ENDOCRINE FUNCTION OF WORKERS EXPOSED TO PBB and PBBO

TERMINAL PROGRESS REPORT

MARCH, 1982

Principal Investigator: Ora Bialik, Ph.D.

University of Pennsylvania School of Medicine
Program for Epidemiologic Research and Training
Nursing Education Building
420 Service Drive S2
Philadelphia, PA 19104

This project is supported by Grant No. I R01 OH 01034-01, awarded by the National Institute for Occupational Safety and Health.

50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO.	2.	3. Recipient's Accession No. PB84 238377

4. Title and Subtitle
Endocrine Function Of Workers Exposed To PBB And PBBO. Terminal Progress Report

5. Report Date

6.

7. Author(s)
Bialik, O.

8. Performing Organization Rept. No.

9. Performing Organization Name and Address
NIOSH, U.S. Department of Health and Human Services

10. Project/Task/Work Unit No.

11. Contract(C) or Grant(G) No.
(C)
(G) I-R01-OH-01034-01

12. Sponsoring Organization Name and Address
Same as box 9

13. Type of Report & Period Covered

14.

15. Supplementary Notes

16. Abstract (Limit: 200 words)

Thyroid and reproductive dysfunction was investigated in workers exposed for at least 240 hours to decabromobiphenyl (13654096) (PBB) and decabromobiphenyloxide (1163195) over a 4 year period. The average period of employment was 3.9; mean age, 34.7. Medical questionnaires, physical examinations, and laboratory tests were conducted. Air samples of PBB in manufacturing area showed 0.18 to 0.23 milligrams per cubic meter for an 8 hour time weighted average. Of 18 workers exposed for 3 years or longer, thyroid nodules were seen in 3; another nodule was seen in a worker exposed to high chlorine (7782505) concentrations. Significant correlation was seen between length of employment and concentrations of follicle stimulating hormone (FSH) in workers exposed to PBB. An abnormal FSH value was found in only one worker. A testicular cyst was found in one exposed worker, and epididymal nodules in two others. No testicular or epididymal nodules were seen among comparisons. No detectable PBB was found in serum. The author concludes that thyroid hyperplasia may result from exposure to PBB, but no definite statement can be made concerning adverse effects on the prevalence of testicular and epididymal nodules because of their prevalence in the general population.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms

NIOSH-Publication, NIOSH-Grant, Air contamination, Air-quality-control, Fumes, Industrial-chemicals, Occupational-exposure, Industrial-hazards, Endocrine-system-disorders, Grant-Number-01034-01

c. COSATI Field/Group

18. Availability Statement:	19. Security Class (This Report)	21. No. of Pages 63
	20. Security Class (This Page)	22. Price

TABLE OF CONTENTS

		Page
1.	SUMMARY	1
2.	LITERATURE REVIEW	3
	2.1 Introduction	3
	2.2 PBBs and PCBs. Comparison of Structures and Properties	6
	2.3 Thyroid Dysfunction Related to PBBs and PCBs Exposure	8
	a. Thyroid Neoplasia in Humans	8
	b. Hypothyroidism in Humans	9
	c. Effects of PBBs on the Thyroid Gland	13
	d. Effect of PCBs on Thyroid Gland	15
	2.4 Reproduction Dysfunction	17
	a. Reproduction Dysfunction Related to PBBs Exposure	17
	b. Reproduction Dysfunction Related to PCBs Exposure	19
	2.5 The PBB Effect on Body Weight	20
	2.6 References	23
3.	THE FIELD STUDY	27
	3.1 The Study Population and Recruitment Procedures	27
	a. Exposed Cohort Group	27
	b. Comparison Group	28
	3.2 Interviewing and Examination Procedures	28
	a. General Procedures	28
	b. Demographic Questionnaire	29
	c. Medical History Questionnaire	30
	d. Physical Examination	31
	e. Laboratory tests	32
	3.3 Protection of Subjects Rights	33
	3.4 Selection and Training of Interviewers	33
	3.5 Procedures for Avoiding Bias	33
	3.6 Procedure to Increase Participation	34
	3.7 Data Processing	34

Page

4. RESULTS 35

4.1 The Industrial Environment 35

a. General 35
b. Industrial Hygienist Evaluations 36
c. Exposure by Job Classification 39

4.2 Demographic Characteristics of the Study Population 42

4.3 Medical and Laboratory Results 45

a. Serum and Fat PBBs 45
b. Thyroid Neoplasia 47
c. Thyroid Hormone 48
d. Reproductive Dysfunction 54
e. Decedent Cases in the Exposed Cohort 56

LIST OF TABLES

TABLE		Page
2.1	Properties of Commercial PBB and PBBO	7
2.2	Experimental Evidence of Thyroid and Reproductive Dysfunction Associated with Oral Administration of PBBs	10
2.3	Experimental Evidence of Thyroid and Reproductive Dysfunction Associated with Exposure to PCBs	16
2.4	Experimental Evidence of Weight Loss Associated with Exposure to PBBs and PCBs	22
4.1	Contaminants Measured in PBBs and PBBOs Manufacturing Area by Sample and Type	37
4.2	Results of Monitoring Exposure to Process Solvents and Raw Materials (ppm)	40
4.3	Total PBBs Serum Levels by Occupational Group	46
4.4	Thyroid Studies in Four Workers Exposed to PBBOs and Found to be Hypothyroid in August, 1978	53

LIST OF FIGURES

FIGURE		Page
2.1	Molecular Structure of PCBs, PBBOs,	5
4.4	Thyroxine T4 By Exposure Groups	49
4.5	Resin Uptake Ratio (RT3) By Exposure Groups	50
4.6	Thyroid Stimulating Hormone (TSH) By Exposure Groups	51
4.7	Follicle Stimulating Hormone (FSH) By Exposure Groups	55
4.1	Period of Employment of 42 PBB and PBBO Workers	43

LIST OF EXHIBITS

EXHIBIT 1 Publicity in Media

1a - News Tribune (ad, 2/28/81 - 3/7/81)

1b - News Tribune - 3/5/81

1c - The Home News - 3/20/81

1. SUMMARY

This final report summarizes the results of the University of Pennsylvania study of thyroid and reproductive dysfunction among male workers who have been involved in the manufacture of decabromobiphenyl and decabromobiphenyl oxide (PBBO). A detailed description of the recruitment procedures of the study population as well as description of the interviewing and examination procedures and all forms used in the field are given in the semi-annual progress report, July 1981.

The study objectives were to identify thyroid and reproductive dysfunction among the employees and to determine the association between these conditions and exposure characteristics.

Forty-two male workers and 69 blue-collar neighborhood controls participated in a field study on March 9-11, 1981. Among the 18 participating employees who had worked for at least 3 years in the plant, five thyroid abnormalities were identified. One worker was diagnosed with carcinoma of the thyroid. Four had other thyroid abnormalities: thyroid adenoma (1), thyroid nodule and hypothroidism (1), borderline TSH (1) and hypothyroidism (1). The latter case was diagnosed in a previous study in 1978, yet by 1981 was spontaneously recovered.

Testicular cyst (1) and epididymal nodules (2) were observed in 3 of the exposed workers, two of whom were employed at the plant for more than 3 years.

Two workers reported severe headaches. The worker with thyroid carcinoma, who had also had a brain operation, was diagnosed with trigeminal neuralgia. Also, the worker diagnosed with hypothyroidism in 1979 sought neurological advice.

Only one control person, who had extremely high serum levels of PCBs, 33,000 mg/ml, in 1978, had a thyroid nodule. No thyroid dysfunction or testicular or epididymal nodules were identified among the other controls.

A significant Pearson correlation coefficient was found between thyroid stimulating hormone (TSH) and length of employment of the plant workers ($p < 0.05$). However, no new hypothyroid cases were diagnosed.

Sixteen healthy children were born to 12 of the 33 ever-married exposed workers during or after their employment at the plant. No stillbirth was reported in this group; one spontaneous abortion was reported as a result of trauma.

No detectable level of serum PBBs was observed in the study. However, few workers have detectable PBBs fat levels.

Considering the small sample size of the exposed group and the positive finding of rare abnormalities, the hypothesis of severe thyroid dysfunction

related to PBBs human exposure is confirmed. Further studies are required to examine hypothyroidism and reproductive dysfunction related to human exposure to PBBs. Further studies are required to re-evaluate the PBBs serum and fat decay in the human body.

2. LITERATURE REVIEW

2.1 Introduction

Brominated aromatic hydrocarbon compounds manufactured for use as flame retardants provide a potential source of environmental contamination recognized in the last decade. Polybrominated biphenyls (PBBs) and its congeners have a close structural relationship to the widely prevalent polychlorinated biphenyls (PCBs). PBB is a highly lipotropic substance that is not easily metabolized or biodegraded. As a result, PBB remains in the human body and in the general biosphere for extended periods of time. Polybrominated biphenyl oxide (PBBO), an ether, is less inert and slightly more readily metabolized than PBB. PBBO is still very stable, however, as the oxygen bonds are not easily broken.

PBBs have not been previously reported to be associated with cancer in humans. It is noted, however, that PBB manufacture first began in 1970 and both PBB and PCB have been associated with the development of neoplastic liver nodules in rats (Kimbrough, 1979).

Public interest in the effects of exposure to polybrominated biphenyls (PBBs) on human health resulted from a 1973 shipping accident in which Firemaster BP-6* was added to animal feed in Michigan. Thousands of contaminated farm animals had to be destroyed and quantities of animal feed and dairy products had to be removed from the commercial market. Human contact with PBB-contaminated feed and consumption of contaminated dairy products continued until May, 1974 when the affected herds were quarantined. As a result of this accident, there has been statewide low-level exposure of Michigan residents to PBBs.

The effects on human health of exposure to PBBs have been alleged in people who consumed dairy products and other food contaminated with the PBB's. Numbness, balance problems, nausea, stomach pain, appetite change, weight change, liver trouble, hepatitis, fainting, loss of power, sleep disorders, blurred vision, immune dysfunction, light sensitivity, thyroid trouble, headache, fatigue, irritability, anxiety, depression, pink eye, dermatitis, sores, acne, skin color change and hair/fingernail change were some of the more specific complaints reported (Selikoff et al., 1976; Meester et al., 1977; Budd et al., 1978; DiCarlo et al., 1978).

Animals who ingested PBB exhibited anorexia, hair loss, skin roughening, decreased milk production, and weight loss (Jackson, T.F. and F.L. Halbert, 1974). An increase in stillborn and malformed calves was also seen (Isleb, D.R. and G.L. Whitehead, 1975).

* Actual composition: 63% hexa-, 14% hepta-, 10% penta-, 2% tetra- and 11% other brominated biphenyls.

While there is interest in the effects of PBBs on the general community, workers engaged in their manufacture may have had an earlier exposure to higher concentrations than the community: therefore, health effects can best be elucidated in workers as the first approach to risk assessment in man. Workers engaged primarily in the manufacture of PBB represent the ideal study group.

A significant difference in the prevalence rate of hypothyroidism was found among a sample of a cohort of workers at a plant in New Jersey which manufactured, between 1973 and 1978, only decabromobiphenyl and decabromobiphenyl oxide, as compared with control workers (4 out of 35 male PBB/PBBO workers compared with none among 89 male control workers)(Bahn et al., 1980). Although based on small numbers, this finding appears to be the first report of an effect on human health associated with exposure to PBB that is supported by laboratory data. Hypothyroidism could explain some of the symptoms, such as hypersomnia and fatigue, reported by the Michigan farmers (Anderson et al., 1979).

The interest of the scientific community as to possible adverse health effects associated with exposure to brominated aromatic hydrocarbon compounds increased as a result of the accidental PBB contamination in Michigan. Many experimental studies were initiated to determine evidence of toxicity in target organs and processes. In general, these animal model studies found a positive correlation between exposure to PBB (or PCB, closely related in structure) and adverse health effects that were time/dose dependent and not restricted to any individual species. In specific, these studies noted experimental evidence of dysfunction in the following organs and processes:

Thyroid: Increased weight and size of thyroid; Hyperplasia; Increased intrathyroidal iodine; Elevated TSH, T_4, ^{131}I uptake; Hypothyroidism; Reduced serum thyroxine levels; Hypertrophy; and Lesions of the thyroid.

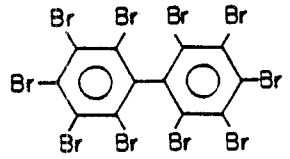
Reproductive Functions: Aspermia; Abortion, stillbirths, and malformations; Infertility; Lesions in testes and epididymides; Increased fetal resorptions; Decreased spermatogenesis; and Hormonal changes.

Body Weight: Anorexia; Weight loss; Emaciation; Decreased food intake; and Inanition leading to death.

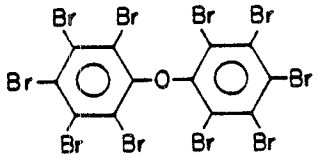
The main focus of the present study was an examination of thyroid and reproductive dysfunction associated with occupational exposure to polybrominated biphenyls. The literature review therefore will concentrate on those animal studies which have considered the thyroid and reproductive effects (see Table 2.1). Weight loss, which was noted in our research, will also be considered in the review of animal model studies.

Figure 2.1

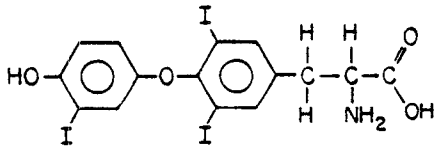
Molecular Structure of Decabromobiphenyl,
Decabromobiphenyl oxide, Triiodothyronine, and Thyroxine



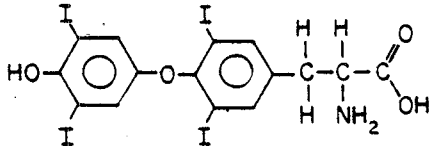
DECABROMOBIPHENYL



DECABROMOBIPHENYL OXIDE



TRIIODOTHYRONINE



THYROXINE

2.2 PBBs and PCBs: Comparison of Structures and Properties

Commercial brominated and chlorinated aromatic hydrocarbon compounds, widely used as fire retardants and pesticides, are characterized by similar structures in which each group of compounds is composed of a biphenyl molecule (two benzene rings) which has undergone varying degrees of substitution with either bromine ions, as in PBBs, or chlorine ions, as in PCBs (see Table 2.2). Similar health effects may, therefore, be produced by exposure to these types of compounds. It should be noted, however, that the lower brominated forms of polybrominated biphenyls appear to be metabolized more slowly than the higher ones, while the lower chlorinated biphenyls are metabolized more rapidly than the higher ones (Ringer and Polin, 1977). Assuming similar effects do exist, structurally related compounds include polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), 1, 2-dibromo-3-chloropropane (DBCP), 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD), kepone, and chloroprene. Norris et al (1973) compared the properties of octabromobiphenyl (OBBP), decabromobiphenyl oxide (DBDPO) and the common PCBs. DBDPO, because of its low mobility and low vapor pressure, has a lower volatility than the common PCBs. The solubility of PBBs and PCBs in water is similar; PCBs are readily soluble in most common organic solvents while DBDPO and OBBP are far less soluble in these.

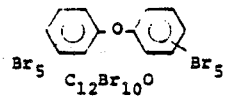
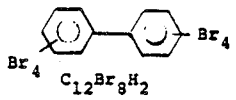
Photodegradation studies comparing DBDPO, OBBP and PCBs have shown that DBDPO and OBBP are readily degraded by UV radiation when they are dissolved in organic solvents such as xylene and octanol. Chlorinated biphenyls do not degrade under the same conditions. The stepwise photoreduction of PBBO and OBBP in xylene leads to formation of lower brominated diphenyl oxides and biphenyls which may be more stable to UV light than the parent compounds. Exposure of DBDPO under "natural conditions," i.e. in water using actual sunlight, causes the compound to degrade but not result in lower brominated biphenyl oxides as degradation products.

In ^{14}C metabolism studies comparing OBBP and DBDPO, it was found that within the first 24 hours, 90.6% ± 1.2 of the ^{14}C activity of the dose administered to the DBDPO-treated rats was found in the feces whereas only 61.9% ± 2.4 of the ^{14}C activity administered to the OBBP-treated rats was found in the feces after 24 hours. By day 2 of the study, all of the ^{14}C activity of the dose administered to the DBDPO-treated rats was accounted for, but only an additional 7% of the activity from the OBBP-treated rats was accounted for by day 2. Norris et al (1975) suggested that DBDPO does not have the potential of OBBP to bioaccumulate.

