PCBs in fish tissue based on concentrations of PCBs in the water column alone. This is true because data developed in recent years indicates that the body burden of compounds like TCDD and PCBs in fish comes primarily from ingestion of food and sediment (Kenaga and Goring, 1980; Shaw and Connell, 1982; Spacie and Hamelink, 1982; Spigarelli et al., 1983; Rand and Petrocelli, 1985; Eisler, 1986; Gobas et al., 1987; Kuehl et al., 1987;

Cook et al., 1990). For example, results reported by Cook et al. (1990) demonstrate that sediments and various food sources represent the most significant sources of lipophilic compounds in fish. This is not surprising given that the majority of PCBs and TCDD introduced into an aquatic system binds to sediment and is not usually detectable in the water column (Fox et al., 1983; Lodge and Cook, 1989). Thus, the concentration of PCBs in fish tissue cannot be predicted solely from the concentration of PCBs in the water column. Nevertheless, this is precisely what the GLI proposes to do by establishing PCB water quality standards using a BAF calculated as the simple ratio of PCB concentration in fish tissue to PCB concentration in the water column. GE submits that a much more complicated model, which has not yet been developed, would be necessary (1) to correlate PCB concentrations in water with PCB concentrations in sediments, (2) to analyze the relative contributions of PCBs dissolved in water, PCBs adsorbed on suspended solids, and PCBs adsorbed on sediments to PCB concentrations in fish tissue, (3) to establish the relative proportions of newly-discharged PCBs that are absorbed directly through gill membranes, that remain in the water column, and that become adsorbed to sediment, given the existing equilibrium between sediment and water column PCB concentrations.[5] Of course, even such a model would need to be adjusted to

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[5] Although field research is still in progress, a variant of the BAF, which we define as the Regulatory Bioaccumulation Multiplier (RBM) (Sherman et al., 1992), may be adaptable for use in establishing water quality standards. The RBM approach, in its current form, is useful in predicting PCB, TCDD and other lipophilic compound uptake by fish, and can be used by regulatory agencies to directly calculate permit limits (not water quality standards) without the need for distribution models. The RBM approach incorporates uptake across gill surfaces, as well as oral uptake from sediment, from food-chain sources, and from colloidal and particulate-bound compounds suspended in the water column.

This can be expressed as an equation:

$$\text{Regulatory Bioaccumulation Multiplier} = \text{RBM} = C_F / C_N$$

where: C_N = total quantity of compound (dissolved and adsorbed) added per unit volume of water (defined as the "nominal" concentration); and

C_F = Concentration in the edible portion of the fish

(continued...)

account for site-specific conditions (e.g., sediment "hot-spots," suspended solids concentration of the ambient water, rate of PCB discharge, and fish species common in the area of concern) in order to accurately predict the impact of water-borne PCBs on fish tissue concentrations.

c. Pitfalls in Calculations of BAFs

As indicated above, GE does not believe that the present state of the science allows for a valid correlation of PCB concentrations in the water column with PCB concentrations in fish tissues. Accordingly, GE believes that further research and model development is needed before a valid basis can exist for establishing water quality standards based on bioaccumulation of super lipophilic chemicals such as PCBs. However, under the assumption that the GLI will propose water quality standards for such compounds based on bioaccumulation, GE feels it appropriate to point out some of the pitfalls of calculating BAFs from data found in the literature.

As noted above, multipliers that have been used to approximate the bioaccumulation of xenobiotic compounds in aquatic environments are generally based on a ratio of the chemical concentration in the fish to the concentration of the compound in the environment. Oftentimes, when regulatory agencies have used BCFs or BAFs, there has been a degree of ambiguity concerning precisely which fish concentrations and which environmental concentrations have actually been measured. For example, with respect to the TCDD concentration in fish (i.e., the numerator in the BAF ratio), one study reported the TCDD concentration in whole juvenile fish weighing less than half a gram each (there was no "edible" portion and lipid content was not reported) (Adams et al., 1986). In another study, the TCDD

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[5] (...continued)

(Sherman, et al., 1991) For TCDD, for example, the wide range of BCFs and BAFs (i.e., <1,000 to 189,000 L/kg) reported in the literature actually fall within a much smaller range (generally below 5,000) if expressed and compared on a consistent basis as defined by the RBM approach.

concentration in the fish referred to whole fish with 19% lipid (Cook et al., 1986; 1991). Other studies report the TCDD content of fish fillet containing 1% lipid. To compare BAF values from different studies requires defining a consistent basis for expressing concentrations in fish. That the GLI has normalized its BAF values to a given lipid content is a step in the right direction.

