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Effects of PBBs on Cattle. I. Clinical Evaluations and Clinical Chemistry

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Toxicosis was induced in pregnant heifers by feeding 25,000 mg/head/day of FireMaster BP-6, a commercial blend of polybrominated biphenyls (PBB). The PBB feeding decreased dry matter intake approximately 50% by 4 days exposure. Emaciated animals became anorexic a few days prior to death at 33 to 66 days. Weight losses of heifers averaged 80 kg. Other clinical signs observed were dehydration, diarrhea, excessive salivation and lacrimation, fetal death, abortion, and general depression as evidenced by depressed heart and respiratory rates. Clinical signs were apparent after 10 days exposure and progressively intensified along with loss of condition until death. Clinicopathologic changes included significantly increased serum glutamic-oxaloacetic transaminase and decreased serum calcium by 30 days exposure. Lactate dehydrogenase, urea nitrogen, and bilirubin were elevated, and serum albumin decreased by 36 to 40 days. Principal urine changes were decreased specific gravity and moderate proteinuria. Pregnant heifers fed 0.25 or 250 mg/head/day for 60 days and nonpregnant heifers fed 250 mg/head/day for 180 days displayed neither clinical signs nor clinicopathologic changes indicating adverse effects from PBB exposure. Post-exposure, all heifers exposed to PBB for 60 days calved normally with zero calf mortality and were successfully rebred. Milk production was not different from control animals. Birth weights of calves from dams exposed to 250 mg PBB/head/day were significantly greater than calves of dams exposed to 0 mg or 0.25 mg/head/day. PBB exposure of dams produced no detrimental effects on calves as indicated by clinical signs, clinicopathologic changes, or performance.

Introduction

In 1974 the industrial fire retardant FireMaster FF-1 (PBB), a pulverized form of FireMaster BP-6 with 2% calcium trisilicate added to prevent caking, was advertently mixed with livestock ration and fed to dairy cattle (*1*). Widespread attention has been focused on the incident, a major concern being the hazard present to the exposed livestock and consumer health. Several field studies have indicated increased cow and calf mortality, decreased milk production, and a wide variety of nonspecific clinical signs attributed to PBB exposure (*2, 3*). However, a field study of contaminated and noncontaminated herds failed to associate PBB exposure with reported signs of toxicosis (*4*). The discrepancies between these field study reports possibly reflected the great variations of levels and durations of exposure, farm management practices, and lack of adequate farm records. The immediate need arose for controlled studies to evaluate the acute and latent health hazard present to cows and their offspring at varying levels and duration of exposure to FireMaster.

Materials and Methods

Sixty dairy animals were involved in seven studies to determine distribution and clearance of FireMaster BP-6 and to evaluate the health hazard present from this residue. Table 1 lists the animals involved in the various experiments, the daily and total amount of FireMaster received, and the duration of the experiment. Specific details of procedures and animals for experiments 1, 2, 3, (*5*); 4 (*6*); and 7 (*7*) have been reported previously.

Experiments 1, 2, and 3 were designed to carefully monitor the short-term distribution and clearance of FireMaster. Changes in health of animals were recorded by attending technicians, but no quantitative procedure was used to evaluate health.

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Table 1. Protocol for seven experiments on the distribution and effects of PBB on dairy cattle.

