THE PBB EPISODE IN MICHIGAN: AN OVERALL APPRAISAL

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I. INTRODUCTION

More than 10 years have passed since the people of Michigan were exposed to polybrominated biphenyls (PBB). The exposure to this flame-retardant chemical occurred when it was substituted accidentally for magnesium oxide in livestock feed. The PBB then was transferred to the human population through food products of animal origin that included meat, milk, and eggs. Although the episode most often was labeled an incident,[1-3] at times it more graphically was labeled a crisis, tragedy, poisoning, and disaster.[4-7] In some contexts, and from some viewpoints, all of these labels have validity.

The Michigan PBB episode is not unique as an example of human exposure to halogenated hydrocarbon chemicals through foods of animal origin. At least 25 incidents of livestock contamination[8] occurred during the 5 years prior to the identification of PBB in 1974. Since then, incidents have included polychlorinated biphenyls in poultry in the western U.S.,[9] heptachlor in all of the dairy herds of Oahu, Hawaii,[10] and a number of smaller incidents of contamination that were less publicized.

The PBB episode differed from other livestock contamination incidents in the length and intensity of the controversies it engendered. The controversies involved the effects of PBB exposure on human and animal health, and on the appropriateness of governmental responses to these issues. There were several reasons why the PBB episode engendered more controversy than other incidents. First, the PBB episode involved exposures to more people and animals than the exposures from the other incidents. Second, the cause could be traced to a single accident and the responsible parties could be identified readily. Third, little biological information on PBB was available at the beginning of the episode. This lack of information left room for doubts when various aspects of the situation were evaluated and acted upon.

The controversies associated with the PBB episode have receded from public awareness. Generally, the controversies were not resolved by interpretations of scientific findings on which there was agreement, but rather they were resolved by political and legal decisions or by the passage of time, which made the questions moot. The major unresolved question that remains concerns the possible long-term effects of PBB exposure on human health. Although a long-term epidemiological study was instituted soon after the exposure was discovered,[11] it is by no means certain that this study will provide a definitive answer because it is difficult to detect subtle effects in epidemiology studies. In addition, the same subjects of study can lead different scientists to different conclusions.[12-14]

Much chemical, environmental, toxicological, and health information on PBB has been added to the meager data base that existed in 1974. The purpose here is to review the PBB episode and to review the research on PBB and relate the findings to developments in the episode and the controversies surrounding it.

II. OVERVIEW OF THE EPISODE

A. Background

The PBB episode originated in the convergence of several industrial, agricultural, scientific, and social trends. These trends cannot be considered causes of the episode, but the trends increased the likelihood that the episode would occur, that it would be detected, and that it would develop controversies.

One trend was the passage of fire safety legislation in the 1960s, which stimulated discovery, production, and application of fire-retardant chemicals.[15] PBBs of varying degrees of bromination were examined as potential flame retardants by at least three companies.[6] Two companies examined a mixture that was predominantly octabromobiphenyl and concluded that it was not suitable as a flame retardant because of its adverse toxicological effects and its persistence as a residue.[6,16-18] One company, the Michigan Chemical Corporation, decided to manufacture a PBB mixture that was predominantly hexabromobiphenyl for use in thermoplastic applications.[15]

A second trend was the increasing size and management sophistication of agricultural enterprises during the 1960s and 1970s. Dairy herd sizes were increasing and a number of innovative feeding techniques were adopted. One large Michigan dairy producer adopted the use of magnesium oxide in dairy cattle rations to buffer the acidity of corn silage and to correct possible magnesium deficiencies in feeds that were grown on deficient soil.[19] The magnesium oxide proved useful and its use was adopted by other Michigan dairy producers. This popularity led Farm Bureau Services, a feed supplier, to formulate a standard dairy feed (No. 402) for general sale that included 0.4% magnesium oxide.[20]

A third trend was the development of analytical techniques that lowered detection limits and eased quantitation of chemical contaminants. Electron capture gas chromatography was a particularly important development in this regard. It is possible that high concentrations of PBB could have been identified and measured without electron capture gas chromatography, but this method was much more sensitive and economical than previous methods. Thus, it was possible to detect PBB in samples in which it was present in small amounts, and it was possible to institute control programs that were much more extensive than would have been possible before this technology was available.

The fourth trend was the increasing public concern over the presence of chemicals in foods and the environment. This trend generally is considered to have received its initial impetus with the publication of *Silent Spring* in 1962. Public concern increased steadily and had reached a high level in the middle 1970s when the PBB episode occurred.

A large contaminating event could have occurred at an earlier time with a chemical similar to PBB. However, it is clear that if contamination occurred at an earlier time, it might not have been detected, or the chemical would not have been recognized as a pervasive contaminant in the environment. Without the easy means of detection and measurement, and heightened public concern, it is doubtful whether an earlier incident could have developed into the legal and political controversies that characterized the PBB episode and other recent examples of food contamination.

B. The Mixup

The Michigan Chemical Corporation began to manufacture PBB under the trade name FireMaster BP-6® at its plant in St. Louis, Mich.[21] in 1970. Yearly production increased steadily until production was stopped in 1974. Total production of PBB was about 5 million lb. Michigan Chemical Corporation prepared a new product, FireMaster FF-1®, in 1972. FF-1 was made by grinding BP-6 and adding 2% calcium silicate as an anticaking agent. This process had a great impact on the Michigan episode because PBB was changed from brown flakes to a white powder.

In addition to fire-retardant chemicals, Michigan Chemical Corporation also produced a number of other chemicals at the St. Louis plant. Feed grade magnesium oxide was one of the other chemicals. FireMaster FF-1® and magnesium oxide were packaged in paper bags with color-coded labeling. But, during a paper shortage, both products were packaged in plain bags with black stenciled labeling and were stored in the same warehouse. During May 1973, some FF-1 was mistakenly included in a shipment of magnesium oxide to the Farm Bureau Services feed mill at Climax, Mich. The amount of FF-1 in the mistaken shipment was not established definitely; it was concluded after a comprehensive consideration of the question that the amount did not exceed 650 lb (295 kg).[20]

Some of the magnesium oxide was used for mixing feeds at the Climax mill and the feeds were sent to farms directly or through retail outlets. In other cases, the magnesium oxide was shipped to affiliated feed mills in the state and used in mixing operations at those locations. At times, FF-1 was added to feed as a total substitute for magnesium oxide. At other times, FF-1 may have substituted for only part of the magnesium oxide. Feeds that were not formulated to contain magnesium oxide also became contaminated because of carryover of PBB from batch to batch in the mixing equipment.[7] Although the typical rate of magnesium oxide use was 0.4%, and one mineral mix contained nearly 2% FF-1,[4] the bulk of the contaminated feed that reached farms had the relatively low concentrations associated with the carryover problem.

Plant production records[20] indicated that the suspected magnesium oxide was used for formulating feed No. 402 as early as July 1973. There also was evidence that FF-1 was used for custom mixing at an affiliated mill during the same month.[22] Although the latter farmers filed damage claims for production losses in August, their exposure had little impact on the ultimate detection of PBB because it was thought that their problem was caused by mycotoxins in moldy corn. The first case of a feed delivery that had an impact on the ultimate recognition and identification of the contamination occurred in September 1973. Most of the other high level exposures occurred in the fall of 1973 before feed No. 402 was withdrawn from sale in December.[22] However, there was one case in which high level substitution occurred as late as February 1974 in a different feed formulation.

Low level contaminations of feeds could have occurred by carryover anytime after the first use of FF-1, and it continued to occur until feed mills were cleaned up after PBB was identified. Mills generally produced feeds with PBB concentrations below the guideline of 0.05 ppm[4] after July 1974. Since it is not possible to remove a persistent chemical completely from an environment to which it has been introduced, it is probable that PBB continued to occur in feeds for some time after clean up. The amounts, however, would have been negligible compared to the amounts present before detection.

C. The Identification

The Halbert Dairy Farm was not the first farm to receive feed with high concentrations of PBB, but the appearance of severe health problems in this herd led directly to the identification of PBB and the actions that followed. The farm had approximately 350 lactating cows and received Farm Bureau feed No. 402 in 9-ton lots in 1973. There was a sudden 50% drop in feed consumption and milk production by the cows in late September. A number of other clinical signs were noted later and described.[23]

The cause of the health problems was not identified as PBB contamination until April 1974. The long identification process involved a number of federal, state, and private organizations that were drawn into the problem by the herd owner, whose persistence was the driving force in resolving the cause of the problem.[19] Common infectious diseases were eliminated and feed No. 402 soon was suspected as the cause of the problem. But, the nature of the toxicant eluded investigators. The feed did not contain excess urea or nitrates, heavy metal concentrations were within acceptable limits, mycotoxins were not detected,

and chlorinated hydrocarbon insecticides were present at the usual background levels. Screens for the insecticides also eliminated many chlorinated industrial compounds such that PCBs would be detected by these methods.

Chance played an important role in the identification of PBB. No progress was made in characterizing the nature of the toxicant until late-eluting peaks were observed when a gas chromatograph inadvertently was allowed to operate several hours longer than usual. Identification of these peaks was speeded up by the chance consultation of the only individual who had experience with PBB and cattle.[19]

D. The Response

Soon after PBB was identified, the U.S. Food and Drug Administration (FDA) established a temporary guideline of 1 ppm in milk and tissue fat,[24] and the Michigan Department of Agriculture (MDA) instituted a program to identify and quarantine contaminated herds.[3,7] Primary emphasis was placed on dairy cattle because magnesium oxide, in theory, was used mainly in dairy feeds. The program soon expanded to include all purchasers of Farm Bureau feeds as the problem of carryover contamination in feed mills was recognized.[7] All herds with high level contamination (>5.0 ppm) were identified and quarantined by the end of May.[22]

It was apparent immediately that it would not be economically feasible to salvage the animals with high levels of PBB.[3] Even if the half-life of PBB was as short as 60 days,[25] it would have required several years for many animals to return to a nonviolative level of PBB. The expense of holding nonproductive animals would have greatly exceeded their value. Therefore, it was decided to depopulate the contaminated farms and dispose of the animals at a burial site on state-owned land at Kalkaska.[3,7] After legal questions were resolved, burial got underway during August and was nearly complete in September.[3,7] Animals buried in the initial phase of the episode when the tolerances were 1 ppm include about 9400 head of cattle, 2000 swine, 400 sheep, and over 2,000,000 chickens.[26] Also, large quantities of contaminated feed and animal products were buried at this time.

When the first analyses of milk were available, it was recognized that farm families who used milk or slaughtered animals for home consumption might have high exposures to PBB. The potential seriousness of the situation was indicated by an estimate that exposures may have exceeded 10 g,[27] which was much greater than the amount of PCB that caused adverse effects in humans in the Yusho incident in Japan.[28] Although many of the Yusho effects are now attributed to the presence of chlorinated dibenzofurans, it was thought then that the effects were caused by PCB and that PCB was the best model to use in the absence of PBB data.[24] In June, the Michigan Department of Public Health surveyed farm residents that were potentially exposed and found no consistent symptoms or adverse health effects could be associated with exposure to PBB.[2] A cohort of 4000 was then enrolled for more thorough studies and observations for chronic effects of PBB exposure. It is still under way.

E. The Developing Controversy

Exposure of cattle to feed that contained over 1000 ppm PBB unquestionably produced adverse production and health effects.[23] However, many clinical signs that were reported for this high exposure were nonspecific and the conditions could occur in any herd for a variety of reasons. As the summer of 1974 passed, some farmers whose herds were exposed to amounts of PBB below the level required for violative residues began to claim herd health damage was caused by low exposure to PBB. In some cases, the farmers and their families also complained of personal health problems, which they attributed to PBB. Thus, the situation that appeared to be nearing its end as the highly exposed animals were buried began its most protracted and controversial phase.

The basis for setting the temporary guidelines in milk and meat was reexamined by the FDA in October 1974. As a result of this re-examination, the guidelines were lowered to

0.3 ppm in fat for both products.[24] The original 1 ppm guidelines were set at the sensitivity limit of the method under the legal theory that the residues were avoidable. The methodology had improved to a point where less than 0.3 ppm could be quantitated, but the FDA now considered the contamination unavoidable and toxicity became the primary basis for setting guidelines. The lowered guidelines had the immediate effect of greatly increasing the number of violative herds, and the ultimate effect was burial of an additional 20,000 head of cattle.

The controversies concerning effects of PBB on human and animal health increased rather than diminished as time passed. In May 1975, the MDA held a hearing to consider changing the guidelines. Epidemiological studies in humans revealed no effect that could be related to PBB and studies in cattle did not indicate adverse effects from nonviolative residue concentrations. Therefore, the MDA decided to maintain guidelines at their existing levels.[6,8]

As controversies on human and animal health effects of PBB continued, the governor appointed an advisory panel in 1976 to review the scientific literature on PBB and to consider three issues. The issues concerned the effects of PBB on human health, the effects of PBB on animal health, and the adequacy of the guidelines. The panel concluded that there was no identifiable effect of PBB on human or animal health, but the panel recommended lowering the tolerances of PBB to 1 ppb.[29] The MDA, however, declined to change the guidelines after a hearing on the report in May.[6,8]

Until the summer of 1976, the PBB controversies largely involved dairy farmers with low level herds, and the controversies focused more on animal health than human health. The disputes of farmers with the MDA had not attracted the attention of the Michigan metropolitan and the national media.[5,6] The situation, however, changed dramatically when it was reported that PBB was present in the breast milk of many Michigan women.[8] The heightened media interest and the new focus on human health made the handling of PBB by the state a major political issue, and bills were introduced in the legislature to reduce the tolerances. Enactment of lower tolerances became probable when the preliminary report[30] of an epidemiology study that appeared to indicate adverse human health effects was released in January 1977. Final legislation, Act 77, lowered the tolerance to 0.02 ppm in body fat of all cull dairy cows offered for slaughter. Unlike the situation under the previous regulations, the finding of a single violative animal did not lead to quarantine and disposal of the whole herd.

F. The Receding Controversy

Passage of Act 77 allayed much of the general public concern, but it did not dampen the media coverage of PBB, which continued as a political issue. Act 77 also did little to resolve the low level herd controversy because it did nothing to ease the burden of proof on the owners of these herds with claims against Farm Bureau Services and Michigan Chemical Corporation. Since herds were not quarantined automatically with a single violative animal, it was still necessary for claimants to establish that PBB caused animal health problems. In addition, the lower tolerance of Act 77 created a new problem. Some farms with high level exposures in 1974 that had been depopulated, cleaned up, and repopulated now were having difficulty producing nonviolative animals because of residual contamination on their farms.[19]

PBB controversies began to recede rapidly in 1978 when state elections settled the political issues, and when the first suit against Farm Bureau Services and Michigan Chemical Corporation was completed. After 15 months of testimony, the judge ruled that there was no evidence for damage to herd health from low levels of PBB, and he ruled in favor of the defendants.[20] The precedent set in this case led to resolution of many other outstanding cases.

Enforcement of Act 77 proceeded without great difficulty except for some disputes over disposal sites for violative animals.[6] Less than 2% of the cull cows were violative, and the percentage decreased rapidly as animals that were in herds in 1974 were culled at the end of their productive lives. Act 77 was allowed to expire in 1982. Areas of residual contam-

Table 1
PROPERTIES OF FIREMASTER BP-6®[21]

Property	Value
Bromine content (%)	75
Softening point (°C)	72
Density at 26°C (g/mℓ)	2.57
Vapor pressure (m*M* of Hg)	
90°C	7.6×10^{-5}
140°C	7.6×10^{-3}
220°C	7.6×10^{-1}
Solubility at 28°C (mg/g)	
Toluene	970
Benzene	750
Chloroform	400
Acetone	60
Water	11×10^{-6}
Decomposition temperature (°C)	300—400

ination on highly exposed farms were identified and corrected by this time.[22] Michigan Chemical Corporation and the state also reached a settlement on clean up of the manufacturing and waste disposal sites in 1982.[8]

III. CHEMISTRY OF PBB

A. General Properties

FireMaster BP-6® had the physical form of brown flakes whereas FireMaster FF-1®, the material involved in the episode, had the physical form of a white powder. The materials were nearly the same chemically because FF-1 was ground BP-6, with 2% calcium silicate added as an anticaking agent. Many papers cited in this review do not make a clear distinction between FF-1 and BP-6, but if lot numbers are provided the distinction can be made. The lot number for FF-1 was 7042 and other lot numbers usually refer to BP-6. Generally, distinctions among lots will not be made because no important chemical or biological differences among lots were noted.