With respect to the environmental concentration (i.e., the denominator in the BAF ratio) a similar problem is apparent. Many studies measure the compound concentration in water. In some cases, the measurement is based on a "whole" water sample; others are filtered or centrifuged. Sometimes a theoretical "dissolved" concentration is used. Other studies have used values based upon the amount of suspended particulate and the concentration absorbed on the particulate. In certain cases, a nominal concentration based on the total amount of compound added to the system is used. Again, however, if the objective is to compare BAF values reported in the literature in order to derive an appropriate value for regulatory purposes, a consistent basis for expressing the environmental or exposure concentration must also be defined. GE believes that lack of consistency among researchers in reporting BAFs for PCBs accounts for some portion of the tremendous variation in the PCB BAFs reported by the GLI technical support document.

The GLI also does not adequately recognize the importance of taking into account the partitioning of organic compounds between the water phase and the lipid phase of aquatic animals. To ensure an accurate measurement of the lipid content in aquatic organisms, a standard methodology is proposed to express lipid content. The lipid content, representative of Great Lakes aquatic organisms, is used to normalize BAFs and BCFs reported in the literature. However, the implementation of these proposed methods are poorly documented and appear not to have been closely adhered to in deriving the BAF for PCBs.

Due to the physical and chemical characteristics of lipophilic compounds, these compounds accumulate disproportionally in the lipid portion of tissues. Therefore, the BCFs and BAFs need to be normalized to an appropriate percent lipid. For the protection of human health, this value should reflect the percent lipid in the edible fish tissue (fillet) of those

species consumed. The assumption of six percent lipid does not accurately represent the edible portion of Great Lakes fish consumed by humans, but is rather a conservative estimate of the percent lipid in all fish in all of the Great Lakes. The GLI reports a mean edible fish lipid content of 5.25 percent (standard deviation = 3.68) for all fish from data pooled for all Great Lakes. This average includes salmonids, non-salmonid game fish and non-game fish species sampled in the Great Lakes. Human fish consumption does not generally consist of all Great Lakes fish species. A greater percentage of game fish species are consumed than non-game species. The average fillet lipid content of salmonids and non-salmonid game fish is 5.02 percent. Thus, ideally, a weighted average representing a species-specific consumption rate of Great Lakes fish would provide a more accurate lipid content value for deriving a water quality criteria protective of human health. This value is likely closer to five percent than six percent.

d. The GLI's Proposed BAF for PCBs

A wide range of BCFs and BAFs have been reported in the literature for PCBs. The GLI recommends a human health BAF for trophic level four of 2,132,232 L/kg, six percent lipid, for all PCBs. This value is derived from a single study conducted by Niimi and Oliver (1988) which reported a BAF of 3,909,091 L/kg for salmon (11% lipid). Depending on the PCB congener or Aroclor examined, reported BAF and BCF values range from 3,000 L/kg to 1,181,818 L/kg for trophic level four fish (USEPA, 1980; Niimi and Oliver, 1988). These widely varying BCFs and BAFs reported in the scientific literature may actually fall within a rather narrow range if expressed and compared on a consistent basis. As noted above, employing the consistent RBM approach for TCDD, for example, the BAFs (which ranged from <1,000 — 189,000) generally fell below 5,000 when expressed as an RBM. An analysis of the PCB literature would likely show similar results. The GLI's recommended BAF of 2,132,232 almost certainly overestimates the accumulation of PCB in fish.

