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OCCURRENCE OF TYPE 2 DIABETES MELLITUS IN A MICHIGAN COHORT EXPOSED TO POLYBROMINATED BIPHENYLS

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OCCURRENCE OF TYPE 2 DIABETES MELLITUS IN A MICHIGAN COHORT EXPOSED TO POLYBROMINATED BIPHENYLS

By

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ABSTRACT

OCCURRENCE OF TYPE 2 DIABETES MELLITUS IN A MICHIGAN COHORT EXPOSED TO POLYBROMINATED BIPHENYLS

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In the summer of 1973 polybrominated biphenyls (PBBs) were accidentally released in large quantities in the environment and as a result some Michigan residents consumed PBB-contaminated farm products for about eight months. A cohort was assembled at the time and cohort members were followed until today. We are interested to verify whether there is a relation between PBB exposure and development of type 2 diabetes mellitus.

Our study population included 1,478 subjects from the Michigan PBB cohort, chosen after a careful selection process. PBB serum determinations were available for all of them. We relied on information from three previously conducted surveys in order to assess type 2 diabetes incidence and to obtain information on several confounders (age, gender, body mass index, smoking and drinking status). All variables in our model were categorical, and our exposure variable had four levels: ≤1 parts per billion (ppb), >1- 3 ppb, >3-5 ppb, and >5 ppb.

Results from our analysis show an increase in type 2 diabetes incidence in women in the >3-≤5 ppb PBB group. PBB serum levels were inversely correlated with the body mass index in women. Also, smoking was weakly associated with an increased diabetes incidence in men.

To Daniel, my husband, who supported me all along the way.

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KEY TO ABBREVIATIONS

BMI= body mass index

CI= confidence interval

LOD= limit of detection

PCB= polychlorinated biphenyl

PBB= polybrominated biphenyl

TCDD= 2,3,7,8-tetrachlorodibenzo-p-dioxin

INTRODUCTION

Background

In the summer of 1973 polybrominated biphenyls were released in large quantities in the environment as a result of the largest accidental contamination incident in the history of the United States. A fire retardant product (FireMaster FF-1®), consisting of a polybrominated biphenyls (PBBs) mixture, was mistakenly added to animal feed instead of magnesium oxide and distributed to farms throughout Michigan. As a result, approximately 295 kg PBBs entered the food web. (11) The first effects became apparent late September 1973, when animals that received the contaminated feed formula began to exhibit symptoms of a mysterious consumptive disease, the cause of which was not identified until April 1974. As a result, Michigan residents, especially farm families, consumed contaminated meat, eggs and dairy products containing high levels of PBB for about eight months before any measure was taken. After the contamination was identified, about 30,000 head of cattle, 2,000 swine, 400 sheep, and over 2,000,000 chicken had to be destroyed.(11) In July 1976, about 4,000 potentially exposed Michigan farm residents and heavy consumers of contaminated farm products were enrolled by the Michigan Department of Public Health in a cohort for further investigations of possible human health effects. This cohort has been followed through the present time.

PBBs are brominated hydrocarbons, with a structure related to other chemical compounds such as polychlorinated biphenyls (PCBs), dioxins and furans. One of

their most important physical properties is that they have a high flammability point, and for this reason they have been used as flame-retardants.

Regarding their biological properties, PBBs are lipophilic compounds, with potential for bioaccumulation and a long half-life (around 10 years) in animals and humans.(35) They are mainly stored in the adipose tissue and can be eliminated through breast milk. Negligible quantities are eliminated through feces.

More than 200 PBB congeners are known, but in the Michigan PBB incident the main congener involved was 2,2',4,4',5,5' hexabromobiphenyl (Figure 1). Another 24 congeners were identified in the FireMaster-FF1® mixture, but they were much less abundant.

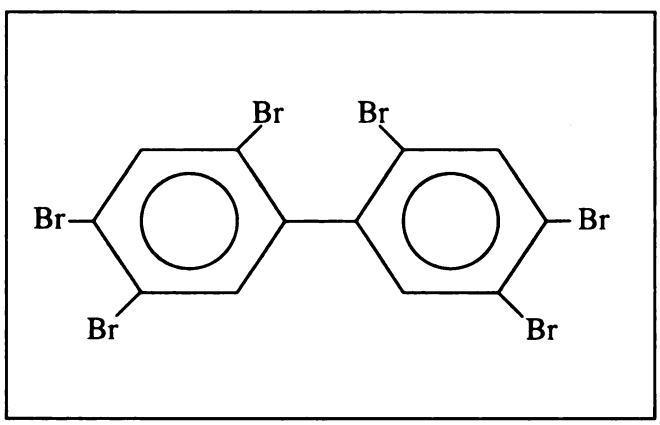


Figure 1: Structure of 2,2',4,4',5,5' hexabromobiphenyl.

The Michigan PBB incident is unique, due both to the high levels of exposure and the number of people exposed. The exposure was well ascertained and the cohort was followed up for 25 years, thus it is of interest to examine the effects that PBBs may have on human health.

Research Question

One of the possible health effects of PBBs in humans may be an association with diabetes mellitus type 2.

In 1999, the World Health Organization provided the following definition for diabetes mellitus: *"The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both."(41)*

It is commonly accepted that type 2 diabetes mellitus is due to insulin resistance and/or a relative insulin deficit. The most important risk factors for this disease were identified to be age, obesity, central adiposity, lack of physical activity, and dietary glucose intake.(31) Another risk factor for type 2 diabetes is a positive family history, due to the fact that a genetical component has been identified.(24)

Our research question is: **"Is exposure to polybrominated biphenyls a risk factor for subsequent development of type 2 diabetes?"** To our best knowledge, no study has found a relationship between exposure to PBBs and an increased incidence of type 2 diabetes cases. However, several studies have found significant associations of exposure to dioxins with diabetes mellitus, which leads us to the belief that PBBs may have a similar effect, due to their similar chemical structure.

A review by Longnecker and Daniels (19) assessed environmental contaminants as possible etiologic factors for type 1 and type 2 diabetes. After a

thorough review of the existing literature, they concluded that there was conflicting evidence regarding environmental risk factors for diabetes, mostly because of weaknesses in the study designs. Incriminated for type 2 diabetes were arsenic, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), and some occupational exposures.

Henriksen et al. (12) found an inverse association between serum levels of dioxin in Vietnam veterans who were participants in Operation Ranch Hand (exposed to Agent Orange, a herbicide containing TCDD), and prevalence of glucose abnormalities (relative risk (RR)=1.4, 95% confidence interval (CI)=1.1, 1.8), diabetes (RR=1.5, 95% CI=1.2, 2.0) and the use of oral diabetes medication (RR=2.3, 95% CI=1.3, 3.9). Unexposed Vietnam veterans were used as controls. They also found that the estimated time to onset for diabetes decreased with increasing dioxin levels. However, the serum levels of dioxins were determined just a few years before the outcome was ascertained; thus, time order is not clear. The association could be explained by a decreased rate of excretion for dioxins in subjects with diabetes/impaired glucose tolerance. Also there was no difference in diabetes prevalence when comparing the exposed versus the unexposed group.(20)

Another study focused on Vietnam veterans that were not exposed to herbicides, and had only background levels of TCDD (≤ 10 ng/kg lipid). Results showed a higher multivariate-adjusted odds of diabetes among those with TCDD levels in the highest quartile compared to those in the lowest quartile (adjusted odds ratio=1.7, 95% CI = 1.0, 2.9). This association was attenuated after adjusting

for serum triglycerides. Causality however cannot be ascertained due to lack of information on the time order of the events.(21)

Pesatori et al. (33) reported an increase in diabetes mortality in women exposed to TCDD as a result of the industrial accident in Seveso, Italy. Based on soil measurements three geographical zones of exposure have been identified: A- highest contamination, B- medium, and R- low contamination, but higher than the background levels. The apparent increase in mortality was found in women residents of zone B (RR=1.9, 95% CI=1.1, 3.2). However, the investigators only adjusted for age as a potential confounder in the analysis, and not for other important risk factors.

