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PROPOSAL FOR A  
GREATER NEW BEDFORD, MA  
PCB HEALTH SURVEY

Prepared by:

Massachusetts Health Research  
Institute, Inc.

-and-

Division of Environmental Health  
Assessment,  
Massachusetts Department of Public  
Health

Date: \_\_\_\_\_

GREATER NEW BEDFORD PCB HEALTH SURVEYI OBJECTIVES

This is a proposal by Massachusetts Health Research Institute and the Massachusetts Department of Public Health to the Centers for Disease Control and the Environmental Protection Agency to do a health effects survey of persons exposed to PCB's, who reside in the greater New Bedford, Massachusetts community. This health effect survey will include two phases: Phase I-consisting of a random sample of the New Bedford Community with blood testing (sample size 1400) to determine the prevalence of PCB contamination in the population. Phase I will also gather limited data to determine route of exposure (occupational versus environmental) and will test the hypothesis of blood pressure correlation with the PCB blood level. Phase II will recruit two groups of about 150 subjects each, most of whom will come from the Phase I study. Phase II will comprise a group of persons with elevated blood PCB levels (greater than 30ppb), and a comparison group with levels at normal background (less than 10ppb). The high group will be matched for age, sex and ethnicity with the comparison PCB group. Phase II will test several specific hypotheses concerning PCB health effects; namely, liver enzyme induction, alteration of lipid metabolism, depressed immune function, and neurotoxicity.

II INTRODUCTIONA) Background Information

This study is designed to investigate possible adverse health effects of polychlorinated biphenyl (PCB) pollution on persons living in the greater New Bedford, Massachusetts area.

The term PCB refers to a class of chemical compounds characterized by the addition of chlorine to the double-ring biphenyl molecule. The number and location of chlorine atoms attached to the PCB molecule are responsible for its chemical properties and relative toxicity. Commercial preparations contained mixtures of the various PCB congeners, with the percentage of chlorine in a mixture generally designated by the last two digits of the trade name (e.g. Aroclor 1242 contains many different PCB isomers with an average chlorine content of 42%).

PCBs are no longer manufactured but their distribution occurs widely in the environment. They are present in all animal species including man. PCBs are predominantly oily liquids with high boiling points, low flammability and low electrical conductivity which make them ideal for use in electrical transformers and capacitors. Other uses have included plasticizers, heat transfer and hydraulic fluids, in pumps and compressors, machine tool cutting oils, lubricants and wax extenders. (1,2)

In New Bedford, PCBs were utilized in the manufacture of capacitors by two corporations: Aerovox Incorporated and Cornell-Dubiler Electronics Corporation. Use began in the early part of the 1940's and continued until 1977 when the EPA banned open system use and manufacture of the compounds. Contamination of the environment resulted mainly from the discharge of PCB-tainted waste water into the Acushnet River estuary by the two capacitor manufacturers. Additional sources included defective capacitors and other debris transported to the New Bedford municipal landfill and contaminated water discharged via sewers to the municipal water treatment plant

(with subsequent incineration of sludge and discharge of treated water to the Acushnet River estuary). (3)

PCBs in the Acushnet River estuary thus entered the aquatic food chain, with subsequent contamination of lobster and fish at levels greater than the 5ppm standard set by the U.S. Food and Drug Administration. Areas of the estuary were closed to lobstering and fishing in 1979 by the Massachusetts Department of Public Health. PCB exposure for the New Bedford residents occurred mainly through ingestion of Acushnet River seafood, and via skin and respiratory absorption for employees at the capacitor plants. In addition, there is potential for exposure via PCB air emission at the municipal waste water treatment facility and at the municipal landfill. The extent of ongoing airborne exposure is unknown, but is probably of much lower magnitude than occupational and food contamination which has occurred.

The health effects of PCBs have been the subject of extensive reviews elsewhere and will only be summarized here. (1,2,4,5,6,7) Chloracne, a specific acneiform eruption consisting of comedones, papules and pustules on body parts not normally affected by teenage acne, has been noted with heavy PCB exposure. Eye discharge, swelling of the extremities and gastrointestinal complaints were prominent in the Japanese Yusho (oil disease) incident. (7) The severity of illness seen in this group is confounded by the presence of polychlorinated dibenzofuran and quaterphenyl contamination along with PCBs in the Yusho oil. Other health effects first documented in the Yusho incident were abnormal complete blood counts, elevated serum triglycerides, abnormal liver function

tests, and decreased sensory nerve conduction time. Of great concern were reproductive abnormalities including stillbirth, low birth weight and hyperpigmentation and other skin changes. Breast milk was found to contain significant PCBs due to its fat content. (7)

Studies in this country, done generally on occupationally exposed workers, have demonstrated skin change including chloracne, allergic dermatitis, and pigment changes; systemic symptoms of headache, nausea, digestive and upper respiratory problems have also been noted, (8,9). No overt illness on the scale of the Yusho poisoning has been demonstrated. Concern about the chronic effects of PCBs as a possible carcinogen and reproductive toxin is warranted based on animal evidence, but to date have not been extensively studied in human populations.

The literature covering occupational and population studies in man at times presents somewhat conflicting conclusions concerning the relationship between PCB blood levels and reported clinical and laboratory tests. For example, there are at least nine studies in which plasma levels of triglycerides, cholesterol and high and low density lipoproteins have been reported, without there being a clear-cut consensus about alterations in these substances (10). A wide array of liver enzyme studies have been reported with a similar lack of consensus. In some instances this has been due to the dissimilarities in the populations being studied.

For the majority of human studies there has been little evidence of clinical disease with the exception of chloracne and pigmentation and the effects reported in the Yusho incident and other high exposure situations. Commonly reported abnor-

malities, while not consistent, need further study to see if the reported abnormalities of lipid and liver metabolism, as well as clinical changes involving the neurological and other systems can be better defined.

The long-range health significance of most reported clinical and laboratory abnormalities remains unknown. The occurrences of cancer cases (e.g. melanoma, rectal) in occupationally exposed persons are still too few to permit any conclusions about excess cancers in PCB workers. There is a suggestive increase in total cancer mortality in the Japanese exposed in the Yusho incident, but it is not clear that this increase is related to PCB exposure (11).

B) The New Bedford Problem

As noted above, there has been exposure of the greater New Bedford population via the environmental and occupational routes. The extent of exposure has been addressed by two pilot studies on volunteer subjects by the Massachusetts Department of Public Health and the Centers for Disease Control. It must be emphasized that in neither of these studies were the volunteers randomly selected (in fact, efforts were made to attract seafood eaters). Some volunteers reported working at the Cornell-Dubilier and Aerovox plants. The first survey, reported in early 1981, involved 21 subjects and found a median blood PCB level of 13ppb with 9 subjects (43%) having levels greater than or equal to 30ppb (12). The Toxicology Laboratory of the CDC uses 30ppb blood PCB as the level below which will be found 99% of "unexposed" blood samples. A second study done by the Massachusetts Department of Public Health and CDC in late 1982, examined 51 volunteer subjects and found a median

blood PCB level of 15ppb with 16 subjects (31%) having levels greater than or equal to 30ppb (13). There were one and three individuals, respectively, in the first and second surveys, with blood PCB levels greater than or equal to 100ppb. Ordinarily these levels are found only in occupationally affected individuals or with overt poisoning.

