

Half-life of Polybrominated Biphenyl in Human Sera

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Polybrominated biphenyl (PBB), a flame-retardant material, was introduced into the food chain in Michigan in 1973 due to a manufacturing and distribution mistake. Following public concern about the long-term health effects of PBB in humans, a cohort of PBB-exposed Michigan residents was assembled in 1975. We initiated this study to determine the half-life of PBB in human sera and to understand how continued body burden relates to the possible adverse health consequences of PBB exposure. To determine the half-life, eligible persons were selected from the cohort if they had at least two PBB measurements 1 year apart and had an initial level ≥ 20 ppb. There were 163 persons who met the criteria with a median PBB level of 45.5 ppb. The estimated half-life is 10.8 years (95% CI, 9.2–14.7 years). The body burden of PBB in exposed persons will decrease only gradually over time. For persons with an initial level of 45.5 ppb of PBB, it will take more than 60 years for their PBB levels to fall below the current level of detection of 1 ppb. Key words: half-life, human sera, Michigan, polybrominated biphenyl. *Environ Health Perspect* 103:272–274 (1995)

Polybrominated biphenyl (PBB), a toxic polyhalogenated aromatic hydrocarbon with bromine substituted on a biphenyl ring, was manufactured in the early 1970s as a fire retardant for use in thermoplastics and carpets. Most laboratory tests identify the 2,4,5,2',4',5'-hexabromobiphenyl component of PBB; this congener occurred in the largest amounts in commercial preparations (1). PBB is stable and resists organic degradation; it is insoluble in water and highly lipophilic (2). PBB in blood sera can be measured by isothermic gas chromatography with electron capture detection, with a lower limit of detection of 1 ppb and an analytic coefficient of variation of between 7.1 and 14.0% (3).

PBB came to the attention of the public in 1974 when it was discovered that about 1000 pounds had been accidentally substituted for magnesium oxide as an additive for cattle feed in Michigan in 1973. Meat and dairy products from contaminated herds were distributed throughout Michigan. To contain the exposure, the Michigan Department of Agriculture quarantined more than 250 Michigan farms and eventually destroyed 30,000 cat-

tle, 1.5 million chickens, and other farm animals, along with their products and by-products (4). By 1978, 96% of breast milk samples from women living in Michigan's lower peninsula contained detectable levels of PBB (5).

The chemical's short-term toxicity in animals has been well described. Studies done in rats and rabbits show that the primary effect is in the liver, where it induces hepatocellular carcinomas and other carcinomas (6), along with immunologic effects, accumulation in the fetus, and fetal abnormalities (7). The short-term effects of PBB in humans are disputed; some studies have noted the appearance of a "PBB syndrome," (8) while others have found no association between exposure and various biochemical and medical outcomes (9–11). The chronic health effects in humans are also unclear (12).

The purpose of this study was to estimate the half-life of PBB in human blood sera in order to contribute to our understanding of how continued body burden relates to the possible adverse health consequences of exposure. We found only one previous report of the half-life of PBB in humans (13). This study gave a median estimate of 12 years with a range of 4.6–94.7 years. This estimate was determined by serum measurements from 15 females and 12 males; the half-life for females and males was similar. An experimental half-life determined in rats using a multicompartment model that was then extrapolated to humans was reported as 6.5 years (14); the elimination of PBB from rat serum has been shown to be first order (15). A linear relationship between PBB concentrations in adipose tissue and in serum with a ratio of approximately 300:1 has been demonstrated; the different congeners of PBB do not have significantly different partition ratios (16,17).

Methods

We used data and participants from the Michigan PBB prospective cohort project, which was started in 1975 and was previously described by Pirkle et al. (18). The Michigan investigators enrolled people in the study if they were residents of farms quarantined because of PBB in milk detected at 300 ppb, in eggs detected at 50 ppb ($N = 2148$), or if they were recipients

of food products from quarantined farms ($N = 1421$). Participation was over 95%. Subjects answered a questionnaire, provided a blood sample, and were followed over time to contribute new blood samples and answer follow-up questionnaires.