Experiment	Animals	Status[a]	PBB Exposure: Daily amount, mg	PBB Exposure: Duration days	PBB Exposure: Total dose to body weight ratio, mg/kg BW	Post exposure study, days
1[b]	1 Cow	P L	3000	1	4.59	1100[c]
	1 Cow	P L N	3000	1	5.95	10
2[b]	1 Calf	N	0.54	44	0.78	—
	1 Calf	N	d	95		44
3[e]	1 Calf	N	25,000	9	5000	—
4[e]	2 Heifers	P N	0	60	0	—
	1 Heifer	P L N	0	60	0	170
	3 Heifers	P L	0	60	0	640[c]
	2 Heifers	P N	0.25	60	0.0375	—
	1 Heifer	P L N	0.25	60	0.0375	170
	3 Heifers	P L	0.25	60	0.0375	640[c]
	2 Heifers	P N	250	60	37.5	—
	1 Heifer	P L N	250	60	37.5	170
	3 Heifers	P L	250	60	37.5	640[c]
	6 Heifers	P N	25,000	32–60[f]	~ 2650	—
5	3 Calves		g	160		475[c]
	1 Calf	N	g	160		10
	3 Calves		h	160		475[c]
	1 Calf	N	h	160		10
	3 Calves		i	160		475[c]
	1 Calf	N	i	160		10
6[e]	1 Heifer	P L	250	180	90.0	500[c]
	5 Heifers	P	0	202	0	200[c]
	4 Heifers	P	250	202	100	200[c]
7[e]	2 Cows	N	25,000	25	1470	35
	2 Cows	N	0	25	0	35

[a] During course of experiment animals were: P = pregnant; L = lactating; N = necropsied.
[b] Lot 158RP of FireMaster BP-6 was used.
[c] Under continued observation—days as of 10-1-1977.
[d] Calf from Experiment 1.
[e] Lot 6244A of FireMaster BP-6 was used.
[f] All animals moribund between days 33 and 66.
[g] Calves from Experiment 4, 0.0 mg/day heifers.
[h] Calves from Experiment 4, 0.25 mg/day heifers.
[i] Calves from Experiment 4, 250 mg/day heifers.

All but one of the animals involved were necropsied. The surviving animal is currently under observation with health, breeding, and milk production records being maintained.

Experiment 4 was designed to systematically and quantitatively evaluate the health, performance, and residue dynamics of pregnant heifers given 0 to 25 g of FireMaster for 60 days. Feed intake and body weight measurements were recorded, along with frequent clinical evaluations performed by a veterinarian. Clinical evaluations included the grading of general health and eight reported clinical signs of PBB toxicosis (*2*) on a 1-10 scale, plus measurement of heart rate, respiration rate, and body temperature (*6*). In addition, blood and urine were collected for clinicopathologic determinations. Following parturition, milk production and breeding records were maintained. Three animals from each group were allotted to necropsy for histological examination of tissues. Of these, two were necropsied on day 61 and the other and her calf 10 days postpartum. All moribund animals were also necropsied.

In experiment 5, feed intake and growth of the calves of the heifers from experiment 4 were recorded, along with clinical evaluations and clinicopathologic determinations. In addition, the attending technician recorded daily ratings of health and evaluated the appetite, breathing, eyes, and stool of each calf daily for 180 days. Blood and urine sampling for clinicopathologic determinations is being continued.

Experiments 6 and 7 were toxicity studies designed to monitor specific target organ effects from PBB exposure. However, clinical observations and blood and urine were collected to give additional information on the overall health hazard present to dairy animals from PBB exposure.

In all experiments the animal that were dosed were given the FireMaster in gelatin capsules with a balling gun to insure that the total dose was received and to reduce cross-contamination. Management practices were followed that minimized housing effects, reduced cross-contamination, and assured that all animals had a similar environment.

The clinical evaluations of animals were performed at frequent regular intervals throughout the experiments. Previously recorded evaluations were not available to the veterinarian at the time of each clinical evaluation to minimize bias. Blood for clinicopathologic determinations was collected by venous puncture in untreated (serum) and sodium fluoride treated (whole blood) vacuum tubes. Urine was collected by induced micturition, filtered, and stored with benzoate preservative. The following serum and plasma parameters were determined: glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase (AP), lactate dehydrogenase (LDH), total protein, albumin, glucose (total reducing sugars), bilirubin, urea nitrogen (BUN), uric acid, creatinine, cholesterol, calcium, and inorganic phosphorus. Globulin and the albumin: globulin ratio were calculated. Urinary reducing sugars, calcium, potassium, and specific gravity were measured. Urine was screened for the presence of glucose, protein, ketones and blood. Color and appearance were evaluated and the urine sediment was examined for the presence of epithelial cells, erythrocytes, leukocytes, crystals, casts, and mucus. Detailed descriptions of each method and typical coefficients of variation for the chemical determinations have been reported (*8*).

