CENTERS FOR DISEASE CONTROL
USDA PVPCP Epidemiology Course, 1991

A MIXED BAG IN MICHIGAN

Objectives

After completing this case study, the student should be able to:

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

Part I

In September 1973, a farmer in southwest Michigan noticed a decrease 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 hematomas, abscesses, abnormal hoof growth, alopecia, and thickening of hte skin. Others developed cachexia and died within 6 months. The farmer and his veterinarian ruled out the usual infectious diseases, but could not diagnose the illness.

Both men suspected something 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?

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Part II

The company 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 12 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 revealed the presence of an unexpected 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), notified of the PBB finding on April 26, immediately initiated inspections of feed mills throughout the state. On April 30, 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.

QUESTION 2: What should the Michigan Department of Agriculture do now?
What should the U.S. Department of Agriculture do now?
What should the U.S. Food and Drug Administration do now?
What other agencies, if any, should be involved? What should they do?

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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 ppm PBB (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 PBB in milk fat. On May 29 and June 12, respectively, FDA established further quarantine guidelines of 0.3 ppm PBB in animal feeds and 1 ppm PBB 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 ppb.)

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 state epidemiologist in Michigan, charged with the responsibility for assessing the human health impact of this chemical contamination problem. How would you proceed?

The chemical structure of PBB is analogous to that of polychlorinated biphenyls (PCBs), with bromine atoms in place of chlorine atoms. At the time of the Michigan problem, relatively little toxicologic information was available regarding PBB, particularly with respect to human health effects. It was assumed, however, that PBB might have characteristics similar to PCB, perhaps with even greater biologic activity. A prominent feature of PCB 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 been associated with chloracne (a distinctive acne-like skin lesion), and with abnormalities in liver, kidney, and peripheral nervous system function. In rats, PCB has been shown to produce hepatic cancer. (Subsequent studies have shown similar oncogenic effects in rats fed PBB.) Other animal studies have suggested that PCB exposure may produce immunologic alterations as well as fetal aberrations and abnormalities in growth and development.

The first action taken by MDPH epidemiologists, with the help of local health departments, was to interview and examine families living on quarantined farms. By the end of July 1974, interviews in person or by telephone had been conducted with over 90% of both quarantined farm families and other families identified by quarantined families as having consumed produce directly from quarantined farms. In 211 persons, extensive health questionnaire interviews were conducted and samples of blood and urine were collected for clinical laboratory testing (complete blood count, urinalysis, SMA-12). The purpose of this work was to identify patterns of PBB-associated illness and to define the nature and extent of human exposure. It appeared from information gathered that over 250 persons had been exposed on quarantined farms and that about 500 others had also been exposed by eating produce from such farms. 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.

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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 PBB) and medical history, with emphasis on changes in health since mid-1973. In 214 persons, physical examinations were performed, as well as electrocardiograms, standard clinical laboratory tests on blood and urine, and measurements of serum PBB level.

QUESTION 5: 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.

Serum PBB (ppm)	Quarantined Farms				Non-Quarantined Farms			
	Adults		Children		Adults		Children	
	#	%	#	%	#	%	#	%
<0.002	3		0		21		0	
0.002-0.019	43		8		52		29	
0.020-0.099	19		10		1		1	
0.100-0.499	11		3		0		0	
0.500-2.260	6		7		0		0	
Total	82		28		74		30	
Median level	0.014		0.035		0.003		0.006	

QUESTION 6: Compute percent distributions, then graph and describe the data in Table 1. 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 (10 or more) to permit statistical analysis. These were rash, anxiety, tiredness, headache, numbness, and balance problems.

QUESTION 7: Assuming that none of the 78 conditions were truly associated with quarantine status (e.g., under the null hypothesis for every condition), what is the likelihood that the p-value for one condition would be equal to or less than 0.05?

In fact, no 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.

Condition		Serum PBB (ppm)					
		< 0.002		0.002 - 0.019		0.020 +	
		#	%	#	%	#	%
Rash	Increased severity	1	4%	5	5%	4	11%
Anxiety	Increased severity	2	8%	6	6%	7	20%
	Increased frequency	2	8%	3	3%	6	17%
Tiredness	Increased severity	3	12.5%	6	6%	9	26%
	Increased frequency	3	12.5%	4	4%	9	26%
Headache	Increased severity	2	8%	8	8%	4	11%
	Increased frequency	5	21%	9	9%	6	17%
Numbness	Increased frequency	1	4%	2	2%	2	6%
Balance Problems	Increased severity	1	4%	5	5%	5	14%
	Increased frequency	1	4%	5	5%	4	11%
Total Participants		24	100%	97	100%	35	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. 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 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 10: Calculate the required sample size for each peninsula, assuming that the prevalence of detectable PBBs in lactating women was 25%, 50%, or 75%.

The investigators 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 were identified. 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. Describe the strengths and weaknesses of this sample 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

PBB level (ppm)	Number of women	
	Lower peninsula	Upper peninsula
Non-detectable	2	24
< 0.05	16	15
0.05 - 0.09	17	2
0.10 - 0.49	15	1
0.50 - 0.99	2	0
1.0 and above	1	0
Total	53	42

QUESTION 12: Interpret the data in Table 4. Extrapolate the findings to the entire Michigan population. Discuss the limitations of this extrapolation.