Participants from the cohort were eligible for inclusion in our analysis if they: 1) lived on a quarantined farm or consumed food products from such a farm; 2) had at least two PBB level determinations between 1976 and 1982 that were a minimum of 1 year apart; 3) were over 18 years of age at the time of their first PBB level measurement; and 4) had an initial PBB level determination of at least 20 ppb. We included the age requirement because continued growth may affect measured PBB levels and half-life (19,20). We restricted the study to those with initial PBB levels above 20 ppb because the possibility of continued low-level exposure would have artificially slowed decline of PBB levels among those with low initial levels. Measurements between 1976 and 1982 were used because only initial weight information on participants was available, and changing body mass index may affect half-life. Also, fewer PBB measurements were made after 1982.

For a one-compartment model using first-order kinetics, the initial and subsequent concentrations of a substance are related by the formula $C_t = C_0 e^{-\lambda t}$ where C_0 represents concentration at initial time, C_t represents concentration at later times, and λ is the rate of decline (21). After taking logarithms and rearranging, this formula is equivalent to $-\lambda = \Delta \log(C) / \Delta t$, where $\Delta \log(C)$ is the change in the log of PBB measurements and Δt is the change in time between the measurements. The estimated half-life is then equal to $\log(2) / \lambda$.

We estimated λ for each individual using simple linear regression of eligible PBB measurements and the times between them. We estimated the half-life using two methods in order to better summarize the data. The first method used the median of the individual λ values to estimate the half-life. Confidence intervals (CI) were calculated using distribution-free techniques (22). The second method used the mean of the individual λ values. Weighting subjects according to the number of available PBB measurements for sensitivity analysis did not change the results. The SAS system was used for calculations (SAS Institute, Inc., Cary, North Carolina).

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Results

A total of 163 persons met the eligibility criteria (Table 1). The study population was 69% male, and 63% lived on quarantined farms. The mean level of PBB was 172.8 ppb (range 20–1900 ppb) and the median was 45.5 ppb. The mean age in 1975 was 40.4 years (range 18.1–73.5 years), and the mean initial body mass index in 1975 was 25.2 (range 17.2–40.7). On average, men had higher PBB levels, greater body mass index, and were older than women, whereas people who lived on quarantined farms had higher mean PBB levels than others.

Using the median of the individual λ values (Table 2), the estimated half-life of PBB in human sera was 10.8 years (95% CI, 9.2–14.7 years). The half-life for women was 18.5 years (9.5–40.1 years) and for men was 10.2 years (8.5–12.4 years). The estimate for residents of quarantined farms was 10.9 years (8.5–15.2 years) and for consumers of meat and dairy products from such farms was 10.8 years (8.9–15.8 years). Only in the highest quartile of body mass index was the estimation of half-life different in men and women (men: 14.2 years, women: infinite years, $p < 0.01$ for the median test).

Using the mean of the individual λ values, the estimated half-life of PBB in human sera was 10.8 years (95% CI, 7.4–19.9 years). The half-life for women was 13.0 years (6.3–infinite years) and for men was 10.0 years (6.7–20.0 years). The estimate for residents of quarantined farms was 10.2 years (7.3–16.6 years) and for consumers of meat and dairy products from such farms was 12.1 years (5.7–infinite years).

Tables 3 and 4 present selected characteristics about the PBB measurements used for this study. Over 65% of participants contributed two eligible PBB measurements, while most of the remainder provided three measurements. The amount of time between the first and last eligible measurement ranged from 1 to 6 years, with counts being approximately equal for spans of 1, 2, 3, and 5 years, and lower for spans of 4 and 6 years.