Results and Discussion

These results are intended to provide an overview of our clinicopathologic findings from studies of the effects of FireMaster in dairy cattle. Seven separate experiments were conducted over a period of three years under varying conditions and with differing objectives. The various doses of FireMaster given were 0.25 mg, 250 mg, 3 g, and 25 g daily for periods of 1 to 202 days. In addition, calves were exposed *in utero* and through consumption of milk from contaminated dams. The results obtained are reported in two primary categories: exposures which elicited a toxic response and exposures which did not.

Exposures Which Did Not Elicit a Toxic Response

The first study with FireMaster was designed to obtain information on short-term residue dynamics. Toxicosis was not expected, so the protocol did not include measurements of clinicopathologic responses. No clinical signs or lesions in necropsied animals that could be attributed to PBB exposure were observed in mature cows given single 3 g doses or in calves which received the residue *in utero* or through milk from contaminated dams (*5*).

Studies to quantitate, clinicopathologic responses precisely were designed and conducted because of the increasing evidence of toxicity reported in field studies of contaminated animals. Pregnant heifers in experimental groups that were exposed to 0.0, 0.25, and 250 mg FireMaster/daily for 60 days did not exhibit signs of toxicosis (*6*). Intake of dry matter and body weight significantly increased for the three groups. Feed efficiencies were not different among the three groups. Heart rate, respiration rate, and body temperature were unaffected and mean general condition scores from clinical evaluations improved (Table 2). The change in the condition of the animals was attributed to improved management and nutrition. Clinicopathologic values of blood and urine samples remained within reported normal ranges for cattle (Table 3) giving no indication of a toxic response attributable to PBB. No gross pathologic changes or changes in tissue sections were observed in animals necropsied (*17*).

Animals that were not necropsied have remained under study throughout their lactation. A relationship between exposure to PBB and milk production, incidence of mastitis, and the number of insemina-

Table 2. Average general condition scores from clinical evaluations for heifers given various doses of PBB for 60 days.[a]

Time, days	General condition score[b]			
	PBB, 0.0 mg/day	PBB, 0.25 mg/day	PBB, 250 mg/day	PBB 25,000 mg/day
-10-(-1)	7.9	7.8	8.4	8.2
1-10	8.0	8.1	8.2	7.8
11-20	8.3	8.4	8.0	6.7
21-30	8.5	8.4	8.5	5.9
31-40	8.5	8.5	8.3	4.2
41-50	8.6	8.3	8.4	4.7
51-60	8.5	8.5	8.5	4.8
61-80	9.1	9.1	9.2	—[a]
81-110	9.3	9.4	9.1	—
111-150	9.6	10.0	9.7	—
151-190	10.0	10.0	10.0	—

[a] All heifers given 25,000 mg/day were moribund and necropsied by day 66.

[b] Condition rated on a 1-10 scale, 10 = excellent condition.

Table 3. Clinicopathologic values for bovines.

Component	Observed pretreatment values mean ± SE[a]	Reported values in bovine range	Reference
Blood			
Glucose, mg/dl	80 ± 1[b]	36–70	(*9–12*)
Bilirubin, mg/dl	0.12 ± 0.01	0.0–1.4	(*11–13*)
Uric acid, mg/dl	0.78 ± 0.04	0.0–2.08	(*9, 11, 12*)
Urea nitrogen, mg/dl	7.6 ± 0.4	6–27	(*10–12, 14*)
Cholesterol, mg/dl	93 ± 4	50–230	(*9, 12, 14*)
Creatinine, mg/dl	1.06 ± 0.03	1.0–2.1	(*10, 12, 14*)
Phosphorus, mg/dl	7.2 ± 0.2	4.0–7.83	(*11, 12, 14*)
Calcium, mg/dl	9.3 ± 0.1	9.35–12.2	(*12, 14*)
Total protein, g/dl	7.0 ± 0.1	5.5–8.0	(*11, 12, 14, 15*)
Albumin, g/dl	3.1 ± 0.1	2.3–3.7	(*10, 12, 14, 15*)
Globulin, g/dl	3.8 ± 0.1	3.0–5.1	(*10, 12, 14, 15*)
Alkaline phosphatase, mU/ml	108 ± 6	50–400	(*12*)
Glutamic-oxaloacetic transaminase, mU/ml	68 ± 2	50–150	(*12*)
Lactate dehydrogenase, mU/ml	1020 ± 47	< 2000	(*12*)
Urine[c]			
Specific gravity	1.031 ± 0.002	1.025–1.045	(*16*)