Cranmer et al. conducted in 2000 a study involving TCDD-exposed subjects living within 25 miles of the Vertac/Hercules Superfund site in Jacksonville, Arkansas. The main finding was that plasma insulin concentrations, at fasting and 30, 60, and 120 min following a 75 g glucose load, were significantly higher in the group with high blood TCDD levels. Nevertheless, the sample size was small (69 subjects) out of which seven constituted the 10^{th} percentile of the serum TCDD distribution. This finding suggests that high blood TCDD levels may cause insulin resistance.(8)

A study conducted in the Czech Republic focused on occupationally exposed workers and found a positive association between TCDD exposure and impaired glucose tolerance. The study design was case series, with a sample of 55 subjects, out of which 22 had an abnormal glucose tolerance test (GTT). (32)

Studies regarding TCDD exposure and its relation to diabetes provide diverse results. The biological plausibility of a diabetogenic effect has been established by an *in vitro* study conducted by Enan et al. This study showed that TCDD can decrease the cellular glucose uptake in human luteinizing granulosa cells in culture.(10)

To our best knowledge, the only study involving both PBBs as one of the exposure variables and diabetes mellitus as one of the outcomes of interest was a mortality study among white male workers potentially exposed to various brominated compounds including PBBs.(40) The overall mortality of the cohort was below expectations when compared to the standard age and calendar time adjusted mortality for white males in the United States. Several subgroups of causes of death were also below expectations (cardiovascular diseases, non-malignant respiratory diseases, and diseases of the digestive system). This result is probably due to the "healthy worker effect", explained by the fact that working groups very often have lower total mortality than the general population as the latter includes people unable to work due to illness or disability. However, mortality from diabetes mellitus was significantly raised for this cohort. This study has no biological measure of exposure, and furthermore, the potential for multiple exposures makes it hard to interpret the results.

Another documented risk factor for diabetes is obesity, usually measured by the body mass index (BMI), which is calculated as weight/(height)^2 and is measured in kg/m^2. According to the World Health Organization criteria for assessing overweight and obese patients, the normal range for body mass index is

18.5-25 kg/m^2; a person with body mass index of less than 18.5 is considered underweight, between 25-30 kg/m^2 overweight and above 30 kg/m^2 obese. (28) According to existing literature, excess body fat is a major risk factor for developing type 2 diabetes mellitus, because of its association with insulin resistance.(4)

Smoking is another risk factor for developing non-insulin dependent diabetes mellitus, according to some studies.(15, 38) Ko et al. have found that smoking is an independent risk factor for type 2 diabetes in Chinese men, but not in women due to the low prevalence of smoking in Chinese women.(14) Another report from Wannamethee et al. showed the same relation in men, after adjusting for body mass index, age and other potential confounders.(37)

In conclusion, in any analysis involving type 2 diabetes mellitus as the outcome, a multitude of factors need to be considered.

METHODS

Study population

The Michigan PBB cohort was first assembled in 1976. Potentially exposed farmers, heavy consumers of contaminated farm products and their families were surveyed for the first time and enrolled in a cohort study (n=4,128 subjects). The second major survey took place between 1991 and 1993, when 3,581 subjects participated. The first two surveys (enrollment 1976 and re-characterization 1991) made use of two questionnaires (Appendix), containing general questions as well as detailed questions concerning the subjects' general health status and lifestyle factors. The third major update (2001), with 3,449 participants, consisted of a short mailed questionnaire (Appendix) containing specific health questions focused on five health conditions: asthma, diabetes, thyroid disease, systemic lupus and rheumatoid arthritis.

The Michigan PBB cohort is a dynamic population. Between the three surveys the cohort population varies, as shown in Figure 2.

A total of 2,379 study subjects participated in all three major surveys (enrollment 1976, re-characterization 1991 and update 2001). As seen in Figure 2, 1,050 subjects participated only in the enrollment survey, 105 only in the re-characterization and 218 only in the last major update. We also found that 472 participants responded to the first and second survey only, 625 to the second and third surveys only and 227 to the first and third. Overall, the number of subjects that responded to a survey in the Michigan PBB cohort was 5,076. For the purpose of our analysis we examined a population of 1,478 subjects. This

number was the result of applying several exclusion criteria, as is illustrated in Figure 3.

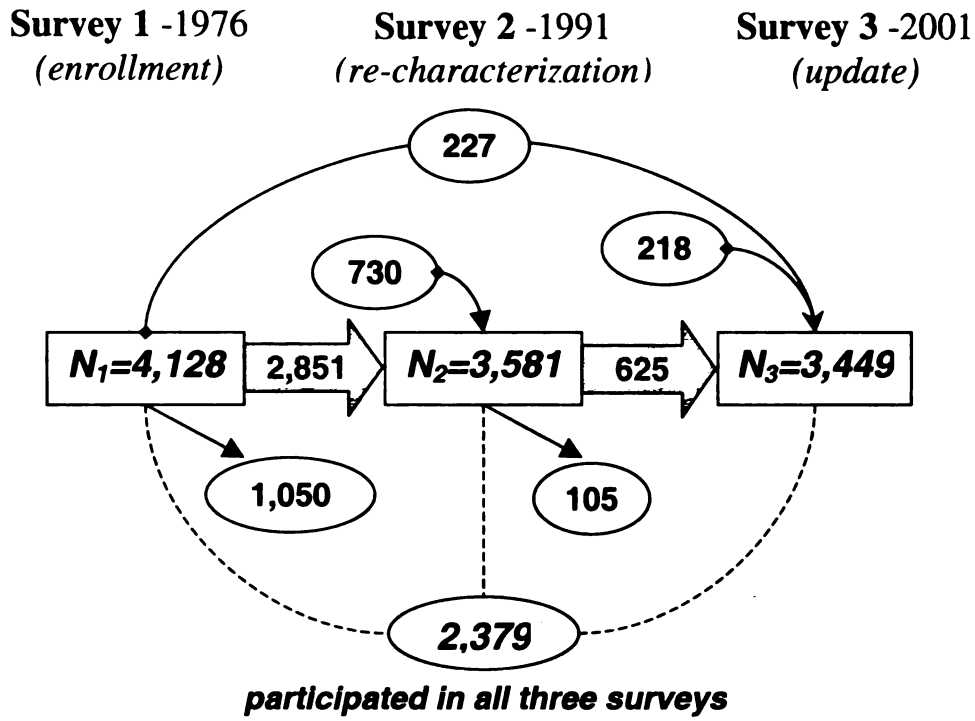


Figure 2: Dynamics and composition of the Michigan PBB cohort.

Starting from 5,076 subjects, we first eliminated those that did not participate in the enrollment survey and at least one other survey (re-characterization 1991 and/or update 2001), after which we acquired a population of 3,078 subjects. This included the 2,379 subjects that participated in all three surveys, the 472 subjects that participated in the first and the second surveys and the 227 subjects that participated in the first and the third surveys. We chose not to include those subjects that participated only in the second and third surveys (n=625) because data on their exposure status is not available at this time.

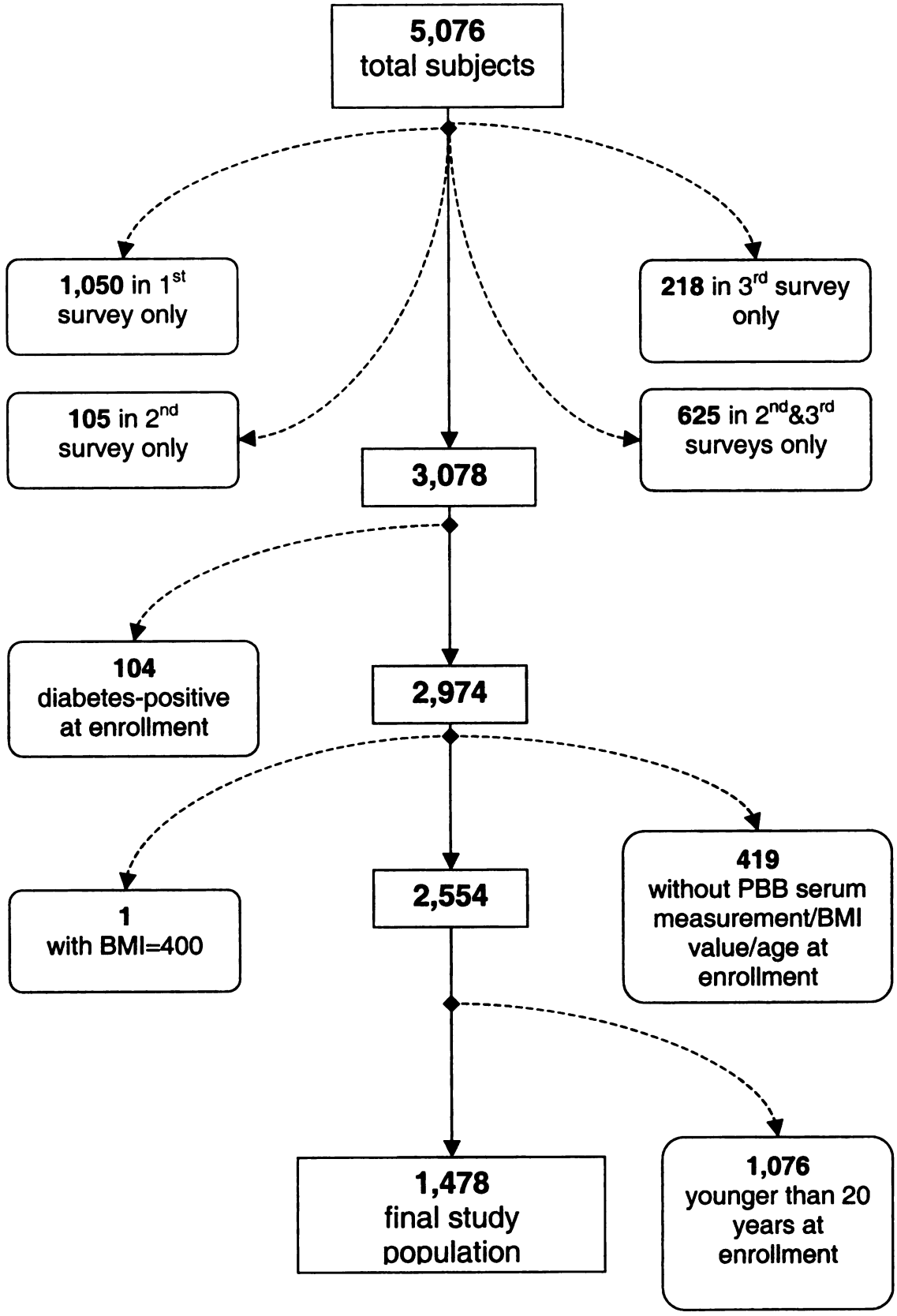
Furthermore, we excluded those individuals that reported diabetes at enrollment (n=104), due to the fact that we considered this to be the best

possibility of estimating the "true" diabetes incidence (new diabetes cases occurring after exposure).