The finding of moderately elevated PCB levels presumably due to fish consumption is supported by a CDC study which showed positive correlation of fish consumption and PCB level in a small community in Alabama (14). Levels were similar to those found in New Bedford. No correlation was found between PCB level and occurrence of illness or weight loss, use of medical care or medication, heart disease, or reproductive abnormality. However, a positive correlation of diastolic blood pressure with PCB level was found independent of age, sex and obesity. Abnormalities of serum cholesterol and gamma-glutamyl transpeptidase were also found (15).

C) Needs Answered By Proposed Study

As noted above, greater New Bedford represents a geographic situation where there has been a well-defined environmental pollution and moderate human contamination documented in a volunteer group of the population. No occurrence of illness relatable to PCBs has been noted by the local medical community, however, there is definite public concern about possible health effects. The question of cancer mortality and hypertensive mortality are being addressed in parallel reviews for possible epidemiologic studies by the Massachusetts Department of Public Health.

The questions which this proposed survey will address are the following:

1. To define the prevalence of elevated blood PCB levels in the New Bedford population.
2. To establish the determinants of increased PCB exposure and to develop a basis for risk factor identification.
3. To determine whether there is a relationship between PCB levels and specific illnesses.
4. To study, in depth, certain postulated biological sequelae of PCB intoxication (i.e. liver enzyme induction; altered lipid metabolism; altered immune status; neurotoxicity and blood pressure).

The first and second objectives have both health research and policy implications. Based on available knowledge, there has not been a community-wide survey of PCB levels in an urban environment such as New Bedford. Information obtained by random sampling will add to the knowledge about baseline PCB levels, and together with questions on occupation and diet, help delineate exposure routes in the general population. From a public health viewpoint, determination of the true prevalence of elevated PCB levels will help in allocating resources for further study of the matter and in decision-making about seafood quarantine as well as harbor clean-up.

The third objective needs little explanation. It would be accomplished by selecting individuals with high PCB levels from the prevalence sample, and comparing them with an appropriate control group with low PCB levels. End points would be developed from medical history, physical examination and laboratory tests.

The fourth objective would add to the now scanty human toxicity data on PCBs. Review of the literature on PCBs reveals a discrete number of postulated biochemical and phy-

biological effects that have yet to be well defined. Direction of resources to these specific areas, as opposed to a "shotgun" screening for health effects, makes more sense based on current knowledge of PCB toxicity. The elucidation of a specific biologic marker for PCB toxicity would be of great help in future PCB exposure studies.

The effects of PCBs on the liver have been noted in animal and human studies. Compared to controls, rats fed Aroclor 1260 developed significantly more hepatocellular carcinomas (16). In humans with PCB exposure, abnormal liver function tests have been documented: elevated SGOT (9), elevated gamma-glutamyl transpeptidase (15), elevated BSP excretion (17), and combinations of the above (18).

In addition, the induction by PCBs of hepatic microsomal enzyme systems has been shown in animals (1) and in man by antiprene clearance (9, 19). Of interest is a recent report from Italy which documented hepatic microsomal enzyme induction due to TCDD exposure in Seveso using measurement of urinary d-glucaric acid (20). In the currently proposed study, it is planned to address the question of liver toxicity by comparing high PCB versus low PCB groups. Evaluation of liver function by routine liver function tests including gamma-glutamyl transpeptidase, and estimation of enzyme induction by urinary d-glucaric acid are planned.

Related to the above liver changes is the finding of hepatic porphyria in animals exposed to TCDD or PCBs (4). Similar findings have been reported in human workers exposed to TCDD, but as yet no information is available on the relation of human PCB exposure to porphyria. It is therefore planned to measure urinary porphyrins patterns and delta-aminolevulinic acid

levels in New Bedford residents with high PCB levels.

Abnormalities of lipid metabolism in humans exposed to PCB include elevated serum triglyceride levels (1) and elevated serum cholesterol levels (15). These abnormalities are due probably to the toxic effects of PCBs on the liver. In New Bedford it is planned to measure cholesterol, triglycerides and high density lipoproteins.

The question of altered immune function due to PCB exposure is less well studied. In a Taiwanese episode of PCB poisoning, total T-lymphocytes, active T-lymphocytes and Th lymphocytes were decreased in exposed persons compared to controls. This seemed to explain the decreased cellular immunity in these patients as documented by skin test (21). IgA and IgM serum concentrations were also decreased.

Polybrominated biphenyl, a compound related to PCB, was shown to decrease the number and function of T and B lymphocytes in exposed Michigan farmers (22). The above data, although preliminary, suggests that there are significant alterations in immunological competence in these patients particularly with respect to T helper (Th) cell function. The observed deficiencies in B cell immunoglobulin synthesis may well be secondary to depressed Th function rather than a separate defect. In order to test this hypothesis, it is planned to evaluate the highly PCB-exposed New Bedford residents using the latest techniques in T and B lymphocyte fractionation as well as skin tests with standard antigens, and compare them to the low PCB group.

Victims of the Yusho PCB poisoning episode in Japan complained of numbness and dysesthesia of their extremities,

and had decreased sensory nerve conduction times (23). For this reason, it will be important to evaluate highly exposed New Bedford residents with a detailed neurologic examination, including tests of neurobehavioral performance. Because of the unpleasant nature of the test, nerve conduction times will not be routinely measured but may be used in selected cases as clinically indicated.

Reports of neurobehavioral effects of PCB and PBB exposure in adults and children are sparse and unclear. Two recent publications have described behavioral testing of the same set of PBB exposed children at different ages and have yielded conflicting results. Seagull (24) has reported an inverse relationship between fat PBB levels and several tests of developmental ability in children, 2 to 4 years of age. Schwartz and Rae (25) tested the same group approximately two years later and found relatively little evidence of behavioral dysfunction. In discussing these two papers, Nebart et al (26) have identified several methodological flaws which partially explain these discrepancies.

In a report of PBB-exposed adults, a high rate (67%) of "reactive depression" was reported. This group was highly selected and no comparison group was tested. Although no reports exist regarding behavioral effects of PCB exposure, the structural similarity to PBBs makes it likely that the potential for neurobehavioral toxicity would be similar.

In many investigations of toxic exposure, behavioral effects such as mood changes, memory disorder, and difficulty in concentrating are reported by exposed individuals. Although

some of these complaints are undoubtedly reactive, exclusion of an organic etiology can be established only after careful epidemiologic study which investigates causal relationships.

