U.S. EPA H.R.O.C. Meeting

Hudson River PCBs Superfund Site Reassessment
Community Interaction Program

Hudson River PCBs Oversight Committee
Wednesday, March 8, 2000 - 7:30 p.m.
Saratoga Springs, New York

AGENDA

Welcome & Introduction	Mel Hauptman, Acting Chair HROC, USEPA
Committee Report-Outs (20 minutes)	Mel Hauptman, Acting Chair
Guest Speakers on PCB Toxicity	Renate Kimbrough, M.D. (30 minutes)
	Jim Cogliano, Ph.D. U.S. EPA (30 minutes)

Questions & Answers

Hudson River PCBs Site Reassessment RI/FS
June 10, 1999 (Updated March 8, 2000)

Milestone	Completed	To Public
PHASE 1 Report	✔	Aug 1991
PHASE 2 Field Sampling Program - 1992 to 1994	✔	N/A
Database Report (DBR)	✔	Nov 1995
Preliminary Model Calibration Report (PMCR)	✔	Oct 1996
Data Evaluation & Interpretation Report (DEIR)	✔	Feb 1997
Low Resolution Sediment Coring Report (LRC)	✔	Jul 1998
Human Health Risk Assessment Scope of Work	✔	Jul 1998
CD-ROM Database Reissue	✔	Jul 1998
Peer Review 1 - Modeling Approach - Begins	✔	Jul 1998
Peer Review 1 Meeting	✔	Sept 1998
Ecological Risk Assessment Scope of Work	✔	Sept 1998
DBR, PMCR, DEIR Responsiveness Summary	✔	Dec 1998
Peer Review 2 - DEIR & LRC - Begins	✔	Jan 1999
LRC Responsiveness Summary	✔	Feb 1999
Peer Review 2 Meeting	✔	Mar 1999
Human Health Risk Assmt SOW Responsiveness Summary	✔	Apr 1999
Ecological Risk Assmt SOW Responsiveness Summary	✔	Apr 1999
Baseline Modeling Report (BMR)	✔	May 1999
Human Health Risk Assessment (HHRA) Upper Hudson	✔	Aug 1999
Ecological Risk Assessment (ERA)	✔	Aug 1999
Addendum HHRA - Mid-Hudson	✔	Dec 1999
Addendum ERA - Future Risks for Lower Hudson	✔	Dec 1999
Peer Review 3 - BMR - Begins	✔	Jan 2000
Revised BMR	✔	Jan 2000
BMR Responsiveness Summary	✔	Feb 2000
Response to Peer Review 1 Comments	✔	Feb 2000
Peer Review 3 Meeting		Mar 2000
HHRA and ERA Responsiveness Summaries		Mar 2000
Peer Review 4 - HHRA & ERA - Begins		Mar 2000
Peer Review 4 Meeting		May 2000
PHASE 3 Feasibility Study Scope of Work (FS SOW)	✔	Sept 1998
FS SOW Responsiveness Summary	✔	Jun 1999
FS Report		Dec 2000
PROPOSED PLAN		Dec 2000
RECORD OF DECISION (including Responsiveness Summary)		Jun 2001

PCBs: Environmental Considerations

Jim Cogliano, Ph.D.
Chief, Quantitative Risk Methods Group

United States Environmental Protection Agency
National Center for Environmental Assessment
Washington, D.C.

PCBs: Environmental considerations

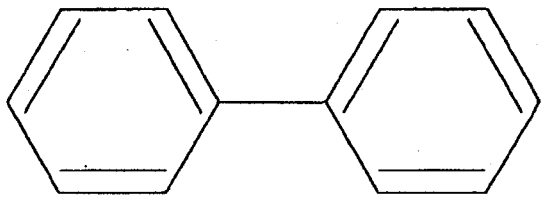
- PCBs in the environment
- PCBs in living organisms
- Health effects of concern

PCBs

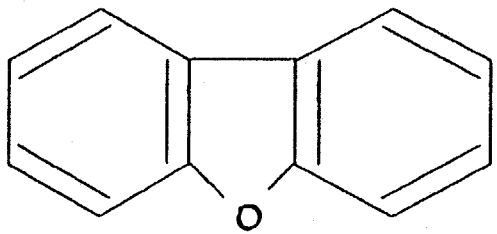
- Chlorine substitution
- Congeners
- Homologues
- Aroclors