Another step was to exclude an additional 420 subjects, 419 of which did not have data available on exposure or on body mass index or on age at enrollment; one additional subject was excluded because of a body mass index value of 400 (erroneously recorded data on height and weight).

Finally, we chose to limit our analysis to those individuals 20 years of age or older at enrollment, thus totaling 1,478 subjects for our analysis. This was due to the fact that we wanted to differentiate, as accurately as possible, type 1 from type 2 diabetes; as type 2 diabetes is more common in subjects 45 years of age or older, we wanted to have a plausible timeframe for the development of the disease.(41)

Figure 3: Study population and selection criteria



Questionnaires and definition of variables

-Copies of the sections of the questionnaires we used are provided in the appendix.

Three standardized questionnaires were developed, one for each survey. The first two questionnaires were administered as in-person interviews, while the third one was a mail-in questionnaire. Questions enabling us to determine various potential health outcomes, among which diabetes, were included. Using information from the first questionnaire, we were able to define the following variables: age at enrollment, gender, height and weight at enrollment (used to calculate the body mass index for the participants), and smoking status and alcohol consumption at the time of the first interview. Gender was observed by the interviewer and marked accordingly. Date of the interview or attempted interview was also recorded. The remaining variables were defined on the basis of the following questions:

1. When were you born?
2. What is your height and weight today?
3. Have you smoked at least 100 cigarettes during your entire life?
4. Do you smoke cigarettes now?
5. Do you ever use alcoholic beverages (such as liquor, wine, or beer) or are you a total abstainer? (if the answer is NO, go to the next question):
6. Have you always been a total abstainer?

The outcome, diabetes, was ascertained by answers to the following questions:

In the enrollment questionnaire:

1. Have you had sugar in your urine, high blood sugar or diabetes?

In the re-characterization questionnaire:

1. Has a physician ever told you that you had diabetes?
2. Has diabetes been a problem during the past year?
3. Have you taken a prescription medication for diabetes during the past year?

In the update 2001 questionnaire:

1. Have you ever had diabetes?
2. Did you have diabetes in the past five years?
3. Have you seen a doctor for diabetes in the past five years?
4. Were you hospitalized for diabetes in the past five years?
5. Did you take any prescription medication for diabetes in the past five years?

Diabetes was coded as "YES" for all three questionnaires if the answer to the question "have you ever had diabetes" was positive.

PBB serum determinations

In our analysis we used data on serum PBB levels (at least one determination) of the participants. The samples were analyzed at the Michigan Department of Public Health laboratories, using gas chromatography with electron capture detection.(3, 17, 29) When measuring PBB serum levels with this method, the denatured serum sample first goes through an ether-ethyl or hexane-ether extraction and then through either a Florisil or Florisil and silica gel

column. The size of this peak in the serum sample is then measured comparative to the size of this peak in a control sample containing a known quantity of FireMaster-FF1®. According to the existing literature, these methods of PBB detection have coefficients of variation of 7.1-14.0% and recovery ranges of 80-90%.(30) The limit of detection (LOD) for PBB in serum is 1 part per billion (ppb). The methods of PBB detection were based on the main PBB congener, 2,2',4,4',5,5' hexabromobiphenyl.

Statistical analysis

Since our analysis is based on data for a self-reported condition during three consecutive surveys, we first wanted to verify the quality of the data. For this purpose we chose to examine the agreement between answers in the three surveys. The special conditions under which the enrollment was conducted (massive environmental exposure with unknown health effects along with public awareness and distress) are cause for concerns about over reporting of various health conditions, especially in the first survey. We chose to examine the reliability of the questionnaires by comparing answers between the first and second and also between the second and third surveys. Although the agreement between surveys in this case will not be independent of the diabetes incidence, as a false positive answer the first time may be followed by a true positive answer due simply to disease incidence, we chose to use as a measure of agreement between surveys the positive predictive value.

In order to eliminate the false-positive answers in the first survey we decided to start our analysis from the population that was diabetes-free at enrollment. We

constructed a generalized linear model to estimate the effect of our explanatory variables (PBB exposure level, body mass index, age, smoking and drinking status) on our response variable (diabetes). For each individual in our study, p_i denotes the probability of presence of the characteristic of interest (diabetes). This probability is related to individual explanatory variables. Our model for p_i is given by:

$$Log(\frac{p_i}{1-p_i}) = (\beta_0+\beta_1 x_{i1}+\beta_2 x_{i2}+\ldots+\beta_n x_{in}),$$

where $(x_{i1}, x_{i2} \ldots, x_{ip})$ represent p explanatory variables in the i^{th} subject.

Let $\eta_i = \exp(\beta_0+\beta_1 x_{i1}+\beta_2 x_{i2}+\ldots+\beta_n x_{in})$, then $p=\frac{\eta_i}{\eta_i+1}$. The parameters β_0, β_1, ..., β_n are estimated through the maximum likelihood method.

We used SAS- PROC GENMOD statement to fit this model to our data. Before running this procedure, a dataset was created in which the total number of individuals within each combination of explanatory variables was calculated, and for each such profile the number of diabetes cases was found. This reduces the analysis to a binomial model.

A second model was developed in which the actual count of diabetes cases (for each covariate profile, e.g. PBB in the 3-5 ppb group, age at enrollment between 20-45 years, body mass index in the 25-30 kg/m^2 group, female, current smoker and total abstainer from alcohol) was modeled as a Poisson variable. We use person-years of follow-up as the offset variable in applying the GENMOD procedure.

To describe the Poisson model let the count Y_j = number of diabetes cases in the j^{th} category, with t_j as the total person-years of follow-up for that category. Then log E $(Y_j/t_j)= (\beta_0+\beta_1 x_{j1}+\beta_2 x_{j2}+\ldots+\beta_n x_{jp})= \eta_j$, where Y_j has a Poisson distribution with mean= exp $(\eta_j t_j)$. Again, the parameters β_0, β_1, β_2, ..., β_p are estimated through the maximum likelihood method.

In other words, these two models allow us to estimate the PBB exposure effect on diabetes incidence (cases/total sample size) and incidence density (cases/person years of follow-up), respectively, within different strata of our study population. Although the two models may seem similar, the important differences are:

1. Binomial model: Y_i has a binomial distribution (η_i, p_i) where η_i= the number of individuals in the ith category and pi= the probability of diabetes in that category.
2. Poisson model: Yj is a Poisson variable with mean= exp $(\eta_j t_j)$, where $\eta_j= (\beta_0+\beta_1 x_{j1}+\beta_2 x_{j2}+\ldots+\beta_n x_{jp})$.

Note that for both models all our explanatory variables were categorical.

Our main outcome variable, diabetes, was treated as a dichotomous outcome (yes/no). Diabetes was coded as "YES" if the subject reported having the disease/condition at least once during the second or third survey and as "NO" if they never reported the condition.

Our main exposure variable was defined using the PBB serum measurement at enrollment, the only measurement available at this time. The serum PBB levels were grouped into four levels, based on their distribution within the study

group. (Appendix- Figure 5) More than 95% of all the serum PBB determinations were below 50 ppb. The highest PBB determination was 1,900 ppb. Due to the fact that the PBB levels were not normally distributed, we chose one group as those subjects with PBB serum levels below or equal to the limit of detection for the method used (LOD=1 ppb). The rest of the distribution was divided into three additional groups. Thus four groups of exposure were defined: ≤1 ppb, >1- 3 ppb, >3-5 ppb, and >5 ppb.

Age at enrollment was categorized into three groups: 20-<45 years, 45-<60 years and ≥60 years. This approach was chosen in view of the fact that the age of 45 years is considered a critical point in the epidemiology of diabetes mellitus and screening is most often recommended after this age.(22, 25) However, seeing as diabetes incidence increases with age after 45 years as well, we chose another cutoff point at 60 years of age.