Some physical properties of BP-6 are listed in Table 1. Low solubility in water and resistance to degradation are two important features of PBB. Solubility in river water is higher than the listed value,[31] but this higher solubility may be due to adsorption to suspended particles. PBBs are chemically unreactive, but some degradation may occur under strong alkaline conditions.[32] PBBs readily undergo photolysis and these reactions will be discussed later.

B. Composition

1. PBB Congeners

Commercial PBBs were produced by bromination of biphenyl with elemental bromine in the presence of a catalyst.[15,33] As a result, all PBBs are mixtures of bromobiphenyls and brominated products of contaminants that were present in the starting material. Theory allows the formation of 209 brominated biphenyls, but far fewer have been synthesized in a pure form on a laboratory scale.[33] Although polychlorinated biphenyls (PCB) and PBBs are manufactured by similar processes, bromination of biphenyl proceeds in a manner that yields a less complex product than chlorination of biphenyl to an equal degree.[34]

After 2,2′,4,4′,5,5′-hexabromobiphenyl was originally identified in 1975 as the major component of BP-6,[34] a succession of reports appeared on the identification and relative abundances of other bromobiphenyl congeners in the BP-6 mixture. In the most recent work, 25 congeners were separated and identified by retention time on capillary column chro-

Table 2
COMPOSITION OF FIREMASTER FF-1® AND BP-6®[34—39]

Congener	Structure	Abundance (%)
1	2,2′,4,5,5′-	2.4—3.9
2	2,3′,4,4′,5-	1.0—5.7
3	2,2′,3,4′,5′,6-	0.8—2.2
4	2,2′,4,4′,5,5′-	53.9—68.0
5	2,2′,3,4,4′,5′-	5.3—12.3
6	2,3′4,4′,5,5′-	3.0—8.0
7	2,3,3′,4,4′,5-	1.0—2.9
8	2,2′,3,4,4′,5,5′-	7.0—27.3
9	2,2′,3,3′,4,4′,5-	0.3—1.7

matography.[35] The relative abundances of the congeners that usually are seen with routine gas chromatography are in Table 2. Congener numbers were assigned in their usual order of elution.[36]

A striking feature of the PBB mixture is the greater than 50% abundance of a single congener, 2,2′,4,4′,5,5′-hexabromobiphenyl. The second most abundant congener is 2,2′,3,4,4′,5,5′-heptabromobiphenyl. There are several reasons for variations in the reported abundances of the PBB congeners. FireMaster FF-1®, which was involved in the Michigan incident, contained 2% calcium silicate as an anticaking agent which was not present in BP-6. As in all industrial processes, there is variation among lots and most reported values are from different lots of PBB. Variations within lots of the commercial mixture also may occur.[34] The techniques used to establish the relative abundances is another cause of variation. In many cases, the differing electron capture responses of the various congeners within the mixture were not taken into account. Thus, values in Table 2 only give an approximate range of composition and it is not possible to provide a precise composition for the material that was introduced into the Michigan environment.

2. Minor Constituents

The potential for highly toxic trace contaminants in the commercial mixture must be considered when evaluating the hazards of PBB. In the case of PCBs, the presence of chlorinated dibenzofurans appeared to have been a significant contributor to the toxic response that was observed in the Yusho incident.[40] PBB is manufactured by a process similar to that used for PCB, and it was reasonable to expect that the analogous brominated contaminants would occur in PBB.

Brominated dibenzofurans were the potential contaminants of most concern because high toxicity would be anticipated.[32] They were not detected in FF-1 or BP-6 at detection limits of about 0.5 ppm,[38,41] but brominated dibenzofurans were formed by pyrolysis of PBB and PBB metabolites.[42,43] Penta- and hexabromonaphthalenes were minor constituents in BP-6 and FF-1, but precise identification and reliable quantitation was not performed because of the lack of authentic standards.[38,41] Nominal concentrations in the PBB mixtures were 150 ppm pentabromonaphthalene[38] and 25 to 70 ppm hexabromonaphthalene.[38,41] Other minor constituents of PBB were detected,[38,44] but simple biological tests suggested that these constituents did not contribute importantly to toxicity and little further work was done on their identification.[38]

C. Analyses

Electron capture gas chromatography has been the method of choice for the detection and quantitation of PBB in foods, feeds, and other materials since PBB was identified as a feed contaminant in 1974.[15,32] The gas chromatographic properties of individual bromobiphenyls

and commercial mixtures have been described.[33,45,46] In general, retention times and electron capture responses increase with increasing bromination. Most routine methods for PBB analysis were adapted from established methods for chlorinated hydrocarbon insecticides and PCBs. Since PBBs elute late compared with chlorinated hydrocarbons and PCBs, it is necessary to use elevated temperatures or light column loadings to allow analyses to be conducted in a reasonable time period.[32] The highly brominated congeners that occur in commercial mixtures are resolved well on a number of columns.[45,46]

High sensitivity of PBB analyses can be achieved with proper conditions and expenditure of effort, but for most applications maximum sensitivity is neither required nor an efficient use of research or regulatory resources. Typically, concentrations of PBB as low as 10 ppb in fatty foods,[47] 3 ppb in dry feeds,[48] and 1 ppb in blood serum[30] can be detected and quantitated by routine methods. However, coefficients of variation become large as concentrations approach the limit of sensitivity of the method, and values that are near the limit must be interpreted with caution.

Recoveries of PBB in established methods are in the range of 80 to 90%. The solvent system that is used for sample extraction can affect recovery. Poor recoveries often were obtained with hexane, which was used commonly for chlorinated hydrocarbon extraction. Recovery could be improved by use of hexane:ether mixtures[49] or methylene chloride[48,50] for extraction. Sample extracts usually are cleaned up with florisil[32] or gel permeation chromatography.[47,51] PBBs can be eluted from florisil with petroleum ether, and elimination of diethyl ether from the usual method of elution has provided a cleaner sample for quantitation.

PBB adsorbs to glass more tenaciously than other halogenated hydrocarbons, and it is not removed easily by the usual cleaning methods.[52-54] This adsorption to glassware can lead to erroneous values, particularly when concentrations in samples are low.[53] Carryover of PBB from samples of high concentration to those of low concentration is a serious problem when samples of widely varying PBB concentrations are analyzed at the same time. This problem can be overcome by the use of disposable glassware.[54]

Nearly all quantitation of PBB was based on the most abundant hexabromobiphenyl congener;[32] however, most samples of biological origin have different congener distributions than the original material. This method of quantitation has been convenient, but reported values may not reflect the actual hazard of the residue because some of the other congeners are more toxic than the most prominent hexabromobiphenyl.

It is desirable and often necessary to confirm the identity of PBB when dealing with residues of environmental origin. Thin layer chromatography, ultraviolet irradiation, and mass spectrometry have been used for confirmation. Thin layer chromatography has not been used often because of its lack of sensitivity.[47,55] Ultraviolet irradiation has been the most common routine method of confirmation. A sample with presumptive PBB is irradiated under prescribed conditions and gas chromatographed to observe the disappearance of hexabromobiphenyl and the formation of pentabromobiphenyls.[45,55,56] Mass spectrometry, usually in conjunction with gas chromatography, has been used for confirmation and at times it has been used for quantitation. Mass spectrometry is more sensitive than electron capture detection, and it can be useful for samples in which there is a special interest or need to quantitate low concentrations.[45,46]

Capillary column gas chromatography of PBB has been performed occasionally, but it has not been used routinely. Improved separation of less brominated congeners can be obtained by capillary column, but it does not possess advantages over ordinary columns for the more brominated congeners.[57] High performance liquid chromatography also was not useful because of low resolution of the more brominated congeners.[45]

IV. ENVIRONMENTAL FATE

A. Photolysis

PBB dissolved in methanol or hexane is readily degraded by ultraviolet light. Commercial BP-6, which predominantly contains hexa- and heptabromobiphenyls, yielded a mixture of tetra- and pentabromobiphenyls after a short irradiation.[58] Concurrent irradiation of 2,2′,4,4′,5,5′-hexachlorobiphenyl indicated that rates of degradation of bromobiphenyls are more rapid than rates for chlorinated analogs. Debromination in the *ortho* position was preferred in all cases when a series of individual bromobiphenyls that contained from two to eight bromines were irradiated in methanol or hexane.[45,59] Debromination was most rapid with 2,2′,4,4′,5,5′-hexabromobiphenyl. A recent photolysis study of BP-6 in which the analyses were by high resolution gas chromatography confirmed the reductive dehalogenation pathways.[35] However, unlike the results of single congener studies, preferential loss of *ortho* bromines did not occur.

The environmental and toxicological significance of photodecomposition of PBB has been speculated upon but has not been evaluated. Composition of PBB in soils at the manufacturing site had enhanced concentrations of pentabromobiphenyls, which could be derived most logically from photolysis of the more brominated starting material.[37] On the other hand, composition of PBB in soils of highly contaminated farms showed little evidence for change in composition or photolytic degradation.[31,53] Clearly, photolytic degradation of PBB would require direct access of light to the compound. This condition is more likely to occur at manufacturing sites with spills on the surface than on farms where PBB was mixed in feed, manure, or soil. Air and water also might be favorable for PBB photolysis in the environment, but these conditions have not been studied.

Photolysis products are more toxic than the original PBB after short irradiations.[60,61] This finding may be of some importance in assessing hazards associated with spills or waste disposal sites; however, in contrast to short-term laboratory irradiations, photolysis in the environment would be a continuing process that might carry degradation beyond the toxic stage.

B. Fate in Soil

Information on the fate of PBB in soil is limited, but this limited information is consistent with what would be predicted from work with PCBs and other halogenated hydrocarbons. PBBs are readily adsorbed to soil and degrees of adsorption increase with increases in organic matter of soils.[62] Absorptive capacities of soils are much greater than any conceivable amount of PBB that would have been applied through waste or manure disposal on contaminated farms. Laboratory studies indicated that leaching would not be an important route of PBB movement in the environment.[62] Subsequent studies of highly contaminated farms indicated that PBB did not move below 15 cm except where there was a history of physical mixing of the soil.[22]

There was little evidence of degradation of the major hexa- and heptabromobiphenyl congeners of PBB when they were incubated with soils for periods as long as 1 year.[31,53] There was some inconsistent data to suggest that pentabromobiphenyl congeners could degrade slowly. Photolyzing a ^{14}C-PBB mixture before incubation with soil enhanced the rate of degradation as measured by $^{14}CO_2$ production. Enhanced degradation of photolyzed PBB is consistent with observations that the less chlorinated PCBs are metabolized more readily in most biological systems, including soil.[63,64]

C. Plant Uptake

There is little or no plant uptake and translocation of PBB. PBB was not detected in the foliage of orchard grass or tops of carrots grown in a soil with low organic matter at PBB concentrations as high as 100 ppm.[53] Concentrations in the range of 20 to 40 ppb were

detected in carrot roots grown in the 100 ppm soil, but the residue probably was associated with the outer surface. No ^{14}C uptake was observed by autoradiography of corn and soybean seedlings grown in ^{14}C-PBB-treated soil.[65] Some ^{14}C was associated with the roots, but most activity could be removed by solvent washing. Small amounts of PBB also were taken up by edible roots of radishes, carrots, and onions. The PBB probably was associated with the root surface.[41]

In addition to plant uptake and translocation, portions of plants suitable for human or animal consumption also could become contaminated by volatilization and redeposition of PBB from soil surfaces, or by movement of contaminated dust from the soil to the plant. Neither of these processes was important on the most heavily contaminated Michigan farms. The highest concentration of PBB in field soils on these farms was about 300 ppb. All crops or harvested feeds from this field and fields with lower concentrations had no detectable PBB at a 1-ppb sensitivity level.[22]

D. PBB in the Environment

With few exceptions, significant environmental concentrations of PBB in the U.S. are found only in limited areas of Michigan.[66] The areas include sites where PBB was manufactured and used, sites of manufacturing waste disposal, sites of contaminated animal disposal, and areas on farms that received highly contaminated feeds in 1973 and 1974.[67,68] The limited extent of areas in the environment with PBB reflects the small amount that was produced. The chemical and physical characteristics of PBB are such that it would be ubiquitous in the environment if it had been produced in amounts equal to the production of PCBs and some chlorinated hydrocarbon insecticides.

The largest repository of PBB is the Gratiot County landfill, which received about 160,000 to 190,000 lb (72,000 to 85,000 kg) of PBB as waste disposal from the manufacturing plant.[68] Test wells within the landfill site have had concentrations of PBB in water in the range of 0.5 to 26 ppb. Test wells outside of the landfill area had trace amounts of PBB that ranged from 0.1 to 4.4 ppb, but PBB was not detected in domestic wells near the landfill.

About 100 lb (45 kg) of PBB were contained in animal feed and other products that were buried at the Kalkaska disposal site.[68] The site was located in an area with a low water table and there was a clay layer between the buried animals and the ground water level. The site was capped to prevent water penetration and no PBB has leaked into ground water.

Concentrations of PBB in soil of some areas around the manufacturing site were greater than 1000 ppm.[37,66] Runoff from these unsecured sites and from the sewer outfall of the plant led to contamination of the downstream portion of the Pine River. Concentrations in sediment were as high as 77,000 ppb near the sewer outfall, decreased with distance downstream, and were still as high as 100 ppb 29 mi downstream.[67] Concentrations in sediment did not change significantly in the 3 years after PBB manufacture stopped.

Concentrations of PBB in water of the Pine River were 0.01 to 0.07 ppb as far as 12 mi downstream, but concentrations at greater distances were less than the detection limit of 0.01 ppb.[67] PBB was detected in resident fish from the plant area at concentrations up to 1.33 ppm, and concentrations as great as 0.3 ppm were found as far as 30 mi downstream. Caged minnows placed in the river had bioconcentration factors as great as 10,000 after exposure for 2 weeks. High bioconcentration factors for PBB are typical of persistent lipophilic compounds, but the factors for PBB are lower than the factors for corresponding PCBs.[69,70] Significant concentrations of PBB were also found in ducks taken from the river.

Approximately 650 lb (290 kg) of PBB was mixed in cattle feeds and delivered to farms in 1973 and 1974. About 50% of this amount probably was excreted in the feces of the exposed animals[71] and remains on the farms in places of fecal deposition or manure disposal. Most of this is located on the 20 to 25 farms that received feed in which PBB was substituted

for magnesium oxide.[22,72] Fields that received contaminated manure had soil concentrations as high as 300 ppb,[53] whereas cattle exercise lots that were not resurfaced had concentrations as high as 1000 to 2000 ppb.[22,72] Generally, PBB on farms did not move from areas of fecal deposition, manure disposal, and waste disposal except for limited areas that received runoff from cattle lots. Areas of residual PBB presented a source of exposure to animals on farms if animals had direct access to contaminated soils. The major route of animal exposure was through soil consumption because crops grown on contaminated soil were free of PBB. Continued exposure of animals, and humans through consumption of animal products, could be prevented by resurfacing or restricting animal use of contaminated areas.[22]

V. METABOLISM AND DISPOSITION

A. Absorption

Absorption of organochlorine compounds from the GI tract generally is considered an efficient process and absorption may exceed 90% of the ingested compound.[63] Some studies indicate that PBB has a similar high efficiency of absorption, but other studies indicate a much lower efficiency of absorption. It is not possible to evaluate absolute absorption because some PBB is recycled to feces in bile and by diffusion across intestinal membranes. However, these processes proceed at low rates and general conclusions concerning absorption can be drawn from short-term observations after single doses.