Sites of deposition of both OBBP and DBDPO were the liver and adipose tissue. The bromine content in these tissues increased rapidly in the OBBP-treated rat, while the bromine content of the livers of the DBDPO-treated rats plateaued after 30 days and after 180 days on test was not significantly different from the control. A statistically significant trend toward low-level accumulation of bromine in the adipose tissue of DBDPO-treated rats was noted. Bromine was not eliminated from

Table 2.1

Properties of Commercial Decabromodiphenyl Oxide and Octabromobiphenyl.

	DBDPO	OBBP
Structure	 $C_{12}Br_{10}O$	 $C_{12}Br_8H_2$
Percent Bromine	83	82
Molecular weight	960	786
Melting Range, °C	290-306	200-250
Decomposition point, DTA	425°C	435°C
Volatility, TGA (10°C/min.)		
% Weight Loss		
< 1	300°C	250°C
<10	330°C	310°C
<50	370°C	350°C
Vapor pressure, mm Hg		
@250°C	<1 mm	
@278°C	2 mm	
@306°C	5 mm	
Solubility @ 25°C		
Water	20-30 ppb	20-30 ppb
Cottonseed oil	600 ppm	1,700 ppm
Solubility in Organic Solvents g/100 g solvent		
Acetone	0.05	1.80
Benzene	0.48	8.10
Chlorobenzene	1.60	18.70
Methylene bromide	0.42	7.40
Methylene chloride	0.09	3.90
o-Xylene	0.87	10.00
Octanol:Water Partition Coefficient		
	172,000	340,000

adipose tissue of the OBBP-treated rats and there was only partial elimination from the liver of these rats after 90 days on recovery. The low level of bromine accumulated in adipose tissue of the DBDPO-treated rats remained unaffected during the 90 days on recovery diets, whereas bromine was readily cleared from the liver of these rats during the first 10 days on recovery (Norris et al., 1973, 1975).

In comparing heptabromobiphenyl and hexabromobiphenyl, Ringer and Polin (1977) noted that the lower brominated biphenyls appear to be metabolized more slowly than the higher ones, while the lower chlorinated biphenyls are metabolized more rapidly than the higher ones. Thus, in discussing the results of studies using PBBs and PCBs it is important to consider exactly what chemical form of the substance was present in the compound of interest.

2.3 Thyroid Dysfunction Related to PBB and PCB Exposure

a. Thyroid Neoplasia in Humans

Thyroid neoplasia is categorized in two groups as: (1) thyroid adenomas and the "solitary nodule" or (2) thyroid carcinoma. The incidence of thyroid adenoma, defined as an encapsulated benign neoplastic growth, was studied in a population sampled in Framingham, Massachusetts. Four percent of those studied were found to have a palpable thyroid nodule or nodules. Of these, half were considered multinodular and half solitary. New modules appeared at a rate of 0.1 percent per year. It is suggested that the prevalence of clinically detectable nodules is probably between 1 and 3 percent while a much higher figure is obtained if autopsy studies are included. Also, there appears to be an age-related increase in thyroid weight and nodularity (Degroot et al, 1979).

Most adenomas are diagnosed as being follicular and histologically look like the normal thyroid gland, although there is usually a discrete fibrous capsule. Some pathologists classify all papillary lesions of the thyroid as carcinomas while others indicate that some of these lesions may be adenomas. About half of all single nodules, on sectioning, have a gelatinous appearance and large colloid-filled follicles within a poorly demarcated capsule. These are classified as follicular adenomas by some pathologists and as "colloid nodules" by others. Adenomas grow slowly, remain dormant for years, must be 0.5-1 cm in size before they can be palpated, and are typically asymptomatic. Pathological evidence suggests that, in rare cases, adenomas can transform into invasive carcinoma since sequential change from hyperplasia to adenoma formation to invasive carcinoma has been found in patients with congenital goitrous hypothyroidism. These changes can be produced in experimental animals. In addition, studies have shown that nodules which are "cold" on isotope scan typically are unable to transport iodide into the thyroid due to a

specific deletion of the transport mechanism. Also, they are unable to maintain a concentration gradient for iodide between the thyroid cell and serum, even though the peroridase function may be intact in the cell.

Studies by the Mayo Clinic suggest a rising trend in incidence of thyroid cancer in the last decade. The incidence of thyroid carcinoma is about 36 new cases per million people per year with a death rate of about 9 in one million per year. The ratio of females to males with the disease is 2:1 and the variety of tumor is age-related. Recent studies have indicated that a high prevalence (5.7 percent) of unsuspected small carcinomas may exist in adults. These are generally below 0.5 cm in largest dimension, usually papillary in nature and believed to behave in a relatively benign manner, although their relationship to clinically diagnosed cancer is not yet known.

Thyroid hyperplasia, followed by abnormal formation and ultimately malignance, has been produced in experimental animals by iodide deficiency, long-term goitrogenic drug administration, exposure of the thyroid to external radiation or radioiodine, or by a combination of these. It should be noted that a common factor in all of these experimental situations is prolonged thyroid stimulation by TSH. It should also be noted that thyroid hyperplasia in man, induced by congenital metabolic defects, may lead to abnormal formation and eventual degeneration to carcinoma in patients who are unrecognized and untreated for decades.

Histologically, thyroid carcinomas may be found in different forms. Papillary lesions tend to be infiltrative, multicentric, with little tendency to invade blood cells and have multiple intraglandular foci and may have abundant psammoma bodies. Follicular carcinomas are more frequently encapsulated but vessel and capsule invasion are not uncommon. Most lesions have papillary and follicular elements: 15 to 20 percent classifiable as pure papillary; 60 percent, mixed papillary and follicular; and 15 to 20 percent, pure follicular tumors. The remainder are undifferentiated or poorly differentiated tumors.

b. Hypothyroidism in Humans

Hypothyroidism has been defined in physiological terms as decreased thyroid secretion which, when due to thyroid disease itself, is sufficient to activate the normal defense against thyroid deficiency, i.e., increased secretion of pituitary thyrotropin (TSH). The increase in TSH secretion may correct or so nearly correct the deficiency in thyroid hormone production that no clinical manifestations of hypothyroidism may be apparent, except for some degree of thyroid enlargement or an elevation of serum TSH concentration (Degroot et al, 1979).

The relative prevalence of the various forms of hypothyroidism is uncertain and in many areas of the world is most commonly caused by iodine deficiency. No recent figures are available on the prevalence of hypothyroidism in the United States. In a community survey conducted recently in Whickham, England, 2.8 percent of males of all ages had elevated serum concentration of thyrotropin (Tunbridge et al, 1977.)

Table 2.2 Experimental Evidence of Thyroid and Reproductive Dysfunction Associated with Oral Administration of Polybrominated Biphenyls

Species	Exposure/Dose Levels	Duration	Toxic signs, target organs and processes	Ref./Year
Cattle				
Heifers and bulls (6-18 months)	Suspect feed ad libitum	6 months	Aspermia, prostration, liver, testicles, spermatozoa, hyperkeratosis.	Jackson et al.(1974)
Cows	Feed contaminated with Firemaster BP-6	?	Stillborn and malformed calves. Abnormal hoof growth. Decreased production. Liver abnormalities.	Moorhead (1977)
Cattle	PBB-contaminated feed	?	Testes, spermatozoa, Infertility. Reduced milk production.	Cook (1978)
Cows/calves	0.1,1.0,10 or 100 mg/kg body weight/ day Firemaster BP-6 (65%hexa-, 14%hepta-, 11%penta-, 10%other)	2-12 weeks	Time/dose-related lesions in testes, epididymides.	Robl (1978)
Chickens				
Chickens	5, 10, 20 ppm PPB in diet	8 weeks	No effect on egg production, Hatchability , progeny growth gains.	Lillie et al. (1975)
Chickens	45 ppm PBB in diet 125 ppm in diet 625 ppm in diet	? ? 	Hatchability depressed. Egg production declined. Egg production ceased.	PBB Sci Adv Panel (1976)
Chicks	As above	?	Liver, spleen, thyroid, heart, male hormone	PBB Sci Adv Panel (1976)

* Adapted from Kingsley, K. Polybrominated biphenyls (PBB) environmental contamination in Michigan, 1973-1975. Environmental Research 13, 74-93, 1977.

Table 2.2 (continued) Experimental Evidence of Thyroid and Reproductive Dysfuntion Associated with Oral Administration of PolybrominatedBiphenyls

Species	Exposure/Dose Levels	Duration	Toxic signs, target organs and processes	Ref./Year
Chickens	?	?	Reduced colloid vacuolization suggesting hypothyroidism	Ringer and Polin (1977)
Immature chickens	?	?	Increased thyroid weight	Ringer (1978)
Rats				
Rats, timed-pregnant	50 ppm PBB 100 ppm in 1000 ppm diet	Days 7-20 of pregnancy	Fatal gastrointestinal hemorrhage. Decreased fetal weight, late fetal mortality, exencephaly, cleft palate, hydronephrosis.	Corbett et al. (1975)
Rats	100 PBB in diet	?	No reproductive interference, birth defects or cytogenetic aberrations.	Ficsor et al. (1976)
Rats	10 or 100 ppm PBB in iodine excess diet	60 days	Increased thyroid size	Sleight et al. (1978)
	100 ppm PBB in iodine adequate diet	60 days	Mild hyperplasia in thyroid	
Rats	1 mg/kg PBB/day 3 & 6 mg/kg PBB	20 days	Increased introthyroid iodine. Depressed T_4 level which was time- and dose-dependent. Increased liver weight. Increased thyroid weight.	Allen-Rowland (1981)
	6 mg/kg PBB		Elevated TSH levels. Increased thyroid uptake of 131_I	
Pregnant Rats	Firemaster BP-6		No fetal effects. Growth delay, enlarged livers, delayed vaginal opening due to postnatal exposure from nursing.	Harris et al. (1978) Rickert et al. (1978)

-11-

Table 2.2 (Continued) Experimental Evidence of Thyroid and Reproductive Dysfunction Associated with Oral Administration of Polybrominated Biphenyls

Species	Exposure/Dose Levels	Duration	Toxic signs, target organs and processes	Ref./Year
Mice				
Mice	50 ppm PBB 100 ppm in 1000 ppm diet	Days 7-18 of pregnancy	Decreasing fetal weight with dosage. Weak teratogen. Fat storage.	Corbett et al. (1975)
Pregnant Mice	0, 100, 200 PBB in diet	Days 4-16 Days 8-16	Dead or resorbed fetuses. Fetal body weight down.	Corbett et al. (1975)
Pregnant Mice	0, 50, 100 ppm PBB in diet	Days 8-16	No effects in offspring.	Preache et al. (1976)
		Postnatal 1-29	Mortality of offspring increased.	
Mice	10 ppm Firemaster PB-6	14 days	Hexabromobiphenyl in testicles.	Corbett et al. (1978)
Mice	PBB-supplemented standard diet	?	Increased susceptibility to renal and hepatic damage.	Kluwe et al. (1978)
Other				
Rhesus Monkeys	PBB (simulated human exposure levels in Michigan accident)	Pre-breeding	Hormonal changes. Five low birth weights, one stillbirth, one abortion.	Allen et al. (1979)
Male Cockerels	Firemaster BP-6	?	Decreased testicle and body weight. Increased thyroid weight.	Ringer et al. (1978)

-12-

c. Effect of PBBs on the Thyroid Gland

The finding of hypothyroidism in the New Jersey workers (Bahn, 1980) is supported by Allen-Rowlands (1981) that described a significant decrease in serum thyroxine (T_4) concentration in rats after administration of PBB. This response was both time and dose dependent. Serum thyrotropin (TSH) concentrations in these animals were elevated (personal communication, J. Seifter). Subnormal serum T_4 concentrations five months after cessation of exposure in these rats suggest that the effect of PBB may be persistent (personal communication, J. Seifter).

Allen-Rowlands et al., (1981) in a study in which rats were fed 1,3 or 6 mg/kg PBB per day for a period of twenty days reported that plasma T_4 levels were significantly depressed ($p<0.05$) by all treatments except the 10-day 1 mg PBB/kg regimen ($p<0.1$). There was a significant decline in T_4 levels ($p<0.02$) from days 10 to 20 in rats treated with 1 mg/kg PBB and also in rats treated with 3 and 6 mg/kg ($p<0.05$). The effect was time- and dose-dependent. An increase in mean thryoid weight was seen following 3 and 6 mg/kg doses of PBB. (Thyroid weights were not obtained following 1 mg/kg PBB treatment). Plasma TSH levels were elevated as compared with controls following 20 days of PBB at 3 and 6 mg/kg doses, but only the 6 mg/kg dose produced statistically significant elevation. PBB administration at 6 mg/kg also produced an increase in the 5-hour thyroid uptake of ^{131}I. In general, PBB treatment caused a significant increase in the amount of intrathyroidal iodide (I^-) as compared to that in vehicle-treated controls.

Two months following the last 1 mg/kg administration of PBB, thyroid weights remained significantly depressed as compared to controls. The same trend was noted with the 3 mg/kg-dosed animals. Substantial amounts of PBB were found in the thyroid glands after 20 days of PBB (treatment) and 5 months after the last PBB administration. No significant depression in the mean PBB tissue concentration in the thyroid was found 5 months post-treatment as compared to the level at cessation of treatment. Increased liver weight was noted following PBB administration, together with an increase in microsomal UDP-glucuronyltransferase activity; UDP-glucuronyltransferase is responsible for glucuronidation of T_4 and tri-iodothyronine prior to biliary excretion.

Allen-Rowlands et al. suggested that the ability of PBB to induce UDP-glucuronyltransferase activity in rats may result in accelerated metabolism of peripheral thyroid hormones and thus contribute to the reduced T_4 levels seen in the study. Other hypotheses were that reduced binding of T_4 to plasma proteins may accelerate metabolism, or that PBB may interfere with the normal synthesis and/or secretion of thyroid hormones. Preferential sequestration of PBB in the thyroid

suggests that PBB may bind to thyroidal macromolecules and affect incorporation of radioiodine into intrathyroidal amino acid. Or PBB may act in some manner to inhibit organification of iodide by peroxidase. Allen-Rowlands et al. concluded that exposure to PBB resulted in disruption of the normal homeostatis of the pituitary-thyroid axis and that this bioactive chemical exhibited persistent and deleterious effects.

Thyroid hyperplasia was first observed in a 30-day dietary feeding study of rats in 1973 at Dow Chemical, U.S.A. Laboratories (Norris et al, 1973). In the study which used octabromobiphenyl (OBBP)[a] and decabromadiphenyl oxide (DBDPO)[b] thyroid hyperplasia was observed at all levels of OBBP feeding (1.0, 0.1 and 0.01% OBBP or about 800, 80 and 8 mg/kg/day) and at the 1.0 and 0.1% dietary levels of DBDPO. It was suggested that the thyroid hyperplasia might have been a physiological response to competition between bromine and iodine in the thyroid gland. According to the researchers, high dosage levels with materials containing bromine in quantities as great as in OBBP and DBDPO could produce such an effect (see figure 2.1).

Ringer and Polin (1977) found thyroid hyperplasia in chickens fed PBB. It was noted (unpublished) that the gland exhibited reduced colloid vacuolization suggesting hypothyroidism. Ringer and Polin suggested that the effect of PBB on the thyroid is related to enhanced catabolism of thyroxine in the liver. However, the lack of linear effect over the whole range of PBB levels versus the thyroidal weights in chicks suggested other factors also contributed to the hypothyroidism and glandular size. In another study by Ringer (1978) of the effects of PBB on immature chicks, increased thyroid weight was also noted.

Rat studies indicate that the iodine content of the diet influences the increase in thyroid size and weight and thyroid hyperplasia following exposure to PBB (Sleight et al, 1978). By day 30 at 10 and 100 ppm PBB in the diet there were significant increases ($p < 0.05$) in the thyroid size of rats fed an iodine deficient diet as compared to rats fed the iodine-excess diet and no PBB. By day 60 significant increases ($p<0.05$) in thyroid size were found in rats fed an iodine excess diet and 10 or 100 ppm PBB. Mild hyperplasia of the follicular epithelium and a change from the normal low cuboidal epithelium to one which had a more columnar appearance were noted in the thyroid glands of rats fed an iodine-adequate diet and 100 ppm PBB. Irregular follicle size and increased cellularity were also found. The thyroid glands from iodine-deficient rats and from rats

[a] Actual chemical composition by vapor phase chromatography and mass spectrophotometry: 45.2% octabromobiphenyl (OBBP), 47.4% nonabromobiphenyl, 5.7% decabromobiphenyl, and 1.8% heptabromobiphenyl.