Another important risk factor for the development of diabetes was body mass index at enrollment, calculated as self-reported weight (measured in kilograms) divided by squared self-reported height (measured in meters). Our body mass index variable was a composed variable, due to the fact that in the dataset the height was registered in feet and inches, and the weight in pounds. We used standardized transformations of height and weight to the metric system.(36) We used the body mass index at enrollment as a categorical variable with three levels (<25, 25-<30 and >=30 kg/m^2). We chose to include both the underweight and normal categories into a single group (<25 kg/m^2) because of small sample size in the underweight group.

Smoking status and alcohol consumption at enrollment were two other important variables we defined, with four groups each: "total abstainer", "former user, "current user" and "status not available". These two variables were not included in the final models and were used for descriptive purposes only, due to the fact that after conducting a stepwise backward elimination procedure, they were not considered to be confounders of the relationship between PBB exposure and our outcome, diabetes.

The number of person-years of follow-up was calculated from the date when the subject entered the study until the first survey date when the subject reported having been diagnosed with diabetes; otherwise the end of the follow-up period is represented by the completion date of the last questionnaire.

All analyses were carried out using SAS software, release 8.2.

RESULTS

In order to estimate the accuracy of the data, we calculated the positive predictive value of a positive answer in the first survey for a positive answer in the second or third survey. Using all the reported diabetes cases in the first survey, we estimated a positive predictive value of only 35.1% (the probability that a positive answer in the first survey would be followed by a positive answer in the second survey is only 35.1%). Between the second and third survey, we calculated a positive predictive value of 80.6%.

Due to the low positive predictive value of answers from the first survey, we eliminated all diabetes cases declared at enrollment. As a result of this and other presented selection criteria already, our study population (Table 3) consisted of 1,478 subjects, out of which 99.8% were Caucasian. Both genders are almost equally represented (49.8% males and 50.2% females). We additionally found that 65.1% of the subjects in our selected population had ages between 20-45 years at enrollment, while the rest were above 45 years. Regarding the calculated body mass index, most of the subjects were either in the normal (43.6%) or in the overweight (37.0%) category, with only 6.8% underweight and 12.6% obese. As to smoking status within our study group, at enrollment 59.8% were non-smokers, 13.8% were past smokers and 24.6% were actively smoking. We could not establish the smoking status for 26 subjects (1.8%). Alcohol consumption was also ascertained, and we found that 32.9% of the subjects were total abstainers at the time when the enrollment took place, while 60.4% were consuming alcohol in variable quantities, and 3.1% were categorized as

former alcohol consumers. We could not determine alcohol consumption for 53 subjects (3.6%).

Regarding PBB exposure, 382 (25.8%) of the study subjects had a serum PBB level below or equal to the limit of detection, and 428 (29%) had levels above that, but below or equal to 3 ppb. (Table 2) The lowest number of subjects was 201 (13.6%) in the greater than 3- below or equal to 5 ppb group. The highest exposure group had 467 subjects (31.6%).

We also wanted to compare our chosen study group with the group of those subjects that participated only in the first survey, our "lost to follow-up" group (Table 2). From the lost to follow-up group, totaling 1,050 people, we chose a comparison group of 583 people, using the same inclusion criteria as for the study group except for participation. We did this for comparison purposes. We found that the "lost to follow-up" group members had a significantly higher age at enrollment, had a slightly higher proportion of male participants and had a higher body mass index than the study group. Additionally we found statistically significant differences with regards to smoking and alcohol consumption at enrollment; however we believe these differences to be small and detectable only because of the high statistical power (a result of the rather large sample size we worked with). We did not detect any difference in the PBB levels within the two groups.

One additional analysis conducted in a population of 2,157 adults (20 years or older) that only participated at enrollment revealed that body mass index in women was significantly and inversely correlated ($p=0.0088$) with the date of

enrollment, association that persisted even after adjusting for age, smoking and drinking status and PBB serum levels. The association did not change after eliminating several outliers with a lower body mass index that were enrolled after 1980.(Appendix A- Figure 7) We did not detect this type of relation for men. (Appendix A- Figure 6)

One important concern was that, in theory, any exposure could exert what is sometimes called a "harvesting effect", referring to the premature death of the most susceptible individuals as a result to the exposure, before the epidemiological surveillance has time to identify the cases. We addressed this problem by estimating the overall mortality (using death certificate information) due to diabetes (recorded as the first cause of death) in the 1,050 subjects that only participated at enrollment and we found only six diabetes-related deaths (0.6%). We suspected that diabetes may have been underreported as a cause of death, in favor of some other complications and closely-related conditions. In light of this concern, we examined the mortality data that was available for the 1,050 subjects that only participated in the first survey. We found that 314 (29.9%) of the total 1,050 subjects were deceased; and only 6 deaths (0.6%) were attributable to diabetes. We further determined that 144 deaths (1.4%) were attributable to cardiovascular causes. Since renal complications are also frequent, we additionally found 6 deaths due to renal conditions (0.6%). It is, of course, unreasonable to assume that all deaths of cardiovascular and renal causes are diabetes-related. However, our goal was to compare the deceased population group with our study population with regards to the exposure. We

found no significant difference between the two populations with regard to PBB exposure levels and thus disproved our initial "harvesting effect" hypothesis.

Another analysis took into consideration all the 1,050 subjects that were lost to follow-up as opposed to a group of 2,974 subjects (before excluding those younger than 20 years at enrollment and those without a PBB serum determination available) (Figure 3). The alternate analysis did not provide any additional significant differences within the two groups.

Within our study population (n=1,478) there were no notable differences in characteristics between the PBB exposure levels, except for gender and body mass index. (Table 3) We noted that more males (43.1%) were in the highest PBB as opposed to only 20.2% females. In the lowest PBB exposure group, the situation was reversed, as only 11.7% males contrasting with 39.9% of the female participants fell in that group. We also detected that less obese people (23.5%) were in the highest (>5 ppb) PBB group versus 35.0% normal/underweight. This last finding enticed us to examine the relation between PBB and body mass index, and with this purpose we ran a logistic model that provided evidence of an inverse relation between PBB and body mass index that was significant even after stratification by gender, for males as well as for females.

Our final model included six covariates, alongside our exposure variable, PBB serum level: age at enrollment, gender, body mass index, smoking and drinking status at enrollment. When using the first model (based on odds ratios) we estimated that the odds for diabetes were not significantly different between the

four PBB exposure groups. (Table 6) Using odds ratios, when compared to the reference level (the lowest PBB exposure group: 0-1 ppb) we found no significant increase or decrease in diabetes occurrence in the other three groups. The highest odds ratio for diabetes (1.28), was found in the 3-5 ppb group; it was however not statistically significant (95% Confidence Interval (CI) = 0.76, 2.17).

The body mass index at enrollment was significantly correlated with increased diabetes odds. (Table 6) When compared to the reference level (the lowest body mass index group: <25 kg/m^2), the next highest body mass index group had a statistically significant increase of diabetes odds, (3.70 times in the second group versus the reference group (95% CI= 2.45, 5.58) and 9.51 times in the third group versus the reference (95% CI= 6.03, 15.00).

According to our data, women have 1.33 times increased diabetes incidence compared to men (95% CI=0.92, 1.90). Also, past smokers are at a slightly increased risk for developing diabetes when compared to non-smokers, although not statistically significant: incidence ratio=1.56 (95% CI= 0.97, 2.51).

The Poisson (incidence-density) model offered approximately the same results, but using incidence ratios. (Table 7) No significant differences were found when taking into account the person-years of follow-up. With regards to PBB exposure levels, the incidence ratio was highest in the 3-5 ppb exposure group: 1.25, (95% CI= 0.79, 1.99).

Regarding body mass index, when compared to the reference level (the lowest body mass index group: <25 kg/m^2) the upper two groups showed increased diabetes incidence (3.26 times in the second group versus the

reference group: (95% CI= 2.21, 4.81) and 6.94 times in the fourth group versus the reference (95% CI= 4.61, 10.45).

Both our models indicated the lack of effect of PBB exposure on the occurrence of the outcome in question (diabetes). A statistically significant increase in diabetes incidence was only detected for women when stratifying by gender. We found that women in the >3-5 ppb exposure group have a significantly higher diabetes odds or incidence when compared to the reference level in both our statistical models (first model: odds ratio=2.20 (95% CI= 1.12, 4.34); second model: incidence density ratio=1.82 (95% CI= 1.04, 3.19).