One inference concerning absorption can be drawn with certainty. More brominated biphenyls are absorbed less efficiently than less brominated biphenyls. For example, less than 10% of ^{14}C-labeled Congener 4 (Table 2) was excreted in the feces of rats when the compound was administered in corn oil,[73] but 62% of a ^{14}C-labeled dose of octabromobiphenyl in the same vehicle was excreted in the feces in 24 hr.[18] A less dramatic but similar trend is seen consistently when the relative concentrations of Congeners 4 and 8 in feces are compared while BP-6 is fed.[71,74,75] Fecal concentrations of Congener 8 were enhanced relative to concentrations of Congener 4, which indicates that Congener 8 was less efficiently absorbed.

Similar to the rats noted above, hens excreted only 9% of Congener 4 when BP-6 was added to the diet in a solvent that was allowed to evaporate before feeding.[75] In contrast, 60 and 38% of ^{14}C-labeled Congener 4 doses suspended in methyl cellulose and dissolved in corn oil, respectively, were excreted in feces of monkey.[76] Cattle fed either single or daily doses of ground BP-6 in capsules excreted about 50% of the doses in feces.[71,74] These limited data suggest that there can be twofold differences in absorption of PBB, but data are insufficient to provide explanations for the differences.

Livestock on Michigan farms were exposed to FF-1 in the same physical form as the BP-6 used in the cattle studies. Confirmation of low absorption of crystalline PBB by cattle was provided by estimates that 40 to 60% of PBB to reach farms in 1974 was present in soils of lots where cattle deposited feces or in fields where manure was spread in 1978.[72] In contrast, except for chemical plant workers who were exposed mainly through inhalation or dermal contact,[77] humans were exposed to PBB that was dissolved in fat of meat and milk, and the rat-corn oil model might be more appropriate for assessing absorption.

B. Distribution

1. General

The distribution of PBB among tissues follows similar patterns in all species. As expected from the solubility characteristics of PBB, highest equilibrium concentrations on a wet tissue basis are adipose tissues.[78] Concentrations are usually an order of magnitude lower in most muscle and organ tissues. Liver and glandular tissues are usually higher,[17,71] and lung[79] and nervous tissues[71,80] are usually lower in concentration than muscle and other organ tissues.

Much of the variation in concentrations among tissues can be accounted for by variations in fat concentrations of the tissues.[71,80] However, even when concentrations are expressed on a fat basis rather than a wet tissue basis, there are some deviations from uniform concentrations among tissues. Concentrations in liver are often,[74] but not always, higher than concentrations in other tissues.[80] Conversely, concentrations in kidney and lung are usually lower, and concentrations in nervous tissue are notably lower than concentrations in other tissues.[71,80] Low concentrations in nervous tissue may reflect barriers to transport of PBB across membranes or lower solubility of PBB in the phospholipids of nervous tissue.

The relationships among concentrations are different when animals are not at equilibrium with respect to dosing regimen or body composition. Concentrations in liver are very high relative to other tissues immediately after dosing and these high concentrations decline relatively as equilibrium concentrations are established.[17,73,78] Although not as dramatic, other organ tissues and muscle tend to follow a similar pattern. Generally, this phenomenon is most pronounced in tissues that have the highest blood flow rates relative to tissue mass.[81] Changes in physiological status that cause mobilization of fat from adipose or other tissues can change the concentration relationships until equilibrium is re-established. Parturition and initiation of lactation is an example of a time when marked changes in body composition occur.

2. Predictors of Body Burden

Quantitative relationships among PBB concentrations in blood serum, adipose tissues, milk, and excretory products are of considerable practical as well as scientific interest. Fat is the largest repository of PBB in the body and concentrations in fat can provide an index of body burdens and exposure. Since collection of blood serum or breast milk samples are simpler and less invasive than collection of body fat samples, use of serum or breast milk concentrations would be indicated if they are reliable estimators of body fat concentrations. However, both milk and serum have limitations. Breast milk can be obtained from only a small part of the population and serum has low PBB concentrations relative to concentrations in body fat. Thus, there will be times when PBB is present in fat, but its concentration is below the detection limit in serum.

Correlation coefficients of PBB concentrations in serum and body fat generally are above 0.90.[82-84] Analytical errors tend to be proportional to concentrations and misleading relationships can be obtained if the data contain a few high value outliers.[84] For this reason, relationships are estimated most appropriately by using logarithmically transformed concentration values. Ratios of fat to serum concentrations were 363:1 for the general population[82] and 300:1 for farm residents[84] in two studies of Michigan subjects. Marked differences can occur among different segments of the population. Lowest ratios were in pregnant females; intermediate ratios were in other females and male chemical workers; and highest ratios were in farm workers and other males.[83] Stability of a ratio would depend on a person being at equilibrium with respect to PBB intake and fat mobilization. For example, ratios in rats rose from 221:1 to 723:1 between 6 and 36 weeks after a single dose exposure.[78] and observations in cattle indicated that pregnancy, lactation, and body weight change could affect the ratios.[71] Despite these shortcomings, serum concentrations do provide a reasonable basis for estimating human exposure.

Breast milk samples were used to survey the extent of exposure of the general population. The ratios of concentrations in milk fat to body fat were in the range of 0.7 to 0.9:1.[82,83] This technique for evaluating body burden appears promising, and it would be more sensitive than serum at low concentrations of PBB in fat. The major limitation of the technique is that it would not be applicable to segments of the population in which lactating women would not provide a representative sample.

In contrast to its limited usefulness in humans, estimations of body fat concentrations and

exposures from milk fat concentrations are quite useful in the dairy industry because most of the subjects of interest are lactating. Milk-fat-to-body-fat ratios of cows no longer receiving PBB averaged about 0.4:1.[71,80,85] The ratio is much lower than the ratio in humans, and the lower ratio may reflect the much higher milk fat production relative to body weight that occurs in cows.

C. Metabolism

Many PBB congeners are persistent in biological systems. This observation and the extensive literature on analogous PCBs[63] would lead one to expect little or no metabolism of the more brominated PBB congeners. Conversely, the frequent absence or change in relative concentrations of some congeners would lead one to infer that these congeners are metabolized. Metabolism of PBB congeners and mixtures was studied by several in vitro and in vivo methods and the expectations generally were confirmed.

One in vitro method was to measure rates of disappearance of congeners when individual congeners or the PBB mixture was incubated with rat liver microsomes in the presence of NADPH and atmospheric O_2.[86,87] No metabolism occurred when microsomes were not induced, or when microsomes were induced with 3-methylcolanthrene. Rapid metabolism of Congeners 1 and 3 (Table 2) occurred when microsomes were induced with phenobarbitol. None of the other congeners that occur normally in PBB were metabolized. Bromobiphenyls that do not occur in PBB also were studied and all compounds that had at least one unbrominated *para* position were metabolized, but no metabolism occurred when both *para* positions were brominated.

A second in vitro approach was to incubate compounds with induced rat liver microsomes and to examine the incubation mixture for metabolites.[88] This technique was used only to investigate Congener 4 and a model compound, 4-monobromobiphenyl. The 4-monobromobiphenyl yielded hydroxylated metabolites, but only small quantities of polar lipophilic products were found after incubation of Congener 4.

The in vivo metabolism of model mono- and dibromobiphenyl compounds was studied in rats.[89-91] Several hydroxylated metabolites were found with the monobromobiphenyls and 4,4′-dibromobiphenyl. In one case, BP-6 was fed and a trace of an unidentified pentabromobiphenylol was detected.[89] A metabolite, 6-hydroxy-2,2′,4,4′,5,5′-hexabromobiphenyl, was identified in the feces of dogs fed BP-6.[42] The metabolite was not present in the liver, and it was suggested that the metabolite may have formed in the GI tract by microbial action. No evidence of hydroxylated bromobiphenyls was found in the milk of cows with PBB residues as high as 900 ppb on a whole milk basis.[92]

The discrepancies in results of in vivo and in vitro metabolism studies are probably not as great as they appear, and they may be of little practical importance. Metabolite yields were low in all in vivo studies. This includes studies with monobromobiphenyls, which one would expect to be the most readily metabolized. Maximum yield of metabolites in vivo was about 7% of the starting compound in the case of 4,4′-dibromobiphenyl.[89] In vitro studies are short and measurements of disappearance of the parent compound will involve analytical errors. Thus, it may not be possible to detect low rates of metabolism in vitro.

In vitro studies indicate that a nonbrominated *para* position is required for metabolism of bromobiphenyls.[86] In contrast, metabolism of 4,4′-bromobiphenyl occurred in vivo.[89] The in vivo result is more consistent with the usual finding that metabolism of PCBs only requires the presence of two adjacent unchlorinated positions.[63] These discrepancies are somewhat academic because mono- and dibromobiphenyls are not present in the commercial mixture. No study provided evidence for significant metabolism of the more abundant congeners in PBB.

D. Elimination

Elimination of PBB, as quantitated by Congener 4, from the body is a slow process. Since there is little or no metabolism of the more abundant PBB congeners, PBB can be eliminated only as the parent compounds through several physiological processes. Processes that were demonstrated to occur include biliary or intestinal excretion with elimination in feces, production of fat-containing products, such as milk or eggs, and transfer to the fetus and associated products of conception. Two of the three processes never occur in males and they apply only to a part of the female population. Elimination of PBB through the oily secretions of the skin was suggested,[73] but this route has not been evaluated. Excretion of PBB in urine is not expected because of the insolubility of PBB in water. The few instances in which low concentrations of PBB were reported in urine may have been caused by cross-contamination with feces.

1. Biliary and Fecal Excretion

Concentrations of PBB were measured in the bile of humans,[83] rats,[73] monkeys,[76] and cattle.[71,74] Concentrations in bile of humans were about half of the concentrations in serum, whereas concentrations in bile of cattle were two to three times greater than concentrations in serum. There is little quantitative data on rates of biliary excretion because rates of bile flow were measured only in the study with rats. But, concentrations of PBB in the bile of animals cannulated 7 days after a single dose were too low to quantitate.[73] Diffusion across intestinal membranes is a second contributor to fecal excretion. Studies in a monkey with a biliary bypass indicated that diffusion may have accounted for about half of PBB excreted in feces.[76]

Quantities of PBB excreted in feces of experimental animals are small compared to total body burdens. Cumulative excretion of an intravenous dose in rats was only 6.6% in 42 days.[73] Monkeys fed a single dose of PBB excreted about 0.5% of the dose per day from 10 to 42 days after dosing.[76] Inferences of low rates of excretion in feces can be drawn from the relatively low fecal concentrations in humans[83] and cattle[71,93] that are no longer being exposed to PBB. Rates of PBB excretion in feces are clearly small relative to body burden, but it is the only route of elimination available in many females and in all males.

2. Placental Transfer

Placental transfer was demonstrated by analyses of tissues from young that had no access to maternal milk, or by analyses of cord serum, placental membranes, and fluids. Although the evidence demonstrates placental transfer of PBB, the evidence also demonstrates that there is a barrier to this transfer because concentrations of PBB in tissues of the fetus or offspring are much lower than concentrations in corresponding maternal tissue.

Concentrations of PBB in cord serum and placental membranes of pregnant women were in the range of 0.1 to 0.15 times the concentration in the maternal serum.[83] The ratios of PBB concentrations in amniotic and allantoic fluids to serum in cattle were in a similar range.[71] Concentrations in blood of calves at birth were 0.37 times concentrations in maternal blood, and a similar value was found for the relationship of fetal and maternal fat.[93] Pigs from sows fed PBB had detectable residues at birth, but concentrations were much lower than concentrations in the same tissues of the dams.[94]

Although there is placental transfer of PBB, the amount of PBB in an offspring that is derived from placental transfer becomes a small part of the body burden if the offspring is allowed to nurse. Pigs from dams that were fed PBB during gestation and the subsequent lactation had a fivefold increase in residue concentrations from birth through the 4-week nursing period.[94] The pigs also had a fourfold increase in body weight and it is concluded that at least 95% of the 4-week body burden was derived from milk. A similar conclusion can be drawn from a study in which rat pups were nursed under various cross-fostering

regimens.[95] Concentrations of PBB in offspring invariably will exceed concentrations in the dam after only a short nursing period.

3. Milk

Milk is the most important route of excretion in females that are lactating. The quantitative significance of this route has been established only in cattle and it only can be inferred for humans and other species from concentrations of PBB in milk or accumulations in nursing offspring. Although nursing during lactation represents a route of elimination of a chemical for an individual, it should be recognized that it is only a transfer of the chemical from one member of the population to another member that may be more sensitive to the chemical. Thus, dairy cattle, which produce large quantities of milk that can be discarded, represent the only species in which lactation can be an effective means of eliminating a toxicant from a population of animals or from human foods.

Concentrations of PBB in milk fat typically exceed concentrations in diet during exposure. In cows, concentrations in milk fat at steady state are about three to four times the concentrations in the diet.[74,96] Concentrations of PBB in milk fat also exceeded concentrations in diets of rats[79] and swine[94] during exposure and higher values in milk fat presumably would occur also in other species. The amount of PBB excreted in milk of cows at steady state is about 20 to 25% of the daily intake. Data on total excretion in milk of other species are not available, but excretion should be less in most species that were not selected genetically for high milk production.

As noted previously, there is a close correlation between concentrations of PBB in milk fat and body fat when equilibrium is reached after exposure. Ratios of concentrations of PBB in milk fat to body fat were 0.7 to 0.9:1 in humans[82,83] and about 0.4:1 in cows.[71,80] Clearance of PBB from the body depends on these ratios and the quantity of milk fat produced relative to the quantity of fat in the body. Both factors change with the progression of lactation and the fractional clearance is less in late lactation than in early lactation. Although milk is the most important route of excretion, a high-producing cow will excrete much less than 1% of its body burden in milk per day.

4. Eggs

Concentrations of PBB in hen or quail eggs are about 1 to 1.5 times concentrations in diets during exposure.[75,97,98] Elimination by this route can account for 50% of the daily dose if egg production is not affected adversely by the treatment. Efficient transfer of PBB from body stores to eggs also occurs when birds are no longer being exposed. This is illustrated by the 28-day biological half-life of PBB in hens, which is substantially shorter than half-lives that were reported for any other species.[75]

E. Enhancement of Excretion

The long biological half-lives of PBB mean that target organs of humans and animals will continue to be exposed for a long time after the initial exposure. The significance of this potential lifetime exposure is not known, but the situation has led to investigations of possible means to enhance the elimination of PBB. The salvage of economically important animals was another reason for studying means to enhance excretion.

Treatments that were investigated included activated carbon in rats and cows,[99,100] cholestyramine in rats and monkeys,[76,100] mineral oil in rats and monkeys,[76,101] high-fiber diets in rats,[101] and phenobarbital in cows.[99] The effect of restricted caloric intake to enhance fat mobilization also was investigated.[100] No treatment had a significant effect on body burdens of PBB even though treatment periods were from 3 to 6 months long. Short-term increases in fecal excretion of PBB were noted with mineral oil and cholestyramine in the monkey studies,[76] but these increases were not large enough to have an important effect on body burden.

The lack of efficacy of these treatments can be readily understood in light of the pharmacokinetic and metabolic characteristics of PBB and the potential mechanisms of action of the treatments. Potential mechanisms include binding of PBB in the lumen of the GI tract to prevent reabsorption of PBB excreted in bile (activated carbon, cholestyramine, and fiber), increasing PBB pool size in the lumen of the GI tract (mineral oil), and inducing microsomal enzymes in the liver to increase rates of PBB metabolism (phenobarbital). Clearly, the low rate of PBB excretion in bile[81] and the negligible metabolism of PBB provide little hope that the treatments would be efficacious.

