Centers for Disease Control and Prevention
Case Studies in Applied Epidemiology
No. 813-D11

A Mixed Bag in Michigan: The PBB Story

Student's Guide

Learning Objectives
After completing this case study, the participant should be able to:

- ☐ Describe the role of each government agency involved in a contaminated food situation.
- ☐ Discuss different options for studying the human health effects following an environmental exposure.
- ☐ Calculate sample size requirements for a community survey.
- ☐ Discuss the reasons for and limitations of a registry following an environmental exposure.

This case study was originally written by Clark Heath in 1981. It was revised by Tom Gomez and Richard Dicker in 1991. The current version was revised and updated by Richard Dicker in 2000 with input from Dori Reissman and the other EIS Summer Course instructors.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

PART I

In September 1973, a farmer in southwest Michigan noticed a decline in the feed consumption and milk production of his 400 dairy cows. Within 20 days, feed consumption had dropped by about 50% and milk production had declined from 13,000 lb. per day to 7,600 lb. per day. The farmer noted other clinical findings such as increased urination and lacrimation, but rectal temperatures remained normal. Some animals developed bruises, abscesses, abnormal hoof growth, hair loss, and thickening of the skin. Others developed cachexia and died within 6 months. The farmer and his veterinarian ruled out the usual infectious diseases, but could not establish a diagnosis.

Both men suspected that something was wrong with the feed. Each day, each cow was fed up to 15 lb. or more of 24%-protein pellets, plus a mixture of alfalfa and corn silage. Because the local corn silage was low in magnesium, magnesium oxide was added to the grain mixture at the feed plant before pelleting. The pellets were supplied by Farm Bureau Services, Michigan's largest feed distributor and a subsidiary of the state's most important farmer organization, the Michigan Farm Bureau.

Question 1: What might you do to determine whether the feed was the cause of the herd's unusual illness?

PART II

The Farm Bureau Services denied knowledge of any problems with the feed. Nevertheless, the farmer removed the feed from the main dairy farm, and took it to another farm where calves are raised. There, the farmer gave twelve 6- to 18-month-old heifers and bulls a steady diet of the suspected feed pellets. After 6 weeks, 5 of the 12 animals had died. Interestingly, rats and mice which had long been present in and around the feed storage building were completely eradicated. Autopsy findings of the calves consistently showed liver damage, leading the farmer and his veterinarian to postulate a hepatotoxin as the cause of the mysterious illness.

In early 1974, the feed company began its own feeding trials and chemical analyses. In March, gas chromatography of the feed left running by mistake during the lunch break unexpectedly revealed the presence of a series of peaks corresponding to the family of **polybrominated biphenyls** (PBBs). PBBs, marketed as *Firemaster*, were produced as a flame retardant for plastics by the Michigan Chemical Corporation (MCC). This company also sold magnesium oxide under the trade name *Nutrimaster* to Farm Bureau Services, which added the substance to dairy feed. According to MCC, these two products were distributed in distinctive color-coded bags: *Firemaster* in bright red and *Nutrimaster* in bright blue.

The U.S. Food and Drug Administration (FDA) was notified of the PBB finding on April 26, and immediately initiated inspections of feed mills throughout the state. Four days later, an FDA inspector discovered a half-empty paper brown bag in a Michigan feed mill. Stenciled across the top of the bag was the name, *Firemaster*. Further discussions with MCC representatives revealed that they had run out of color-coded bags in spring 1973, so they used plain brown 50-lb. bags for both *Firemaster* and *Nutrimaster*. They were distinguishable only by the name stenciled across the top. In May 1973, an estimated 10 to 15 bags of *Firemaster* were mistakenly shipped to feed mills as *Nutrimaster*. The *Firemaster*, similar to *Nutrimaster* in both consistency and color, was incorporated into feed pellets and sold to Michigan farmers. Thus, the mix-up had gone undetected for almost a year.

Question 2: Who are the stakeholders in this situation? What are their concerns? What are their responsibilities?