Without stratifying for gender, we did not identify any significant effect of smoking or drinking on diabetes odds or incidence, with either of the models we used. In a backward elimination technique, both smoking and alcohol consumptions were eliminated. However we chose to keep them in the final model due to previous work stating that these two variables should always be accounted for when using the Michigan PBB cohort data in any kind of analysis. (26)

When stratifying for gender however, men that are past smokers had an increase in diabetes odds or incidence when compared to nonsmokers for both our statistical models. Subjects in the category of current smokers also had a slight increase in diabetes incidence; however that was not statistically significant. In our first model, there is a 2.3 times increase in diabetes odds in past smokers (95% CI= 1.28, 4.27). For current smokers the odds ratio is lower– 1.71, (95% CI= 0.96, 3.03). The results for the second model are very similar. For

past smokers, the incidence ratio is 1.98 (95% CI= 1.17, 3.33). For current smokers, the incidence ratio is 1.56 (95% CI= 0.93, 2.61).

DISCUSSION

This study investigated the influence of environmental PBB exposure on diabetes mellitus incidence in adults of a Michigan cohort. Our findings suggest that there is no effect of PBB exposure on self-reported diabetes incidence. In our model that was not stratified by gender, the only variable for which we detected a significant increase in diabetes incidence is body mass index at enrollment. The increase in diabetes odds or incidence with higher body mass index is evident from both our models, as well as from the crude diabetes incidence values (Table 1). This dramatic increased risk of developing type 2 diabetes with increasing body mass index is in concordance with multiple other studies.(6, 7, 27) In fact, body mass index has long been established as a risk factor for diabetes mellitus.(5, 23)

When stratifying for gender however, in a binomial model, we found that women in the >3-≤5 ppb group had an odds ratio of 2.2 when compared with the lowest PBB group (95% CI: 1.1, 4.3). Results from the Poisson model are similar: incidence ratio 1,8 (95% CI: 1.0, 3,2). A two-way tabulation of diabetes incidence in all PBB levels stratified by body mass index illustrates these findings. (Figure 4) This led us to explore the body mass index- PBB serum levels association. The surprising finding was that PBB serum levels were inversely correlated with the body mass index after stratification by gender. This association has at least two possible explanations:

- High PBB levels could produce a decrease in body mass index as part of a "wasting syndrome", as was described in early studies of contaminated animals.

(2, 9, 18); yet the levels of PBB to which the animals were experimentally exposed were much higher than what was measured in humans.

- Serum PBB levels are higher in persons with a lower body mass index as opposed to those overweight and obese for the same PBB intake, as a result of a dilution effect. For further clarification, it is very important that PBBs are lipophilic substances and bioaccumulate over time. The serum PBB concentration is dependent on the total PBB body burden, as well as on the body mass index (a measure of the total body fat). Thus a person with a lower body mass index (and thus a lower percentage of adipose tissue) will transfer a larger amount of PBBs to the blood compartment as opposed to an overweight person.(13, 34)

Both explanations are plausible. To verify the first direction of the association, we looked at body mass index variation as a function of the time period during which enrollment took place. If the "wasting syndrome" hypothesis was true, we would expect the body mass index to decline over time in the enrollment part of the cohort. Indeed, our finding showed that body mass index decreases with later date of enrollment for adult women enrolled between 1976 and 1984, which comes to support the first explanation, that high PBB exposure could produce a decrease in body mass index over time. (Figure 7) This finding also explains the significant increase in diabetes incidence in women only. However the fact that we did not find a decline in body mass index for men advises for caution when interpreting the sense of the association.

Another significant increase in diabetes incidence was found in the "past smokers": men that have a smoking history but have quit smoking before the

enrollment interview. This finding is in concordance with other studies that have reported that smoking is an independent risk factor for diabetes. (16, 39) Our data is in agreement with these findings, showing that smoking is less prevalent in women than in men, and there is no association between diabetes incidence and smoking in women. We could probably explain the lack of effect in the current smokers group by the fact that they are younger and thus probably exposed for a shorter period of times than past smokers.

One of the major strengths of this study is the fact that the study population was followed for about 25 years, a large time frame which theoretically provides the opportunity for the development of the outcome (diabetes). Another important strength is that PBB serum measurements are available at enrollment, which is vital for assessing time order (in this case, we would be positive that the outcome followed the exposure). This is a relatively large cohort, which gave us the possibility of carefully choosing our study population without minimizing power.

One concern that emerged during this study was detection bias. We were concerned about the fact that self-reporting is not the ideal way of detecting any type of medical condition, with regards to the possibility that the disease exists but has not yet been diagnosed by a physician. This problem may not be so grave in the sense that this is a particular situation: huge environmental accident, that received a lot of publicity, thus people were concerned and were probably more likely to see a physician (not necessarily true however, especially for the later years).

This study is also limited with regard to the differentiation between type 1 and type 2 diabetes. We tried to limit this type of bias as much as possible by selecting only people 20 years of age or older at enrollment and by eliminating the pre-existing diabetes cases. However a possibility still remains that some cases of type 1 diabetes emerged later in life or that some type 2 diabetes cases in the younger population that was excluded were overlooked. There were 41 diabetes cases within the group who was less than 20 years at enrollment; 14 of them occurred in children less than 10 years of age at enrollment. We also addressed that, and conducted a secondary analysis without excluding those people younger than 20 years at enrollment; results were not significantly different than what we reported above.

Another area of potential bias was selection of the study population. The first concern was that 1,050 people participated only in the first survey, and thus were lost to follow-up to the remainder of the study. This concern was addressed by looking at any possible differences between our study group and the 1,050 lost to follow-up cohort members. We found that the lost to follow-up group were older and had a higher body mass index. Since both age and high body mass index are risk factors for type 2 diabetes development, the possibility of bias is present and has to be taken into consideration. If some diabetes mellitus cases are present in the loss to follow-up group, and if they are associated with high levels of exposure, it could lead to underestimating diabetes incidence in the higher exposure group, thus diminishing the calculated incidence ratios.

There is the possibility that PBB exposure may have produced a "harvesting effect"; if present, this would cause us to underestimate the increase in disease incidence due to the exposure, and thus bias our result towards the null. We addressed this issue and found no difference in the PBB serum levels between the deceased group (of the 1,050) and the rest of the study population.

Information bias, if present, would be due to the fact that people who were more likely to be highly exposed may have also been more likely to report any kind of health condition, including diabetes. Thus we would have a problem not only with overreporting and false positive answers, but also (theoretically) with underreporting some real diabetes cases in the lower exposure groups. This phenomenon varied in time, and is likely less important in later surveys. For the enrollment survey, we believe that public awareness and concern were too high and that any over reporting is very likely to be equally distributed among the exposure groups. This is documented by the low positive predictive value of a self reported diabetes case in the enrollment survey. Several studies have shown that Michigan farmers after the PBB incident had a higher rate of reporting of several health conditions and unspecific symptoms when compared with a similar Wisconsin group. These studies did not find a relation between PBB levels and reporting a health problem.(1)

Another concern was the fact that the study population is formed by farm and farm-produce consumer families that were recruited on a "most likely to have been exposed" basis. This may mean that the observations are not independent, and that we have to account for the intra-family effect. An additional analysis was

conducted taking this effect into account. An additional variable was used to characterize a subject' affiliation to one family and data were analyzed adjusting for family appertaining status. This analysis returned the same results as before, so we can safely say that the intra-family effect is negligible in this case.

In conclusion, we found an increase in type 2 diabetes incidence in women in the >3-≤5 ppb PBB group. This finding led to the surprising discovery that PBB serum levels were inversely correlated with the body mass index in women. Also, smoking was weakly associated with an increased diabetes incidence in men. To our best knowledge, this is the first study that examines this possible relationship between PBB exposure and diabetes mellitus. Still, due to the inherent limitations, we have to interpret these results cautiously.

Table 1: Crude diabetes incidences in different groups of our study population (n=1,478)

Variable		Number of cases	Total number of subjects	Crude incidence (%)
Age group at enrollment (years)	20-45 years	115	962	11.9
	45-60 years	59	407	14.5
	>60 years	17	109	15.6
Gender	Male	93	736	12.6
	Female	98	742	13.2
Race	African-American	0	2	0
	White (Caucasian)	191	1474	100.0
	Other	0	2	0
Body Mass Index at enrollment (kg/m^2)	<25	39	744	5.2
	25-<30	90	547	16.4
	≥30	62	187	33.1
Smoking status at enrollment	Non smoker	108	884	12.2
	Past smoker	34	204	16.7
	Current smoker	45	364	12.4
	Status not known	4	26	15.4
Alcohol consumption at enrollment	Total abstainer	67	487	13.8
	Former user	7	46	15.2
	Current user	108	892	12.1
	Status not known	9	53	17.0
PBB serum measurement at enrollment (ppb)	≤ 1	52	382	13.6
	1 < - ≤ 3	51	428	11.9
	>3 - ≤ 5	31	201	15.4
	> 5	57	467	12.2

Table 2: Characteristics of the group that only participated at enrollment versus the study population