Successful use of cholestyramine to lower body burdens of kepone in humans[102] and phenobarbital to enhance metabolism of dieldrin in cattle[103] has led to temptations to apply these and other therapies to humans or livestock exposed to other persistent chemicals. These temptations should be resisted not only because of the unlikelihood of efficacy, but more importantly, because potential side effects have received little study and are poorly understood. For example, adverse liver effects and more pronounced effects of PBB were found in rats fed high fiber, or mineral oil and high fiber, diets.[101] All proposed treatments are nonspecific and could cause nutrient deficiencies and other side effects. Thus, side effects of a therapy possibly could be more serious than the adverse effects of exposure to the original toxicant.

F. Pharmacokinetics

Pharmacokinetic models can provide a means for tracking past and future PBB concentrations in tissues of humans and animals. If the model is appropriate these concentrations can be related to past exposure. Estimates of exposure are particularly useful for proper interpretation of epidemiological studies.

The distribution and kinetics of single doses of PBB are the same regardless of the route of administration in rats.[73] This finding presumably would apply to other species. Concentrations in blood are highest immediately after dosing and decline rapidly as PBB is taken up from blood by liver and muscle tissues.[81,104] Concentrations in blood, liver, and muscle then decline less rapidly as the dose is redistributed to adipose tissue. Thereafter, concentration declines in all tissues are parallel and reflect a low rate of excretion, which is predominantly through the bile, but with some apparent readsorption in the intestinal tract.[81] Generally, a three-compartment model is adequate to describe the major features of PBB behavior.[104]

A pharmacokinetic model for humans was developed by scaling and extrapolating quantitative pharmacokinetic results from rats.[81] The estimated half-life of body burden in man was 6.5 years. Half-lives would be shorter in lean individuals and longer in obese individuals. Predicted concentrations in adipose and other tissues would, however, be higher in lean individuals and lower in obese individuals. When estimates of PBB concentrations in milk of a highly exposed herd[93] were applied to the model, the predicted serum PBB concentrations of humans in 1974 agreed closely with observed values.[2]

Kinetics were examined in domestic species to estimate exposure of these species, and to estimate the amounts of PBB that might have been transmitted to humans.[71,93,96] Generally, adequate data exist only for dairy cattle and the models used for cattle were less sophisticated than those described for rats. Major emphasis in cattle was to describe concentrations in milk, but time trends of concentrations in serum are similar.[93] Milk fat concentrations reach a steady state in about 20 to 30 days after feeding of PBB begins.[71,96] Steady state concentrations are in the range of 3 to 4 times the concentration in the diet, and milk excretion accounts for 20 to 25% of intake. Concentrations in milk fat probably parallel concentrations in serum, muscle, and liver somewhat analogously to the changes in concentrations in these tissues in rats. The limited information on a time course of body fat concentrations suggests that equilibrium usually was not reached in most short-term studies.

Concentrations in milk fat of cows decline rapidly for a short time when PBB feeding is stopped.[96] This decline is comparable to the rapid initial decline in rat serum[73] and probably is related to redistribution of PBB from blood and liver to body fat. When a new equilibrium is established, milk fat and body fat concentrations decline in a parallel manner. Large discrepancies exist in the reported half-lives for the slow phase of the biphasic decline. This was caused by measuring the half-lives under different circumstances of exposure and for different lengths of time. Short exposure periods, which provide little time for redistribution to fat, and short observation periods have led to estimates of half-lives as short as 10.5 days[105] and 58 days.[96] In reality, concentrations probably reflect a multicompartment system and half-lives were as long as 6 months in long-term studies with lactating cows.[71] Although data are not available, half-lives in nonlactating animals presumably are longer because these animals would not have milk as a route of excretion.

G. Differential Behavior of Congeners

Quantitation of PBB in most research studies, as well as all regulatory work, was based on the concentration of the most abundant PBB congener, 2,2′4,4′,5,5′-hexabromobiphenyl (Congener 4). However, it was noted early that relative abundances of congeners change in biological and environmental systems.[25,63] These changes can be important if the congeners differ in their relative toxicity, and if the more toxic congeners become concentrated relative to Congener 4 when passing through biological systems. Toxicological work carried out with the original PBB mixture would then underestimate the degree of hazard associated with a given exposure. Some differential behavior may be due to analytical artifacts introduced by differential recovery of the congeners or by adsorption of congeners to the glassware.[53] However, many changes in composition are consistent and reproducible, and they appear real.

Congeners 1 and 3 (Table 2) are metabolized in vitro.[87] Consistent with the finding of metabolism is the absence of Congener 3 from serum of exposed dairy farmers and from serum of rats 4 days after a single dose of PBB.[106] Although Congener 1 was detected, its concentration relative to Congener 4 was greatly diminished in these two instances.

Changes that occur in the abundances of the more brominated congeners probably are related to the differential rates of movement across intestinal membranes or from blood to depot fat. Relative concentrations of Congener 8 are enhanced consistently in feces, indicating that it is more poorly absorbed than other congeners.[71,75,96] Its relative concentration in milk, eggs, and body fat is lower at the time it is fed, which also indicates poor absorption and transport to body fat. When dosing stops this congener will rapidly disappear from milk as well as the serum of dairy cattle because little is stored in fat.[71] In contrast, short-term studies indicate that Congener 8 is efficiently absorbed by rats and that its concentration relative to Congener 4 did not change in serum after 4 days.[106] In contrast, Congener 8 was greatly diminished from its original relative concentration in serum of dairy farmers and chemical plant workers who were sampled several years after exposure.[106]

Data on other congeners are less consistent and relative concentrations depend on exposure conditions. When samples are taken during or shortly after exposure, relative concentrations of Congener 2 are not greatly diminished and may be enhanced in some cases.[71,106] On the other hand, its concentration was greatly diminished in serum of dairy farmers several years after exposure.[106] Congeners 5 and 6 follow trends similar to the trend for Congener 2. Congener 7 is generally absent from samples taken a long time after exposure.[106] Although in vitro work suggests that Congeners 2 and 7 are not metabolized,[87] both have adjacent unhalogenated positions. This is the condition required for metabolism of PCB[63] and it is possible that Congeners 2 and 7 are metabolized at rates too low to detect in short-term in vitro studies.

VI. BIOLOGICAL EFFECTS AND TOXICITY

A. General Toxicity

The onset of clinical signs is delayed somewhat in animals that receive toxic doses of PBB. This delay, and the persistence of PBB in the body which causes long-term exposure to the target organs from a single dose, tend to blur the usual distinctions that are made between acute and chronic exposure. The patterns of development of clinical signs are similar in most species after exposure to toxic doses.

1. Overt Clinical Signs and Lethality

The first response to a high exposure of PBB is a decrease in feed consumption, which may lead to a total refusal of feed if concentrations of PBB are high enough.[107-109] Concomitant reductions in weight or weight gain and functions such as milk production by cows[19,23] and egg laying by hens[109] also will occur. When exposures were somewhat lower, reductions in weight gain of rats occurred within reductions in feed consumption.[108,110] Reduction in efficiency of feed utilization might be inferred, but this finding was not consistent in all species. Increased efficiencies of feed utilization were indicated in growing pigs[111] and reductions of production and weight in hens were accounted for completely by reductions in feed consumption in paired feeding studies.[112]

As the condition progresses, animals become moribund and die. Rats that became moribund or died had a hunchback posture, rough hair coat, and sunken eyes, appeared dehydrated and emaciated, and were lethargic.[108] Cattle that later died had many of the same appearances, but they also had excessive salivation, lacrimation, and diarrhea and depressed heart and respiratory rates.[107]

Acute toxicity of PBB as measured by the classical LD_{50} is quite low. The oral LD_{50} of BP-6 was 21.5 g/kg in rats.[113] Octabromobiphenyl also had low toxicities with an oral LD_{50} >17 g/kg in rats and >12.5 g/kg in bobwhite quail.[114] These values were determined in 7-day observation periods and the doses were considered the highest that it was practical to administer. The LD_{50} for dermal toxicity of octabromobiphenyl in rabbits was in the range of 2 to 10 g/kg.[114] The lower dermal LD_{50} may reflect differences in species sensitivity rather than a more sensitive route of administration.

A classical LD_{50} value is not a good indicator of toxicity of PBB because it gives no consideration to subacute effects and manifestations of acute effects that develop slowly. When observation periods are longer, the LD_{50} is lower. An LD_{50} of about 4.4 g/kg total dose was estimated by the Spearman-Karber Method for both male and female rats when they were dosed daily and observed for 30 days.[108] When these rats were observed for 60 days, LD_{50} values were 3.7 g/kg for males and 1.4 g/kg for females. Dose-related shortening of survival time occurred at daily doses as low as 0.3 mg/kg in lifetime studies with rats and mice.[115] The total dose was about 200 mg/kg. On the other hand, survival rates through 26 months were not reduced in female rats given a single dose of 1000 mg/kg at 2 months of age, or 12 doses of 100 mg/kg each from 2 through 5 months of age.[116] Thus, dosing regimen as well as magnitude of the dose may affect the degree of toxic response.

Studies in which survival, feed consumption, and/or weight change were measured after high doses of PBB are listed in Table 3. This summary provides a means of comparing acute responses in different species, but conditions of the studies varied widely and the values must be interpreted with caution. All studies employed a range of exposures and animals were observed for at least 30 days, but observation periods were as long as 1 year in some cases. The table is divided into two parts: studies in which animals were administered specified doses that are expressed as milligram per kilogram body weight, and studies in which animals were fed diets of specified concentrations. Feed consumption values were not recorded in many cases, and it is not possible to convert diet concentrations into ac-

Table 3
DOSES OF PBB THAT PRODUCE LETHALITY, REDUCTIONS IN FEED CONSUMPTION, AND WEIGHT CHANGE IN VARIOUS SPECIES

	Lethality		Feed consumption		Weight change		
Species	Effect	No effect	Effect	No effect	Effect	No effect	Ref.
			Total dose (mg/kg)				
Cattle	2650	37.5	2650	37.5	2650	37.5	117
Cattle		71					118
Rat, male	2200	660	2200	660	660		108
Rat, female	2200	660	660		660		108
Rat		660			660	66	119
Rat		390			390	130	120
Mouse		660				660	119
Mouse		390				390	120
Dog					244	61	121
			Diet concentration (ppm)				
Rat		500	500	100	500	100	122
Quail	1000	100	1000	100	1000	100	97
Mouse	1000	100					123
Hen	640	200	200	64	200	64	112
Hen			125	25	125	25	98
Pig		200	20		20		111
Guinea pig	100	10	100	10	100	10	122
Mink	6.25	1.0			2.5	1.0	124

cumulated doses. A rough estimate can be made if there are accepted values for average feed consumption by classes of animals in a species. For example, a diet concentration of 1000 ppm would be equivalent to a dose of 100 mg/kg/day if a class of animals typically consumes 10% of its body weight in feed per day.

The PBB dose required to produce a lethal response was consistent among most mammalian and avian species. Generally, total doses >1000 mg/kg or diet concentrations >500 ppm were required. Two species are noteworthy exceptions. Guinea pigs are about one order of magnitude more sensitive and mink are nearly two orders of magnitude more sensitive to PBB than other species. The high sensitivity of mink to PBB is similar to the high sensitivity of this species to PCB.[124] Reductions in feed consumption and weight gain usually occur at doses lower than doses required to produce significant death losses. On the other hand, the lifetime studies with mice and rats[115] suggest that some reduction in survival time might occur in any group of animals with reduced feed consumption if the observation period is long enough.

2. Hematology and Clinical Chemistry

Changes in hematology and serum clinical chemistry values generally were unremarkable in all species. With few exceptions, significant changes in values only occurred when animals exhibited distinct signs of toxicosis from high exposures to PBB. The data were not entirely consistent among species or among studies of the same species.

Hemoglobin and pack cell volumes were lowered in rats and mice of both sexes when PBB was given at rates of 30 mg/kg/day for 30 days.[108,125] Total white blood cell counts and leukocyte differentials were within normal ranges, but platelets were decreased. Similar hematological results were obtained in rats that were exposed to as little as 3 mg/kg/day when the exposure period was 6 months.[126] Congener 4 (Table 2), when fed to rats at rates

equivalent to amounts of Congener 4 supplied by a given dose of the PBB mixture, had no effect on hematological values except for a decrease in platelets.[125] Packed cell volumes and hemoglobin values also were reduced when cockerels were fed diets of 75 or 150 ppm.[127] There were gradual decreases in packed cell volume, red blood cell and white cell counts in a juvenile monkey fed 300 ppm PBB.[128] No significant hematological changes occurred in growing pigs that were fed diet concentrations of 200 ppm,[111] or in cattle that exhibited toxicosis from total intakes of over 2500 mg/kg.[129]

Glucose and triglyceride concentrations were reduced in rats and mice that received doses high enough to reduce weight gains.[125,126] In contrast, glucose concentrations were not reduced in rats that received comparable doses in short-term studies[110] or in cattle that received toxic doses.[130] Total protein concentrations generally were decreased, and these decreases were associated with decreases in albumin concentrations.[126,128,130] An exception was the increased protein concentrations that were associated with increased β-globulins in short-term studies with rats.[125] Blood urea nitrogen was not affected in rats at any dose,[110,125,126] but it was increased significantly in cattle that had received a toxic dose.[130] This difference between species might be related to differences in the major target organs, which were liver in rats and kidney in cattle.

Serum enzyme changes that are indicative of hepatotoxicity occurred in some cases when high doses of PBB were administered, but morphological changes in hepatocytes were a more sensitive indicator of liver damage.[126] Gamma-glutamyl transpeptidase was elevated consistently in rats and mice.[125,126] Alkaline phosphatase was unaffected in rats,[125,126] but was decreased in newborn pigs from exposed dams.[94] Serum glutamic pyruvic transaminase was unaffected in rats,[110,125,126] but was increased in mice[126] and monkeys.[128] Lactic dehydrogenase was significantly decreased in pigs,[94,111] but it was increased in cattle.[130] Glutamic oxaloacetic transaminase was unaffected in pigs,[111] but it was increased significantly in cattle.[130] It is clear that there were no consistent changes in serum enzymes that are associated with PBB toxicosis.

Cholesterol was the only blood constituent that was affected significantly in any species at exposure rates less than the rate required to produce overt toxicosis. Dose-related increases in cholesterol concentration occurred in rats,[110,126,131] and these increases were significant at dietary concentrations of PBB as low as 5 ppm.[110] Increases in cholesterol concentrations were associated with increases in liver peroxidation in the liver and decreases in retinol and α-tercopherol concentrations.[131] In contrast to rats, serum cholesterol was increased in cattle that had received a toxic dose[130] and decreased in monkeys as toxicosis was produced.[128]

3. Morphological and Histopathological Changes

Liver is the site of the most prominent gross morphological and histopathological changes due to PBB in many species. Changes in liver were similar among rodent species.[108,110,122,125,132-134] Although changes in livers of other species were often similar to the changes in rodents, changes at a given dose were often less severe.[94,109,135] Cattle are notably different from other species in that little change in liver occurs at toxic doses.[117]

Usually, effects of PBB on rodent livers resemble those that are described more extensively for PCB.[40] An increase in liver weight is a characteristic response to PBB exposure. Significant liver weight increases occurred in rats that were fed diets with PBB concentrations as low as 1 ppm for 30 days.[122] The enlargement is associated with induction of microsomal enzymes, and it is dose related.