Similarity of PCBs to dibenzofurans and dioxins

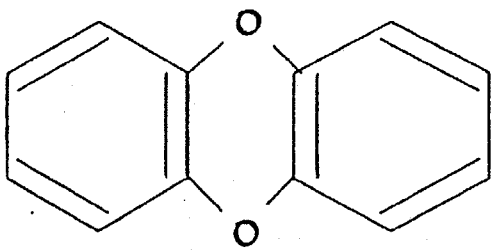
PCBs



Polychlorinated dibenzofurans



Polychlorinated dibenzo-*p*-dioxins



Typical composition of some Aroclor mixtures

	Aroclor 1016	1242	1248	1254	1260
Mono-CBs (%wt)	2	1	—	—	—
Di-CBs	19	13	1	—	—
Tri-CBs	57	45	21	1	—
Tetra-CBs	22	31	49	15	—
Penta-CBs	—	10	27	53	12
Hexa-CBs	—	—	2	26	42
Hepta-CBs	—	—	—	4	38
Octa-CBs	—	—	—	—	7
Nona-CBs	—	—	—	—	1
Deca-CB	—	—	—	—	—
Chlorine content (%)	41	42	48	54	60
Production, 1957–1977 (%)	13	52	7	16	11

"—" denotes less than 1%.

Sources: Adapted from U.S. EPA (1996), Cogliano (1998).

Environmental fate is related to chlorine substitution

1 ..... Chlorine content 10

Higher ..... Volatility ..... Low

Higher ..... Solubility in water ..... Low

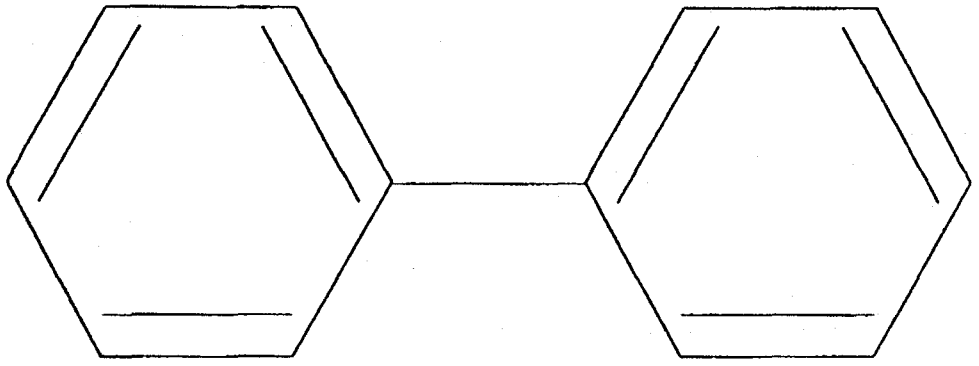
Low ..... Adsorption to soil and sediment ..... High

Low ..... Persistence in the environment ..... High

PCBs partition in the environment

Air —	Higher proportion of lower-chlorinated congeners
Water —	Higher proportion of lower-chlorinated congeners
Soil —	Higher proportion of higher-chlorinated congeners
Sediment —	Higher proportion of higher-chlorinated congeners

Metabolic fate is related to chlorine substitution



Oxidative metabolism is facilitated by the absence of chlorines in adjacent positions

PCBs bioaccumulate in the environment

- Each link in the food chain passes on congeners most difficult to eliminate
- PCB composition can be significantly altered

Which exposure pathways are of greatest concern?

- Bioaccumulated mixtures
  - Fish
  - Birds that eat fish
- Contaminated soil and sediment

PCBs and cancer

Mayes (1998) tested Aroclors 1016, 1242, 1254, and 1260 in rats

- All cause significant increases in liver cancer
- Some Aroclors increased thyroid cancer in males
- Potency differs for these mixtures

These mixtures contain overlapping groups of congeners that, together, span the range of congeners most often found in environmental mixtures

Conclusions

- All PCB mixtures can pose a risk of cancer
- There is a basis for distinguishing the cancer potential of different environmental mixtures

PCBs and cancer

Mayes (1998) tested Aroclors 1016, 1242, 1254, and 1260 in rats

- All cause significant increases in liver cancer
- Some Aroclors increased thyroid cancer in males
- Potency differs for these mixtures

These mixtures contain overlapping groups of congeners that, together, span the range of congeners most often found in environmental mixtures