[a] Mean of day −1 samples for heifers given 0.0, 0.25, 250, and 25,000 mg PBB/day for 60 days or until moribund.
[b] Total reducing substances.
[c] Individual single samples.

tions required per conception was not evident in these studies (Table 4). Milk production was considered adequate for these grade heifers as superior animals with good milk production potentials had not been selected for toxicity studies.

Calves from the above dams were exposed to FireMaster through placental transmission and their dams' milk. Mean birth weights of calves were 35, 38, and 44 kg from dams fed 0.0, 0.25, and 250 mg/day for 60 days. Weight gains of calves by day 42, weaning, were 18, 15, and 13 kg and after 180 days 107, 121, and 113 kg. Clinicopathologic data revealed no significant changes suggesting a toxic response associated with FireMaster exposure.

Table 4. Summary of mean daily milk production, incidence of mastitis, and insemination of heifers exposed to PBB.

PPB concn, mg/day (for 60 days)	Average daily milk production, kg	Days (no.)	Treated clinical mastitis (no.)	Inseminations (no.)
0.0	16.2	305	2[a]	3
0.0	13.0	292	1[b]	1
0.0	16.6	299	0	4
0.25	18.4	292	0	1
0.25	15.1	269	0	1
0.25	19.6	305	1	4
250	16.8	305	0	1
250	12.7	305	0	2
250	16.0	305	2[c]	2

[a] Mastitis related to an injury to the teat.
[b] Mastitis related to a prepartum injury and resulted in the loss of production of one quarter for the entire lactation.
[c] Persistent mastitis necessitated discontinued milking of one quarter on day 127 of lactation.

In order to determine if prolonged exposure would elicit a toxic response, one pregnant and four nonpregnant heifers were given 250 mg FireMaster daily for 180 or 202 days. Clinicopathologic determinations indicated no toxic effects that could be attributed to PBB exposure. The pregnant heifer had dystocia at parturition, which resulted in the stillbirth of a 56.4-kg calf. Necropsy of the calf revealed no abnormalities. The reproductive tract of the cow regressed normally, and she was rebred.

In summary, analysis of clinicopathologic data showed no toxic response in animals given either a single 3 g dose of FireMaster or continuous doses of up to 250 mg/day to give an accumulative dose of up to 50.5 g. Actual mean concentrations of PBB residue in fat tissue exceeded 30 parts per million in animals fed 250 mg/day, exceeding the FDA interum guideline by 100 times. The toxic syndromes observed in field studies of contaminated animals were not evident in any of these experimental animals. Although at present there is no suggestion of toxicity, the animals will remain under study throughout their productive lifetimes.

Exposures Which Elicited a Toxic Response

Toxicity was induced in six pregnant heifers fed 25 g doses of FireMaster daily for 32 to 60 days. These animals consumed between 0.8 and 1.5 kg of

FireMaster. Intake of dry matter was reduced 50% by 4 days exposure and declined to approximately 1 kg by 30 days (Table 5). Subsequently, body weight was significantly reduced with losses of 80 kg among heifers surviving 40 days (Table 5). Heart and respiratory rates progressively decreased (Table 5). Excessive lacrimation and salivation were observed as early as day 11 and increased progressively in severity. Dehydration and emaciation developed and persisted throughout the trial. In four of the heifers, diarrhea developed and persisted from 3 to 9 days with occasional tenesmus. Three heifers aborted on days 30, 33, and 38, and three had retained dead fetuses when necropsied. All heifers were moribund within 33 to 66 days.