PART III

Farm Bureau Services feed containing *Nutrimaster* was immediately recalled. Shipments of Michigan dairy products outside the state were halted. The Michigan Department of Agriculture began testing animals and dairy products on farms suspected of PBB contamination. MCC recalled all *Nutrimaster* on May 2. On May 10, FDA established a farm quarantine guideline of 1 part per million (ppm) PBBs (fat basis) in milk and milk products. On that same date the first farm was quarantined by the Michigan Department of Agriculture based on a level of 34 ppm PBBs in milk fat. On May 29 and June 12, respectively, FDA established further quarantine guidelines of 0.3 ppm PBBs in animal feeds and 1 ppm PBBs in meat fat. (In November 1974, as a result of improved laboratory technology, these guidelines were lowered by FDA to 0.3 ppm in milk, meat, poultry, and dairy products, and 0.05 ppm in eggs and in feed. In October 1977, state law further reduced the limit in milk to 20 parts per billion (equal to 0.02 ppm).

The Michigan Department of Public Health (MDPH) was contacted in mid-May 1974, because of concerns regarding possible human health problems on several of the quarantined farms. By that time, approximately 50 dairy and 50 non-dairy farms had been quarantined.

Question 3: Picture yourself as the Director of the Michigan Department of Public Health, charged with the responsibility for assessing the human health impact of this chemical contamination problem. How might you proceed?

The chemical structure of PBBs is analogous to that of polychlorinated biphenyls (PCBs), with bromine atoms in place of chlorine atoms. In 1974, relatively little toxicologic information was available regarding PBBs, particularly their effects on human health. It was assumed, however, that PBBs might have characteristics similar to PCBs, perhaps with even greater biologic activity. A prominent feature of PCBs and related compounds is their marked tendency to concentrate in fat and hence to remain in tissues for a long time. Human health effects at relatively high doses in occupational exposure settings have included chloracne (a distinctive acne-like skin lesion), and with abnormalities in liver, kidney, and peripheral nervous system function. In rats, PCBs have been shown to produce hepatic cancer. Other animal studies have suggested that PCB exposure may produce immunologic alterations as well as fetal aberrations and abnormalities in growth and development.

MDPH decided its first priority was to determine the nature and extent of human exposure and to identify patterns of PBB-associated illness. MDPH epidemiologists, with the help of local health department staff, attempted to interview and examine all family members living on quarantined farms, plus other families identified by quarantined families as having consumed produce directly from quarantined farms. They identified over 250 persons living on quarantined farms and about 500 others who had been exposed by eating produce from such farms. By the end of July 1974, they had conducted comprehensive health interviews, either in person or by telephone, with over 90% of both

groups. In addition, they collected blood and urine samples for clinical laboratory testing (complete blood count, clinical chemistries, and urinalysis) from 211 participants. Samples of blood from these participants were also banked for future analysis.

No clear patterns of clinical illness were seen.

Question 4: With these general findings in hand, what kind of study, if any, would you do next? List and explain your reasons for doing whatever you propose.

PART IV

In the fall of 1974, MDPH epidemiologists conducted a study in which they collected interview, medical, and laboratory data from residents of quarantined dairy farms and from residents of an equal number of non-quarantined farms matched by geographic area and randomly selected from lists of dairy producers. Personal interviews were conducted with 298 participants: 165 from 25 quarantined farms and 133 from 25 non-quarantined farms. The interviewers collected detailed information regarding environmental exposures (including PBBs) and medical history, with emphasis on changes in health since mid-1973. In addition, 214 participants underwent physical examinations, electrocardiograms, standard clinical laboratory tests on blood and urine, and measurements of serum PBB level.

Question 5: What type of study is this? What are the particular strengths and potential weaknesses of this study design?

Table 1 shows the serum PBB levels found in adults and children from quarantined and non-quarantined farms.

Table 1. Serum PBB levels in residents of quarantined and non-quarantined farms, MDPH study, 1974

	Quarantined Farms				Non-Quarantined Farms			
	Adults		Children		Adults		Children	
Serum PBB (ppm)	#	%	#	%	#	%	#	%
<0.002	3	3.7%	0	---	21	28.4%	0	---
0.002-0.019	43	52.4%	8	28.6%	52	70.3%	29	96.7%
0.020-0.099	19	23.2%	10	35.7%	1	1.3%	1	3.3%
0.100-0.499	11	13.4%	3	10.7%	0	---	0	---
0.500-2.260	6	7.3%	7	25.0%	0	---	0	---
Total	82	100%	28	100%	74	100%	30	100%
Median PBB level (ppm)	0.014		0.035		0.003		0.006	

Question 5: What type of study is this? What are the particular strengths and potential weaknesses of this study design?