In 1976, two further health studies were undertaken regarding residents exposed to PBB. One study was a long-term follow-up study jointly managed by MDPH and CDC. The other was a cross-sectional study conducted by the Mt. Sinai School of Medicine. Both studies have focused on persons living on quarantined farms or consuming produce received directly from such farms.

The long-term follow-up study was begun in April 1976 to monitor the possible appearance of 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. MCC workers and their families, and
6. volunteers.

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

Table 5. Enrollment in MDPH/CDC long-term follow-up study.

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

QUESTION 13: 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 14: List and discuss reasons for and against launching a long-term registry follow-up effort in this particular health hazard situation.

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Part V - CONCLUSION

The consequences of the contamination in Michigan have been enormous, since the error went undetected for a number of months. As a result, most Michigan residents consumed contaminated milk, beef and other products and some estimates report nearly 90% of Michigan's residents have measurable PBB levels in their bodies[1]. It is noteworthy 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]. Approximately 295 (650 kg) of PBB were involved in the incident, of which about 250 kg was fed to livestock; with 50% excreted in the feces. It is estimated that 94 kg of PBB entered the Michigan population before PBB was detected and regulatory actions were taken [2]. It is clear, according to Fries[2], that early detection is much more important for reducing human exposure from a single episode of chemical contamination than is the stringency of regulatory action. 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 (3,000 lb of butter, 34,000 lb of dry milk). The State of Michigan has spent (as of a 1987 reference[1]) 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 (PHBs)[3]. These include about 4000 Michigan farmers exposed during the PBBs contamination incident in 1973-74, over 200 members of farm families exposed to PCBs that were used to line their silos, and about 600 Lake Michigan shoreline residents who ate large amounts of fish contaminated with PCBs. To date, the Michigan Department of Public Health has not 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 although there is some evidence of adverse reproductive outcomes although the effects appear to be small[3].

In addition to collecting interview and medical record data from members of these cohorts, periodic measurements of serum and adipose PHB levels have been made. These studies of PHB-exposed populations have shown a correlation of blood and adipose PBB and PCB levels with exposure, but as mentioned, no convincing evidence of toxicity due to these exposures has been found[3]. The Michigan Department of Public Health states that more intensive study is needed to determine if subtle, adverse effects have occurred in members of each cohort or their offspring[3].

Based on longitudinal studies of PBB-exposed Michigan farmers undertaken in 1976-77 and again in 1981-83 by Bekesi et al.[4], the presence of a toxic syndrome related to this chemical has been established. This syndrome is characterized by effects on the neurological and musculoskeletal organ systems in a large segment of the Michigan residents. The low numbers and impaired functions of T lymphocytes observed some 8 years after the onset of PBB exposure in the studied group of Michigan dairy farm residents suggest persistence of a PBB-induced immune deficiency.

REFERENCES

1. Aust SD, Millis CD, Holcomb, L. Relationship of basic research in toxicology to environmental standard setting: the case of polybrominated biphenyls in Michigan. Arch Toxicol. 1987; 60:229-37.

2. Fries GF. The PBB episode in Michigan: An overall appraisal. Crit Rev Toxicol. 1985; 16:105-56.

3. Kamrin MA, Fischer LJ. Workshop on human health impacts of halogenated biphenyls and related compounds. Environ Health Perspect. 1991; 91:157-164.

4. Bekesi JG, et al. Immunotoxicity: Environmental contamination by polybrominated biphenyls and immune dysfunction among resident of the state of Michigan. Cancer Detect Prev Suppl. 1987; 1:29-37.

5. Jackson TF, Halbert FL. A toxic syndrome associated with the feeding of polybrominated biphenyl-contaminated protein concentrate to dairy cattle. J Am Vet Med Assoc 1974;165:437-439.

6. Brilliant LB, Wilcox K, Von Amburg G, et al. Breast-milk monitoring to measure Michigan's contamination with polybrominated biphenyls. Lancet 1978;2:643-646.

7. Landrigan PJ, Wilcox KR, Silva JT, Humphrey HEB, Kauffman C, Health CW. Cohort study of Michigan residents exposed to polybrominated biphenyls: epidemiologic and immunologic findings. Ann NY Acad Sci 1979;320:284-294.

8. Anderson HA, Wolff MS, Lilis R, et al. Symptoms and clinical abnormalities following ingestion of polybrominated-biphenyl-contaminated food products. Ann NY Acad Sci 1979;320:684-702.

9. Wickizer TM, Brilliant LB, Copeland R, Tilden R. Polychlorinated biphenyl contamination of nursing mothers' milk in Michigan. Am J Public Health 1981;71:132-137.

10. Wolff MS, Anderson HA, Selikoff IJ. Human tissue burdens of halogenated aromatic chemicals in Michigan. JAMA 1982;247:2112-2116.

11. Reich MR. Environmental politics and science: the case of PBB contamination in Michigan. Am J Public Health 1983;73:302-313.