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BREAST-MILK MONITORING TO MEASURE MICHIGAN'S CONTAMINATION WITH POLYBROMINATED BIPHENYLS

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Summary In 1973 and 1974, several thousand Michigan dairy farms were contaminated by polybrominated biphenyls (P.B.B.) as the result of an industrial accident. An unknown quantity of contaminated meat and dairy products entered the food chain before contaminated farms were quarantined. To determine the extent of human exposure, P.B.B. concentrations were measured in human breast milk, which was collected in a random-sample survey from nursing mothers throughout Michigan. 96% of 53 samples from Michigan's lower peninsula and 43% of 42 samples from the less densely populated upper peninsula contained detectable levels of P.B.B. These data indicate that about 8 million of Michigan's 9·1 million residents have detectable body burdens of P.B.B.

Introduction

THE polybrominated biophenyls (P.B.B.) were widely employed until recently as flame retardants in the plastics industry. Commercial P.B.B. consists principally of hexa-brominated biphenyl, but also contains measurable quantities of the di- through octa-brominated isomers, as well as traces of brominated naphthalenes.[1] In 1973 and 1974, as the result of a packaging and shipping error, several hundred pounds of P.B.B. were substituted for magnesium oxide, a dairy-cattle nutritional supplement, and distributed in cattle feed throughout Michigan. In exposed cattle a devastating and often fatal syndrome developed—anorexia, weight-loss, epidermal changes, decreased milk production, and increased fetal wastage.[2–4] To limit human consumption of meat and dairy products contaminated with the chemical, 800 farms were quarantined and over 30 000 cattle, 3 500 swine, and millions of chickens and eggs were destroyed. The Michigan Department of Agriculture termed the event "the most costly and disastrous accidental contamination ever to occur in United States agriculture".[5] An estimated 10 000 to 12 500 persons who lived on contaminated farms or who had directly received the produce of those farms were heavily exposed to P.B.B., nearly all having detectable blood-levels of the chemical.[6] Some exposures were occupational, but most resulted from the ingestion of contaminated meat and dairy products. Human exposure to P.B.B. was initially assumed to be limited to this group.

In June, 1976, during a screening survey for pesticide residues, the laboratory of the Michigan Department of Public Health discovered that breast milk from 4 of 5 Michigan mothers, none of them from quarantined farms, contained P.B.B. The single woman with a Michigan address whose milk was negative for P.B.B. was a recent immigrant to the United States. She had arrived in Michigan after the bulk of P.B.B.-contaminated food had been removed from the state's food chain. 5 women from other states, tested at the same time, had no traces of P.B.B. in their milk. To document more fully the extent of human breast milk contamination, we collected milk specimens from a probability sample of nursing mothers throughout the state. Because of the highly lipophilic nature of P.B.B. and an apparently stable partition of the chemical in blood, adipose tissue, and milk fat, the survey would provide information about P.B.B. contamination in the state's general population.

Study Population and Methods

Our objectives were, first, to estimate the proportion of lactating women in Michigan with detectable P.B.B. in breast milk, and, second, to use the results of the breast-milk survey to estimate the levels of P.B.B. in the general population of the state.

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 P.B.B. were more widely distributed in the lower peninsula (L.P.) than in the upper peninsula (U.P.). To meet the first objective, we judged it adequate to make peninsula-wide inferences using an 85% confidence interval with width plus or minus 10%. On the assumption that 50% of lactating women in Michigan would have detectable P.B.B., the necessary sample sizes were reckoned at 41 in the U.P. and 55 in the L.P. The population in the L.P. from which the sample was drawn consisted of all lactating women who gave birth in hospitals during the week of Aug. 15–21, 1976. In the U.P., because of a much sparser population, all lactating women who gave birth during the month of August were included in the survey population. Since the distribution of P.B.B. levels was known to be highly skewed, we chose the population median and percentiles in preference to mean and standard deviation as measures for statistical comparison.

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 L.P. 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 L.P. for the study period was found later to be 2537 (300 in the U.P.).

54% of women matched to random numbers decided not to breast-feed and they were not contacted again. An attempt was made to contact, screen, and enrol 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 breast-feeding before samples were collected. Of the 59 remaining women, 5 could not be contacted and 1 refused to participate. The 53 women who provided samples of milk represented a response-rate of 90%.

In the upper peninsula, through a similar process, a random sample of 49 lactating women were identified. 3 could not be contacted, 4 refused to participate, and 42 provided samples—a response rate of 86%.