Finally, the application of a single BAF to estimate all PCB congener accumulation in fish assumes that all PCBs accumulate at the same rate. However, the degree of chlorination and the molecular positions of chlorination affect both the rates of uptake and depuration. The biological half-life, based on whole-body tissues analysis, for specific PCB

congeners range from as low as 5 days for 3,3'-dichlorobiphenyl, to 196 days for 2,5,4'-trichlorobiphenyl, to 890 days for 2,5,3',5'-tetrachlorobiphenyl, to over 1,000 days for many penta-, hexa-, octa-, and decachlorobiphenyls (Niimi and Oliver, 1983). Results reported by Lech and Peterson (1983) reveal that higher chlorinated PCBs bioaccumulate to a greater extent than lesser chlorinated PCBs. In general, mono-, di-, and trichlorobiphenyl congeners can be metabolized by fish more efficiently than higher chlorinated congeners (Lech and Peterson, 1983). A BAF for lesser chlorinated PCB congeners (mono-, di-, and trichlorobiphenyl) and one for the higher chlorinated congeners (penta-, hexa-, hepta-, octa-, and decachlorobiphenyls) should be developed to more accurately estimated the accumulation of total PCBs in fish tissue.

D. THE GLI'S USE OF TOXIC EQUIVALENCY FACTORS (TEFs)

Toxic Equivalency Factors (TEFs) were developed to estimate the relative carcinogenicity of structurally similar compounds during the late 1970's when it became apparent that dioxin congeners other than 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) had been released into the environment, particularly from combustion sources (USEPA, 1989c). Early attempts to assign relative toxicity values were developed for assessing risk associated with emissions of chlorinated dibenzo-p-dioxin (CDDs) and chlorinated dibenzofurans (CDFs) from the high temperature incineration of PCBs and the combustion of municipal wastes (USEPA, 1981, 1982). In 1989, EPA proposed interim guidelines for estimating the risks associated with mixtures of CDDs and CDFs following the International Toxic Equivalency scheme (I-TEF) developed through an international project under the auspices of the North Atlantic Treaty Organization's Committee on Challenges of Modern Society (NATO/CCMS) (NATO, 1989).

The TEF methodology involves the assignment of a TEF value of 1.0 to 2,3,7,8-TCDD. TEF values for the other remaining congeners range from zero to one and represent an estimate of relative toxicity using 2,3,7,8-TCDD as the reference measure of toxicity. With the exception of 2,3,7,8-TCDD, hexa-CDD and CDFs, all the TEF values are estimated from short-term *in vivo* and *in vitro* acute toxicity data from rodent studies (USEPA,

1989c, 1991a; NATO, 1989). For each congener, one or more of the following endpoints were used to derive the TEF value: enzyme induction, immunotoxicity, thymic atrophy, body weight gain, potential bioaccumulation, teratogenicity, and lethality. For example, an I-TEF of 0.5 was assigned to 1,2,3,7,8-penta-CDD based primarily on mouse lethality data. The rationale for using such a scheme, of course, is to predict carcinogenic potency for compounds for which chronic carcinogenicity bioassays have not been conducted. Clearly, the appropriateness of this approach rests upon the scientific validity of extrapolating from toxic endpoints such as lethality to tumorigenesis.

For most dioxin and furan congeners, the supporting evidence for the assignment of a TEF in the regulatory setting is not convincing. EPA (1989c) acknowledges this and states:

> With the exception of 2,3,7,8-TCDD, the 2,3,7,8-hexaCDDs and 2,3,7,8-TCDF, the TEFs are not based on the results of major animal (reproductive, carcinogenic) studies. Generally, TEFs are based on estimates of the relative toxicity in *vitro* tests whose relationships to the chronic effects of concern is largely presumptive [emphasis added].

Recently, Dr. Phillip Cook of USEPA, at a March 20, 1992 meeting of the Dioxin Ecotoxicology Subcommittee of the SAB, questioned the use of TEFs for dioxins, furans and PCBs[6] based on "uncertainties with interspecies and endpoint extrapolations" and recommended that TEFs not be used by the GLI to establish effluent standards until additional research is completed. (See Appendix K.)