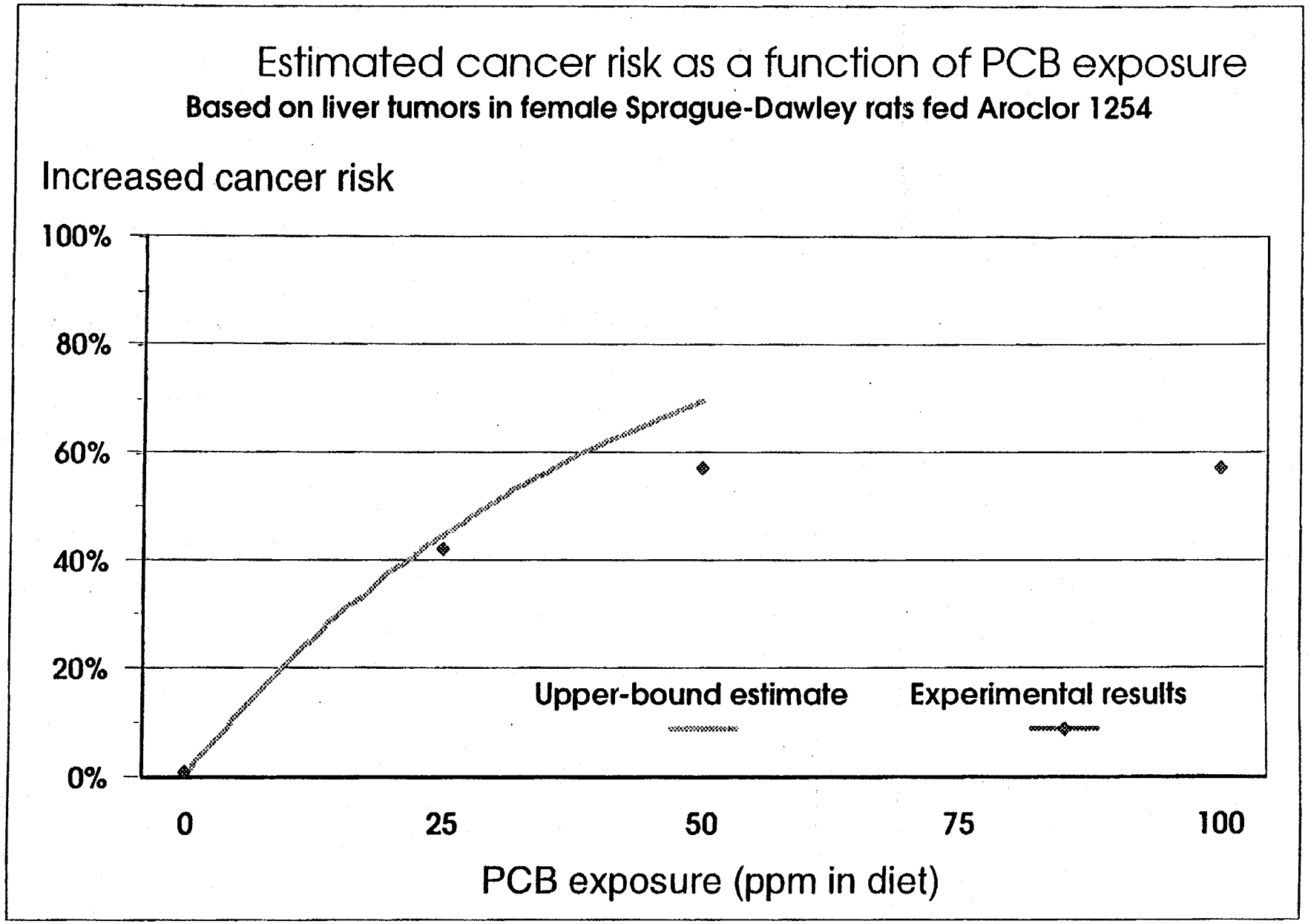
Conclusions

- All PCB mixtures can pose a risk of cancer
- There is a basis for distinguishing the cancer potential of different environmental mixtures

Liver tumor incidences from the 1996 rat study

Mixture	Dose	Females	Males
Aroclor 1260	Control	** 1/85 (1%)	** 7/98 (7%)
	25 ppm	10/49 (20%)	3/50 (6%)
	50 ppm	11/45 (24%)	6/49 (12%)
	100 ppm	24/50 (48%)	10/49 (20%)
Aroclor 1254	Control	** 1/85 (1%)	7/98 (7%)
	25 ppm	19/45 (42%)	4/48 (8%)
	50 ppm	28/49 (57%)	4/49 (8%)
	100 ppm	28/49 (57%)	6/47 (13%)
Aroclor 1242	Control	** 1/85 (1%)	7/98 (7%)
	50 ppm	11/49 (24%)	1/50 (2%)
	100 ppm	15/45 (33%)	4/46 (9%)
Aroclor 1016	Control	** 1/85 (1%)	7/98 (7%)
	50 ppm	1/48 (2%)	2/48 (4%)
	100 ppm	6/45 (13%)	2/50 (4%)
	200 ppm	5/50 (10%)	4/49 (8%)