Women who agreed to participate were sent a questionnaire and a kit containing supplies and instructions for obtaining breast-milk samples by manual expression and for storing them until collection by local health departments. Results were sent to each participant's physician.

TABLE I—DISTRIBUTION OF P.B.B. IN HUMAN BREAST-MILK SAMPLES IN MICHIGAN

P.B.B. range in breast-milk fat in p.p.m.	No. of Women	
	Lower peninsula	Upper peninsula
Total	53	42
Non-detectable	2	24
<0·05	16	15
0·05–0·1	17	2
0·1–0·5	15	1
0·5–1·0	2	—
1·0 and above	1	—

Chemical Analysis

Breast-milk samples were tested for P.B.B. by the Michigan Department of Public Health. The method was that of the Food and Drug Administration for pesticides in milk, on a micro-scale,[7 8] omitting the acetonitrile partitioning step to improve recoveries of P.B.B.

Results

51 (96%) of 53 breast-milk samples from women in the L.P. contained detectable P.B.B. The median was 0·068 p.p.m., the highest 1·2 p.p.m. In the U.P., 43% of samples had detectable P.B.B. The highest value in the U.P. was 0·320 p.p.m.—about a quarter the highest value found in the lower peninsula.

Table I shows the number of samples falling within selected ranges of P.B.B. values. The skewness of the sample data and the difference between peninsulas are obvious. The confidence limits for the percentiles corresponding to certain P.B.B. levels are displayed in fig. 1 for the more heavily populated L.P.

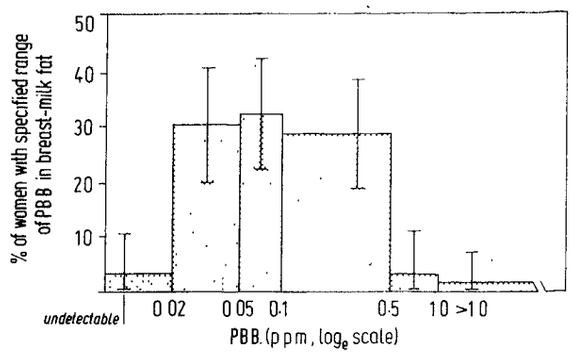

Fig. 1—85% confidence intervals about the percentage of lower-peninsula women with a specified range of P.B.B. in breast milk.

At the time of this study, there were no conclusive data on the toxicity of P.B.B. in man. We were therefore unable to specify a "safe" level of P.B.B. in breast milk or otherwise to advise mothers on the relative risks and benefits of breast-feeding at various P.B.B. levels. Charts such as table II were distributed to all physicians in the state, and these helped to put individual values in the general context.

Discussion

There is no reason to believe that P.B.B. consumption would have been limited to women who subsequently became pregnant, lactated, and were randomly chosen for this study. These data, therefore, are presumptive evidence that most people in Michigan have detectable levels of P.B.B.

There are many drawbacks to using these data for quantitative estimation of P.B.B. body-burdens in the entire population. First, the study included only women 15–45 years old. It is possible that lactating women have dietary preferences which affect the quantity or type of food consumed. Women who breast feed may have different socioeconomic status and therefore differential risk of dietary exposure to P.B.B. And physiological changes during pregnancy or lactation may influence the mobilisation of P.B.B. between body compartments and thus distort the relationship between total body burden and P.B.B. concentration in milk relative to other tissues.

Despite such reservations, these are the only data on P.B.B. exposure derived from a probability sample in the state of Michigan, and they may give a crude indication of the number of people with detectable P.B.B. in their bodies. Of the 1976 population of 9 104 000, 8 777 000

TABLE II—RANGE FOR PERCENTAGE OF LOWER AND UPPER PENINSULA WOMEN WITH P.B.B. LEVELS EXCEEDING SPECIFIED LEVELS IN BREAST-MILK FAT

Range*	% Lower peninsula	% Upper peninsula
Detectable	89·5–99·2	31·8–53·9
0·05 p.p.m.	56·7–75·4	2·3–16·2
0·1 p.p.m.	24·6–43·3	0·1– 9·8
0·5 p.p.m.	1·8–13·0	
1·0 p.p.m.	0·1– 7·8	

*Each range is an 85% confidence interval about the true percentage of lactating women in Michigan's general population exceeding those levels and takes sampling error into account.