Question 6b: What types of graphs could you use to display the data in Table 1?

Question 6c: Using a separate sheet of paper, graph the data in Table 1.

Question 6d: Describe the data in Table 1 and in your graph(s).

Question 6e: What implications do these data have for future studies and for future public health action?

Questionnaire responses were examined for illness first occurring, or intensifying, after May 1, 1973. Of 78 different health questions asked, only 6 conditions showed sufficient numbers of positive responses to permit statistical analysis. These were rash, anxiety, tiredness, headache, numbness, and balance problems.

Question 7: Assuming that none of the 78 conditions was truly associated with quarantine status (e.g., under the null hypothesis for every condition), what is the probability that a statistically significant ($p < 0.05$) will be found for at least one of the 78 conditions?

In fact, no statistically significant differences between quarantined and non-quarantined groups were seen in frequency, severity, or duration of the 6 more common or the other 72 less common conditions. The frequencies of the 6 more common conditions by serum PBB level are shown in Table 2.

Table 2. Frequency of selected symptoms by serum PBB level, MDPH study, 1974

		Serum PBB (ppm)					
		< 0.002		0.002 - 0.019		0.020 +	
Condition		#	%	#	%	#	%
Rash	Increased severity	1	4%	5	5%	4	11%
Anxiety	Increased severity	2	8%	6	6%	7	19%
	Increased frequency	2	8%	3	3%	6	16%
Tiredness	Increased severity	3	12.5%	6	6%	9	24%
	Increased frequency	3	12.5%	4	4%	9	24%
Headache	Increased severity	2	8%	8	8%	4	11%
	Increased frequency	5	21%	9	9%	6	16%
Numbness	Increased frequency	1	4%	2	2%	2	5%
Balance	Increased severity	1	4%	5	5%	5	14%
Problems	Increased frequency	1	4%	5	5%	4	11%
Total Participants		24	100%	95	100%	37	100%

Question 8: Interpret these data. What are the limitations of these data?

By the end of February 1975, the Michigan Department of Agriculture had quarantined over 300 farms, with approximately 15,500 dairy cattle, 3,500 swine, 500 sheep, and 1,500,000 chickens. These animals, together with thousands of pounds of eggs and dairy products, were eventually destroyed. The economic problems caused by these agricultural control measures underscored public concern and uncertainty about the extent of the problem and its possible implications for human health. The PBB incident became a hot political issue in the race for Governor of Michigan. Such was the setting in which several further epidemiologic studies were developed over the next several years.

Within the human body, fat serves as the largest repository for PBBs. Concentrations in fat tissue provide a reliable index of body burden and exposure, but require invasive procedures. Breast milk concentrations correlate well with those in fat tissue, but can only be obtained from a small proportion of the population (lactating women). Serum levels are more easily obtained,

but correlate less well with fat tissue concentrations.

The observation made in the 1974 MDPH study that persons from non-quarantined farms had detectable levels of serum PBBs led to efforts to define more clearly the extent of PBB distribution in the general population of Michigan. One group of researchers proposed to do a population-based survey to measure PBB levels in breast milk of lactating Michigan women.

Question 9: What factors enter into the computation of required sample size for a population-based survey?

The survey was designed to yield separate estimates of detectable PBB levels in breast milk for the state's two geographically distinct peninsulas, because the distribution of contaminated animals and quarantined farms suggested that PBB were more widely distributed in the lower peninsula (LP) than in the upper peninsula (UP). The estimated population of the LP in 1976 was 8,777,000; the UP estimated population was 327,000. The investigators judged it adequate to make peninsula-wide inferences using an 85% confidence interval (t=1.44) with width plus or minus 10%.

Question 10a: Estimate the number of births in one week in the LP, and the number of births in one month in the upper peninsula. Use an estimated U.S, population of 250,000,000, and roughly 3,000,000 births per year, and assume no seasonality in births. (Note: the U.S. population and number of annual births are now higher.)