Although pitfalls exist in doing such studies (27), a strategy for monitoring neurobehavioral toxicity in occupational groups has been described recently, which is equally useful in studying community groups. We propose to apply this approach, described in detail in the appendices, to PCB-exposed persons and a comparison group of non-PCB-exposed. The neurobehavioral tests will be done in a "blinded" manner, so that neither the subject nor the investigator is aware of the serum PCB level.

A single report has raised the provocative question of a relationship between blood PCB level and diastolic blood pressure (15). The relationship between PCB level and diastolic blood pressure remained following correction for age, sex, body mass and social class. Such a relationship has not been documented in other PCB health studies. Given the ubiquitous nature of PCB in the environment, it is certainly worthy of further study. The New Bedford population is an ideal study group because of the moderate PCB levels in a non-occupational group. Because a large number of subjects will be needed to control for age, sex and obesity, it is planned to measure blood pressure during the initial large-scale prevalence phase of the study (Phase I).

### III. METHODS

#### A) General Description

This study is designed as a two phase health effects study to determine the prevalence of PCB exposure in the New Bedford

community and to test several specific hypotheses concerning health effects of elevated blood PCB levels. The two pilot surveys mentioned earlier (12, 13) documented elevated PCB levels in non-occupationally exposed New Bedford residents. Although it is unlikely that overt illness such as in the Yusho incident will be present with such moderately elevated PCB levels, there is evidence from animal and human studies to warrant concern about chronic health effects, including carcinogenicity. Therefore, an accurate estimate of prevalence is necessary.

This will be accomplished by a random sampling of the greater New Bedford community from current city census lists. (Every Massachusetts city and town is required to do an annual census of voting age residents). This sample must be of sufficient size to allow confident modeling of the entire community between ages 18 - 65, and its size will therefore be dictated by considerations of statistical sampling criteria. In order to minimize costs per subject, at this stage only brief demographic and exposure data will be obtained. A single blood sample for PCB level will be taken, and blood pressure plus height and weight will be measured as indicators of body habitus.

B) Pretesting

As part of Phase I and Phase II, a period of time (approximately two weeks) will be devoted to pre-testing all aspects of each phase. This will include pre-testing of the random selection techniques, case contact methods by telephone and direct contact, pre-testing the questionnaires for content, intelligibility and ease of administration. In addition, a

small number of persons will be asked back a second time to run through the entire test procedure to validate both content and methods of obtaining data. Also, as part of the pre-test, blood samples will be taken and processed in the same manner as for the actual Phase I. These samples will be handled and reported to the Phase I pre-test subjects in the same manner as the actual Phase I subject.

This pre-test process will be repeated during the start-up period of Phase II. This will be a more involved pre-test period since, in addition to validating the questionnaire administration, data entry methods and testing and retesting of some subjects for the questionnaire, there will be a requirement to pre-test the methods to be used by the neurobehavioral and immunological study components of the project. Every aspect of these project elements will be run during a period of two weeks to be sure that administration of the physical examination, neurobehavioral tests, blood sample processing and storing for shipment are all thoroughly tested and understood by project staff before undertaking to study the Phase II subjects.

During Phase I, attention will be paid to non-respondents and dropouts, and this will be included in the analysis. Based on the experience with earlier pilot studies, and the continuing media coverage of the PCB problem, a high participation rate of approximately 85-90% is expected.

C) Public Awareness

Media coverage will be assured by frequent informational briefings to the newspapers, radio and television media. In

addition, community awareness of the project will be achieved through public meetings conducted under the sponsorship of the New Bedford Forum. The latter is an organization comprising leading citizens of the greater New Bedford area for the purpose of meeting, discussing and otherwise informing the greater New Bedford community of issues of concern and importance. By these means we expect to reach the majority of the greater New Bedford population. In these efforts, special attention will be given to the fact that there are many ethnic groups present many of whose representatives have limited ability with the English language. These groups, in particular the Portuguese and Spanish speaking groups, will be addressed through all available informational media in the language of concern.

Other issues of concern in conducting both phases of this study relate to the fact that: (1) many persons will find it difficult to keep appointments due to their reluctance to lose time away from their jobs; (2) some persons will not have a readily available method of transporting themselves to the project.

Consideration will be given to conducting some of the study activities during certain week-day nights, or during the week-end. Neither of these options is likely to be popular with the study subjects. Therefore, it is planned to direct enlist the cooperation of all employers to release the employees for the period needed to conduct the questionnaire and physical and laboratory tests. In part, employer awareness will be achieved through the news media, the New Bedford Forum direct telephone calls and letters, and support solicited from organizations such as the Chamber of Commerce and business organizations.

IV. Phase IA) Study Population

The greater New Bedford area (includes Fairhaven, Dartmouth and Acushnet) has approximately 140,000 inhabitants. The population, for the purposes of this study, is defined as males and females residing for at least 5 years within the area between the ages of 18 and 65. Those under 18 are excluded because of difficulty comparing the pediatric with the adult age groups, and the fact that although they comprise a significant proportion of the population, children have lower PCB levels than adults (12). For this reason and because clinical effects are likely to be related to duration of exposure children will not be included, even though the frequent sensitivity of children to toxic agents is recognized. In addition, getting informed consent is more difficult.

The city boundaries provide a suitable geographic limitation for the study since both capacitor factories are within them, and the Acushnet River estuary follows the city limits of New Bedford and Fairhaven. The population is generally blue collar in nature, with a high unemployment rate due to the depressed economy of the area. There are relatively few blacks in New Bedford (2.6%), a small Spanish-speaking population (5.0%), and a significant Portuguese ethnic group (49%), which will necessitate some bilingual personnel as part of the study. A significant number of area residents have worked at some time in one of the two capacitor factories, introducing occupational contact with PCBs as one source of exposure. Fish and lobster consumption is relatively common, although since 1979 there has been no legal taking of these foods from the polluted area.

B) Sampling Technique

The study population will be obtained by a random sampling of persons 18 to 65 years of age whose names will be derived from censuses of the four communities. The selection process will proceed by first selecting by random number the page of the census. After selection of the page, another random number will be used to pick out the subject to be contacted for the health survey. The name, address, age and sex of the person will be recorded, including other information such as previous residence, occupation, and place of national origin.

The telephone directory for the greater New Bedford area will be used to determine whether the person selected for the survey has a telephone. If the name and address of the individual is found in the telephone directory a call will be made and the person's listed name and address will be verified against the city resident list. If the telephone directory does not give the selected individual's name, the list of corresponding (similar) surnames and address will be checked. If the directory shows a person with the same surname and address as the selected subject, then a telephone call will be placed to determine whether the selected subject resides at the address of the listed telephone number. The number will be dialed, and when the phone is answered, verification of the correct number and listed name will be done. If there is no answer, three additional attempts will be made at later times. Once the correct household is reached the caller will ask to speak with the person selected for the study. The caller will briefly explain the study. Identifying information will be confirmed during this call and entered into the Phase I sample.