Discussion

The main strength of this study is that it represents the first large investigation of the half-life of PBB in humans. After the accidental exposure of the population of Michigan to PBB, the product was no longer manufactured. It is no longer a potential environmental hazard. Therefore, the information in this study represents a unique occasion to understand the effects of PBB. Individual serum values have been collected over almost 20 years since the registry was begun. The accuracy of the methods

Table 1. The study population by gender and exposure group

	N	PBB (ppb)		BMI		Age (years)	
		Mean	Range	Mean	Range	Mean	Range
Overall	163	172.8	20–1900	25.2	17.2–40.7	40.4	18.8–73.5
Female	51	145.8	20–1150	24.8	17.2–40.7	40.0	18.8–66.0
Male	112	185.1	20–1900	25.4	19.5–37.1	40.5	18.1–73.5
Farmer	102	198.5	20–1900	24.9	17.2–40.7	40.8	18.8–73.5
Consumer	61	130.0	20–1194	25.8	19.5–35.2	39.6	18.1–68.5

Abbreviations: PBB, polybrominated biphenyl; BMI, body mass index.

Table 2. Half-life values of polybrominated biphenyl for different groups

Group	Half-life, years (95% CI)	
	Median	Mean
All	10.8 (9.2–14.7)	10.8 (7.4–19.9)
Women	18.5 (9.5–40.1)	13.0 (6.3–infinite)
Men	10.2 (8.5–12.4)	10.0 (6.7–20.0)
Farmers	10.9 (8.5–15.2)	10.2 (7.3–16.6)
Consumers	10.8 (8.9–15.8)	12.1 (5.7–infinite)

used to determine PBB levels was high (23).

This study has several limitations. The study does not represent a random sample of Michigan residents exposed to PBB. It is heavily weighted to the subpopulation of farmers who had the most direct exposure to the compound, their neighbors, and direct customers. In addition, the study population was chosen from people who had a PBB level of at least 20 ppb. It is not known how this subset of the cohort may differ from the entire cohort or from other Michigan residents. Generalization of the results of this study to the total cohort and to the population at large must be made with caution.

PBB levels were not determined at equal time intervals for all subjects, the same number of measurements were not obtained for each subject, and we found substantial variation in the λ values for each subject. In addition, the body mass index of each subject was only recorded at initial entry into the registry. Therefore, it was not possible to control for the effect of change over time in body mass index on the estimated value of λ . In addition, blood samples were not uniformly taken after subjects had fasted. We could not determine which samples represented fasting PBB levels and which did not. Therefore, all measurements were used.

PBB is a highly lipophilic compound which is primarily stored in adipose tissue; however, not enough adipose samples were collected to allow the estimation of PBB adipose half-life. The rate of equilibrium at low levels of contamination between adipose tissue and blood is not fully known. However, a very high correlation between adipose tissue and blood serum for PBB has been shown (17). Also, lactation is a major route for excretion of PBB (Davis MK, Centers for Disease Control, personal communication), but

Table 3. Number of serum samples per participant

No. of samples	Count	Percent
2	107	65.6
3	50	30.7
4	6	3.7

Table 4. Number of years between first and last polybrominated biphenyl measurement per participant

No. of years	Count	Percent
1	35	21.5
2	37	22.7
3	32	19.6
4	6	3.7
5	42	25.8
6	11	6.7

information on breastfeeding was not available. However, when we excluded PBB measurements for women starting 30 days before delivery and up to 180 days after delivery, the values for the half-life did not change.

In addition, this study assumed a point exposure of the cohort to PBB, (i.e., essentially everyone was exposed to the contaminant at the same time for the same amount of time and then no more). If continued low-level exposure did occur, for example, on farms that were the most heavily contaminated, we may have overestimated the half-life of PBB because the analysis did not account for the possibility of continued exposure. However, when we split the subjects based on their first PBB determination (less than or greater than 100 ppb), there was no statistically significant difference between the calculated half-lives for those with high first measurements and those with low first measurements, either overall or for any of the subgroups (Wilcoxon, $p > 0.5$).

In conclusion, the estimated PBB half-life in humans is approximately 11 years, although the confidence intervals were quite wide. Thus, the body burden of PBB of exposed people, in the absence of other exposures, will decrease only gradually over time. For people with the median level of exposure (about 45 ppb), it will be more than 60 years from the time of their exposure before their serum levels fall below the current level of detection.

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