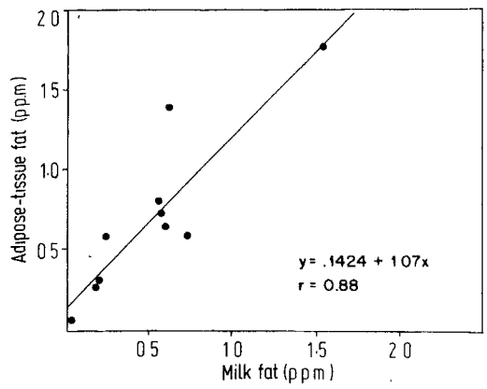

Fig. 2—P.B.B. concentrations in adipose-tissue and breast-milk fat.

lived in the L.P. and 327 000 in the U.P. Extrapolation of 85% confidence intervals to the general public yields an estimate of 7·9 to 8·7 million people in the lower peninsula with detectable P.B.B.—if the nursing mothers are representative of the total population. The estimate in the U.P. is 104 000–176 000 people. These calculations suggest that 9 out of 10 people in the state have been exposed to P.B.B.

We would expect similar results if adipose tissue of nursing mothers were used instead of breast milk. Fig. 2 displays ten paired specimens of adipose tissue and breast milk showing good correlation (r=0·88) and almost equivalent values (1·07:1). However, if blood were used as the surveillance tissue, we would expect only about 3 000 000 Michigan residents to have detectable P.B.B. Fig. 3 displays P.B.B. analyses done on paired specimens of breast milk and serum. There is a reasonably good correlation (r=0·81). However, in the Michigan Department of Public Health laboratory, gas chromatography with electron-capture detection gives a limit of detection in venous blood of 0·001 p.p.m., which corresponds to 0·1 p.p.m. in breast milk. Of the 51 women in the L.P. with detectable P.B.B. in milk, only 18 had levels exceeding 0·1 p.p.m. As a surveillance tissue blood seems to be less than half as sensitive as breast milk.

The U.S. National Human Pesticide Monitoring Program measures human exposure through a proportional, stratified random sample of adipose tissues collected by cooperating pathologists from post-mortem and surgical specimens.[9 10] However, it is difficult to translate necropsy or surgical-biopsy values into population inferences. Patients undergoing surgery are an unhealthy part of the population, and tissue taken after death presents questions of decomposition, chemical reaction, and even intertissue migration. Previous investigators have analysed adipose tissue,[11–20] serum,[17–28] placenta,[28 29] urine,[30–32] and hair.[33 34] While serum is more convenient, adipose tissue is often favoured because many pesticides and toxic chemicals are fat-soluble. In our experience breast milk is easily available; it does not require invasive procedures and lends itself well to probability samples of the population.

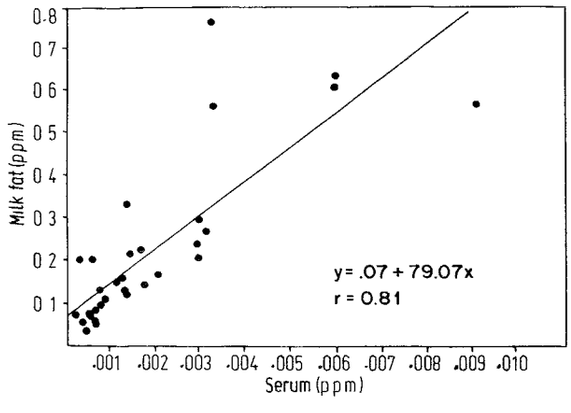

Fig. 3—P.B.B. concentrations in milk fat and serum.

Before recommending breast milk as a surveillance tissue for other lipophilic chemical pollutants, certain clarifications are needed. Because the breast is emptied only periodically, there may be wide fluctuations in the quantity of chemical in each "batch" of milk. Analysis of milk fat (which comprises about 4% of breast milk) seems to reduce this fluctuation, because the chemical

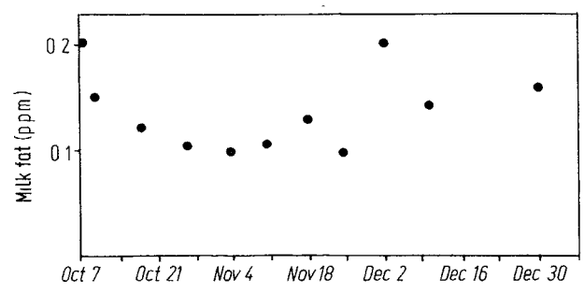

Fig. 4—P.B.B. concentrations in milk fat of a woman sampled repeatedly.