[b] Actual composition by vapor phase chromatography and mass spectrophotometry: 77.4% decabromodiphenyl oxide (DBDPO), 21.8% nonabromodiphenyl oxide and 0.8% octabromodiphenyl oxide.

fed the iodine-excess diet and 100 ppm PBB had an appearance similar to that of the normal thyroid gland of the rats fed an iodine-adequate diet and 0 ppm PBB. Sleight et al, noted that PBB causes histologic changes in the thyroid gland which were similar to the changes in the thyroid gland of rats given polychlorinated biphenyls (PCBs) which were reported by Collins et al (1977).

d. Effect of PCB s on the Thyroid Gland

Collins et al. (1977) found that in rats polychlorinated biphenyls (PCB's) produced ultrastructural lesions in thyroid follicular cells and reductions in serum thyroxin levels which were time- and dose dependent. Acute effects of PCB consisted of accumulation of lysosomal bodies and colloid droplets in follicular cells with luminal surface microvilli abnormalitites. Chronic administration (12 weeks) of PCB (50 and 500/250 ppm) resulted in striking distention of many follicular cells with large lysosomal bodies with strong acid phosphatase activity and colloid droplets, blunt and abnormally branched microvilli, and mitochondrial vacuolation. These changes were associated with a highly significant reduction in serum thyroxine with both the low and high dose of PCB. Follicular cells underwent moderate compensatory hypertrophy and hyperplasia after remaining responsive to the lowered thyroxine level following PCB feeding for 4 and 12 weeks. They were smaller and more columnar than in the controls and often present in multiple layers lining thryoid follicles, although occasionally as papillary projections of hyperplastic follicular cells into the lumen. Because PCB compounds significantly enhance the peripheral metabolism of thyroxine and reduce the binding of thyroid hormones to serum proteins, the serum thyroxine and protein-bound iodine levels are lowered in rats. This suggests that the thyroid changes noted reflect an increase in lowered blood thyroxine levels. The changes found were similar to changes reported following thyroid stimulation by thyrotropin.

Histopathological lesions of the thyroid, parathyroid, and testes followed dosing of male Sprague-Dawley rats with 50 ppm of the PCB photomirex (Villeneuve et al, 1979). Lesions of the thyroid consisted of a progressive reduction in colloid and follicular atrophy. Lesions of the testes included marked tubular degeneration and complete cessation of spematogenesis. Thyroid/parathyroid changes included moderate bilateral reduction in follicle size and colloid density and pronounced follicular atrophy with severe colloid depletion and focal epithelial exfoliation. There was also increased height of thyroid epithelial cells. It was noted that the lesions observed in the thyroid/parathyroid represented a "rather severe toxic response" (Villeneuve et al, 1979).

Five ppm of the PCB aroclor 1254 (54% chlorine) was found to stimulate anatomically the liver weight, adrenal weight and thyroid histology of

Table 2.3 Experimental Evidence of Thyroid and Reproductive Dysfunction Associated with Exposure to Polychlorinated Biphenyls

Species	Exposure/Dose Levels	Duration	Toxic signs, target organs and processes	Ref./Year
Rats				
Rats	50, 250, 500 ppm PCB	12 weeks	Time/dose-dependent reduced serum thyroxine levels. Lowered iodine levels. Ultrastructural lesions in thyroid follicular cells. Thyroid hyperplasia and hypertrophy.	Collins (1977)
Rats, weanling	50 ppm PCB Photomirex	28 days	Lesions of thyroid, parathyroid and testes; aspermia	Villeneuve (1979)
Pregnant Rats	PCB	?	Increased fetal resorptions.	Beaudoin et al. (1977)
Other				
Female mink	5 ppm PCB Aroclor 1254*	9 months	Hypothyroidism. Increased T_4 levels and peripheral degradation of thyroxine except during estrus and pregnancy. Infertility.	Byrne (1975)
Monkeys	PCB	Pre-breeding	Hormonal changes before breeding; abortion, stillbirth, low birth weight.	Allen et al. (1979)

*54 percent chlorine

-16-

female mink (Byrne, 1975). In the mink, PCB generally increased T_4 levels and peripheral degradation of thyroxine except during estrus and pregnancy. Those mink fed 5 and 2 ppm PCB were relatively hypothyroid only at estrus and the reproductive season and they failed to bear young. The PCB fed at 0.5 ppm consistently increased T_4 levels above those in controls.

Table 2.3 summarizes the experimental evidence of thyroid and reproductive dysfunction associated with PCB exposure.

2.4 Reproduction Dysfunction

a. Reproduction Dysfunction Related to PBB Exposure

The effects of polybrominated biphenyls have been associated with various changes in the reproductive function of exposed animals and with teratogenic effects in laboratory animals. The 1973 contamination of feed with Firemaster BP-6 provided a natural experiment of the reproductive effects of PBB. In addition to non-reproductive changes such as liver abnormalities, decreased resistance to infection, abnormal hoof growth and skin roughening, exposed cattle exhibited decreased milk production and produced stillborn and malformed calves (Moorhead et al, 1977).

Cows fed the contaminated feed exhibited anorexia, decreased milk production and shrinking of udders. Atrophied testicles and aspermia were noted in a bull. Embryonic resorption was suspected when, about two weeks into the problem, cows bred 4-6 weeks previously, started coming back into estrus. Cows given the contaminated feed in the last trimester of pregnancy went 2-4 weeks overdue. Calves were born dead or died soon after birth (Jackson and Halbert, 1974). Ten non-lactating cows died without calving. Four developed hydrops amnii; one died a few days prepartum; two delivered dead fetuses at parturition and one had a live, normal-appearing calf (Jackson and Halbert, 1974).

Of twelve 6-12 month-old heifers and bulls fed the contaminated feed ad libitum, after six weeks, five died. An 18 month-old bull developed left abomasal displacement. Despite his emaciation and weakness, an operation was performed. Liver adhesions to the diaphragm and rib cage were noted. The testicles were atrophied and no spermatozoal motility was found. On semen evaluation many headless and tailless spermatozoa were noted (Jackson and Halbert, 1974).

Following Jackson and Halbert's finding of atrophied testes and aspermia, tissues from contaminated cattle in Michigan were collected and examined for PBB level. As part of the study, the testes were examined. Mature spermatozoa were reduced in number or absent in most of the testes. Other cells in the various phases of spermatogenesis were also absent, resulting in the Sertoli cells' being the only cells

present in the seminiferous tubules. The interstitial cells were normal. In all of the herds examined, milk production was lower than normal; cattle were infertile or subfertile; and feed efficiency was poor (Cook et al., 1978).

Calves and cows were then orally administered known dosages of PBB in the form of Firemaster FF-1 (a pulverized form of Firemaster BP-6). Calves were sacrificed at 2,4,6 and 12 weeks of testing with a dosage of 0.1, 1.0, 10 or 100 mg/kg body weight/day (3.3, 33, 330 or 3300 ppm in the diet). Lesions were observed in the testes which were treatment-associated and related to several factors, including the nutritional status, the age of the animal (prepuberal development) and the duration of exposure to PBB. The severity of the treatment-induced lesions was time/dose related.

Treatment-associated changes were present in the testes and epididymis of all males in the study. Changes described as hypospermatogenesis of the testes and absence of sperm in epididymal ducts were consistent with the age of the animals at prepuberal development. Degeneration of the germinal epithelial cells lining seminiferous tubules was also present in many of the bull calves. Severity of the degenerative change was variable (Robl et al., 1978).

Hexabromobiphenyl has been found in the testicles of mice six hours and 14 weeks after 10ppm Firemaster PB-6 had been fed to the mice for 14 days (Corbett et al., 1978).

In an experimental study involving feeding trials of Firemaster BP-6 to male White Leghorn Cockerels, PBB administration decreased testicular weight and caused depressed body weight as a result of decreased feed intake. In contrast, thyroid weight increased despite the overall body weight loss (Ringer, 1978). Ringer and Polin (1977) also reported changes in the testes of chickens due to PBB feeding.

In yet another study, pregnant rats and mice were exposed to Firemaster BP-6 in the diet. Mice were exposed to either 50, 100 or 1,000 ppm Firemaster BP-6 in commercial rodent chow from days 7-18 of pregnancy, while rats were exposed to the same amount from days 7-20 of pregnancy. Control groups were fed uncontaminated feed of the same type. In rats, Firemaster BP-6 caused a decrease in mean fetal weight with increasing dose of the PBB mixture. Late fetal mortality was exhibited at the 1000 ppm concentration. The mice showed not only decreasing mean fetal weight with increasing dose, but also exencephaly at the 100 and 1000 ppm dose and cleft palate and hydronephrosis at the 1000 ppm dose (Corbett et al., 1975).

Harris et al. (1978) reported no fetal effects in pregnant rats from oral administration of Fire Master BP-6. However, postnatal exposure through exposed lactating mothers caused growth delay, enlarged

livers, and delayed vaginal opening. Rickert et al.(1978) in a similar study of prenatal versus postnatal exposure concluded that exposure from nursing was more significant than placental exposure.

Rhesus monkeys administered doses of PBB which simulated human exposure levels from the Michigan accident exhibited hormonal changes before breeding. The seven offspring included one abortion and one stillbirth; the remainder had low birth weights (Allen et al., 1979). Similar results were noted in rhesus monkeys exposed to PCB's, (Allen et al., 1979).

Four years after the initial contamination of Michigan's food supply, semen samples were analyzed from farmers residing on PBB-contaminated farms, from individuals who had bought food directly from such farms, and from workers employed in the plant which manufactured the Firemaster BP-6. These semen samples were compared to samples from male graduate students at a Michigan university who had consumed little or no PBB-contaminated foods. Although the study was prompted by complaints of decreased libido following exposure to PBBs, researchers found no significant effect on spermatogenesis in the group of PBB-exposed men. There was a significant difference in sperm count in the exposed farmer group as compared with expected normal values in the years 1938 and 1951, but not as compared to those reported in 1974. Sperm count, motility and shape were examined in each case. Results of this study of the effects of PBB on human spermatogenesis may not be conclusive since semen collection did not begin until four years after the contamination. Also there may merely have been a change in spermatogenesis of exposed men from "high normal" to "low normal". In addition, while PBB may have a synergistic effect with other factors known to influence spermatogenesis, all men with possible confounding factors for decreased spermatogenesis were excluded from the study (Rosenman et al, 1979).

It should also be noted that PBB supplementing a standard rodent diet has been found to make mice more susceptible to chlorinated hydrocarbon solvent-induced renal and hepatic damage and to the lethal effects of $CHCl_3$ and CCl_4 (Kluwe et al, 1978).

b. Reproduction Dysfunction Related to PCB Exposure

Administration of PCBs to pregnant rats resulted in increased fetal resorptions, cleft palate, and diaphragmatic hernia (Beaudoin et al, 1977). These results are comparable to effects by PBB reported by Corbett et al (1975). Another natural experiment showed association of reproductive dysfunction in humans exposed to halogenated hydrocarbons. In 1968, PCB-contaminated rice oil in Japan caused liver and eye changes (Yusho disease) in over 1000 adults. New-born Yusho disease, characterized by low birth weight, cola-colored skin, eye disease, spotted skin calcifications, and colored gingiva, was reported in offspring of exposed women (Kuratsune et al, 1972).

Twenty-two day-old weanling rats fed the lipophilic PCB photomirex for 28 days at 0, 0.5, 5.0 or 500 ppm were found to present histopathological lesions of the testes. (All animals in the high dose group, however, died after seven days). Lesions noted in the testes included complete cessation of spermatogenesis and marked tubular degeneration. Lesions of the testes were observed together with lesions of the parathyroid/thyroid and depressed growth at 50 ppm photomirex (Villeneuve et al, 1979).

Human spermatogenesis has been reported to be adversely affected by PCB's (Anon., 1979), and DBCP (Whorton et al., 1979; Milby et al., 1980).

2.5 The PBB Effect on Body Weight

Dietary intake of PBB has been associated with significant weight loss in several animal study populations. Anorexia was noted in the first phase of a clinical course in a 400 cow dairy herd accidentally fed Firemaster BP-6 contaminated in Michigan (Jackson and Halbert, 1974). In the second clinical phase, high-producing cows continued to lose weight for several months after the feeding program was changed, even though their appetites were normal. But, twenty non-lactating cows were seen to lose their appetite several weeks prepartum and failed to get up at feeding time. When the suspected feed was taken to another farm and given ad libitum to twelve 6-18 months old heifers and bulls, five of the twelve calves died and a bull which developed left abomasal displacement was noted to be emaciated and weak. Robl et al. (1978) reported poor weight gains, decreased food consumption and body weight losses among calves fed at the level of 100 mg/kg body weight or 330 ppm in the diet. Cows fed daily oral doses of PBB equivalent to 0.01, 0.1, 1 or 10 ppm in the diet exhibited no unexpected weight loss and, in fact, gained weight. There were no differences in food consumption values among cows at any of the PBB levels.

In pigs studied in laboratory conditions, the average daily weight gain and feed intake following administration of 20 or 200 ppm PBB in the diet were significantly decreased ($p < 0.01$) (Ku et al., 1978). Because the differences between the pigs on the 20 ppm and 200 ppm PBB in the diet were signigicant, it has been suggested that the higher the dietary PBB level, the greater the effect on feed intake and weight gain. The effect of dietary PBB levels on weight gain may be due to reduced feed intake. Such a finding has been confirmed in PBB paired-feeding studies using chickens and Japanese quail (Ringer and Polin, 1977). Death due to inanition was also found by Ringer and Polin (1977). Ringer (1978) noted depressed body weight as a result of decreased feed intake in White Leghorn cockerel chicks fed PBB.

PBB treatment has caused significant decreases in body weight in rats and mice (Tilson et al., 1978). Males were affected more by experimental exposure to PBBs than the females. The weight-decreasing

effect of PBBs was greater at the 60-day test than at the 30-day test in both rats and mice. Firemaster FF-1 at 30 mg/kg-day significantly decreased the body weight of male and female rats at both 30 and 60 days. However, Firemaster FF-1 at 3 mg/kg-day and 16.8 mg/kg-day of 2, 4, 5, 2', 4', 5', -hexabromobiphenyl (HBB), the main component of the FF-1 mixture, had no significant effect on body weight. Analysis showed that female mice were not affected by 30 mg/kg-day of FF-1 nor by the 16.8 mg/kg-day of HBB. Male mice receiving 30 mg/kg-day of FF-1 weighed significantly less than controls at the 30-day test but not at the 60-day test. HBB, however, had no significant effect on the body weight of male mice at the 30-day test but at the 60-day test, males given HBB were significantly heavier than controls. Tilson et al. suggested that loss of body weight or failure to gain weight after PBB administration is manifestation of exposure to relatively high doses of PBBs.

At the cellular level, growth of C3H/10T½ mouse embryo fibroblasts treated with 37 mg/ml HBB or Firemaster FF-1 sharply declined after 8 days whereas growth of cells treated with hexachlorobiphenyl (HCB) was linear. At 5 mg/ml HBB, cell growth was stimulated after 4 and 8 days while Firemaster FF-1 stimulated growth after 8 days (Bairstow et al., 1978).

Decreased weight gain (Kuratsune et al, 1972; Hansen et al., 1976) and reduced feed efficiency (Hansen et al., 1976) have also been reported following PCB intoxication.

Table 2.4 summarizes the experimental evidence of weight loss associated with PBBs and PCBs exposure.