The nature of histological changes in rodent livers depends on dose rates and the length of time between exposure and examination. Microscopic lesions consisted mainly of extensive swelling and vacuolation of hepatocytes when examination occurred within 30 days of exposure.[108,125,132,134] The vacuoles were filled with fat and vacuolated hepatocytes were diffused throughout the hepatic lobules. Guinea pigs had more extensive vacuolation than

comparably dosed rats.[122] Mitochondria of hepatocytes are increased in size[122] and show degeneration as time passes.[122,132,133] There was a dose-related increase in amounts of smooth endoplasmic reticulum.[108,122,125,132,133] Amounts of rough endoplasmic reticulum were decreased in mice.[132]

As time between exposure and observation increases, livers become friable at high doses, and external surfaces become grayish or mottled.[125] Livers fluoresce under ultraviolet light, which indicates hepatic porphyria.[126,134] Lesions are similar to those at earlier times, but at higher dose levels there are more large vacuoles and necrotic areas. The necrotic foci are infiltrated with polymorphonuclear cells and lymphocytes.[125,134] In rats exposed for 6 months, the microscopic appearance was characterized by disorganization of trabecular cords, moderate to marked enlargement of hepatocytes, moderate fatty infiltration, and hyalinization of the cytoplasma of hepatocytes.[126]

Increased liver weights occur in avian species,[109] and vacuolation, swelling of mitochondria, and disruption of mitochondrial cristae were observed.[135] But unlike rodents, increases in smooth endoplasmic reticulum were not remarkable features in birds. Alterations of livers of pigs consisted of fatty change and centrolobular necrosis.[94] Frequently, hepatocytes were swollen, and the cytoplasm was homogeneous. Although liver is the major target organ in most species, and the changes are fairly consistent among species, cattle are a notable exception. Livers of cattle that were moribund from toxic doses of PBB were enlarged but the only changes were glycogen depletion, sinusoidal dilation, and scattered areas of centrilobular fatty degeneration.[129]

Kidneys show little change at toxic doses in most species except cattle. In cattle, kidneys are the most severely affected organs, and they doubled in size in animals moribund from toxic doses of PBB.[129] The kidneys were distended with fluid and pale tan to gray in color. Pararenal lymph nodes were enlarged and edematous. Prominent lesions were dilatation of collecting ducts and convoluted tubules, and tubular epithelial degenerative changes. Despite the extensive morphological damage, effective renal plasma flow rates and glomerular filtration rates were not affected.[136] The only kidney change noted in other species was atrophy of a few glomerular tufts in male rats at high doses.[108,126]

The weight of thymus is reduced as early as 15 days after rats are given high doses of PBB.[125] In 6-month studies, thymus weights of rats were reduced with exposures as low as 0.3 mg/kg/day, but thymus weights of mice were not affected at any exposure.[126] The normal architecture of thymus was obliterated in moribund rats.[108] There was marked atrophy and loss of demarcation between the cortical and medullary regions, and a disappearance of thymocytes. A reduction in weight of the analogous organ in avian species, the bursa of Fabricius, occurs with exposures as low as 10 ppm in cockerels.[135] The bursa had a moderate depletion of lymphoid cells in the medulla.

Spleen weights increased in rats and female mice at high doses in 6-month studies,[126] but were not changed when the same doses were used in 30-day studies.[125] Histopathological changes in spleen are unremarkable except when rats are moribund from high doses. In this case, lymphatic follicles were small due to lack of periarterial lymphoid cells.[108]

Responses of thyroid weight to PBB exposure were inconsistent, but weights generally were not affected except at high doses.[94,108,109,137,138] On the other hand, dose-related cellular changes occurred at diet concentrations as low as 5 ppm.[137] There was hyperplasia and a number of structural alterations of the follicular cells. More prominent changes included luminal surfaces devoid of microvilli and abnormal cytoplasmic projections in the lumin, swollen mitochondria with disrupted cristae, and abnormal lysosomes and colloid droplets in the cytoplasm.

The commercial PBB mixture was hyperkeratotic when it was applied to rabbit ears. This reaction of rabbit skin is specific for compounds that cause chloracne in humans. Fractionation of the mixture indicated that most activity was associated with the more polar fraction.[38,39,139]

Pure Congener 4, the most abundant congener in the mixture, did not produce hyperkeratosis,[39,60] but solar irradiation of this compound yielded a product that caused severe hyperkeratosis.[60]

Hyperkeratosis, particularly around the eyelids, was a characteristic lesion of high PBB exposure in cattle,[85,117,129] and has been associated classically with chloronaphthalene intoxication in cattle.[140] Thus, it is logical to consider the possibility that brominated naphthalene contaminants of PBB contributed to the toxicity of PBB. But, concentrations of bromonaphthalenes in PBB[38,41] appear to be too low for bromonaphthalenes to be important contributors to hyperkeratosis. Therefore, it is probable that one or more of the bromobiphenyls was the cause of this lesion in cattle.

Only the more acute morphological and histopathological changes are discussed in this section. Changes in the liver associated with carcinogenicity and in the thymus associated with immunotoxicity are discussed in other sections. Lesions in other organs and tissues other than those discussed here were reported occasionally.[15,141] But, findings generally were nonspecific and inconsistent among studies and species, so that little importance can be placed on them.

B. Biochemical Toxicity

1. Induction of Microsomal Enzymes

Induction of the mixed function oxidase system is one of the most sensitive biological effects of PBB. This effect has been studied and characterized thoroughly as a response of animals to PBB. The mixed function oxidase system, which has cytochrome P-450 as its terminal oxidase, is located in the endoplasmic reticulum of many mammalian cells.[142] The system is responsible for metabolism of many endogenous compounds and is an important means of detoxification of many exogenous compounds. Inducing agents generally fall into two classes. Phenobarbital (PB) is typical of one class of agents that induce cytochrome P-450 and a wide variety of enzyme activities. 3-Methylcholanthrene (MC) is typical of a second class of agents that induce a narrower range of enzyme activities and cytochrome P-448.

The commercial PBB mixture is a mixed inducer, i.e., it induces enzymes typical of both PB- and MC-type inductions.[143-146] The response is dose dependent in rats and reaches a maximum at about 50 ppm PBB in the diet,[110,147] or at a total dose in the range of 75 to 375 mg/kg.[146] Induction occurred in rats at intakes as low as 1 ppm in the diet for 21 days.[143] This is equivalent to an 8 mg/kg total dose. Induction was detected as early as 24 hr after initiation of the dose.[144] Individual enzymes are induced at different rates and maximum concentrations usually occur within a range of 7 to 28 days after dosing.[148] Enzymes that reach maximum concentrations early are typical of PB-type induction, whereas enzymes that reach maximum concentrations later are typical of MC-type induction.

Enzyme induction occurred in every species tested. The species included mice,[149,150] dogs,[121] pigs,[94] cows,[151] hamsters,[152] and guinea pigs.[152] PBB was a mixed-type inducer in all mammalian species studied except guinea pigs. In this case, PBB caused a PB-type induction only.[152]

Nonmammalian species show some interesting differences from mammals in patterns of enzyme induction. Quail can be induced and the P-450 response is dose dependent in males, but not in females.[97] Peak induction occurs at 20 ppm in males, but no induction occurred at dietary concentrations below 100 ppm in females. Induction also occurs in several species of fresh- and saltwater fish.[153-156] This induction was only of the MC-type, but it was not accompanied by an increased synthesis of cytochrome P-448.[153]

Although the most prominent site for microsomal enzymes is liver and levels of induction are greatest in that organ, induction also was noted in a number of other organs, including kidney,[149,157,158] lung,[149] and mammary gland.[157] In addition to the absolute concentration

of enzymes, some enzymes that were induced in liver were not induced in other tissues. As an example, epoxide hydratase was induced in the liver, but there was no effect, or a decrease, in its concentrations in other organs.

Milk is an important route of PBB excretion in lactating animals. Thus, induction may occur in the offspring that nurse dams exposed to PBB.[94,157,158] Enzymes were not induced at birth in pigs of dams fed 200 ppm PBB, but enzymes were induced after 4 weeks of nursing.[94]

As congeners in the PBB mixture were identified, purified, and synthesized, studies were carried out to determine the activity of these congeners as enzyme inducers. Studies on the fractionated mixtures, or mixtures reconstituted from pure congeners, indicate that most activity associated with the mixture is due to the brominated biphenyls and is not due to potential brominated dibenzofuran or naphthalene contaminants.[159,160]

Congeners 4 and 8 (Table 2), which are the most abundant congeners in the commercial mixture, are strictly PB-type inducers.[161-163] Congeners 2 and 6 exhibit a mixed PB- and MC-type induction.[164-166] Congener 7 is a very potent MC-type inducer.[167]

Studies of congeners isolated from PBB and of model brominated biphenyls have provided clues as to the structural requirements for MC-type inducers. Generally, MC-type induction requires that the molecule assume a planar position. This position is attained most easily when there are no *ortho* bromines.[87] Some peripheral bromines are required as biphenyl is not an inducer. *Para* bromines appear mandatory because the tetrabromobiphenyl without *para* or *ortho* substitution is not an MC-type inducer.

Compounds that cause MC-type induction often are considered to be more toxic than compounds that cause PB-type induction. Studies with pure congeners and model bromobiphenyls of the two induction types tend to support the hypothesis. The toxic effects of BP-6 were more severe in rats than the effects of pure Congener 4,[125,168] and rats showed more recovery from Congener 4 than the mixture.[125] Congener 4 also did not decrease the hatchability of hens eggs.[169] The mixed-type inducers, Congeners 5 and 7, caused more severe effects than BP-6 or Congener 4.[135,165] Two model bromobiphenyls that were MC-inducers caused greater reductions in feed consumption and growth, and more severe liver pathology of rats than equally brominated PB-type inducers.[168,170] Although the studies are suggestive, it cannot be definitely concluded that MC-inducers are the main cause of PBB toxicity because the studies were short term and only involved a limited number of toxicological endpoints.

2. Interaction with Drugs and Toxicants

Pretreatment of animals with PBB alters the effects of a number of drugs and toxic chemicals. PBB increased the lethality of bromobenzene in mice and shortened the time required to produce death.[171] Timing of the PBB dose affected the response, which was more severe at 48 than at 24 hr. Survival time and LD_{50} were lowered for carbon tetrachloride in mice and rats after PBB treatment.[172,173] The severity of morphological damage in liver and kidney was also increased. Both bromobiphenyls and chlorobiphenyls enhanced the effects of mirex-type compounds in rats, but effects were additive and there were no indications of synergism.[174]

In other cases, PBB may reduce the toxicity of exogenous compounds. Pretreatment of mice with PBB reduced the actions of dibromochloropropane (DBCP) and ethylene dibromide (EDB) on the nonprotein sulfhydral content of liver and kidney, and it also increased the LD_{50} of DBCP.[175] Pretreatment with PBB inhibited the renal toxicity of cephaloridine by enhancing its rate of metabolism.[176] Feeding microsomal enzyme inducers, such as PBB, reduced effects of *p*-aminophenol in producing proximal tubal necrosis in rat kidney.[177] Mercaptanic acid excretion was increased fourfold in studies of metabolism of acetaminophen in isolated profused kidney from rats pretreated with PBB.[178] However, uptake of *n*-methyl

nicotinamide and *p*-aminohippuric acid by renal cortical slices was not influenced by PBB treatment.[179]

Pretreatment of 10-day-old rats with PBB enhanced excretion of the liver toxin ouabain and raised its LD_{50}.[180] Transport of ouabain from plasma to bile also was enhanced in 15-day-old rats whose dams were exposed to 50 ppm PBB during pregnancy and nursing.[181,182] The effect did not occur after rats were 21 days or more old. The increased transport was associated with increased hepatic uptake of ouabain, which also was noted in isolated hepatocytes from rats that had been treated with 200 mg/kg of PBB.[183] Although PBB increased the rate of removal of ouabain from the plasma of mice, it had no effect on the LD_{50}.[180,184]

In general, it is concluded that PBB interacts with compounds that are increased in toxicity or detoxified by increased microsomal metabolism. There are no indications that interactions between PBB and other chemicals involve synergism, and there are no indications that interactions would occur if PBB doses are below that required to induce microsomal enzymes.

3. Endocrine Interactions

Mixed function oxidases are important in normal metabolism of many steroid hormones. Thus, alteration of steroid metabolism and function might be expected because of microsomal enzyme induction by PBB. The frequent observation of thyroid hyperplasia in response to PBB exposure is another indication of PBB interaction with the endocrine system.

Serum thyroxine (T_4) was reduced in male rats that received PBB doses as low as 0.3 mg/kg/day for 6 months.[126] The response was less in females and effects were seen only at doses of 1 mg/kg or greater. PBB did not affect triiodothyronine (T_3) in males, but concentrations were reduced at the higher doses in females. Dose- and time-related reductions in circulating plasma T_4 were found in rats fed daily doses of 1 to 6 mg/kg for 10 or 20 days.[185] At the higher doses, thyroid uptake of iodine was increased, but incorporation of iodine into monoiodotyrosine was decreased. There also was an increase in thyroid stimulating hormone (TSH) with PBB treatment. Feeding PBB to pregnant swine at 200 ppm in the diet reduced serum concentrations of T_3 and T_4.[94] Newborn pigs from these sows had lower concentrations of T_3 and T_4 at birth. After nursing for 4 weeks, pigs born to sows fed 100 ppm also had significant reductions in T_3 and T_4.

Microsomes from livers of rats induced with PBB had increased rates of metabolism of progesterone,[186] testosterone,[187] and the estrogens, estradiol, esterone, and ethynylestradiol.[188] There was no effect of PBB induction on the reductive reactions of testosterone.[187] Stimulated metabolism and lower concentrations of progesterone, testosterone, and estradiol in target organs occurred in vivo in rats treated with 10 or 100 ppm PBB in the diet.[189]

In contrast, PBB treatment had little effect on concentrations of circulating steroid hormones. Corticosterone,[190,191] prolactin,[191] luteinizing hormone (LH),[191] and testosterone[190] were not affected in rats. However, high concentrations of PBB did cause a reduction in prolactin in one study.[190] As in rats, circulating concentrations of progesterone and estradiol were normal in cows that had received toxic doses of PBB.[192] These cows also had lower clearance rates of these hormones from blood and a decreased rate of excretion of metabolites in urine and feces.[193]

Clearly, PBB exposure can alter metabolism or circulating concentrations of hormones, but the significance of the alterations is not established. Lower concentrations of thyroid hormones may be a cause of lower feed consumption and growth in chronic studies. Delayed vaginal opening in female rats,[194] regression of comb weights in male chicks,[109] and hypospermatogenesis in male calves[85] suggest the possibility of altered steroid function.

C. Reproduction

1. Embryotoxicity and Teratogenicity

PBB is embryotoxic and teratogenic in some species at high doses. Mice and rats are the

only species in which teratogenic effects were noted. Lack of reports of teratogenicity in other species may be due more to lack of comprehensive studies than to the absence of effects.