The use of TEFs implies that all biological effects of exposure are equivalent and are scientifically valid predictors of carcinogenic potential. Such biological effects include reproductive, immunological, and growth rate effects, as well as induction of certain relatively

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[6] The GLI has proposed to use TEFs to establish effluent standards for PCBs with respect to wildlife protection-based water quality standards, but not with respect to human health-based water quality standards. This is probably due to USEPA's refusal to endorse the TEF approach for use with human health-based standards. (USEPA, 1991a).

non-specific hepatic enzymes, such as aryl hydrocarbon hydroxylase (AHH). Neubert (1991) recently outlined a number of prerequisites which would have to be fulfilled in order to consider the TEF approach scientifically valid. These include:

(1) the actions of the congeners must be strictly additive in the dose range to be evaluated;

(2) the dose-response curves for the various congeners must run parallel;

(3) the organotropic manifestations of all congeners must be identical and present over the dose relevant ranges;

(4) dose-response curves for various toxicological endpoints for a given congener must run parallel;

(5) for extrapolations between species the kinetics must be identical, or differences have to be taken into consideration; and,

(6) with respect to a risk assessment in man, toxic or biological manifestations in the lower dose ranges are of special interest, and LD_{50} values and effects induced by highly toxic doses are of minor importance.

According to Neubert (1991), for most dioxin and furan congeners, most of these issues have not been resolved to date. The author further states that "in fact, there is not a single pair of congeners for which substantial and sufficient information on dose-responses for various toxicological and biological endpoints is available."

Safe (1990) recently proposed an expansion of the TEF scheme to include brominated dibenzo-p-dioxins and dibenzofurans (BDDs and BDFs), PCBs, and polybrominated biphenyls (PBBs). Similar to the I-TEF scheme for CDDs and CDFs, Safe (1990) used various measures of noncancer toxicologic endpoints to derive TEFs for coplanar and mono-ortho coplanar PCBs, as well as for certain diortho coplanar PCBs. These groups of PCB congeners were selected because of commonality with regard to Ah receptor activity and because of the correlation between structure-binding and structure-activity relationships (Safe, 1990).

Safe's hypothesis that all toxic responses to these coplanar compounds are mediated through a common cytosolic receptor protein and involve the induction of various cytochrome P-450 enzymes including AHH is consistent with the research of others (Litterst et al., 1972; Alvarez et al., 1973; Alvarez and Kappas, 1975; Poland and Grover, 1977; Parkinson et al., 1981a; Bandiera et al., 1982; Leece et al., 1985). However, these biochemical responses are not unique to certain coplanar halogenated compounds; i.e., dioxins, furans, and coplanar PCBs. In actuality, the induction of P-450 enzymes is a common toxicologic response to many xenobiotic compounds as well as many naturally occurring compounds such as indoles (Fiala et al., 1985; Hodgson and Levi, 1987).

Although there is little evidence supporting the validity of TEFs for any class of compounds, there is virtually no evidence that TEFs can be used with any degree of certainty to predict the toxicity of PCB mixtures. To the contrary, it can be shown through comparison of TEF predictions with animal studies that the TEF approach has no value whatsoever in predicting the toxicity of PCB mixtures. This matter is discussed in some detail in Appendix L. Recently, Dr. Phillip Cook of USEPA, at a March 20, 1992 meeting of the Dioxin Ecotoxicology Subcommittee of the SAB, presented data developed by Dr. Linda Birnbaum of USEPA indicating that there is a range of two to three orders of magnitude in the TEFs that have been calculated for several PCB congeners. Given this range of data, Dr. Cook seriously questioned whether any of the specific TEF values calculated for PCBs are scientifically defensible. (See Appendix K).

III. CONCLUSION

As discussed throughout these comments, GE believes that the GLI has made several serious errors in deriving the proposed human health-based water quality standards. GE urges the Committee to consider its comments carefully. If the Committee wishes to discuss these comments, or if it has any questions, please call Dr. Stephen B. Hamilton (203-373-3316) or Marion P. Herrington (203-373-3899).

APPENDICES

A. Summary of the Results of the Institute of Evaluating Health Risks (IEHR) Reassessment of Rat Liver Findings.

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