Table 2.4 Experimental Evidence of Weight Loss Associated with Exposure to Polybrominated Biphenyls and Polychlorinated Biphenyls

Species	Exposure/Dose Levels	Duration	Weight Loss	Ref/Year
Cattle	Firemaster BP-6 Contaminated feed ad libitum	?	Anorexia, depressed appetite weight loss	Jackson et al. (1974)
Calves	Firemaster BP-6 Contaminated feed ad libitum	?	Emaciation, weakness, death	Jackson et al. (1974)
Calves	330 ppm PBB	?	Poor weight gain. ↓ food consumption	Robl et al. (1978)
Cows	0.01, 0.1, 1 or 10 ppm PBB in diet	?	No weight loss	Robl et al. (1978)
Pigs	20 or 200 ppm PBB	?	Dose-dependent decreased weight gain and feed intake.	Ku et al. (1978)
Chickens/ Japanese Quail	PBB in diet	?	Decreased weight loss and feed intake. Death due to inanition	Ringer and Polin (1977)
Cockerel Chicks	PBB in diet	?	Decreased weight	Ringer (1978)
Rats/Mice	.03-3.0 mg/kg/day Firemaster FF-1*	30 days dosing	Decreased body weight in male rodents at 30 mg/kg Firemaster FF-1. HBB no effect on male mice at 30 days. Decreased weight effect greater than at 30 days in male rats. No effect at 3 mg/kg FF1 on males. No effect on female mice at 30 mg/kg Firemaster and HBB.	Tilson et al. (1978)
	.168-16.8 mg/kg HBB*	60 days (30 days post-dosing)		

* 2, 4, 5, 2', 4', 5' hexabromobiphenyl (HBB)

-22-

2.6 REFERENCES

1. Allen, J.R., Barsotti, D.A., Lambrecht, L.K. and VanMiller, J.P. (1979). Reproductive effects of halogenated aromatic hydrocarbons on nonhuman primates. Ann NY Acad Sci 320:419-425.

2. Allen-Rowlands, C.F., Castracane, V.D., Hamilton, M.G. and Seifter, J. (1981). Effect of polybrominated biphenyls (PBB) on the pituitary-thyroid axis of the rat (41099). Proc Soc Exp Biol Med 166:506-514.

3. Anderson, H.A., Wolff, M.S., Lilis, R. et al. (1979). Symptoms and clinical abnormalities following ingestion of polybrominated biphenyl-contaminated food products. Health Effects of Halogenated Aromatic Hydrocarbons. Ann NY Acad Sci 320:684-702.

4. Anon. (1979). PCBs linked to male sterility. Science News 116:183.

5. Bahn, A.K., Bialik, O. Oler, J., et al. (1980). Health assessment of occupational exposure to polybrominated biphenyl (PBB) and polybrominated biphenyl oxide (PBBO). EPA 560/6-80-001.

6. Bairstow, F., Hsia, M.T., Norback, D.H. and Allen, J.R. (1978). Toxicity of Firemaster FF-1 and 2, 2', 4, 4', 5, 5'-hexabromobiphenyl in cultures of C3H/10T½ mammalian fibroblasts. Environ Health Perspect 23:321-327.

7. Beaudoin, A.R. (1977). Teratogenicity of polybrominated biphenyls in rats. Environ Res 14:81-86.

8. Budd, M.L. et al. (1978). Polybrominated biphenyl exposure. Michigan Morbidity and Mortality Weekly Report 27:115-121.

9. Byrne, J.J., Reineke, E.P., Ringer, R.K. and Auerlich, R. (1975). Influences of polychlorinated biphenyl mixture (Aroclor 1254) administration on reproduction and thyroid function in mink (Mustela vison). Fed Proc Fed Amer Soc Exp Biol 34:321. Abstract only.

10. Collins, W.T., Capen, C.C., Kasza, L. et al. (1977). Effect of polychlorinated biphenyl (PCB) on the thyroid gland of rats: Ultrastructural and biochemical investigations. Am J Pathol 89(1):119-130.

11. Cook, H., Helland, D.R., VanderWeele, B.H. and DeJong, R.J. (1978). Histotoxic effects of polybrominated biphenyls in Michigan dairy cattle. Environ Res 15:82-88.

12. Corbett, T.H., Beaudoin, A.R., Cornell, R.G. et al. (1975). Toxicity of polybrominated biphenyls (Firemaster BP-6) in rodents. Environ Res 10: 390-396.

13. Corbett, T.H., Simmons, J.L., Kawanishi, H. and Endres, J.L. (1978) EM changes and other toxic effects of Firemaster BP-6 (polybrominated biphenyls) in the mouse. Environ Health Perspect 23:275-281.

14. Degroot, L.J., Cahill, G. F. Jr., Odell, W.D. et al. (ed.) (1979). Endocrinology, Vol. 1. New York: Grune and Stratton, Inc.

15. DiCarlo, F.J., Seifter, J. and DiCarlo, V.J. (1978). Assessment of the hazards of polybrominated biphenyls. Environ Health Perspect 23:351-365.

16. Ficsor, G. and Wertz, G.F. (1976). Polybrominated biphenyl non-teratogenic C-mitosis synergist in rat. Abstract CA-7, p. 37., Seventh Annual Meeting, Environmental Mutagen Society.

17. Hansen, L.G., Wilson, D.W., and Byerly, C.S. (1976). Effects on growing swine and sheep of two polychlorinated biphenyls. Am J Vet Res 37:1021-1024.

18. Harris, S.J., Cecil, H.C. and Bitman, J. (1978). Embryotoxic effects of polybrominated biphenyls (PBB) in rats. Environ Health Perspect 23:295-300.

19. Isleb, D.R. and Whitehead, G.L. (1975). Polybrominated biphenyls: An agricultural incident and its consequences: I. The agricultural effects of exposure. Proceedings at the Ninth Annual Conference on Trace Element Substances in Environmental Health, 47-54.

20. Jackson, T.F. and Halbert, F.L. (1974). A toxic syndrome associated with the feeding of polybrominated biphenyl contaminated protein concentrate to dairy cattle. J Am Vet Med Assoc 165:437-439.

21. Kimbrough, R.D. (1979). The carcinogenic and other chronic effects of persistent halogenated organic compounds. Health Effects of Halogenated Aromatic Hydrocarbons. Ann NY Acad Sci 320:415-418.

22. Kingsley, K. (1977). Polybrominated biphenyls (PBB) environmental contamination in Michigan, 1973-1975. Environ Res 13:74-93.

23. Kluwe, W.M., McCormack, K.M. and Hook, J.B. (1978). Potentiation of hepatic and renal toxicity of various compounds by prior exposure to polybrominated biphenyls. Environ Health Perspect 23:241-246.

24. Ku, P.K., Hogberg, M.G., Trapp, A.L. et al. (1978). Polybrominated biphenyl (PBB) in the growing pig diet. Environ Health Perspect 23:13-18.

25. Kuratsune, M., Yoshimura, T., Matsuzaka, J. and Yamaguchi, A. (1972). Epidemiological study of Yusho, a poisoning caused by ingestion of rice oil contaminated with a commercial brand of polychlorinated biphenyls. Environ Health Perspect 1:119-128.

26. Lillie, R.J., Cecil, H.C., Bitman, J. and Fries, C.F. (1975). Toxicity of certain polychlorinated and polybrominated biphenyls on reproductive efficiency of caged chickens. Poultry Sci 54:1550-1555.

27. Meester, W.D. and McCoy, D.J. (1977). Human toxicity of polybrominated biphenyls. Clin Toxicol 10:474.

28. Milby, T.H. and Whorton, D. (1980). Epidemiological assessment of occupationally related, chemically induced sperm count suppression. J Occup Med 22:77-82.

29. Moorhead, P.D., Willett, L.B., Brumm, C.J. and Mercer, H.D. (1977). Pathology of experimentally induced polybrominated biphenyl toxicosis in pregnant heifers. J Am Vet Med Assoc 170:307-313.

30. Norris, J.M., Ehrmantraut, J.W., Gibbons, C.L. et al. (1973). Toxicological and environmental factors involved in the selection of decabromobiphenyl oxide as a fire retardant chemical. Applied Polymer Symposium 22:195-219. See and cf. to our citation number 31.

31. Norris, J.M., Kociba, R.J., Schwetz, B.A. et al. (1975). Toxicity of octabromobiphenyl and decabromobiphenyl oxide. Environ Health Perspect 11: 153-161.

32. PBB Scientific Advisory Panel. (1976). Report to William G. Milliken, Governor, State of Michigan, on polybrominated biphenyls (PBB). May 24.

33. Preache, M.M., Cagen, S.Z. and Gibson, J.L. (1976). Perinatal toxicity in mice following maternal dietary exposure to polybrominated biphenyls. Abstract 192, 15th Annual Meeting, Society of Toxicology, Atlanta, GA, March 14-18.

34. Rickert, D.E., Dent, J.G., Cagen, S.Z. et al. (1978). Distribution of polybrominated biphenyls after dietary exposure in pregnant and lactating rats and their offspring. Environ Health Perspect 23:63-66.

35. Ringer, R.K. and Polin, D. (1977). The biological effects of polybrominated biphenyls in avian species. Fed Proc 36:1894-1898.

36. Ringer, R.K. (1978). PBB fed to immature chickens: Its effect on organ weights and function and on the cardiovascular system. Environ Health Perspect 23:247-255.

37. Robl, M.G., Jenkins, D.H., Wingender, R.J. and Gordon, D.E. (1978). Toxicity and residue studies in dairy animals with Firemaster FF-1 (polybrominated biphenyls). Environ Health Perspect 23:91-97.

38. Rosenman, K.D., Anderson, H.A., Selikoff, I.J. et al. (1979). Spermatogenesis in men exposed to polybrominated biphenyl (PBB). Fertil Steril 32(2): 209-213.

39. Selikoff, I.J. et al. (1976). Health effects of exposure to polybrominated biphenyls. Results of a clinical field survey Nov. 4-10, 1976. Interim summary report to National Institutes of Environmental Health Sciences. ES 00928.

40. Sleight, S.D., Mangkoewidjojo, S., Akoso, B.T. and Sanger, V.L. (1978). Polybrominated biphenyl toxicosis in rats fed an iodine-deficient, iodine-adequate or iodine-excess diet. Environ Health Perspect 23:341-346.

41. Tilson, H.A., Cabe, P.A. and Mitchell, C.L. (1978). Behavioral and neurological toxicity of polybrominated biphenyls in rats and mice. Environ Health Perspect 23:257-263.

42. Tunbridge, W.M.G., Evered, D.C., Hall, R. et al. (1977). The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol 7: 481-493.

43. Villeneuve, D.C., Ritter, L., Felsky, G. et al. (1979). Short-term toxicity of photomirex in the rat. Toxicol Appl Pharmacol 47:105-114.

44. Whorton, D., Milby, T.H., Krauss, R.M. and Stubbs, H.A. (1979). Testicular function in DBCP exposed pesticide workers. J Occup Med 21:161-166.

3. THE FIELD STUDY

3.1 The Study Population and Recruitment Procedures

a. Exposed Cohort Group

The study cohort is 100 male, 8 female and 4 deceased employees of Hexcel/Fine Organics and Saytech, Inc. who were exposed for at least 240 hours to PBB from January 1, 1973 to March 30, 1977 or to PBBO from April 1, 1977 to March 1, 1981.

After the grant for this study was awarded in September, 1980, the investigators from the University of Pennsylvania approached Saytech, Inc. for assistance in contacting their employees. However, in July, 1980, the Saytech plant was purchased by Ethyl Corporation of Baton Rouge, Louisiana, who decided not to cooperate with this study.

All efforts to gain the company's cooperation were in vain. Even the local congressman at the time, Edward J. Patten, refused to become involved. The investigators therefore contacted the study group directly. The 42 workers who had participated in the 1978 study assisted in identifying 25 additional workers. Twenty-two additional workers who took part in the annual physical examination given by Hexcel in January, 1978 were also contacted by letters addressed to the workers, in care of Saytech. Eleven letters were returned as "unknown." Fifty-five (70 percent) of the 78 identified workers agreed to participate in the study, including 33 current employees.

In February, 1981, a local coordinator was contracted to schedule the appointments by telephone and to send a letter of informed consent after each phone call.

Efforts were made to recruit additional workers by placing an ad in the local newspaper, The News Tribune, inviting all workers who were exposed to PBB or PBBO to contact the investigators (Exhibit 1a). As a result of the ad, the local newspaper interviewed the Principal Investigator, and an article describing the study appeared in The News Tribune (Exhibit 3b). Following the field study, a second article appeared in The Home News (Exhibit 3c).

In November, 1981, the investigators met with company representatives: Mr. Robert Ortleb, Vice-president; Mrs. Laverne J. Makfinsky, Manager, Technical Compliance; and Mr. Jonathan Jacoby, Supervisor of Industrial Hygiene, Ethyl Corporation, to discuss the study findings as published in the Semi-Annual Progress Report, July 1981. Following the meeting the companies responded to the workers' requests to

release medical and employment records. Also, the company reviewed our industrial hygienist's evaluation of the work environment. Trade secret information was eliminated from this report at the company's request.

b. Comparison Group

An external comparison (control) group allows information about the general population to be obtained. A control group also helps to eliminate bias in the field work and analysis of blood samples in the laboratory.

The study's control group was comprised of two subgroups. The first subgroup included male control subjects who participated in the 1978 study, matched by age (± 5 years) with the plant workers. These subjects were randomly selected from the 1978 controls and invited by letter to participate. Appointments were arranged by phone and confirmed by a follow-up letter. Because of the small number of women employees at Saytech, no female controls were asked to participate.

A second subgroup of neighborhood controls was supposed to be randomly selected from a telephone directory. Each exposed worker was matched with three people from the same neighborhood, and a letter was sent to these people describing the objectives of the study. Telephone interviews were used to select male controls in the same age range and who had not worked with PBB, PBBO, or bromine.

Problems arose in assembling this second subgroup. Too much time was spent on contacting these people. Also, the lists from the telephone directory included many widows, along with elderly people who did not fit the age criteria for the study. Therefore, each exposed worker and each control subject who consented to participate in the study was asked to recommend a male friend from his neighborhood. The coordinator verified that these friends met the study requirements and then scheduled appointments.

3.2 Interviewing and Examination Procedures

a. General Procedures

Interviews and examinations were conducted from March 9 through March 11, 1981 at Our Lady of Victories Parish Center, Sayreville, New Jersey. This site was selected because it was near the plant and familiar to the community. The physical layout provided ample, well-defined spaces for conducting tests and interviews.

The multi-color pre-coded forms used in the field work (see Semi-Annual Report, July, 1981) included the following: control sheet,

demographic questionnaire, medical history questionnaire, physical examination, labels for blood tests, interviewer's instructions, and two manila folders. Exhibit 3.2 shows the coding instructions for computerized data analysis of the information collected.

All procedures in the field work were designed to maximize objectivity and assure unbiased interviews and examination. Each subject checked into the reception area where he was greeted by an interviewer who verified that his consent form was complete and then "logged him in" on a roster sheet. Next, each subject was assigned a sequential identification (ID) number starting with 301. (The 1978 numbers started with 001.) Each subject was handed a manila folder which included all prenumbered forms required for the field work. Stapled to the folder was a control sheet on which the interviewer noted the subject's name, address, and other identification and demographic data. At this time the interviewer also gave each subject a general description of the procedures to be followed.

The subject carried his folder throughout the day and removed various forms at the appropriate stations. At the termination of each interview, the completed interview and examination forms were checked and placed in the second folder which was kept by the quality-control team.

After checking in at the reception station, the subjects went to stations on a random basis. Random movement was necessary to minimize waiting time, since the administration of the demographic and medical history questionnaires required different amounts of time. After each examination or interview, the responsible staff person noted the subject's time in and out on the control sheet, and removed the appropriate forms from the subject's folder. All completed forms were taken by staff persons to the quality-control station where the forms were reviewed for completeness and assembled in the empty folders.

Before leaving the test site, subjects were checked for a second time to make sure they had completed all tests and interviews. Each subject then signed a statement verifying that he was satisfied with the testing procedures that had been used.

The interviews moved smoothly. No subject had to spend more than ten minutes waiting during the entire interview process which lasted approximately two and a half hours.

b. Demographic Questionnaire

The demographic questionnaire included six distinct areas: residential history (place and year of birth; current address and all residences since 1970); lifetime employment history (place of work, type of work; an open ended question concerning exposure; duration, type, level, and frequency of exposure); (Information from subjects who participated in the 1978 study was updated.); exposure in work

and leisure activities to specific agents (including chemicals known to affect the thyroid or the gonads, or known teratogens); work habits; smoking and drinking habits.