Changes in some clinicopathologic values occurred in these heifers. SGOT and serum calcium had a significant response by day 15. After 30 days exposure SGOT, LDH, BUN, and bilirubin were significantly ($p < 0.01$) increased and serum calcium and albumin decreased from pretreatment normals (Table 5). Although significantly different from pretreatment, albumin and bilirubin did not deviate from the normal range reported for cattle (Table 3). Changes in the urine were not marked. Urine calcium of heifers in group II was lower on days −1 and 15. Concentrations in heifers of Group IV, showed a marked decrease by day 15 and remained lower until necropsy. Urine calcium concentrations of animals in groups I, II, and III were

Table 5. Mean values for clinical and clinicopathologic factors for heifers given polybrominated biphenyls.

		Exposures, mg PBB/day				
		60 days				202 days,
Factor		0.0	0.25	250	25,000	250
Body weight, kg	Pretreatment	385	393	381	372	
	End of dosing	473	512	446	291[a]	
	Parturition	554	529	550	—	
	90 days postpartum	508	500	506	—	
Dry matter intake, kg	Pretreatment	7.3	8.7	6.8	7.9	
	End of dosing	9.5	10.4	8.5	< 1.0	
Heart rate, beats/min	Pretreatment	87	84	88	79	
	End of dosing	85	85	86	51	
	Parturition	78	84	81	—	
	90 days postpartum	74	82	84	—	
Respiration rate, inspirations/min	Pretreatment	44	47	43	46	
	End of dosing	40	38	37	16	
	Parturition	38	46	38	—	
	90 days postpartum	37	40	36	—	
LDH, mU/l.	Pretreatment	918	1184	967	1012	1105
	End of dosing	1107	1193	1094	2600	1126
	Parturition	1250	1231	1095	—	[b]
	90 days postpartum	692	1011	954	—	—
SGOT, mU/l.	Pretreatment	67	70	64	71	63
	End of dosing	73	75	68	154	64
	Parturition	78	80	85	—	—
	90 days postpartum	63	64	52	—	—
BUN, mg/dl	Pretreatment	8.0	7.5	6.7	8.5	10.5
	End of dosing	9.5	9.5	7.0	40.7	7.5
	Parturition	16.2	14.2	17.0	—	—
	90 days postpartum	14.0	11.6	10.6	—	—
Bilirubin, mg/dl	Pretreatment	0.12	0.13	0.10	0.15	0.10
	End of dosing	0.12	0.12	0.13	0.38	0.0
	Parturition	0.47	0.45	0.15	—	—
	90 days postpartum	0.06	0.06	0.06	—	—
Calcium, mg/dl	Pretreatment	9.1	9.2	9.4	9.7	9.2
	End of dosing	9.4	9.7	9.6	8.1	9.8
	Parturition	7.3	9.8	9.8	—	—
	90 days postpartum	9.5	9.9	9.7	—	—

[a] All heifers given 25,000 mg/day became moribund after 32–60 doses and were necropsied.
[b] Nonpregnant heifers.

lower on days 150 and 190 following a ration change to haylage on day 110. Interpretation is difficult because calcium concentrations are based on single samples and not 24-hr collections. Samples taken immediately prior to necropsy revealed a trace to moderate proteinuria, a slight decrease in pH, and decreased specific gravity. The specific gravity decreased from a pretreatment mean of 1.038 to a mean of 1.017 in terminal samples. All animals were maintained as long as possible. When death was impending heifers were necropsied on days 33, 36, 39, 40, 41, and 66. Principle changes were observed in the gall bladder and renal tubules. These and other changes in tissues of the terminally toxic heifers have been reported in detail (*17*).