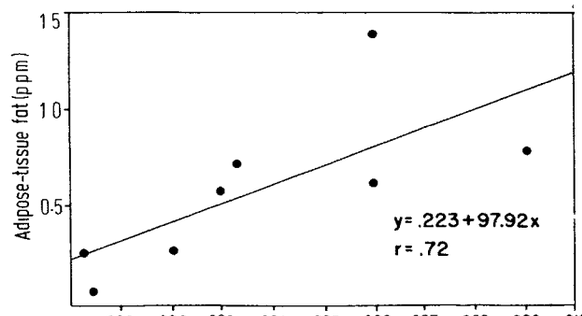

Fig. 5—P.B.B. concentrations in adipose tissue and serum of lactating women.

pollutant is usually passively dissolved in fat.[35] A series can be done to see if chemical levels remain constant over time. We were able to study one woman repeatedly over three months (fig. 4). While there were day-to-day variations, there was no real secular trend.

Earlier investigators[14 15 18 21] tried to find useful, predictable, and repeatable relationships between insecticide levels in breast milk and other tissues. Dyment[22] preferred serum to breast milk after finding no linear relationship between milk and serum levels of four principle chlorinated insecticides. Our data for P.B.B. (which unlike many pesticides are metabolised little and are excreted from the body only in milk) indicate stable linear relationships between adipose, milk, and serum. The largest set of paired P.B.B. values consists of simultaneous specimens of blood and adipose tissue taken from 221 Michigan residents.[36] A high correlation was seen between P.B.B. concentration in these two tissues (r=0·951) and, in the 132 instances where both values

were above detection limits, the ratio of adipose to serum P.B.B. concentrations was 363/1, indicating the high lipid partitioning of the chemical. This ratio fell to 100/1 when only lactating women were studied (fig. 5) showing that fat mobilisation in lactating women seems to alter P.B.B. partitioning. This mobilisation of P.B.B. out of adipose and into milk fat may help explain the nearly equal partitioning of P.B.B. between milk fat and adipose-tissue fat in our small sample of paired specimens.

In our industrial society we can expect further episodes of environmental contamination with little-studied fat-soluble chemicals. If there is a stable relationship between the concentrations of chemical in various tissues, our experience suggests that breast milk can usefully indicate the extent of population exposure.

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Requests for reprints should be addressed to L.B.B.

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AMINOGLUTETHIMIDE IN TREATMENT OF METASTATIC BREAST CARCINOMA

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Summary 42 patients with metastatic breast carcinoma were treated with aminoglutethimide, which inhibits adrenal steroid hormone synthesis. Treatment was stopped in 2 patients before response could be assessed; of the other 40, 15 (37·5%) had an objective response, 1 (2·5%) showed a response in bone but not in soft tissue, and 4 (10%) had complete or very great relief of metastatic bone pain but no radiological evidence of improvement. 19 (53%) of 36 patients with bone metastases responded to treatment (15 had X-ray evidence and 4 had pain relief), as did 5 (45%) of 11 patients with soft tissue metastases, 2 (25%) of 8 with malignant marrow infiltration, 1 (14%) of 7 with lung metastases, and none of 13 with liver metastases. Response was commonest in patients who had previously responded to other forms of endocrine therapy. Side-effects, usually mild and transient, occurred in a few patients; the most important were an initial period of somnolence in 9 patients and a rash in 5.

Introduction

SURGICAL adrenalectomy, first described as a treatment for metastatic breast carcinoma in 1952,[1] has proved to be effective; the overall response-rate is around 30–40%,[2–7] responses being most likely in patients who have previously responded to oophorectomy.[5–7] However, the operation has a significant morbidity[8] and a mortality of 4%–15%.[3 6] Another disadvantage is that often the medical condition of patients in whom the operation might be contemplated is poor; and permanent postoperative hormone replacement is required. For these reasons, effective medical inhibition of steroid hormone production would be attractive.

Aminoglutethimide, developed as an anticonvulsant in the 1950s, was withdrawn from clinical use after reports that it caused adrenal insufficiency.[9] The drug was subsequently shown to suppress synthesis of all adrenal steroid hormones by inhibiting the first step in their metabolic pathway, the enzymic conversion of cholesterol to pregnenolone (fig. 1).[10] It was suggested that aminoglutethimide might be used to achieve a "medical