The questionnaires were developed to obtain the maximum information within the time available. Wherever possible, questions included in the 1978 study were repeated. Certain key questions were asked in several different portions of the interview, to be sure that subjects' answers were reliable. For example, in the lifetime occupational history, questions on exposure to chemicals, fumes, and dust were first asked in an open-ended format ("Did you have in this job any contact with chemicals, fumes, or dust?"). Later, the same questions were asked in a closed format ("Have you ever worked on your job or hobby with ---?").

Both the interviewer and the subject had a list of chemicals that included a description of the possible sources of exposure for each chemical. In addition, an industrial hygienist was contracted to obtain from the workers a detailed description of the manufacturing process of PBB and PBBO. Based on this information, a grading procedure for determining the level of exposure to PBB and PBBO in each job classification was later developed.

c. Medical History Questionnaire

The following were the seven major parts of the questionnaire:

1. Name/address of personal physician.

2. History of hospitalizations, including admission date, length of stay, name and address of hospital, major medical problem and current status of problem.

3. History of physician-diagnosed medical conditions by system, including date of original diagnosis, attending physician, status of condition, and prescribed medication(s).

4. Symptom review by system over last ten years, including dates of occurrence, contact with physician, and current status.

5. Selected lifetime medical conditions.

6. Use of medication(s) within the last year by drug type, including specific drugs, dates of use, and prescribing physician.

7. Family history, pregnancies, and reproductive history of each spouse.

A special emphasis was given to questions on thyroid symptoms, thyroid disease in the family, and other diseases that may affect the thyroid or lead to fertility dysfunction, such as mumps, TB, feucillosis, and leprosy (Isselbacher, K. J. et al., 1980).

All parts of the questionnaire except the fertility history were prepared in a pre-coded form. Internal checks were made on the reliability of drug-use information by asking the subjects to specify, in interviews and in a separate section of the questionnaire, which medications they used for specific medical conditions.

d. Physical Examination

This examination included:

1. Measurements - height, weight, pulse, blood pressure, and bicep skin fold (using a fat caliper).

2. General appearance (subjective) - normal weight, obese, or underweight; sclera - normal or icteric.

3. Thyroid examination.

4. Auscultation of lungs.

5. Testicles - size, descendency, varicocele presence, and nodules.

In order to study properly thyroid and reproductive functions, special attention had to be given to the thyroid gland and the testicles. The lung examination was conducted because it is familiar and comforting to most lay people, and because lung effects are associated with exposure to various chemicals.

Although no particular liver dysfunction related to PBB exposure was identified in the 1978 study, animal studies (EPA 1977) and the Michigan study strongly suggested that the liver should be examined for adverse effects. If no liver problems were found in the present study, chances of producing false negatives, i.e., telling workers they are in good health when in fact they have liver damage caused by PBB exposure, would be reduced.

The anthropometric measurements were taken by a licensed practical nurse. The physical examination was performed by a general practitioner and licensed endocrinologist.

e. Laboratory Tests

Thirty-five cubic centimeters of blood were drawn from each subject and placed in three red top vaccutainers for the following analyses:

Thyroid function - thyroxin (T_4), resin uptake ratio (RT3), and thyroid stimulating hormone (TSH)

Reproductive function - follicle stimulating hormone (FSH)

PBB exposure - gas chromatography with an electron capture detector at 290 degrees centigrade

Each red top tube was marked by a label indicating the test and the study ID. RT3 analysis was done at Bioscience Laboratories, Philadelphia, PA; T_4, TSH and FSH at the University of Pennsylvania Pepper Laboratory. Abnormal results were rechecked and all remaining sera were frozen and stored at Pepper Laboratory for possible future analysis.

Serum PBB analysis was performed at National Medical Services, Inc., Willow Grove, PA. The polybrominated biphenyls included were: dibromobiphenyl, tribromobiphenyl, tetrabromobiphenyl, pentabromobiphenyl, hexabromobiphenyl, heptabromobiphenyl, octabromobiphenyl and nonabromobiphenyl. Positional isomers were treated as a single substance in the analysis (no separation of 2, 2', 4, 4' -tetrabromobiphenyl and 3, 3', 4, 4' -tetrabromobiphenyl, etc.).

The analysis was by gas chromatography with an electron capture detector. Some samples were re-tested to confirm the reproducibility of the findings.

The limit of identification varied with the PBB in question. In general, the reporting limit for dibromo-through heptabromobiphenyl was 5 parts per billion (ng/ml). The higher molecular weight PBB's, with 8 and 9 bromines per molecule, had a reporting limit of 3 ng/ml.

Because PBB is lipotropic, the best indicator of PBB exposure is the level of PBB in adipose tissue. However, obtaining a fat specimen would have required making an incision in a fatty area on the subject's body. Under field conditions, the procedure would be difficult as well as costly; many exposed workers would resist submitting to incisions; and the procedure would be unwarranted for non-exposed workers.

As described in Section 4.3, no subject in the study showed any detectable serum level of PBB. However, since there is a decay of 39 percent of serum PBB in six months (EPA, 1977), few cases who had high serum levels of PBB in 1978 were expected to have detectable serum levels in 1981.

Although fat analysis had not been performed previously on this population, samples of fat tissue were taken from two PBB employees who had exhibited the first and third highest PBB levels in 1978. Simultaneous analyses were done at the National Medical Services, Inc. and at the Laboratory Analysis Section, Division of Environmental Epidemiology, Department of Public Health, State of Michigan. The two laboratories coordinated the procedures to assure compatability of the results.

3.3 Protection of Subjects' Rights

The principles of informed consent and confidentiality, and the subject's access to his examination results were strictly followed.

To reassure the plant employees who wanted to participate in the study, special consideration was given to employment protection. The informed consent letter stated, "We remind you that under Section 11 (c) of the Occupational Safety and Health Act (29 U.S. Code 660(c)) your employer is prohibited by law from any discrimination against you because of your participation in this study." Also, workers were asked to consent to the release of dates of plant employment and the discussion of their personal medical findings with the company's representatives.

3.4 Selection and Training of Interviewers

The team of interviewers consisted of professional interviewers and graduate students in epidemiology and medicine. Prior to the field study, the students had a one-day training session in interviewing techniques and in administering the study questionnaire.

3.5 Procedures for Avoiding Bias

To minimize possible bias, the study was conducted with concurrent controls, chosen from the same local area so that they could participate in the same manner as the plant workers. Appointments were scheduled in a generally random order. Medical and demographic interviews were conducted by different individuals. Workers were informed verbally not to divulge their occupations or whether they participated in the 1978 study, except in the demographic interview. Also, physician and medical history interviewers were instructed not to inquire about these subjects. All blood specimens were identified and analyzed in the same manner.

3.6 Procedure to Increase Participation

To maximize participation, the investigators stressed that the subjects would learn about their own health and be part of a significant research effort. Results from our tests could be sent either to the subject or to his physician, at the subject's request.

Appointments were scheduled from early morning through evening hours. Invasive or uncomfortable procedures such as fat biopsies were eliminated from the study.

3.7 Data Processing

A coding manual (Exhibit 3.2) was designed for transcribing all study data for computer analysis. To avoid bias, the coding was done without reference to employment status. Prior to any statistical analyses, data were cleaned of punching and transcription errors.

4. RESULTS

4.1 The Industrial Environment

a. General

Reconstruction of the work environment is based on the information obtained during the field work from interviews with long term plant employees, on the review of compliance inspections made by the Occupational Safety and Health Administration (OSHA) in 1977 and 1978, and by the company's industrial hygienist in 1980. Trade secret information pertaining to the description of manufacturing processes and operation has been eliminated from this report.

About two million pounds of decabromobiphenyl was manufactured during the period from January 1, 1973 through March 31, 1977. During that time, 95 percent of plant production consisted of decabromobiphenyl, for export only, and decabromobiphenyl oxide (18 percent and 77 percent respectively). From April 1, 1978 to March 1, 1981, about 60 percent of the plant production was decabromobiphenyl oxide, and 40 percent was other brominated fire retardant compounds. Decabromobiphenyl production stopped in April 1978.

The plant is a two-story building, approximately 50' by 75' and 30' high. A portion of open mesh steel flooring between the floors allows ventilation and access for servicing machinery, but also permits the unobstructed flow of chemical contaminants.

There are four distinct manufacturing areas, i.e., the reactor, distillation, centrifuge, and mill areas.

The initial chemical reaction begins when the reactors are loaded with raw materials. (The reactors can handle several different products.) Powders are loaded manually while liquids or gases are loaded automatically. Periodic line transfers of bromine and the manual addition of a catalyst represent the only dusty operation occurring in the reactor area.

Distillation (stainless) involves a sealed system which recovers solvent from the reactors. Several open ports allow workers to make spot checks of the process. Ethylene dichloride is frequently used to purge the lines when necessary.

In the centrifuge area moisture is removed from the product. During the half-hour centrifuge process, the operator checks gauges, drains the holding tank, and checks the drying temperatures. The operator then cuts the dried cake so that it can enter the dryers.

After completing the drying process, the end product is milled to a certain particle size and packed. The dry product is gravity fed to one of two micropulverizing units. There, it is pneumatically conveyed to a hopper which ultimately empties into a 55 gallon cardboard drum lined with a polyethylene bag. The hopper is tapped occasionally to

release the product clinging to the sides. The drum is on a scale which weighs its contents. Occasionally, the drum must be tapped to settle the product. In 1977 these processes created a significant amount of product dust. Also contributing to dusty conditions at that time was the nightly dismantlement and cleaning of the mill. In 1977 no local exhaust ventilation nor general ventilation was intended for control of this problem; also, collected deposits of dust were found on the rafters. The mill operators wore a 3M non-toxic dust mask.

There are two other operations in the plant: cleaning the Neutch and general maintenance. The Neutch is an open 2000-gallon vat with a fabric filter at the bottom. It is used to separate experimental reaction products from the solvents. The cleaning of the Neutch after use takes four hours. Ethylenedichloride, a solvent, is used for rinsing the vat.

Maintenance workers are responsible for repairing line breaks of malfunctioning units throughout the plant.

b. Industrial Hygienist Evaluations

On the basis of a referral from the Environmental Protection Agency (EPA) concerning decabromobiphenyl contamination of the environment surrounding the plant, an industrial hygiene survey was conducted by the Occupational Safety and Health Administration (OSHA) in July and August of 1977, followed by another observation in April, 1978.

The OSHA investigation was concerned with decabromobiphenyl (PBB). Though the company no longer produced this product, checks for past contamination were made. A full-scale industrial hygiene investigation of the plant and persons involved in the manufacturing process was made. This was conducted in order to disclose any violation of current standards. Special attention was paid to employee symptoms of exposure, even though decabromobiphenyl was no longer manufactured.

Table 4.1 summarizes the results of measured contaminant levels of decabromobiphenyl and decabromobiphenyl oxide in the manufacturing area by sample and type. Plant air samples (personnel samplers) showed values of 0.18 and 0.23 mg/m^3 8 hour TWA of decabromobiphenyl. Wipe tests indicated decabromobiphenyl levels up to 8 mg/100 sq. cm. and 0.1 mg/100 sq. cm. on an eating table.

OSHA's inspection of the plant (June 28, 1977 - August 5, 1977) cited violations whch were alleged to have occurred on or about the day the inspection was made unless otherwise indicated in the citations:

Serious violations (October 3, 1977, OSHA Number Y4648 123)

29 CFR 1910.1000(a)(1): Employee(s) were exposed to material(s) in excess of the ceiling value(s) listed for the particular material(s) in table Z-1 of subpart Z of 29 CFR part 1910:

Table 4.1 Contaminants Measured in Decabromobiphenyl and Decabromobiphenyl Oxide Manufacturing Area by Sample and Type (7/14/77, 8/5/77, 4/21/78)

Chemical Name \ Sample Location	Reactor	Centrifuge	Stainless	Mill	Neutch
Ethylene Dichloride (EDC)	1-A <5ppm 1-P ND	1-P 20ppm 2-P 20ppm	1-P <5ppm -	- -	1-P 112ppm* 1-P 288ppm*
Hydrogen Chloride(HCL)	1-S 2ppm+ 3-S 3ppm+	1-S ND 3-S ND	- -	- -	1-P 30mg/m^3* 1-S >40mg/m^3*
Halides ($ASCl_2$)	1-S 0.025ppm	1-S ND 3-S ND	- -	- -	- -
Hydrogen Bromide (HBr)	1-A 0.06ppm	-	-	-	-
Decabromobiphenyl (DBB)	1-W 3.4mg/m^3*	-	1-W 11mg/m^3*	-	-
Decabromobiphenyl Oxide (DBBO)	1-W 3.6mg/m^3*	-	1-W 5.9mg/m^3*	1-P 0.08 2-P 0.21	- -

Date of Sample	Type of Sample	+Mean Concentration
1 - July 14, 1977	A Area	*OSHA Violation
2 - August 5, 1977	P Personal	ND Not Detectable
3 - April 21, 1978	S Spot	- Not Available
	W Wipe	

Source: Occupational Safety and Health Administration - Industrial Hygiene Inspection Worksheets.

Hydrogen chloride exposure to employee engaged in cleaning out the Neutch in the chemical production area.

29 CFR 1910.1000(b)(2): Employee(s) were exposed to material(s) in excess of the acceptable ceiling concentration limit(s) and for a duration exceeding the maximum time period listed for the particular material(s) in table Z-2 of subpart Z of 29 CFR 1910:

Ethylene dichloride exposure to employee engaged in cleaning out the Neutch in the chemical production area.

29 CFR 1910.1000(e): Feasible administrative or engineering controls were not determined and implemented to reduce employee exposure(s):

Neutch cleaning operation in the chemical production area.

Other violations (October 3, 1977, OSHA Number Y4648 123)

29 CFR 1910.132(a): Protective equipment was not used where it was necessary by reason of hazards encountered in a manner capable of causing injury or impairment in the function of any part of the body:

In the chemical production area the employees cleaning out the Neutch were not supplied with protective suits to cover their extremities and prevent skin irritation from HCl mist.

29 CFR 1910.132(a): Protective equipment was not maintained in a sanitary and reliable condition:

In the centrifuge room on the south wall, the eyewash fountain was inoperative.

Other violations (February 22, 1978, OSHA Number Y4648 123)

29 CFR 1910.22(a)(1): Places of employment were not kept clean and in a sanitary condition to guard against disease (toxic material) in that there was evidence of polybrominated biphenyl and polybrominated biphenyl oxide contamination in the following areas:

a) tables in the laboratory
b) cafeteria table
c) tops of lockers in the locker room and the boiler room
d) rafters in the mill room and dryer area
e) desks in the still area, reactor area, and warehouse
f) urinals in the men's room

No violation was observed in OSHA's inspection on April 4, 1978 and there has been no further inspection for PBBs by OSHA.

It should be noted that in 1977 OSHA was not able to gather sufficient data to establish an airborne standard in the plant. However, during our 1981 study, workers reported that conditions have improved since the major clean-up of the plant in the fall of 1978. There are occasional spills of chlorine, bromine, and other raw chemicals in the plant. At such times, respirators are worn by all employees. Records of spills are available only for the period May 1, 1978 to February 1982. Hexcel, Inc. failed to provide the investigators with any information pertaining to the preceding period.*

Following a spill of ethylenedichloride on November 7, 1980, Ethyl Corporation conducted an industrial hygienist evaluation. Ethylenedichloride was at a level of 380 ppm at the spill area of the vibrating hopper.** The personnel and area measurement obtained during that evaluation and the results of the follow-up examination under normal conditions are given in Table 4.2.

c. Exposure by Job Classification

Following the field study, the investigators compiled a list of 32 raw materials and 7 end-products ever present at the plant during the period from 1973 to 1981. Yet, objective assessment of individual exposure to each one of the chemicals by job classification is not available. In the absence of a complete industrial hygiene evaluation only subjective assessment can be made.

At our request, the manager of technical compliance of the company and several long term employees have graded exposure on a scale of zero (no exposure) to five (high exposure) for each chemical and job classification.

Using that information together with the industrial hygiene evaluation, one may conclude that the mill and the centrifuge operators have the highest exposure to the end-products (rated 4 and 5), followed by the maintenance workers and manufacturing supervisors (rated 2-3). All other jobs involve lower exposure (rated 2) to the end-products. Reactor operators, still operators, maintenance supervisors, and janitors all have moderate to high levels of exposures (rated 3 and 4) to the raw chemicals. All other plant workers, i.e., centrifuge operators, warehouse and lab workers, have a relatively low exposure (rated 1 and 2) to raw chemicals.