Single doses of PBB on day 6 of pregnancy in rats caused 100% embryo resorption at doses above 400 mg/kg and caused some resorption at doses of 200 mg/kg.[195] Embryo lethality declined as the dose was given later in pregnancy, and lethality approached control values when high doses were given after day 13 of pregnancy. When rats were given lower levels, but continuous doses through late gestation, fetal deaths were not greater than controls at dietary concentrations as high as 1000 ppm[196] or intakes of 10 mg/day for a total dose of 360 mg/kg.[194] Interestingly, octabromobiphenyl was less embryotoxic in rats than BP-6, and it was fed at rates as high as 10,000 ppm from day 6 through day 15 of pregnancy with no adverse effects.[114,197] Maternal exposure to 200 ppm PBB during pregnancy increased fetal death in mice as measured by resorbed fetuses and decreased the weights of surviving fetuses.[198] Cattle fed a total dose of about 2650 mg/kg had three abortions and three dead fetuses from six treated animals.[107]

Two types of terata occurred in rats that were fed PBB at days 12 and 13 of pregnancy. Cleft palate and diaphragmatic hernia occurred occasionally with intakes of 400 mg/kg and were quite frequent at 800 mg/kg.[195] No terata were noted in rats fed 1000 ppm PBB in the diet,[196] doses of 600 mg/kg on day 6 of pregnancy,[199] or total doses of 360 mg/kg through the latter stages of gestation.[194] Also, no teratogenic effects were found in rats fed octabromobiphenyl at 1000 ppm.[114] Mice were more sensitive than rats to teratogenic effects of PBB. Exencephaly was reported in mice fed as little as 100 ppm and cleft palate occurred at 1000 ppm.[196]

Embryo development was studied in vitro in rats that were given 800 mg/kg PBB on days 9 or 10 of pregnancy and killed after 24 hr.[200] Survival of embryos cultured for 24 or 42 hr was not affected. DNA content was reduced and remained reduced for the 42 hr. PBB treatment retarded development of cultured embryos, but retarded development was not correlated with in vivo observations made earlier.[195] This delayed development tended to be corrected after 42 hr, which led to the conclusion that effects of PBB are transitory when embryos are removed from the contaminated environment.[200,201]

2. Reproductive Performance

In addition to embryo mortality, which was discussed above, overall reproductive performance of animals is determined by fertility and progeny performance. Surprisingly, little work was done in which animals of either sex were exposed before mating so that the effect of PBB on fertility cannot be evaluated. When young nurse, they often receive PBB in milk in amounts that greatly exceed their exposures *in utero*. Thus, animals that are apparently normal at birth may show increased liver weight, decreased growth, and increased mortality as time passes.

Reduced birth weights were reported in mice and rats at intakes of 1000 ppm.[196] Cross-fostering studies with rats indicated that exposures to PBB by the dam at levels >360 mg/kg reduced growth of the progeny.[194] The effect was more severe in males than in females. Concentrations as high as 100 ppm did not produce a significant effect on postnatal mortality or body weight of mice up to 6 weeks of age.[198]

Pigs fed diets with concentrations as high as 200 ppm during gestation had young that were normal at birth.[94] But, mortality was over 50% in these apparently normal young when they nursed their dams that continued to receive 200 ppm. There was no mortality in the young when dams received lower doses. Weight gains were lower at 100 ppm but there was no effect at 10 ppm.

Calves born of cows that had received 250 mg/day PBB for 60 to 202 days during late pregnancy had increased birth weights, which caused some stillbirths due to difficulty in

calving.[202] Birth weights were correlated positively with PBB concentrations in the fat of the dams. Growth, development, and survival were not affected in the calves born alive.

Lower birth weights were found in monkeys whose dams were fed as little as 3 ppm PBB for 6 months and growth in monkeys whose dams had received 0.3 ppm was reduced.[128] Birth weights were reduced in mink fed diets containing 1 ppm PBB.[124] The work with this species is among the few studies in which feeding of PBB was started before the start of gestation. Offspring of mink fed 1 ppm in the diet also had lower growth rates than offspring of controls.

3. Avian Reproduction

Reproductive performance in hens is lowered dramatically by high exposures to PBB.[98,112,203] First, there is a reduction in feed consumption, which is paralleled by a reduction in egg production. Feed consumption and egg production stop when concentrations of PBB in diets exceed 600 ppm.[112] Second, there is a dose-related reduction in the hatchability of fertilized eggs. The reduction in hatchability is not related to the reduction of food intake because hatchability of eggs from pair-fed controls is about the same as eggs from normal controls.[112] Significant reductions in hatchability can occur at dietary concentrations between 30 and 45 ppm.[98] Usually, death of embryos occurs late after an apparently normal development. Many eggs will be pipped but will not hatch. There is no evidence that PBB is teratogenic in chickens.

Chicks from hens fed PBB had higher mortality and lower growth rates than chicks from unexposed hens, and effects were detected when there was 30 ppm PBB in the diet.[98] Results were inconsistent when diet concentrations were 20 ppm. In one study,[204] growth rate was not reduced, whereas in another study,[112] there appeared to be some reduction in growth rate.

Hens will recover after exposures as high as 3000 ppm in the diet when they are returned to clean feed. Time for recovery depends the concentration of PBB in the diet. Egg production and hatchability returned to normal within 2 weeks when hens were fed 120 ppm or less, but 5 to 6 weeks were required when concentrations were 3000 ppm.[98]

Mechanisms for the adverse effects of PBB in hens are not established, but it was established that Congener 4 (Table 2), the most abundant chlorobiphenyl in the mixture, is not the cause of decreased hatchability.[203] Effects caused by PBB on hatchability and progeny survival are similar to those caused by PCB in hens.[204,205] However, unlike mammalian species, avian species appear to be more sensitive to PCB than to PBB for most measures of toxicity.[98,205]

D. Immunotoxicity

Atrophy of the thymus was a frequent observation when cattle and laboratory animals were exposed to high doses of PBB.[108,125,126,129] These observations, and the implication of PCBs as immunosuppressants,[40] suggested that exposure to PBB could lead to a compromised immune system.

Dogs fed PBB for 61 days showed depletion of lymphocytes in the lymph nodes, particularly in the T-cell zones, and a reduction in the IgG-containing lymphol sites in popliteal lymph nodes.[206] Effects were pronounced at doses of 4 mg/kg/day but were mild at doses of 1 mg/kg/day. Animals at the highest dose level also had weight loss and other adverse effects of PBB.

PBB reduced concentrations of serum immunoglobulin isotypes in mice, but results were not uniform in all studies.[119,120,207,208] In one study, IgM and IgG were affected at diet concentrations as low as 10 ppm for 30 days,[207] whereas in another study, IgG was only moderately reduced at diet concentrations as high as 167 ppm for 6 weeks.[208] Reductions in serum immunoglobulins occurred only at the highest dose level of 10 mg/kg/day in chronic studies.[119]

The T-cell-dependent delayed hypersensitivity reaction to sensitization with dinitrofluorobenzene was normal at all dose rates in mice and rats in short- and long-term studies.[119,207]

Antibody production to sheep erythrocytes was reduced in mice fed 160 ppm PBB in the diet for 3 weeks, but antibody production was not affected at 6 weeks.[208] No response of direct plaque-forming cells was found in 6-month studies that represented a higher total dose.[119] The lack of response in longer studies suggests that there is adaption to chronic exposure.

Response to mitogens was variable among species, and rats were the most sensitive species. Reduction in several responses in rats occurred at diet concentrations of 1 ppm fed for 6 months, whereas mice required concentrations of 10 ppm to produce a response in the same study.[119] Mitogen responses in pigs were reduced when pigs were fed 200 ppm PBB in the diet for 12 weeks, but responses were not reduced at 100 ppm.[209] There were no reductions in cows when exposures to PBB were >1000 mg/kg.[210]

Although a variety of immune responses has been recorded, nearly all were recorded at doses that produced other effects, such as liver lesions and decreased weight gains. There also appears to be some variation among species, since rats were more sensitive than mice, and rats appear to be more sensitive than cattle or swine for those parameters that were measured.

E. Carcinogenicity

The BP-6 mixture was carcinogenic in two strains of rats and one strain of mice when it was administered at high doses. Male and female Sherman rats were given a single dose of 1000 mg/kg PBB, and they were observed for as long as 14 months after dosing.[134] Rats had pronounced liver pathology, including neoplastic nodules that occurred mainly in females. Later, studies were conducted in female Sherman rats in which treatments were a single dose of 1000 mg/kg, 12 doses of 100 mg/kg, and a single dose of 200 mg/kg.[116] Atypical foci were almost 100% at higher doses and about 50% at the lowest dose. The incidence of hepatocellular carcinomas was 41 and 68% in rats at the two high doses. Rats given the lowest dose had a 31% incidence of neoplastic nodules. There was no change in incidence of lesions in other tissues.

In another study, Fisher 344 rats and D6C3F$_1$ mice of both sexes were fed daily doses as great as 10 mg/kg for 6 months.[115] Lesions included neoplastic nodules, hepatocellular carcinomas, and cholangiocarcinomas in rats and hepatocellular carcinomas in mice. A significant incidence of lesions only occurred in groups that received the highest dose of 10 mg/kg. Atypical foci in liver were present at lower doses, and a significant incidence occurred at doses as low as 0.3 mg/kg in male rats.

Carcinogenesis in animal test systems is a multistage process that consists of initiation and promotion phases. PBB does not have properties of known initiators. That is, PBB does not bind to DNA[86] or induce chromosome breaks.[110,199,211] PBB does inhibit metabolic cooperation in Chinese hamster cells in vitro.[212] Since this is a property of promoters, it is possible that PBB is a promoter and not an initiator of carcinogenesis.[213] Concentrations of 10 and 100 ppm of the PBB mixture or of pure Congener 4 in the diet were promoters of hepatocarcinogenesis in rats.[214] The mixture was a more effective promoter than Congener 4. In contrast, neither PBB nor several purified congeners were tumor promoters in two-stage mouse skin assays.[215,216]

Overall, PBB was a liver carcinogen under long-term observations in rats and mice. Its behavior is similar to that of PCB in many respects.[40] There is no evidence of tumors in tissues other than liver and the action of PBB appears to be that of a promoter rather than an initiator.

F. Conclusions

Although extensive, this review is not intended to be all-inclusive. No consideration was

given to field reports or epidemiological studies of environmentally exposed animals. These reports, which are considered in a later section, contain a great deal of extraneous information that can be evaluated only with a foundation of experimental findings. There are several other reviews of PBB toxicity that may differ from this review in emphasis and comprehensiveness.[15,40,63,140,217,218]

A variety of toxic responses to PBB were produced in laboratory and domestic animals. None of the responses are produced uniquely by PBB, but several are characteristic of responses produced by halogenated hydrocarbons as a class. Responses that are characteristic of halogenated hydrocarbon toxicosis were typified by induction of microsomal enzymes in all species, liver lesions of rodents, kidney lesions of cattle, hyperkeratosis in several species, and reduction of egg hatchability in avian species. Many responses to PBB, such as immunosuppression, weight loss, and poor reproductive performance are caused by a variety of toxic agents. Although no effect levels were not established in most studies, it is noteworthy that, except for enzyme induction, high exposures to PBB were required to produce effects experimentally.

VII. FARM ANIMAL EXPOSURE AND HEALTH

Controversies in the PBB episode revolved around two underlying issues: effects of PBB on health of cattle and effects of PBB on health of people. Although questions on the effects of PBB on health of people are by far the most important, controversies concerning health of cattle arose first, and publicity surrounding these controversies largely were responsible for bringing issues of human health to popular attention. There is no doubt that high exposures to PBB caused toxic effects in cattle,[23,107] but there is reason to doubt that herds with nonviolative residue concentrations in fat were exposed to amounts sufficient to cause toxic effects.

A. Exposure

Estimates of PBB exposure of cattle herds can be made by applying kinetic models to concentrations of PBB in milk or tissue fat that existed in contaminated herds when they were identified originally. A major uncertainty in exposure estimates made with any kinetic model is lack of knowledge of the time of exposure for most herds. Time of exposure is known for some herds that used feed with high concentrations of PBB,[22] but time of exposure generally is not known for herds that received feeds with low concentrations of PBB due to cross-contamination in feed mills.

Since no exposure to PBB occurred before August 1973,[20,22] maximum potential exposures of herds with low exposures may be estimated if it is assumed that all exposure occurred in August 1973. This assumption will lead to erroneously high values for exposure in many cases, but it will provide a sound basis for making a worst case evaluation of exposure. The claims of adverse effects of PBB in herds with low exposures can then be evaluated by comparing the estimated exposure levels with exposure levels required to produce effects experimentally.

Estimates of maximum exposures that correspond to various milk or tissue fat concentrations at the time of detection are presented in Table 4. Absence of values for some categories of concentration and time after exposure indicate that no herd fit these categories. A model with first-order elimination from a single compartment was used to calculate the estimates. The model is reasonable for lactating cows that are not ingesting PBB.[96] Biological half-lives of PBB are about 180 days in lactating cows when observation periods are long.[219] Concentrations of PBB in milk fat and body fat are correlated highly and concentrations in body fat were about 2.5 times concentrations in milk fat of cows from the Halbert herd sampled about 1 year after exposure.[80] Total doses in milligrams per kilogram were about

Table 4
ESTIMATED MAXIMUM PBB DOSE OF CATTLE BASED ON MILK OR TISSUE FAT CONCENTRATIONS AT THE TIME OF DETECTION[a]

Concentration detected[b]		Months from exposure to detection[c]			
Milk	Tissue	9	12	18	24
100	250	1055			
30	75	317			
10	30	106			
3	7.5	32	45		
1	2.5	11	15	30	
0.3	0.75	3	5	9	18
0.1	0.25	1	2	3	6

[a] It was assumed that exposure occurred in August 1973. Vacant areas indicate that all animals in the concentration categories were identified before the indicated time had elapsed.
[b] Values in parts per million.
[c] Values in milligrams per kilogram.

1.5 tim concentration of PBB in body fat in parts per million when heifers were fed PBB fo lays.[71]

Documented exposure data for the Halbert herd[23] provide a means to check the validity of the projections in Table 4. High producing cows were offered 6.8 kg/day (15 lb) of feed that contained 2900 ppm of PBB for 16 days. Thus, animals were offered approximately 19.7 g/day of PBB, or a total of 316 g for the 16-day period. However, feed consumption was reduced and the dose would have been less. If reduction in consumption in this herd followed the pattern of reduction in feed consumption of animals that were fed 25 g/day experimentally,[107] total intake of PBB would have been about 125 g. This is equivalent to a 250 mg/kg dose in cows that weigh 500 kg.

Contamination in the Halbert herd was identified and the residues were quantitated in May 1974, approximately 7 months after the contaminated feed was used. Average concentration of PBB in milk fat was 34 ppm,[220] which would correspond to 85 ppm in body fat. Using the 180-day half-life, one would project a 191-ppm concentration in body fat at the end of exposure in October. This concentration would be derived from a dose of 285 mg/kg. This projection agrees well with the exposure calculated above and it is concluded that the model used in deriving the values in Table 4 is reasonable.

Although more than 300 Michigan farms were quarantined for having residue concentrations in meat or milk that exceeded the 0.3-ppm guideline, only a small number of these herds had high exposures to PBB.[220] One herd had a concentration in milk fat that exceeded 100 ppm at the time of detection. An additional 12 herds had concentrations in the range of 30 to 100 ppm, and 8 herds had concentrations in the range of 10 to 30 ppm. All of these herds were identified and quarantined in May 1974. Seven herds had milk concentrations in the range of 3 to 10 ppm. All of these herds were identified by July 1974, but most were identified in May. With one or two exceptions, early detection and quarantine were the rule for the 12 herds that had milk concentrations in the range of 1 to 3 ppm. The herds listed above generally were depopulated, although a few farmers retained some animals that they felt had not been exposed to the contaminated feed. These herds accounted for most of the cattle that were destroyed in the first phase of the episode.

Most animals that were destroyed (over 20,000) were from herds that were identified and quarantined after guidelines were lowered to 0.3 ppm in milk and tissue in October 1974. These herds generally were quarantined on the basis of tissue residues, and these residues may have reflected only one or a few violative animals out of a large number of tested animals.

The herds that engendered the controversies on animal health effects of PBB were those in which some animals had detectable PBB but the concentrations did not exceed the 0.3 ppm guideline. It is clear from the projections in Table 4 that exposures in these herds, even using worst case estimates, were very low. Exposures could not have exceeded 10 mg/kg even if exposure had occurred as early as August 1973 and detection as late as August 1975. It should be noted that if exposures to these herds had been higher, the pattern of contaminated herd detection suggests that the herds would have been detected at an earlier time when their milk concentrations would have been in the violative range.