Variable	Category	Population		Chi square	P-value
		Loss to Follow-up (%) (n=583)	Study Population (%) (n=1,478)		
Age group at enrollment (years)	20-45	256 (43.9)	962 (65.1)	143.4	<0.0001
	45-60	178 (30.5)	407 (27.5)		
	>60	149 (25.6)	109 (7.4)		
Gender	Male	317 (54.4)	736 (49.8)	3.5	0.0612
	Female	266 (45.6)	742 (50.2)		
Race	African-American	1 (0.1)	2 (0.1)	Chi square not calculated due to small cell size	
	White (Caucasian)	581 (99.8)	1,474 (99.8)		
	Other	1 (0.1)	2 (0.1)		
Body Mass Index at enrollment (kg/m^2)	≤25	257 (44.1)	744 (50.3)	14.0	0.0009
	25-<30	217 (37.2)	547 (37.0)		
	≥30	109 (18.7)	187 (12.7)		
Smoking status at enrollment	Non smoker	291 (49.9)	884 (59.8)	25.6	<0.0001
	Past smoker	115 (19.7)	204 (13.8)		

Table 2 (continued): Characteristics of the group that only participated at enrollment versus the study population

Variable	Category	Population		Chi square	P-value
		Loss to Follow-up (%) (n=583)	Study Population(%) (n=1,478)		
Smoking status at enrollment	Current smoker	174 (29.9)	364 (24.6)		
	Status not known	3 (0.5)	26 (1.8)		
Alcohol consumption at enrollment	Total abstainer	205 (35.2)	487 (32.9)	14.5	0.0022
	Former user	36 (6.2)	46 (3.1)		
	Current user	330 (56.6)	892 (60.4)		
	Status not known	12 (2.1)	53 (3.6)		
PBB serum measurement at enrollment (ppb)	≤ 1	155 (26.6)	382 (25.8)	0.4	0.9486
	>1 - ≤ 3	162 (27.8)	428 (29.0)		
	>3 - ≤ 5	78 (13.4)	201 (13.6)		
	> 5	188 (32.3)	467 (31.6)		

Table 3: Characteristics of the study population (n=1,478)

Variable	Category	PBB serum levels (ppb) n (%)			
		≤ 1	>1–≤ 3	>3–≤ 5	>5
Age at enrollment (years)	20-45	244 (25.3)	275 (28.7)	129 (13.4)	314 (32.6)
	45-60	106 (26.0)	122 (30.0)	60 (14.7)	119 (29.3)
	>60	32 (29.4)	31 (28.4)	12 (11.0)	34 (31.2)
Gender	Male	86 (11.7)	215 (29.2)	118 (16.0)	317 (43.1)
	Female	296 (39.9)	213 (28.7)	83 (11.2)	150 (20.2)
Race	African-American	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)
	Caucasian	381 (25.9)	428 (29.0)	199 (13.5)	466 (31.6)
	Other	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)
Body Mass Index at enrollment (kg/m^2)	≤25	181 (24.3)	215 (28.9)	88 (11.8)	260 (35.0)
	25-<30	134 (24.5)	164 (30.0)	86 (15.7)	163 (29.8)
	≥30	67 (35.8)	49 (26.2)	27 (14.4)	44 (23.5)
Smoking status at enrollment	Non smoker	255 (28.9)	262 (29.6)	103 (11.6)	264 (29.9)
	Past smoker	38 (18.6)	58 (28.4)	40 (19.6)	68 (33.3)

Table 3 (continued): Characteristics of the study population (n=1,478)

Variable	Category	PBB serum levels (ppb) n (*row %*)			
		≤ 1	**>1–≤ 3**	**>3–≤ 5**	**>5**
Smoking status at enrollment	Current smoker	84 (23.1)	100 (27.5)	55 (15.1)	125 (34.3)
	Status not known	5 (19.2)	8 (30.8)	3 (11.5)	10 (38.4)
Alcohol consumption at enrollment	Total abstainer	138 (28.3)	138 (28.3)	62 (12.7)	149 (30.6)
	Former user	19 (41.3)	13 (28.3)	5 (10.9)	9 (19.6)
	Current user	210 (23.5)	262 (29.3)	127 (14.2)	293 (32.8)
	Status not known	15 (28.3)	15 (28.3)	7 (13.2)	16 (30.9)
Diabetes	Yes	52 (27.2)	51 (26.7)	31 (16.2)	57 (29.9)
	No	330 (25.6)	377 (29.3)	170 (13.2)	410 (31.9)
Person-years of follow-up	*Mean (years)*	*22.1*	*22.2*	*22.3*	*22.1*

Table 4: Diabetes incidence in different body mass index groups (stratification by gender)

	Women			Men		
BMI (kg/m^2)	**<25**	**25-≤30**	**>30**	**<25**	**25-≤30**	**>30**
Cases	22	41	35	17	49	27
Total subjects	425	206	111	319	341	76
Diabetes incidence (%)	5.2	19.9	31.5	5.3	14.4	35.5

Table 5: Diabetes incidence in the different PBB exposure groups (stratification by gender)

	Women				Men			
PBB (ppb)	**≤ 1**	**>1-≤3**	**>3-≤5**	**>5**	**≤1**	**>1-≤3**	**>3-≤5**	**>5**
Cases	42	23	18	15	10	28	13	42
Total subjects	296	213	83	150	86	215	118	317
Diabetes incidence (%)	14.2	10.8	21.7	10.0	11.6	13.0	11.0	13.2

Table 6: Results of the binomial model

Variable		Odds ratio	95% CI†
Age group at enrollment (years)	45-60	1.01	0.71–1.44
RL: 20-45 years*	>60	1.22	0.68–2.19
PBB group at enrollment (ppb)	>1–≤ 3	1.02	0.66–1.59
RL: ≤1ppb	>3–≤ 5	1.28	0.76–2.17
	>5	1.21	0.77–1.89
Body Mass Index at enrollment (kg/m^2)	25-<30	3.70	2.45–5.58
RL: <25	≥30	9.51	6.03–15.00
Gender	Female	1.33	0.92 –1.90
RL: Male			
Smoking status at enrollment	Current smoker	1.32	0.87–2.00
	Past smoker	1.56	0.97–2.51
	Status not known	1.14	0.32–4.14
RL: Non-smoker			
Alcohol consumption at enrollment	Current user	0.94	0.65–1.35
	Former user	0.88	0.35–2.22
RL: Total abstainer	Status not known	1.83	0.74–4.51

**RL: Reference level*
***Total number of cases=191*
† Confidence Interval

Table 7: Results of the Poisson model

Variable		Person-years of follow-up**	Incidence ratio	95% CI†
Age group at enrollment (years)	45-60	8,874.2	1.05	0.77–1.45
	>60	2,019.3	1.30	0.85–2.39
RL:	*20-45*	21,883.0	1.00	–
PBB group at enrollment (ppb)	>1–≤ 3	10,340.7	1.02	0.69–1.51
	>3–≤ 5	4,478.8	1.25	0.79–1.99
	>5	4,468.7	1.19	0.80–1.79
RL:*	*≤1*	8,436.1	1.00	–
Body Mass Index at enrollment (kg/m^2)	25-<30	12,015.5	3.26	2.21–4.81
	≥30	3,984.8	6.94	4.61–10.45
	≤25	16,776.2	1.00	–
Gender	Female	16,509.8	1.25	0.91 –1.73
RL:	*Male*	16,266.7	1.00	–
Smoking status at enrollment	Current smoker	4,513.8	1.26	0.87–1.84
	Past smoker	8,034.8	1.43	0.94–2.18
	Status not known	570.8	1.09	0.36–3.24
RL:	*Non-smoker*	19,657.2	1.00	–
Alcohol consumption at enrollment	Current user	1,025.3	0.94	0.68–1.30
	Former user	19,871.7	0.88	0.39–1.98
	Status not known	1,137.7	1.70	0.79–3.64
RL:	*Total abstainer*	10,741.7	1.00	–

**RL: Reference level*
***Total person-years of follow-up=32,776.5 years*
† Confidence Interval
‡Total number of cases=191

Table 8: Body Mass Index within PBB groups stratified by gender, as well as in the whole study population

	BMI (kg/m^2)	PBB serum levels (ppb) n (%)			
		≤ 1	>1-≤ 3	>3-≤ 5	>5
Women n (%)	<25	155 (52.4)	123 (57.8)	49 (59.0)	98 (65.3)
	25-<30	88 (29.7)	59 (27.7)	25 (30.1)	34 (22.7)
	>=30	53 (17.9)	31 (14.6)	9 (10.8)	18 (12.0)
Men n (%)	<25	26 (30.2)	92 (42.8)	39 (33.1)	162 (51.1)
	25-<30	46 (53.5)	105 (48.8)	61 (51.7)	129 (40.7)
	>=30	14 (16.3)	18 (8.4)	18 (15.3)	26 (8.2)
Total n (%)	<25	181 (47.4)	215 (50.2)	88 (43.8)	260 (55.7)
	25-<30	134 (35.1)	164 (38.3)	86 (42.8)	163 (34.9)
	>=30	67 (17.5)	49 (11.5)	27 (13.4)	44 (9.4)