To estimate prevalence in a large population, the formula for required sample size of a large population is:

$$n = t2p\ (1 - p) / d^2$$

where p = guesstimated prevalence in population (use 0.5 if you don't know)
t = Z-score based on desired confidence level (e.g., 1.96 for 95% confidence)
d = acceptable tolerance (precision, width of confidence interval), e.g., 10%

If the population is small, so that the sample n comprises > 5% of the total population N, calculate final n as:

$$n_f = Nn / (N + n)$$ where N = total population

Question 10b: Calculate the required sample size for each peninsula, assuming that the prevalence of detectable PBBs in lactating women was 25%, 50%, or 75%, and using a lactating LP population of 3,000 and lactating UP population of 300.

Question 10c: Calculate the sample size if the investigators had wanted a 95% confidence level (t = 1.96). Ignore the finite population correction.

Question 10d: Calculate the sample size if the investigators had wanted a 5% tolerance (use t = 1.44). Ignore the finite population correction.

Question 10e: What do you conclude about the factors in the formula?

The investigators, using slightly different values and assumptions, calculated the necessary sample sizes as 41 in the UP and 55 in the LP. They defined the LP population as all women who gave birth in hospitals during the week of August 15-21, 1976 and who chose to breastfeed. Because of the much sparser population in the UP, the UP population was defined as all women who gave birth during the month of August and who chose to breastfeed.

"To obtain a random sample, hospitals throughout the state were asked to identify women who had given birth during the study period. Post-partum women were sequentially assigned numbers as hospitals were contacted. Since at the time of sampling the actual number of births could not be known, a high estimate of 3400 births in the LP was derived based on the previous year's data. Information was then collected only for women matching 330 numbers selected randomly from the integers 1 to 3400. The actual number of live births in the LP for the study period was found later to be 2537 (300 in the UP).

"54% of women matched to random numbers decided not to breastfeed and they were not contacted again. An attempt was made to contact, screen, and enroll a random subset of the remaining matched women. This random subset contained 83 women; 21 were excluded because they too were not lactating. A further 3 had stopped breastfeeding before samples were collected. Of the 59 remaining women, 5 could not be contacted and 1 refused to participate...

"In the UP, through a similar process, a random sample of 49 lactating women was selected. Three could not be contacted, 4 refused to participate, and 42 provided samples..."

Question 11: Calculate response rates for women in the upper and lower peninsulas. Would you worry about biases with this study design and selection process?

The results of this survey are shown in Table 4.

Table 4. Distribution of PBBs in human breast milk fat samples in Michigan

	Lower Peninsula		Upper Peninsula	
PBB level (ppm)	#	%	#	%
Non-detectable	2	3.8%	24	57.1%
< 0.05	16	30.2%	15	35.7%
0.05 - 0.09	17	32.1%	2	4.8%
0.10 - 0.49	15	28.3%	1	2.4%
0.50 - 0.99	2	3.8%	0	–
1.0 and above	1	1.9%	0	–
Total	53	100%	42	100%

Question 12: What proportion of women in the two samples had detectable levels of PBBs in their breast milk? Assuming these samples are representative of the two parts of Michigan, calculate a single overall statewide estimate the proportion of women with detectable PBB levels.

Additional studies have been conducted by the MDPH, federal agencies, and researchers. One study, started in April 1976, was a MDPH / CDC long-term follow-up study. This study focused on persons living on quarantined farms or consuming produce received directly from such farms, to monitor the appearance of possible non-acute health effects in PBB-exposed individuals. Plans for the study gave particular emphasis on assessing eventual patterns of cancer occurrence, especially liver cancer.

Study participants included:

1. residents of quarantined farms,
2. recipients of produce from quarantined farms,
3. persons living near quarantined farms (the "non-exposed" group from the 1974 MDPH study),
4. residents of non-quarantined farms with low PBB levels, including recipients of produce from those farms,
5. Michigan Chemical Corporation workers and their families, and
6. volunteers who contacted the MDPH and requested to participate in the study.

Question 13: Investigators asked each potential participant to provide his / her "informed consent" before enrolling in the study. What would you include in your Informed Consent form?

The number of subjects involved in this follow-up study, and their degree of participation, are given in Table 5.

Table 5. Participation and median blood PBB levels, MDPH/CDC long-term follow-up study.

Group	Persons contacted	Persons Enrolled	Percent Enrolled	Median blood PBB (ppm)
Quarantined farms				
Residents	2,246	2,150	96%	0.004
Produce recipients	1,562	1,488	95%	
Nearby residents	60	57	95%	
Low level farms				
Residents and recipients	356	329	92%	0.002
MCC workers and family members	335	261	78%	0.0045
Volunteers	421	377	90%	0.001
Total	4,980	4,662	94%	0.003

Generally, PBB levels were a little higher in males and in younger participants. The highest rate of subjective complaints (tiredness, headaches, nausea, numbness, and joint pain) was among the volunteers.