During the same phone call, or later call or letter, the person will be given a full explanation of the PCB study and asked to participate. If they agree, they will be told they will be sent a letter confirming their participation in the program, and given an appointment to appear for the Phase I visit. Records of "failure to contact," "refused entry" and "failure to keep appointment" will be kept. Follow-up will be directed at the first and last of these cases.

For the persons selected who do not have a telephone, direct contact will be established with visits by project staff to the address of record. The subject's address will be visited and the residence verified by questioning of residents if the subject is not present. The subject will be informed directly of the project and its purposes and asked to participate. If the subject agrees an appointment will be made for the subject and the subject will be told that a card or letter will follow to confirm the time of the appointment.

If the subject is not at home at the time of the visit by the project staff member, a card with the staff member's name and project telephone number will be left with a request that the subject call within two days. If no telephone call is received, the project staff person will re-visit the subject's address at a time when the subject is most likely to be home and the steps outlined above will be followed.

On an ongoing basis, the accumulated list of persons will be compared to the most recent census for the New Bedford area to assess representativeness of the sample by age, sex and ethnicity. Certain persons may of necessity be excluded, such as those with mental or physical impairments which would not allow

participation in the study. In such circumstances, once it is established that a person cannot participate in the study a brief questionnaire covering the nature of the medical problem, duration, past medical and occupational history and socio-economic indicators will be obtained.

Explanation of the two phase study design will be given at the time of initial contact with the subjects, and included in the written consent. All subjects will be told their PCB level, either at the end of Phase I, or at the end of Phase II for those in that phase. Results of all examinations and tests will be communicated to the subjects. Spanish and Portuguese translation will be provided to assure the participation of persons speaking these languages. Persons with abnormal tests will be advised to see their personal physician.

C) The Phase I Visit

A suite of offices will be rented for use of the study group in New Bedford, preferably in the immediate environs of St. Luke's Hospital, the main local hospital. Contact with local physicians and communication of study goals and results will be maintained on a continuing basis. Any health problems identified by the study will be referred to a local physician for follow-up care, if the subject desires. The Phase I subjects will have appointments staggered throughout the day, allowing approximately one hour per person for completion of an abbreviated questionnaire, three blood pressure measurements, and a single blood drawing. Appointments will have been arranged by direct contact or over the phone during the sample selection process, and confirmed by postcard shortly before the scheduled visit. At the time the appointment is made and confirmed by postcard, the subject will be asked to bring a list

of drugs they are currently taking or have taken over the past 10 years. They will also be asked to bring a list of places where they have worked, and the kind of jobs they held, and the years they worked at each place.

The subject will enter the study office, and register with the secretary who will verify the person's identity with the name on the sample master list and check their name off the list. Next, the subject will proceed to an interview room, where an epidemiologic assistant or public health nurse will first obtain informed consent, based on a simple printed "Phase I Consent Form" previously passed by the appropriate human studies review committees. The form will state the overall purposes of the study, describe the information asked in the questionnaire, and the blood pressure measurements and phlebotomy. Possible risks of participation will be described (estimated to be minimal), and provide assurance of confidentiality as well as communication of the test results to the individual subject. The subject will be informed that all results will be sent directly to him or her and to the family physician if the subject so indicates. Any subject in whom an abnormal clinical finding is noted will be informed of that finding by mail and will be given a recommendation to have the clinical finding further evaluated by their own physician. The project physician will be available to discuss the findings with either the subject or the family physician. If the subject does not have a family physician he or she will be referred to the New Bedford Medical Society for assistance in this matter. In the unusual circumstances where in the opinion

of the project physician the clinical findings are of a sufficiently grave nature to warrant that the subject see the family physician immediately, the subject will be informed to do so and given the reasons directly by the project physician.

The above processes will apply to all physical and clinical laboratory tests. Blood PCB levels will be reported separately. No PCB health-related statements or implications will be given to the subjects.

In the event abnormal laboratory tests are obtained, it is expected that the costs of further investigating the abnormal tests will be borne by the patient.

Consent will be obtained for Phase I only, but the possibility of being asked to participate in Phase II will be stated. The right to refuse entry will be so stated. Forms in Spanish and Portuguese will be available. Once consent is obtained, and after the first blood pressure measurement, administration of the Phase I Questionnaire will begin. This is an administered questionnaire. The subject's name and study number will be entered on the questionnaire and a blood pressure form, upon which the results of 3 blood pressure measurements will be entered. A second blood pressure measurement will be taken at the end of the questionnaire administration. The subject will then proceed to an area of the office selected for phlebotomy by a trained technician, where he or she will await their turn for blood-drawing. Once this is done, the subject will return once again to the waiting area and have a few minutes to relax, eat cookies, ask questions, etc. Height and weight will be measured at this point. The third and final blood pressure measurement will be at the end

of this time and will conclude the Phase I visit, with a reminder to the subject that he or she may be requested to return for Phase II.

D) Phase I Laboratory

a) PCB Analysis PCB analysis will be done on samples using gas chromatography following CDC laboratory procedures as described in the study by Kreiss et al (21), (Appendix 12). Blood will be obtained in special hexane washed, teflon-topped tubes, spun down, and the clot removed. Specimens of serum will be kept frozen until analysis. Analysis will be done by the laboratories of the Massachusetts Department of Public Health.

Quality Control Considerations. The Massachusetts Department of Public Health (MDPH) will have the primary responsibility for performing the total PCB analysis for this study. The quality control objectives for this proposal are based on the following considerations:

1. The quality control program must provide a direct comparison of values between MDPH and CDC laboratories on the basis of both quality control pools and study specimens.
2. CDC will serve as the reference laboratory for the study.
3. Active quality control information is available to MDPH laboratory to make daily judgments concerning the status/performance of individual runs.
4. Quality control data will yield information concerning the provision of PCB measurements for the study specimens at various levels, such that statistically significant differences may be calculated as required.

5. An upper limit will be placed on the acceptable variability for the PCB measurement at the decision levels for entry of subjects into Phase II of the study.

CDC Laboratory Commitments. The Clinical Chemistry Division, CDC, will maintain close surveillance of quality assurance data to insure both the short- and long-term validity of the MDPH PCB results and will have the following responsibilities:

1. Define and validate all methods for analysis of PCBs used by MDPH.
2. Assist MDPH in selection of appropriate equipment required for PCB analysis.
3. CDC has already provided training for selected individuals from MDPH for transfer of PCB methodology.
4. Assist in the design of an internal bench-controlled system for MDPH and establish and maintain an external quality assurance program for that laboratory.
5. Prepare and characterize quality assurance material for both the internal and external quality assurance programs that will be actively maintained in both laboratories.
6. Prepare stock PCB standard solutions for calibration for use in both laboratories. Provide silica gel and 3% SE30 on Gas Chrom to MDPH laboratories to remove effects of lot-to-lot differences.