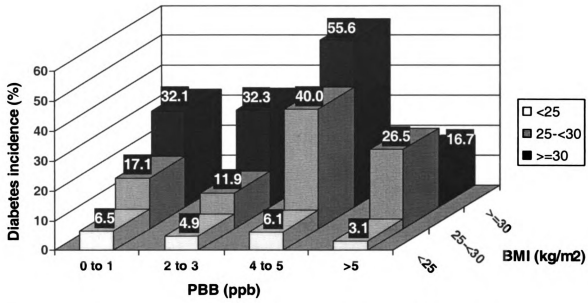


Figure 4: Diabetes Incidence in Women – Stratified By PBB Group and Body Mass Index

APPENDICES

APPENDIX A

Additional Figures

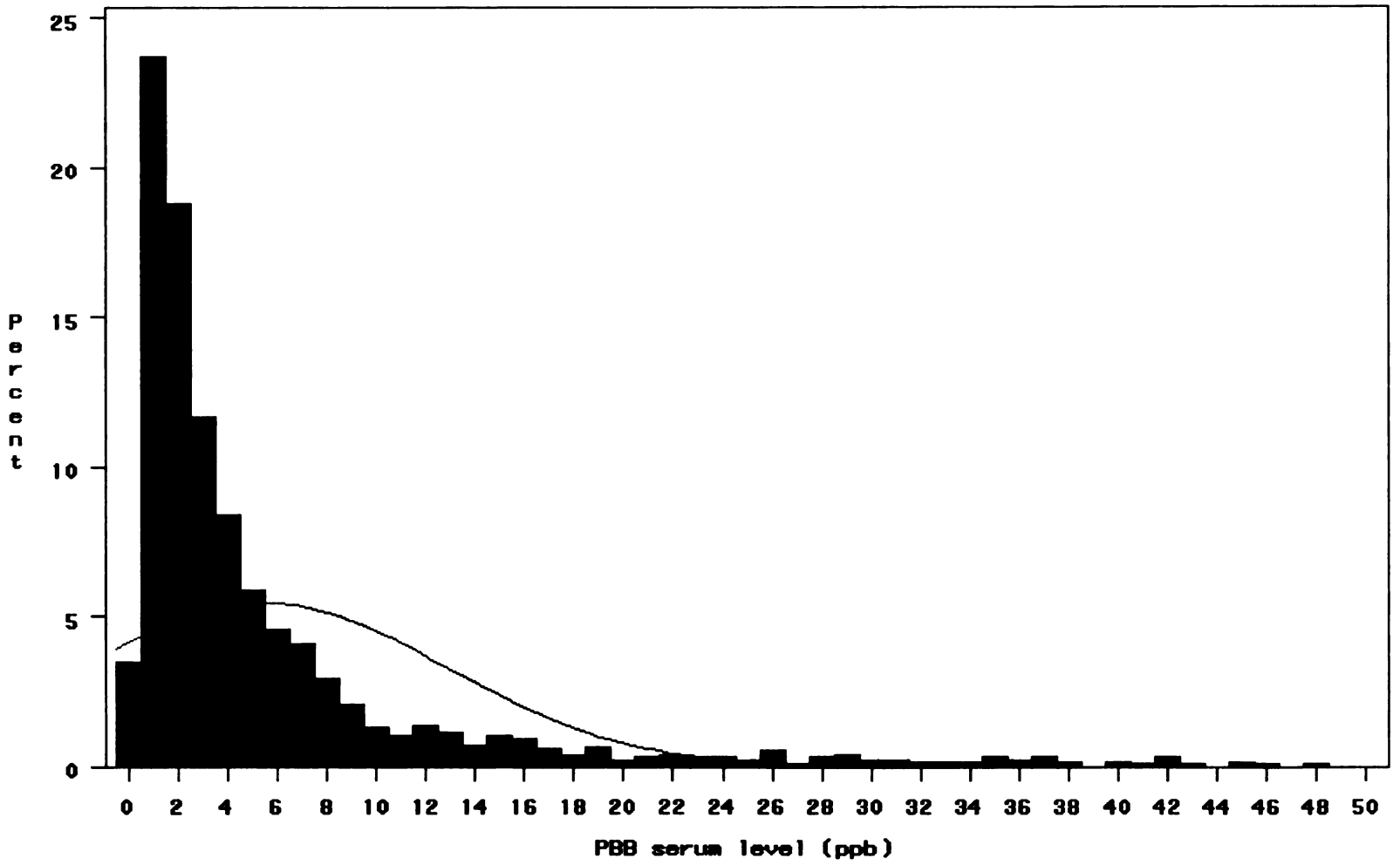


Figure 5: Serum PBB levels – distribution in the study group (up to 50 ppb)