Question 14: How many cases of cancer, and of hepatic cancer in particular, would you expect to occur in the cohort overt 20 years (1973-1992), given expected average annual crude incidence rates of 294.0 and 2.0 cases per 100,000 respectively? (What assumptions does one accept in making this crude comparison?)

Question 15a: What is a registry?

Question 15b: List and discuss reasons for and against launching a long-term registry follow-up effort in this particular health hazard situation.

PART V - CONCLUSION

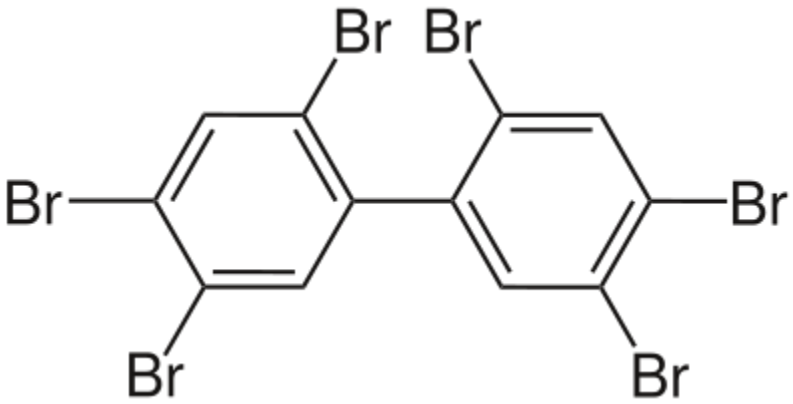
Authorities believe that 10 to 20 fifty-pound bags of *Firemaster* were sent by mistake in place of *Nutrimaster* to the Michigan Farm Bureau Services. The consequences of this mix-up were enormous, since the error went undetected for almost a year. As a result, most Michigan residents consumed contaminated milk, beef and other products – some estimates report nearly 90% of Michigan's residents have measurable PBB levels in their bodies[1]. Authorities estimate that nearly 30% of the potential human exposure had already occurred when health problems in livestock were recognized initially in 1974; and 75% of the exposure occurred before the toxicant was identified as PBB[2].

More than 500 of Michigan's dairy and poultry farms were quarantined in 1973 and 1974. More than 30,000 cattle, 3,500 swine, 500 sheep and 1.5 million chickens died, and 5 million eggs had to be destroyed. In addition, 788 tons of feed and dairy products also had to be destroyed, including 3,000 lb. of butter, 18,000 lb. of cheese, and 34,000 lb. of dry milk. By 1987, the State of Michigan had spent between $75 to $100 million on PBB cleanup and related expenses. The Michigan Chemical Company settled with the Michigan Farm Bureau Services for $20 million and together the 2 firms settled about 700 claims totaling $40 million. There has also been a $14 million settlement between Velsicol (the parent company for MCC) and the State of Michigan.

Michigan populations represent some of the largest cohorts exposed to polyhalogenated biphenyls (PCBs and PBBs)[3]. In addition to the more than 4,000 farm family members exposed to PBBs in 1973-74, over 200 farm family members were exposed to PCBs that were used to line their silos, and about 600 Lake Michigan shoreline residents ate large amounts of fish contaminated with PCBs. To date, neither the MDPH nor CDC has found any syndrome or sign of human illness clearly attributable to exposure to PBB. In general, studies of various PHB-exposed populations to date have not shown a clear increase in mortality or cancer incidence. However, there is some evidence of adverse reproductive outcomes although the effects appear to be small[3]. In addition, at least one investigator has found persistence of low numbers and impaired functions of T lymphocytes observed some 8 years after the onset of PBB exposure.

The Michigan Chemical Corporation stopped producing PBB on November 20, 1974. In 1977, the federal government banned all manufacturing of PBB in the U.S.

As of January 2000, the MDPH/CDC follow-up study continues to be funded, and family participation remains high. However, questions are being raised about how long to continue the study in the absence of any evidence or even suggestion of clear adverse health effects.



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