MDPH Laboratory Commitment. The MDPH laboratory will be considered acceptable when the variability of their PCB results equals that achieved and documented by the Toxicology Branch laboratory or a coefficient of variation of 10%, whichever is greater, and when the analytical systematic bias between the two laboratories is equal to or less than 10%.

1. Validation of MDPH Laboratory will consist of 20 runs with two internal bench controls provided by CDC and three external quality control pools with different levels of PCB.
  2. MDPH Laboratory will calculate appropriate confidence limits for the two internal bench controls based on the first 20 analytical runs. Therefore, the means and units will be used to determine if the PCB analysis is "in control" or "out of control."
  3. The analytical system will be declared "out of control" if one or more of the following events occurs:
    - i. Values obtained from two quality control pools during a single run fall outside the 99% limits (upper and lower).
    - ii. Two consecutive values of one control pool fall above or below the 95% limits.
    - iii. Eight consecutive values for one control pool fall either above or below the mean (high or low trend).
    - iv. Scientific judgement will be made before categorically declaring a system "out of control."
- (b) Specific Isomer Analysis. The CDC laboratory proposes evaluating a subset of the participants with elevated PCB values for the individual distribution of PCB isomers. The technique will involve capillary column gas chromatography followed by mass spectrometric confirmation of the PCB isomers (maximum - 25 samples).
- (c) Chlorinated hydrocarbon screen. Since one of the potential confounding variables in the study may be exposure to chlorinated hydrocarbons, the CDC laboratory proposes screening approximately 5% of the participants in

Phase I for commonly occurring chlorinated hydrocarbons by a gas chromatographic technique (i.e., DDE, heptachlor epoxide, trans-nonachlor dieldrin, oxychlordan, endrin, beta-BHC, gamma-BHC, and hexachlorobenzene).

(d) Heavy Metals Screen. Another confounding variable in the study may be exposure of the participants to heavy metals. It is suggested that screening for an appropriate battery of heavy metals should be conducted in Phase I rather than Phase II. The CDC laboratories propose screening approximately 10% of the participants for lead, arsenic, and mercury, using the following techniques:

<u>Analyte</u>	<u>Specimen</u>	<u>Anticoagulant or Preservation</u>	<u>Method</u>
Lead	Whole Blood	EDTA	Graphite furnace (GF) AAS
Arsenic	Urine	Nitric acid	Zeeman, L'vov GF AAS
Mercury	Urine	Triton-X and sulfamic acid	Cold-vapor AAS

These additional analyses will require the collection of additional Phase I specimens: blood for lead and urine for arsenic and mercury.

E) Phase I Blood Pressure

Will be measured by a method similar to that used by the CDC study (15), (See Appendix 7 for blood pressure protocol). The subject will be seated with legs uncrossed in a straight chair, and the right arm will be at heart level supported on a flat surface. The cuff will be placed, assuring correct size for the arm, and the radial pulse palpated. The cuff will be inflated to a pressure of 200mm Hg. If heart sounds are heard above that pressure the cuff will be reinflated to 240mm Hg.

The stethoscope will be in the antecubital fossa, and the pressure bled off at a constant rate. Systolic blood pressure is recorded at the point when Korotkoff sounds are first noted. Diastolic pressure is recorded as the disappearance (not muffling) of the Korotkoff sounds.

F) Skin Testing

Skin testing will be done with the multi-test CMI. Multi-test CMI is a disposable, plastic applicator consisting of eight sterile test heads preloaded with seven delayed hypersensitivity skin test antigens and glycerin as a negative control. The tests will be applied to the forearm. The Antigens are Tetanus Toxoid; Diphtheria Toxoid; Streptococcus; Tuberculin, Old; Glycerin Control; Candida; Trichophyton Mentagrophytes; and Proteus. The skin tests will be read at 48 hours via home visit by a public health nurse, or by other qualified medical personnel. A positive test will be defined as ten millimeters of induration, and results for each of the seven antigens will be entered in the data set.

G) Phase I Data Processing and Analysis

Collection and processing of data will be carried out by the project director and the staff, with the technical assistance of the staff data processing specialist and the project statistician. All data will be coded, validated and computerized, with indexing by the subject's study number, and safeguards to assure confidentiality.

There are some on-site computer facilities at the Department of Public Health, which are connected to AVCO Computer Services, a major service bureau from which the

Department of Public Health rents computer time. AVCO maintains state-of-art computer hardware and software. They support numerous statistical packages, including SAS and SPSS, two packages which will be used in the analysis of this study. The on-site computer facilities at the Department of Public Health easily accomodate the program check out and execution, and a number of terminals and printers are available to handle high volume input and output.

Statistical methods will be critical for the Phase I sample selection. Care will be exercised to assure that the sampling process does not introduce bias (for example, by under-representing poorer persons with no telephones). Verification of the sample will be ongoing, comparing demographics and socio-economic status with the most recent U.S. Census for the New Bedford area. Maintaining a complete record of those in the chosen sample who either cannot be reached, refuse to participate, or do not keep appointments, will be crucial to assuring sample validity. "Volunteer bias" should be minimized if the guidelines of sample selection are adhered to, and if maximum efforts are made to follow-up on the "dropouts" and urge their participation. Based on other Massachusetts studies, a response rate of 85-90% is anticipated.

The statistical plan for the entire project will be developed by the project statisticians. The implementation of the statistical plan will be done by the Biostatistical Clerk/Data Management Specialist, who will be responsible for the day to day statistical activities under the direct supervision of the project statisticians. The biostatistical clerk will be at the master's degree level and will be responsible for the collection, local storage, validation and transmission (for data

processing) of all data. In addition, the biostatistical clerk will assist in the statistical calculations.

The project statistician will have responsibility for overall supervision of the statistical planning and analysis and will supervise and guide the day to day activities of the biostatistical clerk. He will plan all phases of the statistical work plan. A brief overview of the planned statistical methodology is given in the following sections. During the course of the study a number of graphical techniques will be used to see whether patterns develop which suggest specific statistical techniques.

The Phase I study is a cross-sectional descriptive study of a random sample of 1400 individuals between the ages of 18 and 65 in the New Bedford area. This sample size will be adequate to describe in detail the distribution of PCB levels in the population. The CDC estimates that 1% of an "unexposed" population would be expected to have PCB levels of 30ppb or more. This sample size is sufficient to detect an increase of 1% or more (i.e. a doubling) above this estimate in the New Bedford population at the 5% significance level with 80% power (one-tailed test). This number was estimated by the formula given by Colton in *Statistics in Medicine*, Boston; Little Brown, 1974, page 168. To investigate the correlation between PCB levels and blood-pressure this sample size is sufficient to detect a correlation of .11 or greater at the 5% significance level with 90% power (one-tailed test).