B. Animal Health at High Exposures

A description of the clinical signs associated with feeding PBB-contaminated feed to cattle is available for the Halbert farm.[23] As noted above, average exposure to the cows on this farm was about 250 mg/kg. The contaminated feed also was fed to a group of 6- to 18-month-old calves. If the contaminated feed was the only feed offered, the dose might have been about 58 mg/kg/day when feeding started. The animals became anorexic, but total doses may have reached 700 mg/kg over 6 weeks if feed was consumed at the same rates as in experimental studies.[107] As in all situations involving clinical observations without controls, it was not possible to draw definitive conclusions as to which conditions were caused by PBB and which were unrelated to PBB. On the basis of controlled experiments carried out later, some conditions that often are ascribed to PBB actually were unrelated to exposure.

Controlled studies on high-level exposure of cattle to PBB were initiated in Ohio in 1975.[107] The high dose group of the study was intended to have exposures that approximated exposures in the Halbert herd. In reality, the design of the experiment resulted in exposures that were much higher. The Halbert cows probably consumed about 20 g/day PBB initially, and the Ohio study was designed with one group dosed at 25 g/day. PBB was administered by capsule and dosing continued until animals were moribund. In contrast, cows in the Halbert herd reduced their feed consumption, and their rate of PBB exposure, and the contaminated feed was fed for only 16 days. Thus, the Ohio study involved total exposures of 2060 to 3750 mg/kg, which were about 10 times greater than the estimated exposures in the Halbert herd.

In spite of the wide difference in dose between the Halbert and Ohio animals, there are many areas of agreement on the clinical signs of toxicity. Anorexia, emaciation, dehydration, excessive lacrimation, fetal death, and hyperkeratosis were recorded in both sets of observations.[23,107] Hematological or clinical chemistry changes were not noteworthy in either case, and both sets of animals had some response in appetite when alfalfa hay was offered.

The Ohio animals were nonlactating and became moribund within 4 to 6 weeks. However, some clinical signs in the Halbert animals that cannot be compared directly to those of the Ohio animals appear to have been caused by PBB. Reduction in milk production is the most obvious because it would occur any time feed consumption is reduced. Embryonic resorption was suspected in the Halbert herd, and this suspicion agrees with findings in many laboratory animal species.[195,198] The hypospermatogenesis in a young bull was confirmed in a calf feeding study.[85] Enlarged calves and difficulty in calving also were found in the Ohio studies when the total dose was only 37.5 mg/kg.[118] However, attribution of enlarged calves to lengthened gestation periods was not confirmed.

About 50% of the Halbert calves that were fed the contaminated feed died within 6 weeks,

as did the Ohio heifers. Pathological findings, however, were not reported.[23] The death rate of Halbert cows was much lower (about 24/400) and deaths occurred as long as 6 months after exposure. Pathology reports from ten of the cows did not reveal a consistent pattern of changes, although liver changes were noted frequently. The changes included fatty metamorphosis, large fat vacuoles replacing cells, and amyloidosis. In contrast, liver changes were not notable in the Ohio animals that died in a shorter time period.[129] The findings may not be in disagreement because liver is the major target organ in many species and the Halbert animals had a more chronic type exposure than the Ohio animals. One important difference between the Ohio and Halbert animals was the consistent finding of kidney damage in the Ohio animals. This damage was the same as that caused by chlorinated naphthalenes.[140] Although kidney changes were found in some Halbert animals, these were less significant. The failure to find kidney changes consistently in the Halbert animals could be a reflection of lower exposure levels, or it could be an indication of repair with passage of time. The latter is a possibility because recovery was often noted in cattle with chlorinated naphthalene toxicosis.[221]

Several clinical signs that occurred in the Halbert animals were not observed in the Ohio animals. These included hematomas, abscesses, abnormal hoof growth, hair loss, liver abscesses and necrosis, and metritis. Many of these nonspecific clinical signs probably were not caused by PBB. For example, follow-up studies with a group of the Halbert animals indicated that hoof growth was not exceptional after the hoofs were trimmed.[99] The hematomas may have been caused by bad hoofs, which made animals prone to falls and injury. Increases in infections of the reproductive tract might be expected after difficult calving, but this is not related to an impaired immune function, which does not occur unless animals are moribund.[210]

The Halbert herd was 1 of about 12 herds that had PBB concentrations in milk fat that exceeded 30 ppm when detected. It is likely that all of these herds had some clinical signs of toxicosis. The situation is less clear cut as one goes down the scale of milk concentrations. Feed that was contaminated by cross-contamination in the feed mills was being fed at the time of detection in some cases.[22] Under this circumstance, PBB intakes as low as 0.1 mg/kg/day could produce milk fat residues as high as 20 ppm.[96]

Total exposure of herds with 3 ppm or less in milk fat at detection could not have exceeded the total 37.5 mg/kg dose administered to one group in the Ohio studies.[107] There were no short- or long-term effects of PBB in these animals except for increases in calf weight and induction of microsomal enzymes.[107,129,130,151,202] Neither effect is of particular clinical importance as a sign of toxicity. There was no comprehensive clinical examination of any herd that had milk concentrations in the range of 1 to 30 ppm, but it appears that most animals in these herds were not exhibiting clinical signs when the farms were depopulated.

C. Animal Health at Low Exposures

The highly publicized controversies[5,6,8] on the effects of PBB on cattle health involved herds in which residue concentrations in body fat did not exceed 0.3 ppm. Some owners of these herds claimed that PBB exposure caused the same clinical signs in their herds as were reported in the Halbert herd. A point that often is overlooked, however, is that most owners of herds in the category did not feel that their herds were harmed by PBB. It is clear on examining the projections in Table 4 that average exposure per animal in the low level herds could not have exceeded a total dose of 5 mg/kg even under the extreme assumptions of the model. There is no experimental or epidemiological evidence that this level of exposure would have caused toxicological effects in cattle or in any other species.

Total doses of 1.08 mg/kg PBB were fed to cattle in a research setting in 1972 before the Michigan episode occurred.[96] Although the study was designed primarily to examine residues, no overt signs of toxicosis were observed when PBB was fed, or in subsequent

observation of the cattle in their productive lifetimes.[222] It can be inferred from concentrations of PBB in milk that concentrations in body fat were greater than 1 ppm at the end of dosing and that concentrations would have exceeded 0.3 ppm for some time.

More comprehensive studies were carried out after the incident occurred. As noted above, only two negligible biological effects occurred in the Ohio animals that were fed a total dose of 37.5 mg/kg. These animals had PBB concentrations in body fat that were about 100 times greater than the 0.3-ppm guideline.[71] The Ohio studies[107] also included a group of animals that received a total dose of 0.0375 mg/kg, which produced a body fat concentration of 0.16 ppm.[71] No effect of PBB was found in these animals that were observed through their lifetimes.[118,129,130,202] In another study, no clinical effects of PBB were found in calves fed 0.1 mg/kg for 84 days or cows fed 0.3 mg/kg for 158 days.[85] Concentrations of PBB in body fat of both classes of animals were more than 100 times greater than the 0.3-ppm guideline when dosing ended.

Michigan cattle with low exposures to PBB were the subject of several studies. Cows with known production histories and with PBB exposure were assembled for one study.[223] Mean concentration of PBB was 0.31 ppm in body fat. A comparable group of cows from Wisconsin were assembled as controls. There were no significant differences in the production, health, or clinical lesions of the two groups, which were subjected to the same feeding and management system. The health status of 16 herds with low PBB exposure was compared to the status of 15 herds with no PBB exposure in an epidemiological survey.[224] Productivity and general health conditions between the two groups of herds were similar. Dairy Herd Improvement Association records of exposed and unexposed herds, as indicated by records of residues under Act 77, were analyzed recently.[225] No productive or reproductive characteristic of the herds was affected by PBB exposure.

In conclusion, all published studies on effects of low PBB exposure indicate that it is not possible to detect an effect of PBB at levels of exposure that are insufficient to cause violative residues. The clinical signs associated with high exposures to PBB are nonspecific and most are of such a general nature that they can be caused by many agents that include improper nutrition, mismanagement, disease, or toxic materials other than PBB. Thus, the herds for which owners complained of health or production problems may have had those problems, but the problems must have been caused by some agent or management factor other than exposure to PBB.

VIII. HUMAN EXPOSURE AND HEALTH

A. Exposure

1. General Population

PBB became distributed widely throughout the population of Michigan. This is not surprising since normal marketing channels for dairy products involve mixing of milk from a large number of producers in relatively few processing facilities. In addition, most cull dairy cattle are used for hamburger and processed meat products, which also would receive wide distribution. Thus, the marketing systems have the negative impact of broadening the exposed population and the positive impact of minimizing the exposure of an individual in the population.

Although results of earlier studies suggest that PBB was distributed widely in the urban population,[82] a comprehensive study of the distribution was not conducted until 1978.[226] In this study, serum of adults and children and adipose tissue of adults were examined in a weighted probability sample of the population of the state. The mean concentration of PBB in adipose tissue was 400 ppb, and PBB was detected in 97% of the samples. Detection of PBB in serum is less sensitive, and it only could be detected in 69% of the adults and 73% of the children. Mean concentrations in serum were 1.3 for adults and 1.8 ppb for children.

Application of a pharmacokinetic model[81] to the mean serum concentrations for adults indicates that total exposure was about 9 to 10 mg for an average male with an average adipose content. There was, of course, considerable variation among PBB serum concentrations in serum of individuals. The individual with the highest concentration is projected to have had a total exposure of about 800 to 900 mg.

The incidence of PBB residues in humans was not uniform throughout the state. Average concentrations tended to reflect the areas where the contaminated feed had been used and the marketing channels for dairy and meat products. Thus, average concentrations of PBB were lowest in the upper peninsula where there was little use of PBB-contaminated feed. Higher than average concentrations occurred in the area centered on Muskegan County in western Michigan. This was the area that had the largest number of quarantined farms.

Concentrations of PCB also were measured in the survey.[226] It is interesting that PCB concentrations were about ten times greater than PBB concentrations in most areas of the state. As with PBB, people in the Muskegan area had higher PCB concentrations than people in other areas. It might be speculated that the high PCB concentrations in the Muskegan area reflect the prominence of sport fishing in Lake Michigan which adjoins this area and which has a record of producing PCB-contaminated fish.[227]

2. Groups with High Exposures

Several groups had PBB exposures much higher than exposures of the general population. These groups included chemical plant workers who manufactured PBB, farmers on contaminated farms who consumed their own products, and a group of consumers who purchased products directly from contaminated farms. The greatest variation in exposure involved residents of contaminated farms who consumed their own products. Consumption of home-produced food is a practice that is followed to varying degrees among farmers, and there was great variation among exposure levels of contaminated farms (Table 4).

Workers in the chemical plant that produced PBB had the highest average serum and adipose concentrations of PBB among all of the special groups that had high exposures.[11,77] Chemical plant workers also are different from other groups in that their route of exposure would be mainly by dermal contact or inhalation rather than ingestion with food. Thus, the distribution of congeners in the residue of plant workers was different from the distribution in other exposed groups because there was no intervening animal system to metabolize or selectively excrete some of the congeners.[106] PBB was detected in serum of all chemical plant workers who responded to invitations (55 of 270) for examination.[77] Highest concentrations were in workers directly involved with production of PBB. Four out of ten production workers had serum concentrations greater than 500 ppb and the mean was about 600 ppb. In contrast, the mean of nonproduction workers was only 16 ppb.

Serum samples for PBB analysis were obtained from potentially exposed residents of farms as early as June 1974.[2] Other reports appeared over time, but the most comprehensive data are those obtained in the Michigan Department of Health Cohort Study.[11] Highest individual, mean, and median concentrations occurred in the group composed of residents of quarantined farms. The second highest group was individuals who consumed products from quarantined farms. The lowest concentrations occurred among residents of farms that had PBB exposures too low to produce animals with residues great enough to require quarantine.

The mean concentration of PBB in serum of residents of quarantined farms was 27 ppb and the range was from 0 to 1900 ppb. Applying the pharmacokinetic model, as was done for the general population, indicates that the mean total exposure was about 170 mg per individual and the highest exposure was about 11.7 g. The 11.7-g value agrees well with the high exposure of 9.8 g that was derived from a pharmacokinetic analysis of milk concentrations on a highly exposed farm.[93] Serum concentrations in consumers of products

from quarantined farms were slightly, but not significantly, lower than concentrations in residents of farms. Mean concentration in the residents of nonquarantined farms was 3.5 ppb, and the highest was only 24 ppb. These are equivalent to a mean total exposure of 21 mg and a high exposure of 150 mg per individual. It is interesting that the mean concentration in residents of nonquarantined farms did not differ greatly from the mean of a group of self-selected volunteers who had no known connection with a PBB-contaminated farm. It was found later that some volunteers may have received products from contaminated farms.

B. Epidemiological Studies

Questions that involve the effects of PBB on health of people are more difficult to evaluate and resolve than questions that involve the effects on health of cattle. This is because there was no instance of acute PBB toxicosis in humans with which to compare the potential effects at lower exposures, and there are, of course, no controlled studies on humans. Resolution of health questions were complicated further by the absence of toxicological information on PBB in 1974. But, it was reasonable then, as it is now, to expect that effects of PBB in humans would be similar to the effects of PCB.

It was recognized within days after the identification of PBB that the potential for high exposures existed in farm families that may have consumed home-produced foods. For this reason, an epidemiological investigation was initiated by the Michigan Department of Public Health (MDPH) in June 1974 to compare the health status of people on quarantined farms with people on nonquarantined farms in the same area.[2] Individuals were surveyed for conditions and complaints that were prominent in the Yusho incident that involved human exposure to PCB.[28] Results of this study set a pattern that characterized all subsequent reports on human health effects of PBB. Although a variety of symptoms were reported by both groups, there was no pattern of differences between the groups. No abnormalities of heart, liver, spleen, or nervous system that could be related to PBB exposure were found in physical examinations. There were no differences between groups in urine analyses and blood counts.

Serum concentrations of PBB in residents of quarantined farms were in a range from nondetected to 2.26 ppm. Many residents of nonquarantined farms also had detectable PBB in serum, but the median was much lower than the median of the quarantined group, and the highest concentration was less than 0.09 ppm. The presence of PBB in the nonquarantined farm group led many to question its use as a control group,[5,6] but the conclusions of the study are valid when the data are viewed on a dose-response basis.

After this initial study, MDPH established a cohort of individuals for a long-term study of the effects of PBB.[11] The shorter-term objectives of the study were to determine if there were increases in incidence of acute or subacute illness, biochemical aberrations, and alterations in the outcome of pregnancy. The cohort is to be followed for several decades to determine long-term effects, with particular emphasis on changes in the incidence of cancer.

Six groups of varying potential exposure were included in the cohort. The groups were residents of quarantined farms, recipients of products from quarantined farms, chemical workers and their families, individuals from the pilot study who had low PBB exposures, self-referred individuals who resided on farms that were contaminated with low amounts of PBB, and self-referred individuals who had no direct connection with contaminated farm premises. As discussed in the section above, mean and median serum concentrations of PBB were much higher in the first three groups than in the latter three.

Prevalence of selected symptoms by group was examined and reported above 4 years after exposure.[11] Symptoms generally were most prevalent in the two self-selected groups and were least prevalent in the group composed of chemical workers and their families. The cohort was divided into segments on the basis of serum PBB concentrations in order to examine dose-response relationships. No positive associations were found between serum concentrations of PBB and symptom frequencies. Symptom prevalence was slightly higher

in persons with no detectable PBB in serum than in persons with measurable quantities. No positive dose-response trend existed within any group. Even within the chemical worker and quarantined farm resident groups, the highest prevalence of symptoms was in persons with the lower serum PBB concentrations.