In an experiment designed to measure renal function in PBB exposed animals, two mature cows were given 25-g doses of FireMaster daily for 25 days and necropsied 35 days post dose (*7*). It was clinically apparent that one cow was more severely affected. The other was beginning to show clinical signs when necropsied. Primarily a decreased appetite and weight loss were observed in both with a 30% decrease in body weight of one and a 12% decrease in the other at necropsy. Clinicopathologic responses for the more toxic animal were similar to those observed in the six heifers exposed to 25 g/day (*18*).

The changes in routine clinicopathologic parameters examined in these eight animals have indicated a definite toxic response in dairy animals fed 25 g/day of FireMaster, but were not specific or sensitive so as to provide a clear indication of the exact mechanisms of toxicity. However, target organ effects were indicated. Several parameters suggested that liver was affected by PBB, but necrosis was not evident (*17*). The mild rise in bilirubin values, a good indicator of biliary obstruction and hepatocellular damage, was considered a reflection of gall bladder changes and minimum hepatocellular damage (*17*). Serum values of SGOT and LDH peaked at approximately the time of fetal death and/or absorption and were at least partially attributed to uterine cell necrosis.

The increase in BUN, a good indicator of renal damage, and the decrease in urine specific gravity suggested FireMaster was primarily a renal toxin. This was supported by microscopic examination of renal tissue (*17*). The elevated BUN possibly reflected decreased flow of urine through the tubules, and decreased specific gravity indicated an alteration in the ability of the tubules to concentrate urine (*19*). The primary sites of the renal lesion were distal tubules and collecting ducts which are primarily responsible for the forming of a concentrated urine (*19*). Alterations of intrarenal blood flow or a washout of the corticomedullary concentration gradient are two mechanisms which could affect the flow through and the reabsorption abilities of the tubules. However, recent studies in our laboratory have suggested these mechanisms are not affected in PBB exposed dairy animals (*7*). An effect of PBB on production or action of the antidiuretic hormone (ADH) cannot be entirely ruled out; however, there is no evidence from current work to implicate the role of ADH in this syndrome.

The mild hypocalcemia of toxic animals was possibly due to decreased uptake of calcium from the gastrointestinal tract because of the marked decrease in feed intake of the animals and/or some disruption of the calcium metabolism. Synthesis of the active metabolite of vitamin D (1,25-dihydroxycholecalciferol) which acts directly upon its target organs, the small intestine and the bone to mobilize calcium stores, occurs in the renal tubules (*20, 21*). This suggests that the renal tubular damage may have interfered with 1,25-dihydroxycholecalciferol production or action and possibly affected calcium availability. Decreased serum calcium concentrations were reported in a survey of 16 low-level exposure herds (*4*). In our studies, effects on serum calcium were observed only at extremely high levels of exposure.

The clinicopathologic parameters examined indicated the kidney and possibly the liver as target organs, but were not specific enough to relate an exact mechanism of action of PBB.

In summary, we have gained several insights into the clinicopathological effects of PBBs in dairy cattle. They are categorized as: dose response to toxicity, and physiological and clinical manifestation of toxicity. Firstly, PBB toxicity as determined from clinicopathologic parameters measured in these studies, was not dose responsive. Instead, PBB appeared to be a threshold toxin since toxicity was not evident during exposure and in the two years following exposure in our experimental animals given 250 mg/day or less. Although placental transport of PBB has been demonstrated in these animals (*22*) teratogenic effects have not been observed.

In contrast, the higher dose of 25 g/day elicited an unequivocal toxic response. At this level the animals could no longer tolerate or detoxify the compound(s), and toxicosis was induced. The toxic syndrome was evidenced by a variety of clinical signs, changes in blood and urine chemistry, and a reproducible and specific pathological lesion in the kidney: the mechanisms of PBB toxicity in the kidney or other affected tissues (i.e., liver, gall bladder, etc.) could not be determined. Further research is being conducted in our laboratory to explain the

toxic syndrome through understanding of the primary toxicity to the target organs, the mechanisms by which the clinical signs are elicited, and by distinguishing target organ effects from secondary effects.

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