The primary analytic techniques for the Phase I study will be descriptive methods and measures of association. The distribution of PCB levels in the sample will be investigated

and the prevalence of elevated levels will be computed. It is anticipated that PCB levels are not normally distributed and therefore these values will be transformed so that the distribution approximates a normal distribution before further analysis takes place. The association between PCB levels and blood pressure (also suitably transformed, if necessary) will then be investigated using the Pearson correlation coefficient. Using the analysis of variance, the association between PCB levels and demographic variables such as occupation, will be investigated. If an association between PCB levels and blood pressure is confirmed, the analysis of covariance will be used to investigate further the association while controlling for selected demographic variables.

## V PHASE II

### A. Sample Selection

An important requirement in Phase II will be to study a sufficient number of persons, with attention paid to collecting adequate historical and clinical data to permit for adequate controlling of confounding factors such as smoking, alcohol, weight, occupation, exposures to unusual substances such as heavy metals or to residing in the vicinity of plants which may be emitting toxic substances. The Acushnet River is known to contain heavy metals and organic compounds released by local metal, dye or printing industries. It is not known to what extent these materials may have entered the greater New Bedford population, but it is planned to perform a limited number of analyses for heavy metals such as lead, arsenic and mercury in the persons entering Phase II, and for other pollutants which may be identified.

Phase II will be a cross-sectional, matched pairs study with a high exposure group defined by blood PCB level greater than 30ppm of PCB. As noted elsewhere in this proposal Phase I subjects will be randomly selected and assessed for PCB levels. From this population the comparison PCB group for Phase II will be selected. During Phase I if it becomes apparent that random selection will not provide a sufficiently large group (150 persons) of persons with blood PCB levels greater than 30ppb, an effort will be made to recruit directly persons with large fish and lobster consumption from the Acushnet River as well as a history of occupational contact with PCB. These persons, as well as appropriate controls will have their blood tested for PCB prior to being enrolled in this study. The rationale for this is based on the fact that while Phase I is intended to give an indication of the prevalence of elevated PCB levels in the New Bedford population, Phase II is a study to compare two groups matched as carefully as possible in all respects except levels of serum PCB. If it is necessary to augment the high PCB group, additional controls, appropriate for these additional groups will be selected. In selecting the high PCB Phase II group we hope to have one-half come from a fish-eating population and the other half from an occupational exposure group. The reason for this is that the relative biological retention of the various PCB isomers differs, and this may be reflected by current as opposed to past exposure to PCBs (29).

A further reason for establishing two groups with different sources of PCB contamination is to allow a comparison of the spectrum of PCB isomers in human blood to the isomers present in PCB-contaminated fish and lobsters present in the

Acushnet River. This will permit modeling of the transfer of PCBs from river sediment to aquatic biota to man and may be helpful in determining the levels to which harbor clean-up should be taken. We plan to evaluate clinical laboratory findings in relationship to isomers present.

Phase II groups will be matched by age, sex, socio-economic, geographic and ethnicity with subjects drawn to the greatest extent from the Phase I study but supplemented with controls drawn from populations recruited directly. Both the high and low PCB groups will be called to undergo a more detailed questionnaire on symptoms, illness, habits and past medical history. They will be given a physical examination emphasizing particularly the skin and nervous system. Phase II analysis will directly compare the high and low PCB groups based on the questionnaire, clinical examinations and tests, as well as on other relevant data.

B) The Phase II Visit

The Phase II visit will begin with registration by name and study number and completion of Phase II consent forms. All study personnel, as well as the subject, remain blinded as to the subject's PCB level. The subject will proceed to the laboratory for drawing blood and a urine specimen, after which orange juice and donuts will be available. The more detailed Phase II questionnaire will be administered to some subjects, (see note on next page) while others may proceed to the physical examination in order to facilitate rapid passage through the stations. The questionnaire covers information about past medical history, prior illness, coexisting medical conditions, alcohol and smoking habits, and use of medication, especially

those known to cause liver enzyme induction. A review of symptoms will be obtained including general medical complaints as well as symptoms referable to PCB exposure.

The physical examination will follow a standard format, with special emphasis on measurement of blood pressure and examination of the skin and nervous system as noted above. A physician unaware of the subject's PCB level, will perform the examination. It is anticipated that in evaluating the skin, nervous and other systems, various medical problems will be disclosed ranging from acne to neuromotor dysfunction as well as other problems. In the event that a diagnostic problem is encountered it is planned that the project physician will consult with appropriate medical specialists. Prior to implementing Phase II, conferences will be held between the project physician and each medical specialist who will serve as a consultant. These conferences will identify areas of the physical examination, medical history and laboratory tests which should be incorporated into the final questionnaire forms so as to assure uniformity of the examinations and to maximize the clinical awareness of the project medical staff.

(Note: The full Phase II questionnaire will be developed while Phase I is in progress. It is likely that the experience, insights and information obtained in carrying out Phase I will contribute greatly to the development of a better Phase II questionnaire. Therefore, while the format for the Phase II questionnaire will undoubtedly resemble that of Phase I, no effort has been made at this time to develop the Phase II instrument for the reasons given above.

The same reasoning applies to the development of the forms to be used in performing a physical examination and taking a past history. While there is a general format that will be followed in the physical examination, the special attention which will be paid to the skin and neurological examinations will necessitate development of special forms for these examinations as noted in the following paragraph. For the above reasons, the Phase II forms for physical examination, review of symptoms and past medical history will be developed during Phase I).

Height, weight, and triceps skin fold thickness will be measured by the public health nurse either prior to, or after the physical examination. At this time the nurse will also place a standard skin test panel. The patient will be given three hemocult cards with a return envelope as a screen for gastrointestinal carcinoma. Blood pressure measurements will be interspersed among the physical examination and questionnaire. During the Phase II visit, the subject will be told that the results of all tests will be made known to him, including his PCB level, and that the patient and the private physician will be notified immediately of any medical problem revealed by the study.

C) Phase II Tests

a) Blood Pressure

Blood pressure will be measured as described under Phase I.

b) Skin Testing

Skin testing will be measured as described under Phase I.

c) Neurologic and Neurobehavioral Evaluation A detailed neurologic examination under the direction of Dr. E. L. Baker will be part of every Phase II visit. Assessment of the cranial nerves, reflexes, coordination and motor function will be done, and special attention will be paid to the sensory system, because of the finding of a sensory peripheral neuropathy in the victims of the Yusho poisoning. Finally, as a sensitive index of mental functioning, a panel of neurobehavioral tests will be administered (See Appendix 15). Invasive tests are not

planned routinely, but may be indicated in certain cases.

d) Clinical Laboratory Tests For the Phase II subjects, these will consist of a complete blood count, electrolytes, BUN and creatinine, liver function tests (total bilirubin, LDH, SGOT, SGPT, gamma-glutamyl transpeptidase, alkaline phosphatase, and albumin), serum and immune electrophoresis.