** The Federal standard is 50 ppm (200mg/m^3) as an 8 hour TWA with an acceptable ceiling concentration of 100 ppm. Acceptable maximum peaks above the ceiling of 200 ppm are allowed for 5 minutes duration in any 3 hour period (Key et al, 1977.)

* On 3/30/82, the following statement was received from Hexcel Inc, investigator's office:

"Although we have no official documentation relating to spills at that plant in our possession, from speaking to various people who are involved in the operations, it is my understanding that there was a reported leakage of bromine around 1976 and a leakage of hydrochloric acid fumes around 1978. In addition, in about 1979, Essex Chemical Company which operates a plant next to the previous Hexcel facility had a spill of dioctylpthalate which flowed onto the plant property then owned by Hexcel. Any leakages of a minor nature, i.e., leaking pipe, etc., were considered a day-to-day operational matter and would have been recorded in the operation logs of the facility and not in any personnel files. Consequently, we are unable to supply you with any information regarding leaks of this nature. Such operational information, I understand, is retained at the facility for a very limited period of time."

Table 4.2 Results of Monitoring Exposure to Process Solvents and Raw Materials (ppm)

	DBBO	EDC		CH		BCE		EDB		VCH		TBA	
	S	S	N	S	N	S	N	S	N	S	N	S	N
Reactor Operator	-	4.6	22.0	6.0	9.4	0.9	0.6	0.43	ND	0.48	ND	-	3.8
Reactor Area	-	3.2	8.5	3.8	9.4	0.5	0.3	2.0	0.07	0.54	1.86	-	1.8
Centrifuge Operator	-	36.0	22.0	14.0	13.0	6.6	1.3	0.14	ND	2.06	0.1	-	5.5
Centrifuge Area	-	150.0	9.2	ND	ND	19.0	1.1	1.8	0.14	0.72	4.9	-	-
Stainless Operator	-	10.0	10.0	8.7	12.0	2.0	0.6	0.2	ND	2.61	0.2	-	6.0
Stainless Area	-	11.0	5.6	5.2	17.7	1.5	0.6	0.53	0.08	1.9	6.3	-	-
Mill Operator	1.3												
Mill Area	1.9												
Maintenance		120.0	-	3.3	-	17.0	-	1.8	-	1.8	-	-	-
Extra Operator	-	80.0	-	5.9	-	15.0	-	1.3	-	1.8	-	-	-
ND - Not Detectable	-	<0.03		<0.06		<0.04		<0.01		<0.02		<0.1	
OSHA-PEL Exposure Guideline		50		300		-		20		-		100	
OSHA-PEL/Ceiling	-					1.0/5.0							

DBBO = Decabromobiphenyl oxide
EDC = Ethylene dichloride
CH = Cyclohexane
BCE = 1-Bromo-2-chloro-ethane
EDB = Ethylene dibromide
VCH = Vinyl cyclohexene
TBA = tert-Butyl alcohol

S - Monitoring following a spill on November 7, 1980 (highest result)
N - Monitoring under normal conditions on November 7, 1980 and on February 25, 1981 (highest result)
- Not Available
ND- Not Detectable
* - Exceeds OSHA-PEL Guideline

Source: Ethyl Corp. Industrial hygiene report

-40-

The mill area is the dustiest in the building. As much as 3/8" of dust usually covers the floor, surfaces, and equipment. General ventilation provides the only air supply. Before 1977, some bagging, a procedure which generates more dust than drum filling, was done in this area; the bagging procedure may have contributed to the considerable particulate pollution noted in the area. One employee on each shift monitors the drum filling. In addition, one or two mechanics tear down the mill for its nightly cleaning. As of July 25, 1977, there was no local exhaust ventilation or general ventilation intended for control of the dust and in August, 1977, OSHA reported dust levels of 0.23 mg/m^3 in the mill area. In March 1981, workers reported that conditions had improved since the major plant cleanup in the Fall of 1978. Presumably, there is now less employee exposure to dust in the mill area of the plant.

In general, the centrifuge and the distillation areas have not been described as particularly dusty. Although OSHA noted the odor of HCl, halides, and EDC, in the centrifuge area, their investigations of July 14, 1977 and August 5, 1978 did not reveal any significant levels of these chemicals. The senior operator in the distillation area is responsible for rectifying any problems during this phase of the recovery process. Therefore, he is more likely to be exposed to hazardous substances in this area than any other workers.

Toxic exposure also occurs during periodic cleaning of the reactors. On those occasions workers reported "strong sensations," "dizzy spells," and that they "had to leave area from time to time." It is suggested that leaks from the reactors, associated vessels, and pipelines may have exposed employees to short and acute concentrations of vapors and gases.

Employees may also have been exposed to occasional accidental spills of solvents during cleaning of the neutch, a sporadic operation. Although it has been reported that the operator wears a NIOSH-approved respirator, some employees involved in this operation have complained about "bad fumes" in the area. One employee who has cleaned the neutch also reported a rash from exposure to the chemical in the cake.

The maintenance workers have the most diversified function in the plant and the highest risk of experiencing industrial contaminant exposures. These workers have reported that line breaks or malfunctions occur on the average of twice a month. The building is always evacuated if bromine or chlorine is accidentally released during the line repairs. Maintenance workers neutralize the outage and a self-contained breathing apparatus is worn by anyone in the building.

Maintenance men are also responsible for the periodic changing of full bags on the four dust collectors located in the centrifuge area. This procedure involves a high level of chemical-dust exposure. It should be noted that the worker wears a paper suit and dust mask, yet the protective gear may not afford him complete protection.

All plant chemical operators are trained to do all of the tasks in the plant. A new employee is first admitted at "Labor Grade D," working in packaging and in the mill room for an average period of five months. During the next six months, he is generally trained as a stainless operator and as a centrifuge operator (Laborer Grade C and B). Finally, the workers learn to operate the reactor (Labor Grade A). Depending on the work schedule and the production needs, all plant employees perform any duty in the plant. Consequently, all plant employees have been exposed for at least five months to high levels of end products in the mill room and to moderate to high levels of raw chemicals. Exposure levels vary daily, depending on the employee's duties in the plant on a given day.

4.2 Demographic Characteristics of the Study Population

One hundred and nine male subjects participated in the field study from March 8-11, 1981. There were 42 exposed workers and 67 controls. In addition, 22 exposed workers (16 former employees and 6 current employees) and 34 controls also participated in the 1978 study. This sample represents 44 per cent of the 100 men (45 former employees and 55 current employees) who ever worked at the plant studied.

Only 33 men have worked at the plant for at least three years. A total of 18 employees (55 per cent) participated in the present study.

Figure 4.1 describes the period of employment of the exposed group. Each line in the figure represents the period of one worker's employment. Twenty-two subjects started working at the plant during the time PBB was being manufactured. The average period of employment was 3.9 years (Range: 4 months to 8.08 years)

Twenty people started working at the plant after April, 1977, when the company began to produce PBBOs. The average period of employment for these employees was 1.7 years. (Range: 2 months to 3.6 years)

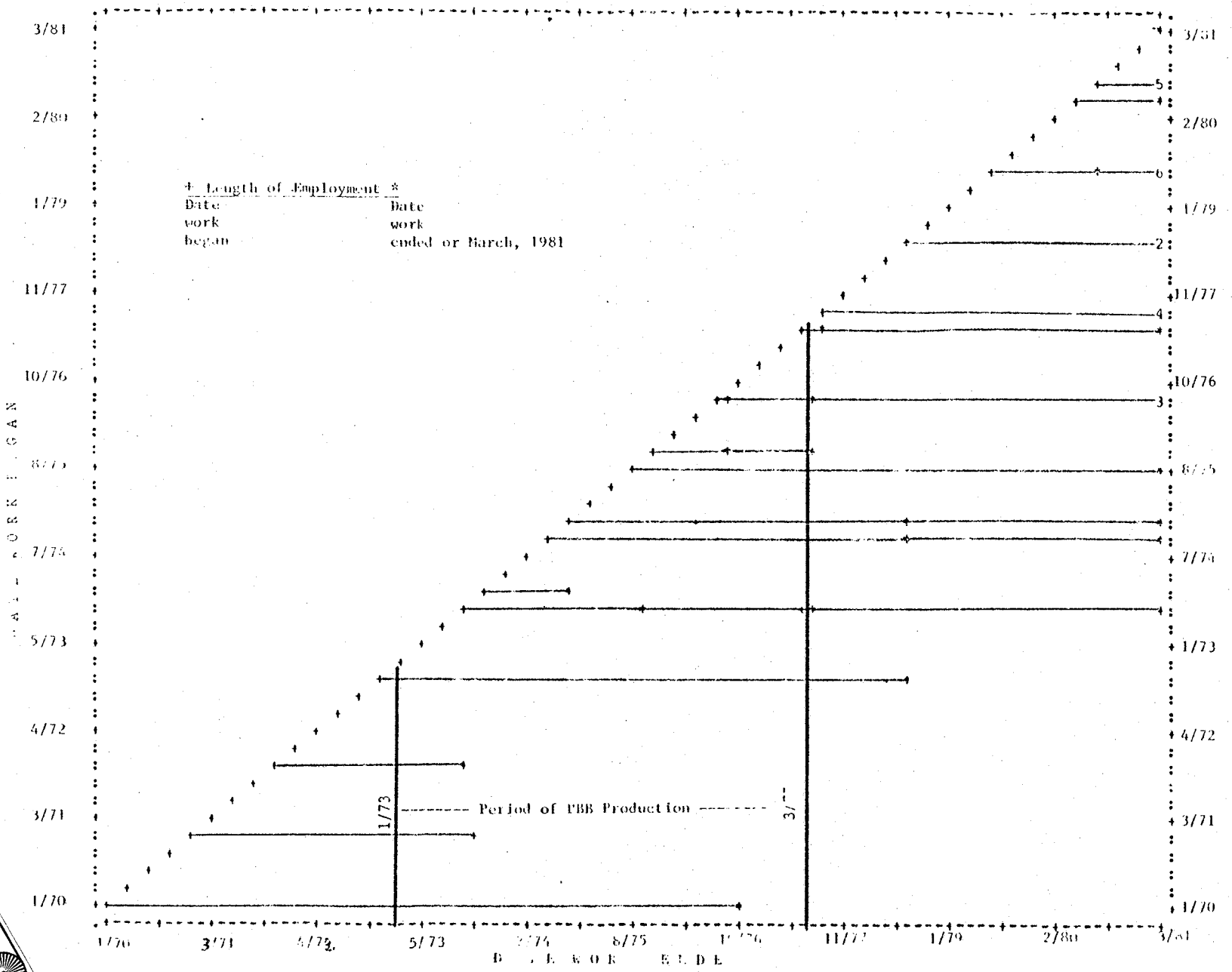
The mean age of the workers was 34.7 years (S.D. 11.0). The youngest worker was 22 years old, and the oldest was 60. In the control group, the mean age was 42.7 years (S.D. 9.8). The youngest control subject was 26 years old, and the oldest was 60.

Those employees who started working after April, 1977 are somewhat younger than the PBB workers who started working in March, 1977 or earlier (mean ages of 33.8 and 37.4 respectively). Most of the subjects were Caucasians. Two blacks and one Hispanic were among the exposed workers. One Hispanic was a control subject.

The average amount of schooling of the exposed workers is similar to that of the controls, 12.6 (S.D. 2.16) and 13.4 (S.D. 2.7) years respectively.

Considering the small sample size of the exposed group, any positive findings of rare abnormalities confirm the hypothesis of thyroid dysfunction related to PBB exposure.

FIGURE 4.1: PERIODS OF EMPLOYMENT OF 42 PBB AND PCB WORKERS



-43-

Because the PBBO workers have been exposed to the chemicals for a short period of time, and since the time span since their last exposure is small, it may be difficult to find evidence of health problems related to industrial exposure to PBBO. Also, in view of the relatively young age of the exposed group, any adverse health effects observed in this group are prominent.

4.3 MEDICAL AND LABORATORY RESULTS

a. Serum and Fat PBBs Levels

PBBs exposure was measured in the blood of all 109 study subjects and analyzed by gas chromatography with an electron capture detector at 290° C. The test was done by National Medical Services, Inc. (See Section 3.2 e)

No subject in the study showed any detectable serum level of PBBs. However, since it is assumed that 39% of serum PBBs decays in six months (EPA, 1977), it was expected that few cases who have had high levels of serum PBBs in the previous study of 1978 would have detectable serum levels of PBBs in 1981. For example, the person who had 1340 ng/ml in August 1978 should have had about 113 ng/ml in March 1981. (See Table 4.3.) In order to evaluate the quality of the serum analysis and the hypotheses concerning the decay rate of PBBs in human serum, samples of fat were taken from two workers who had the highest and the third highest level of serum PBBs in 1978 (Case a: a total of 1340 ng/ml: 40 ng/ml hepta-; 800 ng/ml Octa-; 500 ng/ml nona-; and not detectable level of Deca-; Case b had a total of 132.3 ng/ml PBBs: 12 ng/ml hepta-; 120 ng/ml Octa-; not detectable levels of mona- and deca- and 0.3 ng/ml of C_{12} H9 Br.)

The fat samples were analyzed by the State of Michigan Department of Public Health and by National Medical Services, Inc. The two laboratories were aware of the 1978 study results for the entire group, yet the fat samples were identified by an identification number only.

The Michigan Department of Public Health inserted our two samples in a batch of other human adipose samples and a bovine fat control (Michigan PBBs). As previous samples from these participants contained hepta-, octa- and nona-bromobiphenyls, the laboratory looked for these congeners and decabrom-obiphenyl. Composition of the reference standards is based on a publication on the analysis of polybrominated biphenyls by J.J. de Kok et al (Journal of Chromatography 142 (1977) 367-383). On this basis, the following results were obtained: Case a: 2619 ng/g deca-; not determined level of Octa. and 46.4% Lipid. Case b had 640 ng/g Deca-; 530 ng/g Octa- and 76.3% Lipid.

National Medical Services, Inc. performed the PBBs fat analysis optimizing the laboratory conditions for heptabromobiphenyl ($C_{12}H_3Br_7$), octabromobiphenyl ($C_{12}H_2Br_8$) and nonabromobiphenyl ($C_{12}HB_9$). Tetra-, penta-, and hexabromo-biphenyls were included in the scope of the test semi-quantitatively. Based on the available standard, no hepta-, octa- nor nona was observed.

There were substances observed by gas chromatography which are possibly PBBs, but did not present retention times matching available standards. Gas chromatography-mass spectrometry did not provide evidence for the presence of PBBs. A major component with a retention time of indistinguishable from 2, 2', 4, 4', 5, 5'-hexabromobiphenyl was noted in NMS No. 84313. The concentration is estimated to be 0.1 to 0.4 µg/gram.

Table 4.3
Total PBB's Serum Levels by Occupational Group

Results	PBB Workers		Electricians		Steel Workers		Others		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Not detectable	13	33.3	20	47.6	13	50.0	16	53.3	62	45.3
Not confirmed*	9	23.1	14	33.3	7	26.9	11	36.7	41	29.9
Trace**	3	7.7	3	7.1	2	7.7	0	0.0	8	5.8
Detectable level	14[1]	35.9	5[2]	11.9	4[3]	15.4	3[4]	10.0	26	19.0
Not available	0	-	0	-	0	-	1	-	1	-
Total	39	100.0	42	99.9	26	100.0	31	100.0	138	100.0

* Not confirmed = impossible to confirm any detectable level. For most practical purposes, equivalent to "not detectable".

** Trace = below measurable level

"-" Not included in the total

[1] Serum levels of PBB workers: .5, 2.4, 12.0, 15.0, 20.0, 20.5, 29.0, 40.4, 50.0, 58.0, 94.0, 132.3, 318.0, 1340.0 (ng/mL)

[2] Serum levels of electricians: .4, 1.9, 2.0, 4.0, 6.0 (ng/mL)

[3] Serum levels of steel workers: .3, 1.5, 2.2, 7.8 (ng/mL)

[4] Serum levels of others: 2.2, 5.5, 13.0 (ng/mL)

REMARK: A significantly higher number of PBB workers had a detectable level of PBBs as compared with other workers in the study (35.9 percent as compared to 12.2 percent, chi square = 8.67, $p<0.005$). Among workers with detectable PBB levels, the PBB workers had significantly higher serum levels ($p<0.001$) as compared to other workers ($Z = 3.61$, Mann-Whitney U test).