Another epidemiological study of Michigan farmers exposed to PBB was conducted in 1976 by the Environmental Sciences Laboratory, Mt. Sinai School of Medicine (ESL).[30,228,229] The study involved about 990 farm residents, 55 chemical workers, and a group of Wisconsin dairy farmers who were used as a control. The Michigan farm residents were comprised of three groups. One group was a random sample of individuals from PBB-contaminated farms. The sample was generated from lists of quarantined and nonquarantined farms developed by the Michigan Department of Agriculture. The random sample was augmented by individuals from the most highly exposed farms and by individuals from farms where PBB was not detected in order to provide a wide range of possible exposures. Another group consisted of consumers of produce bought directly from farms that participated in the survey. A third group consisted of self-selected individuals who comprised approximately 50% of the total participants. All subjects completed comprehensive questionnaires on medical histories and symptoms, and they were subjected to physical examinations and certain laboratory tests.

The incidence of symptoms in Michigan farmers was greater than the incidence in Wisconsin farmers.[228,229] The greatest differences were in the broad classifications of neurological and musculoskeletal symptoms. Consumers of products from contaminated farms had an array of symptoms similar to the symptoms of the residents of the farms.[230] Elevated serum concentrations of some liver enzymes and carcinoembryonic antigen were more prevalent in Michigan farmers than in Wisconsin farmers.[231,232] Chemical workers had a higher prevalence of chest and skin symptoms and a lower prevalence of musculoskeletal symptoms than farmers.[233] There is some basis for this observation because chemical workers would have a greater likelihood of dermal or inhalation exposure than farmers.

As was the pattern of the MDPH study,[11] self-selected groups, which had lower PPB concentrations in serum, reported a higher incidence of symptoms than randomly selected groups. Although results of ESL studies were at times interpreted differently from results of comparable studies, there was one area of consistent agreement. Neither sets of studies demonstrated a positive dose-response relationship between PBB concentrations in serum or adipose tissue and the prevalence of symptoms or abnormal clinical measurements.

A complicating factor in interpreting the ESL studies was the low rate of response to invitations to participate by some groups.[229] Responses were 86% for the self-selected groups, about 50% for the randomly selected groups, and less than 20% for the chemical workers and Wisconsin farmers. This differential rate of participation may have introduced a bias into the studies which cannot be evaluated.

C. Special Studies

Several clinical areas received attention in more intensive studies by the MDPH, the ESL, and others. Neurological symptoms were one such area because this class of symptoms was reported more frequently than other classes. Subsamples of the Michigan and Wisconsin groups in the ESL studies were examined in objective performance tests used for the assessment of neuropsychologic disfunction.[234,235] Although prevalence of subjective symptoms was greater in the Michigan group, there were no significant differences between groups in the performance tests. Neither the results of the objective tests nor the subjective symptoms were significantly correlated with serum PBB concentrations.

Memory performance in a battery of tests was similar in chemical workers and farm residents despite the fact that chemical workers had serum concentration of PBB about three times greater than farmers.[236] There also was no relationship between fat concentration of PBB and memory performance. Individuals exposed to PBB who had complained of chronic

undiagnosed illnesses were compared to volunteers in a battery of tests measuring memory, motor strength, and coordination.[237] Differences in measurements between groups were eliminated by adjusting for educational level. The groups differed in the Minnesota Multiphasic Personality Inventory, which suggested an adjustment reaction with depressive symptoms and somatizing defenses. PBB concentrations in adipose tissue did not correlate with performance on any test.

Of 45 individuals, 18 had abnormal lymphoblastogenesis when a group of Michigan farm residents was examined for lymphocyte function.[238,239] In contrast, lymphocyte responses were normal in all 46 farm residents from Wisconsin. There was no relationship between serum concentrations of PBB and the abnormal function. This study is difficult to interpret because little information is given on the selection criteria of the Michigan subjects. Decreased lymphocyte function also occurred in four of ten chemicals workers. The decrease was related to higher plasma levels of PBB.[239] In contrast, immune function was not impaired in randomly drawn groups from the MDPH cohort with high (>300 ppb) or low (<1 ppb) concentrations of PBB in serum.[240] There were no differences in any measure between either group and a control group drawn from MDPH employees. Lymphocyte numbers and functions were not correlated with serum PBB concentrations.

Farm residents and chemical workers with high exposure were systematically evaluated to determine if these high-risk groups suffered adverse effects from their exposure to PBB.[241,242] Few abnormalities were found in objective tests, and these tests provided no findings that were correlated with subjective complaints. A striking finding in the physical examinations was the presence of hepatomegaly in about 75% of the farm residents, but minimal enlargement was the rule and few abnormalities of function were found. Extensive psychological workups failed to identify consistent findings aside from the presence of reactive depression, and there was no evidence to suggest organic brain syndromes. Physical and laboratory findings were not related to PBB concentrations. It was concluded that reactive depression may have been responsible for the high prevalence of constitutional symptoms.

Pediatric aspects of PBB exposure were examined in families of the ESL study.[243,244] Although many symptoms were reported, physical examination failed to reveal any objective alteration that could be attributed to PBB. A striking finding was the statistically significant negative correlation between prevalence of reported symptoms and serum PBB concentrations. Effects of PBB exposure *in utero* were studied in children when they were about 2 years old.[245] Although parents of exposed children tended to report more illness, particularly respiratory illness, than parents of control children, no effects of exposure were found on physical growth, physical examinations, or neurological assessments. There was a suggestion that concentration of PBB in fat was inversely related to performance on selected developmental tests. The children were re-examined 2 years later and there was a divergence of opinion as to whether exposure had an effect.[12-14] One set of authors felt that the children were within normal ranges in all areas assessed. Although an inverse relationship was noted between concentrations of PBB in fat and scores on some developmental tasks, the importance of the findings for later development is unclear.

D. Conclusions

There is little convincing evidence that detectable effects of PBB exposure have occurred in Michigan farm residents. Although a variety of subjective symptoms were reported, the prevalence of these symptoms had no consistent relationship to the extent or types of exposure. In addition, most objective clinical measures have failed to show a significant relationship to PBB exposure.

It is recognized that serum concentrations of PBB are not absolute measures of exposure. Serum concentrations will be influenced by the time of exposure relative to measurement and by certain physiological states of the individual. However, epidemiological studies have

involved individuals with serum concentrations of PBB as low as 0.2 ppb to concentrations as high as 2000 ppb. It may not be possible to use serum concentrations to distinguish between a two- or threefold difference in exposure, but it is possible to distinguish among exposures when there is a 10,000-fold range in concentrations.

One of the more remarkable aspects of the PBB episode is that no identifiable clinical syndrome was produced in any of the most highly exposed farm residents who consumed their products. In the Yusho incident, a clinical syndrome was produced in individuals who had consumed about 2 g of PCB and its associated dibenzofurans. As noted, some individuals in the PBB incident may have consumed as much as 10 g or more of PBB without showing clinical signs of the type that occurred in the Yusho incident. In view of the generally conceded greater biological activity of PBB in many systems, it must be concluded that the dibenzofurans were an important factor in the Yusho incident.

Although no acute or short-term chronic effects of PBB have been identified, the possibility of long-term effects, such as cancer, cannot be ruled out. Induction of liver tumors in rodents is a matter of concern and continued monitoring of highly exposed individuals is a desirable course of action.

IX. CONCLUSIONS

The Michigan PBB episode differs from most other cases of human exposure to persistent chemicals in foods of animal origin because PBB was not a pervasive environmental contaminant nor was it used for routine agricultural applications. The amount of contaminant and potential exposure to the general population were finite. Thus, exposures to PBB were not continuing or repetitious as were the exposures in the cases of widely used chlorinated hydrocarbon insecticides and industrial products, such as PCB. An incident that involves a single introduction of a contaminant into the food chain has the characteristic that exposures of the general population are high early in the incident and decline at rates that depend on the persistence of the material in animals and the environment. This "front-loaded" nature of the exposure to PBB had important implications for the efficacy of any remedial or regulatory action, which can be illustrated by calculating the amount of PBB that appeared in the food supply at various times.

Although one incident of direct substitution of PBB for magnesium oxide occurred as late as February 1974, most PBB was introduced into Michigan livestock herds between August and December 1973.[22] It can be assumed that low exposures followed the same time course as high exposures because most feeds with low concentrations of PBB were derived from cross-contamination in feed mills. The percentage of the total potential PBB that could be transmitted to the general population was estimated by months using information on the time and amounts of PBB that reached herds that had high exposures.[22] The values of Table 5 were calculated by using the experimental findings that 25% of the administered PBB is excreted in milk while PBB is being fed[96] and that 25% is stored in the body and excreted with a half-life of 180 days.[219] Excretion of PBB in milk would be a good indicator of the time course of exposure of the general population because any PBB absorbed by the animal would have a potential for transmission to humans. If it was not excreted into the milk, the meat would be consumed when animals are slaughtered and nonedible portions of the carcass would be rendered and recycled into feed of other animals.

One of the interesting conclusions from the data in Table 5 is that nearly 30% of the potential human exposure already had occurred when health problems in livestock were recognized initially in October 1974. It is also noteworthy that 75% of the exposure occurred before the toxicant was identified as PBB. These data indicate that in an incident that covers a short period of time, significant reductions in exposure of the general population can occur only if there is an early identification of the chemical contaminant. If identification comes

Table 5
FRACTION OF POTENTIAL PBB EXCRETION IN MILK THAT WAS EXCRETED BEFORE DETECTION AND REGULATION IN MAY 1974

Month	Monthly (%)	Cumulative (%)
August 1973	17.0	17.0
September	11.8	28.8
October	7.2	36.0
November	10.0	46.0
December	7.8	53.8
January 1974	3.4	57.2
February	8.6	65.8
March	3.6	69.4
April	3.0	72.4
May	2.8	75.2

Table 6
APPROXIMATE DISPOSITION OF THE PBB INVOLVED IN THE MICHIGAN EPISODE AND THE ESTIMATED HUMAN EXPOSURE AVOIDED BY REGULATION

Item	Amount (kg)
Total	295
Not fed to livestock	45
Fed to livestock	250
Excreted in feces	125
Absorbed by animals	125
In human foods before regulation	94
Exposure avoided by regulation	
Tolerance at 1.0 ppm	15.4
Tolerance at 0.3 ppm	0.75
Tolerance at 0.02 ppm	0.015

late, as it did in the PBB episode, the potential for reducing total exposure of the general population is not great.

The efficacy of regulatory actions in reducing exposures of the general population is illustrated in the estimated disposition of the PBB presented in Table 6. Approximately 295 kg (650 lb) of PBB were involved in the episode. A small amount of the PBB was not fed to livestock because some was recovered before it was mixed in feed and some contaminated feed was returned to the feed mills and held because of the suspicions of a toxic factor. The amount was about 45 kg, which left about 250 kg that was fed to livestock.[7]

About 50% of the amount fed to livestock was excreted in feces.[74] Although a small part of this could recycle through animal consumption of soil, most usually would not enter the human food supply. Thus, 125 kg was absorbed by livestock and potentially could have been transmitted to humans. Applying the 75% figure (Table 5), it is estimated that 94 kg of PBB entered the Michigan population before PBB was detected and regulatory actions were taken. It was noted in a previous section that the average serum PBB concentrations of the people of Michigan indicated a total exposure of about 9 to 10 mg per person. Since the population of Michigan is about 8 million, a total body burden of 70 to 80 kg in the

Michigan population can be inferred. The two methods of calculating average human exposure agree remarkably well.

The regulatory guideline was set at 1 ppm originally, reduced to 0.3 ppm later, and to 0.02 ppm still later. The effect of enforcing these tolerances on the exposure of the general population is listed in Table 6. The values were derived by assuming that all PBB in animals was potentially available to humans over an infinite time span. Body burdens of the violative animals in the first phase were calculated from milk fat concentrations and herd sizes. It was assumed that average animals weighed 400 kg and contained 15% fat. For the second phase, the same animal weights and compositions were assumed and applied to 20,000 animals with an average body fat PBB concentration of 0.5 ppm. Calculation of the efficacy of Act 77 used the same assumptions except the number of animals was 2000 and the average fat concentration was 0.05 ppm. Although there is room for error in these assumptions, the relative magnitude of the values still holds and would be true of any set of assumptions.

The most effective action in reducing general population exposure was the early action in identifying the small number of highly contaminated herds and eliminating them from the food chain. However, the reduction was small when compared to the exposure that already had occurred. When guidelines were lowered to 0.3 ppm the amount of PBB removed from the food chain was only 5% of the amount removed through the initial action even though it involved 4 to 5 times as many animals. The amount of PBB removed from the food chain by enforcement of Act 77, which reduced the tolerance to 0.02 ppm, was negligible by any measure.

The effect of Act 77 can be put into perspective by comparing the amount of PBB that it removed from the food supply (15 g) with the amount that was being excreted into the milk of Halbert herd at the time of detection in 1974. About 4500 kg of milk per day was being marketed when the herd was quarantined. The milk would contain about 180 kg of fat with a PBB concentration of 34 ppm. Thus, about 6 g of PBB per day was entering the Michigan food supply from this herd in May 1974. Any action that speeded up the identification and quarantine of this herd by 2 to 3 days was more effective in reducing human exposures than all of the efforts devoted to the enforcement of Act 77.

It is clear from the data of Tables 5 and 6 that early detection is much more important for reducing human exposures from a single episode of chemical contamination than is the stringency of regulatory action. The process by which PBB was finally identified has been described thoroughly.[19] It is difficult, even with the benefit of the hindsight of 10 years of experience, to see how this process could have been speeded up materially. The most significant breakthrough in the identification process did not occur until February 1974. At this time a concerted effort would have led to an earlier identification of PBB. But even with this gain, exposure only would have been reduced from 75 to 65% of the potential exposure (Table 5).

Before February 1974, there were few clues as to the nature of the agent or compound causing the cattle health problem. Even a massive effort to identify the cause would not have been assured of success. In retrospect, some clinical signs typical of chlorinated naphthalene toxicosis were present in the Halbert herd, but these signs were not prominent. In addition, many investigators were distracted from a consideration of halogenated hydrocarbons by a failure to detect them with the gas chromatography methods then in use.

It was suggested at times that the suspicion of the presence of a toxic chemical should have led to the exclusion of the cattle and their products from the market. However, most acute toxicants to which cattle have been exposed are rapidly metabolized or excreted and pose no continuing residue problem. Heavy metals may be sequestered in bone, a nonedible tissue, and most cattle disease agents are not transmitted to man. Thus, without identification of the agent causing the health problem, there is no legal basis for, and usually no public health benefit from, quarantining a herd of cattle or excluding its products from the market.

The course of events in the PBB episode has been described extensively in the popular literature.[5,6] Although these works provide much interesting information, all are imbalanced in the sense that events are described from the viewpoints of a small group of farmers who felt they were aggrieved parties. These viewpoints do, however, reflect what became the popular perception of the Michigan PBB episode in the media. Popular perceptions often become reality as far as political actions are concerned. Thus, passage of Act 77 probably was a political necessity even though it held little promise of reducing exposure and risk of the general population.

Regulation of a toxic compound in a food supply usually is considered an objective process that is based on underlying scientific findings or principles. However, regulatory decisions often must be made with incomplete knowledge and must involve a considerable amount of subjective judgment. Since the value systems of individuals are different, it is not surprising that controversy is a result of an episode involving food contamination. The policymakers and government technical experts often were described as indifferent, incompetent, or overwhelmed by a situation beyond their understanding in the popular descriptions of the PBB episode.

When viewed in retrospect, these allegations are not valid. Although the amount of toxicological information available on PBB was small at the time of its identification, the underlying assumption of all policymaking was that the compound was similar in effects and behavior to PCB. Tolerances and other recommendations were established consistent with that assumption and with previous policies established for PCB. The greatest failing, if it may be labeled a failing, of state and federal policymakers and their technical advisors was that they did not foresee a changed climate of public opinion concerning environmental chemicals.

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