A lipid profile will be done (cholesterol, triglycerides, heavy density lipoproteins and lipoprotein electrophoresis). If CDC will assist the project by doing the lipid profiles, this will be of particular value given the large national database which the CDC has for comparability.

In addition to these tests we propose that a small sample of Phase II subjects will be studied to determine blood lead levels, as well as the levels of urinary arsenic and mercury. These heavy metals are neurotoxic, and a minimal screen for unusual elevation of these metals will be a part of this protocol. This will be of value in assuring that the neurobehavioral tests will not be confounded by these metals.

Urinary porphyrins and urinary D-glucaric acid are measures of hepatic porphyria and liver microsomal enzyme induction. Methods and laboratory for these tests are available through the CDC Toxicology Laboratory.

Commercial labs do measure the former, but the results may lack the detail and accuracy necessary for the purposes of this study. It would be desirable to have CDC provide some analytical support because of the special interest

CDC has in urinary porphyrins and d-glucaric acid in exposure to toxins, such as occurred at Times Beach, Missouri.

e) Immunological Evaluation This aspect of the study will be under the direction of Dr. R. Ruggles. There will be 2 components to the immunological testing; in vivo and in vitro. The in vivo testing will consist of skin testing of patients to a variety of delayed recall antigens described previously. The in vitro testing will concentrate on evaluating peripheral blood lymphocyte subsets in these heavily exposed subjects (methods described in Appendix 14). Blood lymphocytes will be isolated and the percentage and absolute number of T (E rosette positive), B (surface Immunoglobulin positive) and null ( $E^{-}SIg^{-}$ ) subsets determined. This unfractionated population will also be evaluated by flow cytometric analyses on a fluorescence activated cellsorter (FACS Analyzer) for T cell associated differentiation antigens as defined by monoclonal hybridoma antibodies of the OKT (Ortho Labs) and the Leu (Becton-Dickinson) series. For instance, the numbers of OKT 3, OKT 4, OKT 6, OKT 8, OKT 10 positive cells will be determined in this manner and an estimate of OKT 4 (helper)/OKT 8 (suppressor) ratios obtained. This ratio has proven to be of great value as an index on immunocompetence (immunosuppression). Additional monoclonal antibodies will be used to evaluate B cell function including the determination of individual SIg chains, Fc receptors, C'3 receptors and the Ia and Bl differentiation associated antigens.

An estimate of activated T cells will be obtained by either double fluorescence labelling with OKT 3 and Ia antibodies on whole mononuclear preparations or Ia staining on cell populations further fractionated to select for T cells. If a significant null cell population is found in these samples, this population will be further concentrated and characterized with a panel of monoclonal antigens that includes a cross section of T and B associated differentiation antigens.

A quantitative defect in the Ig synthetic capacity of the total B cell pool will be measured by quantitative serum Ig determinations. The presence of abnormal B cell clones will be screened for by serum protein electrophoresis

The above studies will provide quantitative and qualitative information regarding T, B and null cell populations in these patients, in vivo measures of delayed hypersensitivity and in vivo measurements of B cell function.

D. Phase II

Statistical Analysis

Data processing and some statistical procedures as described above will be utilized. For analysis of the Phase II results, statistical methods appropriate for matched studies will be used. Since most of the outcome measures in this study are continuous, the simple association of each measure with high or low PCB levels will be investigated using the paired t-test. If necessary, the outcome measures will be transformed so that the pair differences follow normal distributions. For a multivariate investigation of the association between PCB

levels and a continuous outcome measure, the analysis of variance or covariance will be used. In the case of a dichotomous outcome measure, McNemar's test will be used (30, 31, 32).

VII. ADMINISTRATIVE

A) Project Director

The study will be headed by a project director, selected by the Assistant Commissioner of Environmental Health, and will be a physician experienced in conducting epidemiological and environmental studies. He will be responsible for recruiting and training of personnel. He will be responsible for implementing all aspects of both phases of the survey including subject recruitment, data collection and validation, coordinating laboratory blood analysis, physical examinations of subjects, maintaining confidentiality of data collected, and reporting to the subjects and the private physician the outcome of the survey evaluation of each subject. The project director will have primary responsibility for maintaining a good relationship with the greater New Bedford community, including the local physicians, citizen representatives, news media, responsible city and state officials, as well as other interested groups such as environmentally concerned groups, the business community and others. Finally, he will be responsible for all data analysis, writing of interim quarterly reports and final reports detailing all aspects of the study, conclusions and recommendations determined to result from the study. Funding will be through the Massachusetts Health Research Institute. The Commissioner of Public Health will guide the release of study results.

B) Project Staff

Under the supervision of the Project Director the following staff will be needed to implement and successfully complete this project. Some of this staff will not be required for the entire project period, and will be released from the project staff accordingly. The 24 month budget for personnel and fringe costs has been adjusted to reflect these staff requirements.

Project Staff MembersDuties and Responsibilities

- |   |  |
|---|--|
| 1. Assistant Project Director                       | Responsible for administrative and management activities. Involved in subject recruitment, public and media contacts and coordinating project activities as assigned by project director.  |
| 2. Public Health Nurse                              | Will assist project director and consulting medical staff in subject examinations. Will place and read skin tests. Will make direct home visits to subjects.   |
| 3. Neurobehavioral Technologist                     | Will administer project questionnaires and perform neurobehavioral evaluation of subjects.   |
| 4. Medical Technologist                             | Will take blood samples and prepare them for PCB and immunological analysis.   |
| 5. Biostatistical Assist/Data Management Specialist | Will be involved in developing forms to be used in study; assist in random selection procedures and selection of study population; validation of data; will oversee data processing and computer programming services; will work under the direct supervision of the project statistician and consultant; will perform statistical |

tests and evaluations as part of the statistical assessment of project data.

#### 6. Epidemiologic Assistants

Will make initial telephone contacts and recruit subjects for health survey. Will explain project and answer questions. Will work with project secretary in scheduling appointments. Will administer questionnaires. Will do medical records abstracting. Will maintain project files. Will help in preparation of tables, graphs and charts for quarterly and annual reports.

#### 7. Administrative Assistant

Will be responsible for delivering of blood specimens to appropriate laboratories for analysis. Will pick up or drop off medical files, project questionnaires and data sheets. Will assist in follow-up contact of "no-shows" as well as assist the epidemiologic assistants and secretary in recruitment of subjects for project, including direct visits to locate the subjects not contacted by other means.

#### 8. Project Secretary

Will be responsible for preparing all correspondence with subjects participating in the project, private physicians and other correspondence as required by the project director and his staff. Will also assist with certain administrative aspects of the project, including arranging for travel, maintaining time sheets, scheduling of subjects, answering of telephones, arranging conferences and other duties as assigned by the project director.