SOURCE: Bahn et al. October, 1980

-46-

The Michigan Department of Public Health observed that the ratio of PBBs (hexabromobiphenyl) levels in fat to that of serum is approximately 500. However, the ratio for higher molecular weight brominated biphenyls may be different as mobility of higher molecular weight species could vary inversely. (Harold A. Price, Chief Laboratory Analysis Section, Div. of Environmental Epidemiology, Personal Communication). Therefore, in spite of the disagreement between the two laboratories concerning PBBs fat levels, one may assume that no detectable level of PBBs should be found. However, those workers who were involved in the PBBs manufacturing may still have detectable fat levels of PBBs.

It should be noted that although the company manufactured primarily decabromobiphenyls, other forms of PBBs were found in the workers' sera in 1978 and in the fat in 1981. Further studies are needed to re-evaluate the PBBs serum and fat decay in the human body.

b. Thyroid Neoplasia

Four thyroid nodules were observed during the field study. Three nodules were seen among the exposed workers who have worked at the plant for at least three years. One nodule was palpated in a worker who was exposed to high levels of chlorine. Consequent to our examination the workers sought further medical evaluation.

Case 1*: A 43 year-old white male PBBs worker was operated on in June 1981 and diagnosed with thyroid carcinoma, mixed follicular-papillary, focal, chronic thyroiditis with focal calcification neurofibroma, subcutaneous.

The microscopic examination report indicated:

"Alteration of the general architecture by abundant proliferation of lymphoid tissue with formation of numerous lymphoid follicles occasionally containing germinal centers. In addition to the proliferation of lymphocytes, there is marked proliferation of fibrocollagenous tissue forming broad band of fibrosis which separates areas of thyroid follicles containing colloid, all of normal appearance. In one area, the thyroid lobe shows a round calcified nodule. This is composed of nests and islands of thyroid follicles within a mass of dense acellular collagen with areas of hyalinization and diffuse calcification. Some follicles still contain colloid, while others are lined by cells with nuclei showing a moderate degree of atypia. Very few also exhibit intraluminal papillary projections. Vascular invasion is not noted. Slide B shows a small portion of skin and subcutaneous tissue. The latter includes a nodule composed of interlacing bundles of Schwann cells."

This worker also had trigeminal neuralgia, and an operation was performed in July, 1980. He worked at the plant as a supervisor for about four years, starting in 1974.

Case 2*: A 50 year-old white male PBBs worker was diagnosed as having thyroid follicular adenoma. Microscopic examination showed a thyroid composed of even-sized follicles lined by a single row of cuboidal cells. A well encapsulated nodule which was composed of thyroid follicles which were irregular in size and ranged from follicles just budding to large lakes of colloid surrounded by a single layer of cuboidal cells, was found. An area of scarring and calcification was also noted.

Serum analysis of thyroid hormone was normal and follicle stimulating hormone (FSH) was slightly elevated (15.5 mIU/ml). This worker also had heart and kidney problems and soft testes. Case 2* has worked at the plant for seven years, starting in 1974.

Case 3*: A 53 year-old male PBBs worker had an 8mm thyroid nodule. Later examination by a radiologist found normal thyroid uptake and scan, with no focal defect observed.

Serum analysis of thyroid hormone levels indicated primary hypothyroidism (TSH = 31.4 μU/ml, TSH = 31.4 μU/ml, T_4 = 4.3 μg/dl, T_3 uptake ratio = 0.66 and FSH = 5.2 nIU/ml.) This worker also was hypothyroid in August 1978, yet refused any medical treatment.

Case 3* worked at the plant for 40 months, starting in 1977.

Case 4*: A 50 year-old male, working in the cigarette industry for 35 years and who in 1978 had a level of 33,000 ng/ml serum PCBs, had an 8mm thyroid nodule palpated by the study endocrinologist. A subsequent examination by a radiologist indicated a slightly enlarged gland on scan although no distinct areas of abnormal uptake were noted. No further medical evaluation was done following the examination by the radiologist.

Slight irregularities of the thyroid were found in a fifth case, a 41 year-old comparison worker. This person had a tonsillectomy in childhood, therefore should be removed from any further analysis.

Considering the small size of the study population of workers exposed for over three years to chemicals in the plant (18 workers in total), the relative rarity of the medical conditions noted in these workers and the animal studies reporting thyroid hyperplasia and other irregularities in a variety of animals, we conclude that thyroid hyperplasia may result from human exposure to PBBs.

c. Thyroid Hormones

Thyroid function was measured by thyroxin (T4), resin uptake ratio (RT3), and thyroid stimulating hormone (TSH). Description of the laboratory results is given in Figures 4.5-4.7. As can be seen, only a few exposed workers had borderline levels of T_4. One case had a low level (0.66) of RT3. One case had a high level (31.4 μU/ml) of TSH, while another case had a borderline level (8.2).

A significant Pearson correlation coefficient was found between TSH and length of employment of the plant workers ($r = 0.2277$, $n = 109$, $p < 0.009$). Also, TSH was correlated with T4 ($r = 0.2157$, $n = 109$, $p < 0.012$).

Among the 22 plant workers employed before March, 1977, (i.e. during the production period of PBBs), the coefficient of correlation between length of employment and TSH is 0.3188 ($p < 0.10$). A similar coefficient is observed among the 20 workers employed after March, 1977, (i.e. during the production period of PBBO), $r = 0.3200$ ($p < 0.10$).

FIGURE 4.4 THYROXINE T4 BY EXPOSURE GROUPS

MIDPOINTS	Workers Employed Before March 1977	Workers Employed From April 1977	CONTROL	CASES WITH UNUSED VALUES FOR GROUP1
10.400)				
10.000)				
9.600)*				
9.200)*			***	
8.800)**				
8.400)		***	***	
8.000)		**	****	
7.600)***		*	*********	
7.200)M****		*	**********	
6.800)****		M	M****	
6.400)*		******	**********	
6.000)*		**	*****	
5.600)**		*	****	
5.200)			******	
4.800)**		*	*	
4.400)		*	***	
4.000)		*	*	
3.600)			*	
3.200)				
2.800)				

GROUP MEANS ARE DENOTED BY M'S IF THEY COINCIDE WITH *'S, N'S OTHERWISE

MEAN	7.091	6.630	6.699
STD.DEV.	1.282	1.299	1.244
S. E. M.	0.273	0.291	0.152
MAXIMUM	9.500	8.500	9.400
MINIMUM	4.700	4.200	3.800
SAMPLE SIZE	22	20	67

ALL GROUPS COMBINED (EXCEPT CASES WITH UNUSED VALUES FOR GROUP1)

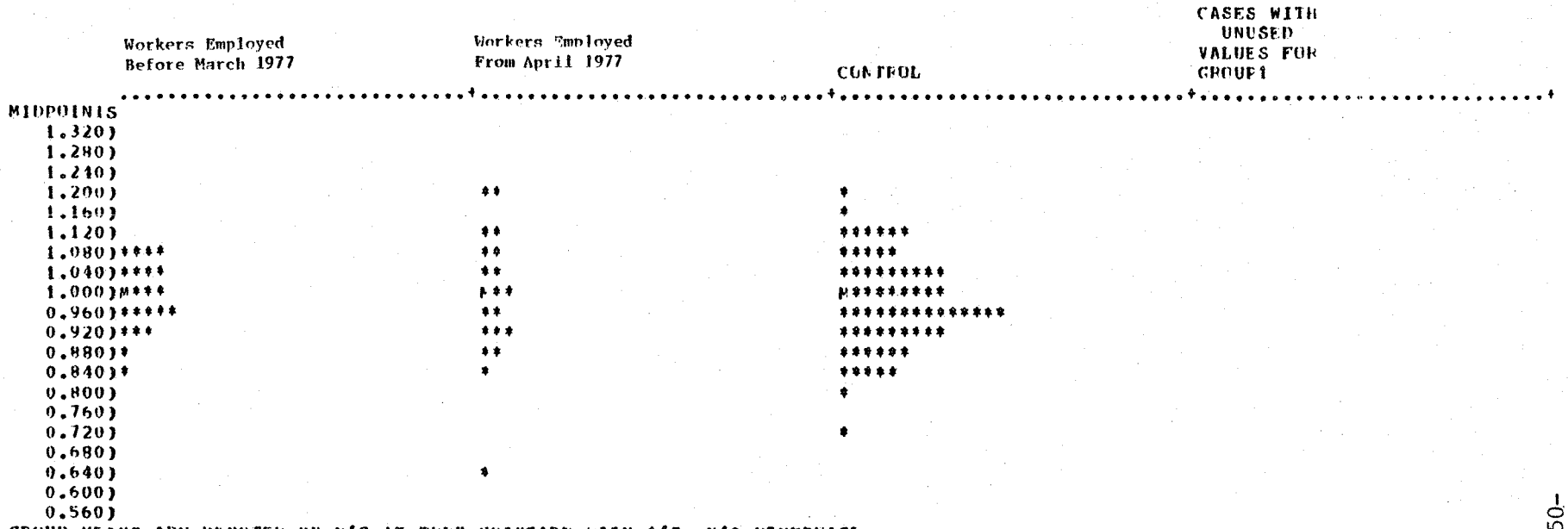
MEAN	6.765
STD.DEV.	1.261
S. E. M.	0.121
MAXIMUM	9.500
MINIMUM	3.800
SAMPLE SIZE	109

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	DF	MEAN SQUARE	F VALUE	TAIL PROBABILITY
BETWEEN GROUPS	2.9975	2	1.4987	0.94	0.3934
WITHIN GROUPS	168.7900	106	1.5924		
TOTAL	171.7875	108			
LEVENE'S TEST FOR EQUAL VARIANCES		2, 106		0.02	0.9787
ONE-WAY ANALYSIS OF VARIANCE					
TEST STATISTICS FOR WITHIN-GROUP VARIANCES NOT ASSUMED TO BE EQUAL					
WELCH		2, 39		0.90	0.4155
BROWN-FORSYTHE		2, 58		0.91	0.4075

-49-

FIGURE 4.5 RESIN UPTAKE RATIO (RT3) BY EXPOSURE GROUPS



GROUP MEANS ARE DENOTED BY M'S IF THEY COINCIDE WITH *'S, N'S OTHERWISE

MEAN	0.993	0.997	0.983
STD.DEV.	0.065	0.130	0.092
S. E. M.	0.014	0.029	0.011
MAXIMUM	1.090	1.200	1.220
MINIMUM	0.840	0.660	0.720
SAMPLE SIZE	22	20	67

ALL GROUPS COMBINED (EXCEPT CASES WITH UNUSED VALUES FOR GROUP1)

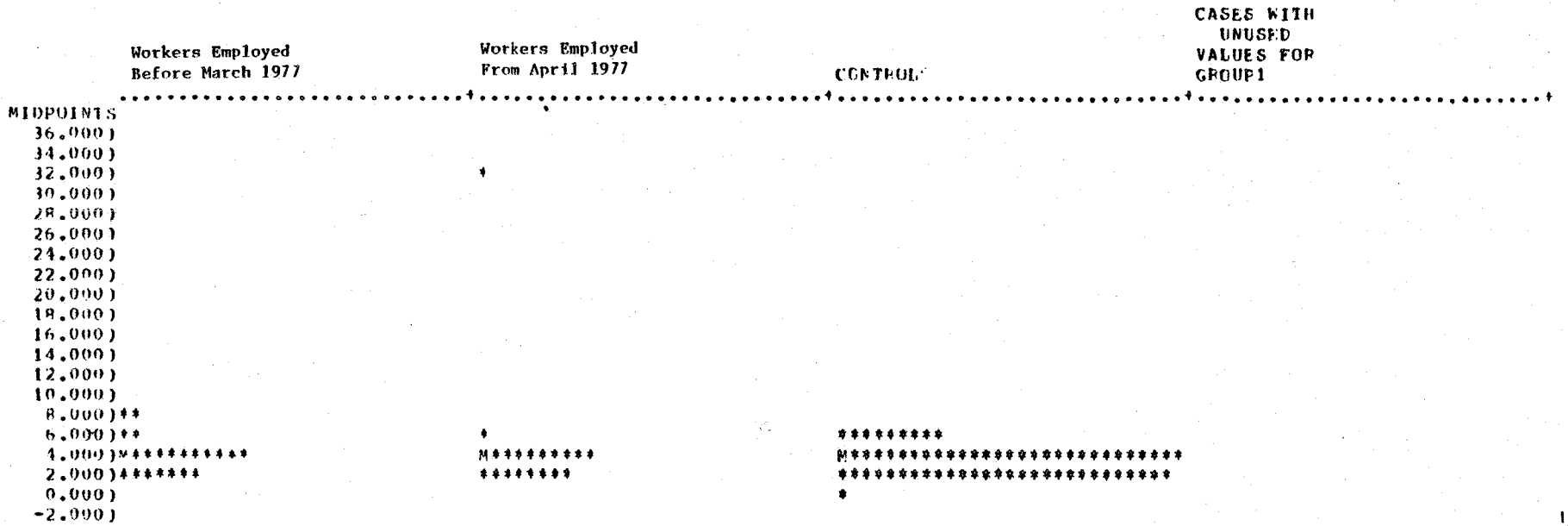
MEAN	0.987
STD.DEV.	0.095
S. E. M.	0.009
MAXIMUM	1.220
MINIMUM	0.660
SAMPLE SIZE	109

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	DF	MEAN SQUARE	F VALUE	TAIL PROBABILITY
BETWEEN GROUPS	0.0039	2	0.0019	0.21	0.8096
WITHIN GROUPS	0.9714	106	0.0092		
TOTAL	0.9753	108			
LEVENE'S TEST FOR EQUAL VARIANCES		2, 106		3.53	0.0328
ONE-WAY ANALYSIS OF VARIANCE TEST STATISTICS FOR WITHIN-GROUP VARIANCES NOT ASSUMED TO BE EQUAL					
WELCH		2, 40		0.22	0.8038
BROWN-FORSYTHE		2, 39		0.19	0.8272

-50-

FIGURE 4.6 THYROID STIMULATING HORMONE (TSH) BY EXPOSURE GROUPS



MEAN	3.991	4.770	3.409
STD.DEV.	1.854	6.315	1.317
S. E. M.	0.395	1.412	0.161
MAXIMUM	8.200	31.400	6.900
MINIMUM	1.200	1.800	1.000
SAMPLE SIZE	22	20	67

ALL GROUPS COMBINED (EXCEPT CASES WITH UNUSED VALUES FOR GROUP1)

MEAN	3.776
STD.DEV.	3.003
S. E. M.	0.288
MAXIMUM	31.400
MINIMUM	1.000
SAMPLE SIZE	109

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	DF	MEAN SQUARE	F VALUE	TAIL PROBABILITY
BETWEEN GROUPS	29.8032	2,	14.9016	1.67	0.1926
WITHIN GROUPS	944.2948	106	8.9084		
TOTAL	974.0980	108			
LEVENE'S TEST FOR EQUAL VARIANCES		2, 106		3.37	0.0381
ONE-WAY ANALYSIS OF VARIANCE TEST STATISTICS FOR WITHIN-GROUP VARIANCES NOT ASSUMED TO BE EQUAL					
WELCH		2, 31		1.31	0.2852
BROWN-FORSYTHE		2, 23		0.83	0.4493

-51-

Reported symptoms related to thyroid dysfunction seem to be more prevalent among the exposed group. No new hypothyroid case was identified in the study group.

Special attention was given to the thyroid function of the four people who showed primary hypothyroidism among the 35 PBBs employees studied in August 1978 (see Table 4.7, also Bahn et al 1980).

Case 1, a 51 year-old, did not participate in the field study. However, special efforts were made to obtain a blood sample from him showing TSH = 24.0 μU/ml; T4 = 4.7 μg/dl and RT3 = 0.86, indicating primary hypothyroid. Physical examination of this worker was performed.

This person worked in the plant for about one year, beginning 1973, before the PBBs production started.

Case 2, a 43 year-old, was taking Syntroid in March 1981, which controlled his thyroid function, (TSH = 3.9 μU/ml, T4 = 9.1μg/dl and RT3 = 1.09). This person was hyperthyroid in childhood and has a mother with enlarged thyroid.

Case 2 was working part time for the company, from March 1971 to May 1973, performing gardening and office cleaning. He also works for another chemical company in the area, doing similar work. Considering his medical history and his relatively low exposure to PBBs, one may question the direct effect of PBBs on his thyroid.