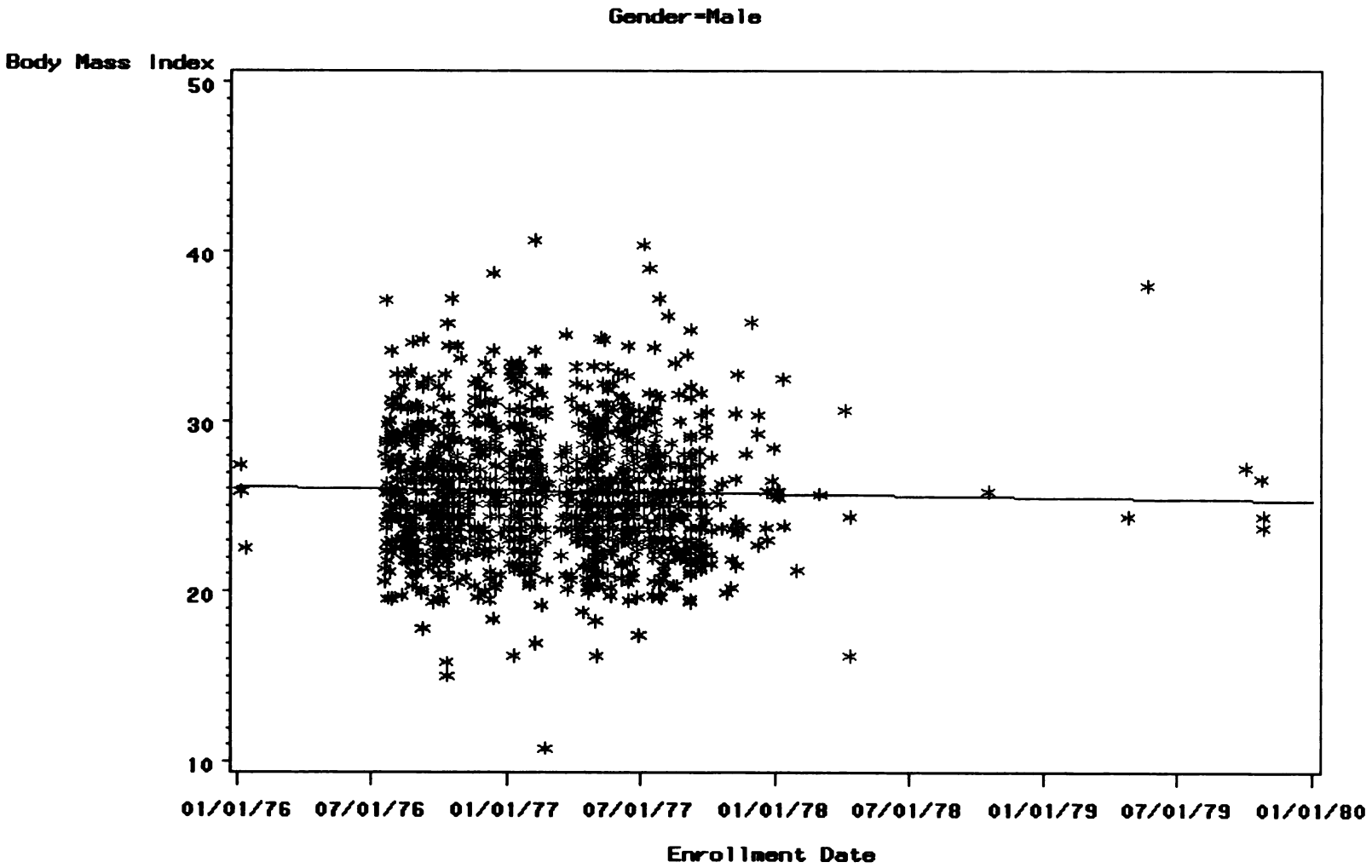


Figure 6: Body Mass Index in Relation to Date of Enrollment in Adult Men

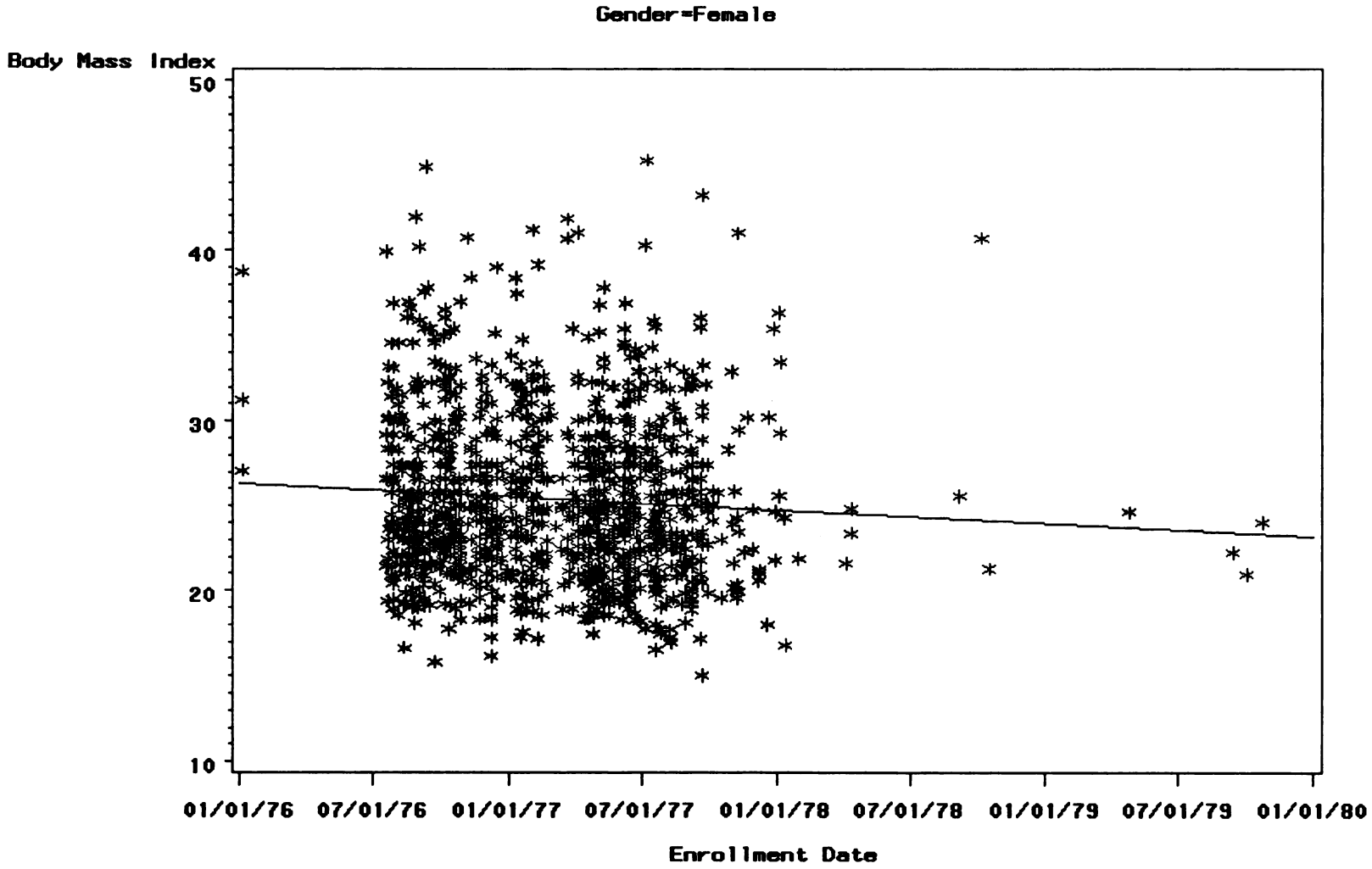


Figure 7: Body Mass Index in Relation to Date of Enrollment in Adult Women

APPENDIX B

ENROLLMENT QUESTIONNAIRE

MICHIGAN PBB COHORT

(SELECTED QUESTIONS)

MICHIGAN DEPARTMENT OF HEALTH

PBB HEALTH QUESTIONNAIRE

LONG TERM SURVEY

(Selected Questions)

2. ID # __ __ __ __ /__ /__ __
Family gp individual

3. 1=Completed, 2= Refusal, 3= Deceased

7. Date of interview or attempted interview:

__ __ /__ __ / __ __ 99= DK
Mo. Day Year

8. Observe race: 1= black, 2= white, 3= other, 9= DK

9. Observe sex: 1=female, 2=male.

10. How old were you on your last birthday? __ __ years

98= 99 or older; 99=DK

11. When were you born?
__ __ /__ __ / __ __ 98= 1898 or before, 99= DK
Mo. Day Year

18. What is your height and weight today?

WEIGHT __ __ __ lbs 99= DK

HEIGHT __ / __ __
ft in

67. Have you had sugar in your urine, high blood sugar or diabetes?

1= YES, at least one

2=NO, none/ DK

69. Did you see a doctor about this diabetes (sugar)?

1=YES

2=NO/ DK

SMOKING AND ALCOHOL INFORMATION:

ASK ONLY PERSONS AGED 16 OR OLDER

Would you answer a few questions about smoking and drinking?

__ NA= wrong age

__ Refused

101. Have you smoked at least 100 cigarettes during your entire life?

No ("Non-smoker"=1)

YES (smoker) → go to 102

102. Do you smoke cigarettes now?

NO ("Past smoker"=2)

YES ("Current smoker"=3)

9= DK

105. Do you ever use alcoholic beverages (such as liquor, wine, or beer) or are you a total abstainer?

NO ("Abstain")

YES ("presently use"= 1) → go to 106

106. Have you always been a total abstainer?

NO ("former user"= 2)

YES ("total abstainer"= 3)

APPENDIX C

RE-CHARACTERIZATION QUESTIONNAIRE

MICHIGAN PBB COHORT

(SELECTED QUESTIONS)

MICHIGAN DEPARTMENT OF PUBLIC HEALTH

INTERAGENCY CENTER ON HEALTH AND ENVIRONMENTAL QUALITY

LONG TERM HEALTH STUDIES

1990-91

OFFICIAL USE ONLY

Sex 1=Female

2=Male

3= Unknown/Missing

STATUS CODE

1. Questionnaire answered by person
2. Questionnaire answered by proxy
3. Interview refused this year
4. Unable to locate
5. Deceased. Date of death ____ ____ __ County of Death _____
   Mo Day Yr
6. Moved out of state
7. Send update questionnaire & newsletter- visit refused
8. Send newsletter only- refused further participation
9. wishes no more contact- refuses further participation

We would like to ask you some questions about your medical history.

3. What is your current weight? _____ pounds *(DO NOT INCLUDE FRACTIONAL POUNDS)*

Have you ever had diabetes? YES ____ NO ____

Has diabetes been a problem in the past year? YES ____ NO ____

Did you receive prescription medication for diabetes in the past year?

YES ____ NO ____

CODING:

1= YES YES YES

2= YES YES NO

3=YES NO YES

4= YES NO NO

5= NO NO NO

6= YES MAYBE* MAYBE

7= YES NO MAYBE

8= YES MAYBE NO

9= MISSING

10= DON"T KNOW

11= NOT APPLICABLE

* MAYBE= Have had, or taken prescription medication, but possibly more than one year ago based on the length of time having passed since the last update.

APPENDIX D

UPDATE FORM

MICHIGAN PBB COHORT

MICHIGAN DEPARTMENT OF COMMUNITY HEALTH

ENVIRONMENTAL EPIDEMIOLOGY

LONG-TERM PBB STUDY PERSONAL UPDATE 2000-2001

Please complete the following information **for the individual listed to the right.** If individual is deceased, give date of death: _____ «V2»-«V3»-«V4»

NAME CHANGE _____

«CURFIRST» «CURMID» «CURLAST»

ADDRESS CHANGE _____

«CURSTREE»

ADDRESS CHANGE _____

«CURCITY», «CURST» «CURZIP»

PHONE CHANGE: _____

«CURAREA» «CURPHONE»

SOCIAL SECURITY NUMBER _____ SS# «SOCNO»

DATE OF BIRTH «DOB»

Please check the appropriate box in **each** column for **each** of the following illnesses or medical conditions that apply to this individual.

Illness or Condition	Ever Had?		Had in the past 5 years?		Saw doctor for in the past 5 years?		Hospitalized for in the past 5 years?		Taken any prescription medication for in the past 5 years?	
	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO
Asthma										
Diabetes										
Rheumatoid arthritis										
Thyroid disease										
Systemic lupus erythematosus (SLE)										
Stiff or painful muscles or joints										
Wheezing or gasping for breath										

For women age 16-60: since **«SINCEUPD»,** have you given birth to any live-born infants? _____Yes _____No.

If yes, please list the names of the infants and dates of birth and if they were breast fed below.

Infant's Name	Date of Birth	Breast Fed	
		Yes	No
		Yes	No
		Yes	No
		Yes	No

Completed by: (your signature) _____ Date _____

EE-100 (Rev 10/00)

AUTHORITY: ACT 368, PUBLIC ACTS OF 1978. COMPLETION: VOLUNTARY

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