VIII. PROJECT REPORTS

The project director and his staff will prepare quarterly reports which will summarize the progress of the study during the preceeding quarter. The following will be included:

- 1) Number of subjects contacted.
- 2) Number of subjects successfully recruited for study.
- 3) Number of refusals and summary of reasons.
- 4) Number of blood samples submitted for analysis.
- 5) Number of blood analysis reports received.
- 6) Summary of financial aspects of conducting the project including personnel costs, supplies and services purchased, equipment required, costs of transportation, building rental fees, telephone services, travel expenses, etc.
- 7) Summary of progress made toward completion of each phase of the study, including questionnaires processed, etc.
- 8) Summary of problems encountered or anticipated and impact they may have on the project (for example, illness amongst the staff).

The project director and his staff will prepare an annual report summarizing the progress of the project during the preceeding year. It will summarize the activities of project staff as well as consultants, and give summary of all data elements collected. It will contain a consolidated report of data given in the quarterly reports in sufficient detail to permit appraisal and evaluation of the overall progress of the project.

Interim reports will be prepared as necessary. It is expected that an early report will be prepared summarizing and

analyzing data based on Phase I. This report will examine the PCB blood levels and blood pressure measurements, looking for a possible relationship between the two. Other Phase I questionnaire data will be evaluated for possible relationships to PCB levels, such as data on seafood intake and occupation.

A final report covering all aspects of Phase I and Phase II will be prepared. This report will consist of a detailed presentation of all data collected and will examine the relationships between PCB blood levels and clinical, laboratory and questionnaire data, using multiple statistical tests, including multivariate analytical methods, to test for significant correlations.

It is anticipated that a number of journal articles will be written as a result of this study. In general, authors will include representatives from each of the institutions involved: the Massachusetts Department of Public Health, Harvard School of Public Health, University of Massachusetts, Southeastern Massachusetts University and Centers for Disease Control. The first author should represent the institution that contributed most to the particular phase of the study described in the article and will usually be the person who prepared the article. Certain specialized articles need not be co-authored by representatives of all of the involved institutions.

REFERENCES

1. USEPA: Polychlorinated Biphenyls-Ambient Water Quality Criteria (Criteria & Standards Division, Office of Water Planning & Standards USEPA) Wash. D.C.
2. NIOSH: Criteria for Recommended Standard...-Occupational Exposures to Polychlorinated Biphenyls. DHEW Public NO. 77-225 Wash. D.C. 1977
3. Weaver, G.: PCB Pollution in New Bedford, Mass. Area: A status report. Massachusetts Coastal Zone Management, Boston 1982
4. Kimbrough, R.D.: The toxicity of polychlorinated polycyclic compounds and related chemicals. Crit. Rev. Toxicol 2:445-498 1974
5. Zimmerman, N.: Polychlorinated Biphenyls in Great Lakes Fish-Toxicological justification for lowering acceptable standard to 2ppm. Toxic Substance Control Commission, Lansing Michigan 1982
6. Wasserman, M. et al: World PCB's Map: Storage and effects in Man and his biologic environment. Ann. NY Acad. Sci. 320:69, 1979
7. Kuratsune, M. et. al: Epidemiologic study on Yusho. Environ. Health Perspect. 1:119-128 1972
8. Letz, G.: The Toxicology of PCB's: State of California, Dept. of Health Services, Berkeley, CA. 1982
9. Fischbein, A. et. al: Clinical findings among PCB-exposed capacitor manufacturing workers, Ann. NY Acad, Sci. 320:703 1979
10. Drill, V.A. et al: Potential Health Effects in the Human From Exposure to Polychlorinated Biphenyls (PCBs) and Related Impurities. Report prepared by Drill, Friess, Hoop, Lommis and Shaffer, Inc. Consultants in Toxicology, Arlington, Virginia Jan. 25, 1982
11. Urabe, H. et al: Present State of Yusho Patients. Ann. NY Acad. Sci. 320:273-276, 1979
12. Telles, N.C.: Letter to Representative Roger Goyette, Massachusetts Department of Public Health. May 20, 1981
13. Telles, N.C.: The New Bedford Study-Preliminary findings. Massachusetts Department of Public Health, Environmental Health Assessment, March 23, 1982

REFERENCES

14. Kreiss, K. et al: PCB levels in a community with exceptional exposure to DDT, Triana, Alabama. Public Health Service, CDC Atlanta, EPI 79-44-4, 1980
15. Kreiss, K. et al: Association of blood pressure and PCB levels. JAMA 245 (24): 2505-2509, 1981
16. Kimbrough, R.D. et al: Induction of liver tumors in Sherman strain female rats by PCB Aroclor 1280. J. Natl. Cancer Inst. 55:1453, 1975
17. Ouw, H.D. et al: The use and health effects of Arclor 1242, a PCB in the electrical industry. Arch Environ. Health 31: 189, 1976
18. Maroni, M. et al: Occupational exposure to PCB's in electrical workers II-health effects. Brit. J. Indus Med. 38:55, 1981
19. Alvares, A.P. et al: Alterations in drug metabolism in workers exposed to PCBs. Clin Pharmacol Ther. 22:140, 1977
20. Ideo, G. et al: Increased urinary D-glucaric acid excretion by children living in an area polluted with TCDD. Clin. Chimin. Acta 120:270, 1982
21. Ding-Jen Chang, et al: Immunologic evaluation of patients with polychlorinated biphenyl poisoning: determination of lymphocyte sub-populations. Toxicol and Appl Pharm 61:58, 1981
22. Bekesi, J.F. et al: Immunologic dysfunction among PBB exposed Michigan dairy farmers. Ann. NY Acad. Sci. 320:717-728, 1979
23. Marai, Y and Yoshigoro, K.: Peripheral neuropathy in chlorobiphenyl poisoning. Neurol 21:1173, 1971
24. Segull, E.A.W.: Developmental abilities of children exposed to polybrominated biphenyls (PBB). AJPH 73:281-285, 1983
25. Schwartz, E.M and Rae, W.A.: Effect of polybrominated biphenyls (PBB) on developmental abilities in young children. AJPH 73:286-289, 1983

REFERENCES

26. Nebert, D.W. et al: Possible effect of neonatal polybrominated biphenyl exposure on the developmental abilities of children. AJPH 73:286-289, 1983
27. Feldman, R.G. et al: Neuropsychological effects of industrial toxins: A review. Am J Indust. Med. 1:211-227, 1980
28. Baker, E.L. et al: Monitoring neurotoxins in industry: development of a neurobehavioral test battery. J. Occ Med. 25:125-130, 1983
29. Wolff, M.S. et al: Body burden of polychlorinated biphenyls among persons employed in capacitor manufacturing. Int. Arch Occup Environ. Health 49:199-208, 1982
30. Anderson, A., et. al: Statistical Methods for Comparative Studies, John Wiley and Sons New York, 1980
31. Fleiss, J.: Statistical Methods for Rates and Proportions, John Wiley and Sons, New York, 1973
32. Snedecor, G. & Cochran, W.: Statistical Methods, Ames, Iowa: Iowa State University Press, 1967