Case 3, a 24 year-old, had no aid from a physician, and no signs of primary hypothyroidism were observed in March, 1981. (TSH = 6.5 μU/ml, T4 = 7.7 μg/dl and RT3 = 0.98). Case 3 has been working in the plant since October, 1974, and had the highest PBBs level (1340 ng/mL) in August 1978, and fat level of 2619 ng/g decabromobyphenil in 1981.

Case 4, a 53 year-old, did not seek any aid from a physician. In our physical examination a thyroid nodule was found (see Case 3*, section 4.3.b). His TSH level was high 31.4 μU/ml, and the other laboratory results were T4 = 4.3 μg/dl and RT3 = 0.66. Case 4 has been working at the plant since December, 1977, during the decabromobiphenyl oxide period.

The phenomenon of reversibility as observed in Case 3 was unexpected, because primary hypothyroidism if untreated is not known to be reversible. If there is an association between PBBs exposure and primary hypothyroidism, possibly the lower level of PBBs in this blood (or fat) as compared to these levels in 1978 may explain the fact that the primary hypothyroidism of Case 3 has reversed itself.

To examine the phenomenon of reversible hypothyroidism, the investigators contacted the personal physician of Case 2 and advised the physician to stop giving thyroid medication to his patient. Consequently, his TSH level increased to a level of about 100 μU/ml. However, since the thyroid condition of Case 3 may be attributed to pre-medical conditions, the last approach may not have been an appropriate one. Furthermore, since Case 3 also had the highest

TABLE 4.4

Thyroid Studies in Four Workers Exposed to PBB's and PBBO's and Found to be Hypothyroid in August, 1978.

Subject	Age	Employment Period	Serum Thyrotropin	Serum Thyroxine* (T_4)	Free-Thyroxine Index	Thyroid Antibodies		Family History of Thyroid Disease
						Antithyroglobulin	Antimicrosomal	
	yr		*μU/ml*	*μg/dl*				
Case 1	49	2/72-4/73	24.0	4.7	4.0	<1:100	1:6,400	None
Case 2	41	3/71-5/73	50.0	4.0	3.8	1:6,400	1:25,600	None
Case 3	22	10/74-8/78	46.0	3.8†	3.5	<1:100	1:6,400	Hyperthyroid aunt
Case 4	50	12/77-8/78	30.0	5.1†	3.6	<1:100	1:25,600	None
Normal ranges			<1.5-8.0	4.5-11.5	3.8-10.8	<1:100	<1:100	

*To convert μg/dl to nmol/liter, multiply by 12.87.

†Seven mo before this study Case 3 had a serum T_4 of 9.0 μg/dl, and Case 4 had a serum T_4 of 5.6 μg/dl (normal range, 3.9-14.7).

Source: Bahn et.al. (1980a)

PBBs serum level, one may question the validity of the hormone assays. Therefore, standard assays for TSH and T4 were analyzed in 1340 ng/ml and other PBBs levels. There was no change in the assays, indicating no interaction between the tests for thyroid hormones and PBBs serum concentration. In other words, Case 3 has had a spontaneous hypothyroidism recovery.

d. Reproductive Dysfunction

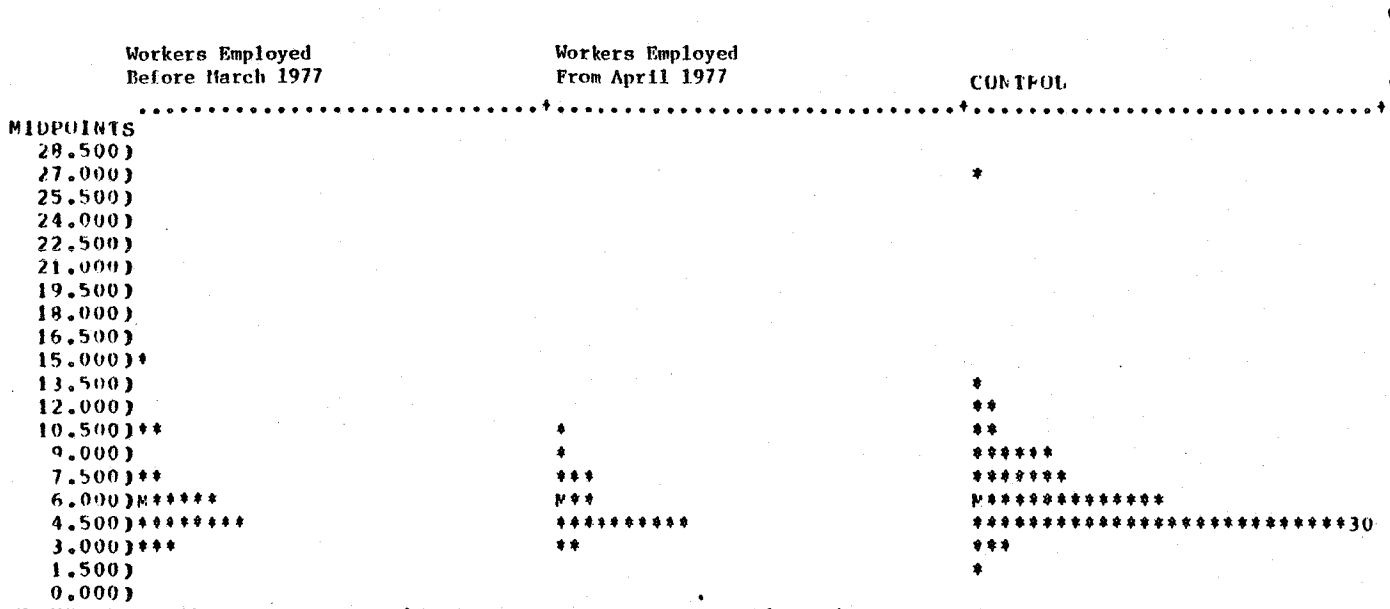
Reproductive function was measured by follicle stimulating hormone (FSH).

Significant correlation was found between length of employment of the plant workers employed before March, 1977 and FSH levels ($r = 0.4766$, $n = 22$, $p < 0.05$). Smaller correlation ($r = 0.2815$) was found among the other plant workers. Table 4.8 describes the FSH distribution among the study population. Only one case had an abnormal level (15.5 nIU/ml) of FSH: his testes are also somewhat soft (August 1981, as reported by his personal physician. See also Case 2*, Section 4.3.b.)

A testicular cyst was found in one worker, and epididymis nodules in two other exposed workers. These thre workers have worked at the plant for at least three years. No testicular and epididymis nodules were observed among the 69 controls. The person with testicular cyst also had the third highest PBBs serum level in 1978 (see Case b, Section 4.3.a.) Considering the prevalence of testicular and epididymis nodules in the general population, no definite statement can be made concerning the PBBs adverse effect on these conditions.

Sixteen healthy children were born to 12 of the 33 workers who were ever married and had been exposed during or after their employment at the plant. No stillbirth was reported in this group; one spontaneous abortion was reported as a result of trauma.

FIGURE 4.7 FOLLICLE STIMULATING HORMONE (FSH) BY EXPOSURE GROUPS



MEAN	5.959	5.690	6.278
STD.DEV.	2.914	1.818	3.522
S. E. M.	0.621	0.407	0.430
MAXIMUM	15.500	9.800	27.700
MINIMUM	2.800	2.900	2.100
SAMPLE SIZE	22	20	67

ALL GROUPS COMBINED (EXCEPT CASES WITH UNUSED VALUES FOR GROUP1)

MEAN	6.106
STD.DEV.	3.142
S. E. M.	0.301
MAXIMUM	27.700
MINIMUM	2.100
SAMPLE SIZE	109

ANALYSIS OF VARIANCE TABLE

SOURCE	SUM OF SQUARES	DF	MEAN SQUARE	F VALUE	TAIL PROBABILITY
BETWEEN GROUPS	5.9091	2	2.9545	0.30	0.7448
WITHIN GROUPS	1060.0076	106	10.0001		
TOTAL	1065.9167	108			
LEVENE'S TEST FOR EQUAL VARIANCES		2, 106		0.63	0.5363
ONE-WAY ANALYSIS OF VARIANCE					
TEST STATISTICS FOR WITHIN-GROUP					
VARIANCES NOT ASSUMED TO BE EQUAL					
WELCH		2, 49		0.49	0.6180
BROWN-FORSYTHE		2, 70		0.41	0.6623

-55-

e. Decedent Cases in the Exposed Cohort

Death certificates for four white male deceased PBB workers indicated the following immediate causes of death and contributing conditions:

Selected Characteristics and Cause of Death for Decedent PBB Workers

	Worker A	Worker B	Worker C	Worker D
Age	54	63	59	56
Occupation	Chemical operator	Maintenance	Chemical operator	Maintenance
Dates of Employment	11/7/69 to 1/4/76	5/20/71 to 4/4/76	2/30/70 to 5/15/78	2/26/69 to 12/2/77
Dates of Death	1/4/76	4/4/76	5/16/78	12/2/77
Immediate Cause of Death	Acute myocardial infarction due to coronary sclerosis	metastatic bronchogenic carcinoma	electrolyte imbalance due to peritonitis, associated with massive ascites due to partial cirrhosis	metastatic lung cancer
Contributing Cause of Death	von Recklinghausen's disease	--	diabetes mellitus, arteriosclerotic heart disease	--
Autopsy	No	No	Yes	--

Because a total of only four known deaths has occurred, a meaningful comparison could not be made with expected deaths.

EXHIBIT 1 a and b

The ad in the News Tribune 2/28/81 - 3/7/81

110 Personal Special Notices

ENDOCRINE DYSFUNCTION STUDY — Of workers exposed to PBB's & PBBO's scheduled from March 9th thru March 11th, 1981, in Sayreville, N.J. All current and former workers of Saytech, Inc. & Hexcel Fine Organics are invited to participate. Please call 536-9402.

The News Tribune March 5, 1981

Saytech workers to undergo new thyroid tests

By DAVE SCHRATWIESER
News Tribune staff writer

SAYREVILLE — The University of Pennsylvania will conduct tests on workers at Saytech Inc. next week to determine the accuracy of 1978 tests that revealed four cases of primary hypothyrodism in workers at the plant.

Dr. Ora Bialik of the University of Pennsylvania said yesterday that the 1978 medical evaluation of workers at the Saytech plant (formerly Hexcel) showed that four males of a sample group of 35 men had "an unexpectedly high prevalence of primary hypothyroidism."

The tests were conducted on workers who manufactured polybrominated biphenyls (PBBs) and polybrominated biphenyl oxide (PBBOs). The plant ceased production of PBBs in 1977 after the U.S. Environmental Protection Agency banned the manufacture of the chemical.

According to the results of the "occupational health-effects study" published in the New England Journal of Medicine, concern over the toxic effects of PBBs on human beings arose when the chemical was accidentally fed to livestock in 1973 in Michigan.

Dr. Bialik said the 1978 tests were "not conclusive" enough and that the University of Pennsylvania, operating under a $139,000 federal grant, wished to test workers and their relatives once again to "define the test results" further.

"This is not a threatening situation to outsiders. It may be a threatening situation for the workers, but we're not sure. That's why we need the second test," Dr. Bialik said.

"We found four primary cases of hypothyroidism which we believe are the result of contact with either PBBs or PBBOs," she explained. "Hypothyroidism is a treatable condition and we did notify each of the four individuals involved about the test results within several months after the tests."

The study results state that the "common exposure of these four men to PBBs and PBBOs and bromine suggests that these substances could have caused the hyporthyroidism. The development of thyroid abnormalities in animals given PBBs and PBBOs supports this hypothesis."

All test results and information about the conditions under which the tests were conducted were forwarded to each of the four individual's doctors. Each of the four was advised to consult his physician.

Dr. Bialik said that hypothyroidism, if left untreated, could develop into a heart condition. It also could involve thyroid gland problems and liver complications.

She emphasized that the findings were "clinical results" and that the follow-up tests would give a "clearer picture" of the first study's findings. The new tests will be conducted from Monday through Wednesday.

Dr. Bialik also explained that the tests were conducted on 89 control groups made up of relatives and neighbors who came into contact with workers from the former Hexcel plant.

There were no signs of hypothyroidism in the control groups.

She said none of the four workers reported taking thyroid medication, visiting a physician for thyroid problems, or being told that he had a thyroid problem within five years of taking the 1978 tests.

The physical examinations of each participant did not reveal any thyroid enlargement, she said. No obvious signs of hypothyroidism were present on physical examination in any subject, according to Dr. Bialik.

Dr. Gilbert B. Meyers, corporate medical director for the Ethyl Corp., which purchased the former Hexcel facility last July, recently told the workers at the Saytech plant on lower Main Street that he had "serious reservations about the soundness of the test results."

Dr. Meyers said he doubted the findings of the tests because the sample group on which the 1978 tests were conducted was "too small."

He claimed the researchers should have drawn their conclusions from a larger sample group that included workers from the four other PBB- and PBBO-producing companies in the United States.

Meyers said that while the Ethyl Corp. would not be involved in, or sanction, the new tests, "the workers are free as individuals" to participate in the tests.

He said the company offers a comprehensive physical examination and tests to all of its workers.

The company's medical program includes tests for thyroid conditions, 25 different blood analyses, electrocardiograms for workers over 40, and a series of other physical examinations.

EXHIBIT 1c

The HomeNews FRIDAY, MARCH 20, 1981

PBB hazard probe stalled

By LAURA SANDERS
Home News staff writer

SAYREVILLE – A University of Pennsylvania research team which two years ago discovered evidence of thyroid changes among chemical workers at Saytech Inc. encountered opposition from the company when it returned last week for a follow-up study.

"We are not cooperating with the study," said Prescott Rowe, spokesman for Ethyl Corp., Saytech's parent corporation. "We have serious reservations about the soundness of the study and its conclusions."

The original study, performed in August 1979, tested 35 Saytech volunteers – men who worked in jobs exposing them to fire retardant chemicals known as polybrominated biphenyls (PBBs) or polybrominated biphenyl oxides (PBBOs) or both.

The researchers found four workers whose blood changes signaled a condition called primary hypothyroidism, a slowdown in thryoid activity which can cause arteriosclerotic heart disease if left untreated. The workers asked the researchers to withhold their names from Saytech, said Ora Bialik, head of the investigating team from the university's Department of Epidemiological Research and Training.

In 1978, none of the workers tested showed nodules, which are signs of more serious – possibly malignant – thyroid problems, Dr. Bialik said. When the researchers returned to Sayreville last week for follow-up tests, however, they detected nodules in several men, she said.

Because the examiners were not told which subjects were chemical workers and which subjects were selected from a control group of non-chemical workers, she said she could not know yet if those with nodules were the ones who exhibited blood irregularities in 1978.

The control group consisted of steel and electrical workers and volunteers from the general community, who were matched for age, sex and race with the Saytech workers. No thyroid problems were discovered in the control group in 1978.

When the 1978 study was done, the researchers promised the company anonymity in return for its cooperation. When the research results were published Jan. 3, 1980 in the "New England Journal of Medicine," neither Saytech (then Hexcel Corp.) nor its then parent company, Cities Service Co., were identified.

In July 1980, Saytech was sold to Ethyl Corp.

Ethyl's corporate medical director, Gilbert D. Meyers, recommended Saytech cease to cooperate with the Pennsylvania researchers, citing flaws in the study.

In a letter to Saytech workers dated Oct. 23, 1980, Dr. Meyers said he found "no statistically significant difference" in tests on the control group and Saytech group and that "no obvious signs of hypothyroidism were present on physical examination of any subject."

Dr. Bialik said four of 35 workers showed signs of hypothyroidism while no thyroid illness was detected among 89 control group members. One of the four workers showed cell concentrations of PBB four times higher than those of the person with next highest reading and 100 times higher than the highest reading in the control group, she said.

PBB first came to national attention in Michigan in 1973, when it was accidently mixed into cattle feed, causing blocked milk production, defective offspring and death in the cattle.

In 1977, a U.S. Environmental Protection Agency survey discovered PBB contamination in water and soil surrounding the Saytech plant and in the workers. Saytech, then Hexcel, agreed to implement a pollution control program. Meanwhile, the EPA commissioned the University of Pennsylvania research team to study the workers for clues to the health effects of PBB contamination in humans.

-58-