**Statistically significant ($p<0.05$) by Cochran-Armitage trend test.
Hepatocellular adenomas, carcinomas, cholangiomas, or cholangiocarcinomas in rats alive when the first tumor was observed.
One control group supported all experiments.
Source: Brunner (*1996*), reported by U.S. EPA (*1996*); Mayes (*1998*).



Three tiers of environmental PCBs

HIGHEST RISK AND PERSISTENCE

- Food chain exposure
- Sediment or soil ingestion
- Dust or aerosol inhalation
- Early-life exposure (all pathways and mixtures)

LOWER RISK AND PERSISTENCE

- Ingestion of water-soluble congeners
- Inhalation of evaporated congeners
- Dermal exposure, if no absorption factor has been applied

LOWEST RISK AND PERSISTENCE

- Congener or homologue analyses verify that congeners with more than 4 chlorines comprise less than 1/2% of total PCBs

Less-than-lifetime exposure to the more persistent mixtures may pose disproportionately high risks

Mixture	Dose	Less-than-lifetime exposure	Lifetime exposure
Aroclor 1260	Control	** 1/85 (1%)	** 1/85 (1%)
	25 ppm	4/24 (17%)	10/49 (20%)
	50 ppm	3/24 (12%)	11/45 (24%)
	100 ppm	17/24 (71%)	24/50 (48%)
Aroclor 1254	Control	** 1/85 (1%)	** 1/85 (1%)
	25 ppm	5/24 (21%)	19/45 (42%)
	50 ppm	7/24 (29%)	28/49 (57%)
	100 ppm	6/24 (25%)	28/49 (57%)
Aroclor 1242	Control	** 1/85 (1%)	** 1/85 (1%)
	50 ppm	3/24 (12%)	11/49 (22%)
	100 ppm	6/24 (25%)	15/45 (33%)
Aroclor 1016	Control	1/85 (1%)	** 1/85 (1%)
	50 ppm	0/24 (0%)	1/48 (2%)
	100 ppm	0/24 (0%)	6/45 (13%)
	200 ppm	0/24 (0%)	5/50 (10%)

**Statistically significant ($p<0.05$) by Cochran-Armitage trend test.
Less-than-lifetime experiment involved rats dosed for 52 weeks and killed after 104 weeks.
Source: Brunner (*1996*), reported by U.S. EPA (*1996*).

Bioaccumulated PCBs may be more toxic and more persistent than the Aroclors

- In mink fed Great Lakes fish, reproductive toxicity and liver toxicity were greater than for other mink fed equivalent amounts of Aroclor 1254
- In monkeys fed a mixture representative of PCBs found in human milk, long-term behavioral impairments have been found
- In people eating Great Lakes fish, the rate of decline in serum PCB levels was much smaller than what has been reported for people exposed to Aroclors in the workplace

Noncancer effects of PCBs

PCBs have significant adverse health effects other than cancer, including

- Learning deficits
- Neurological effects
- Immune dysfunction
- Thyroid effects
- Hormonal effects

Recent studies raise new concerns about environmental exposure

Study of children whose mothers ate L. Michigan fish

3 days	Motor immaturity, ⇓ ability to quiet, ⇑ startle, ⇓ reflexes
7 months	⇓ short-term memory
4 years	⇓ verbal scale, ⇓ memory scale, ⇓ activity, ⇓ short-term memory, ⇓ visual discrimination
11 years	⇓ full-scale and verbal IQ, ⇓ work and reading comprehension, ⇓ memory and attention

Highest PCB group . . .

had average IQ 6 points below average

3x more likely to have low IQ

2x more likely to be 2 years behind in reading ability

Study of children whose mothers ate L. Ontario fish

Infancy	Abnormal reflexes, ⇑ startle, ⇑ tremor
12 months	⇓ habituation
36 months	⇓ general cognitive index

Study of PCBs from food (N. Carolina)

Early infancy	⇓ reflexes, ⇓ activity
6–12 months	⇓ psychomotor development
24 months	⇓ psychomotor development
3, 4, 5 years	No effect on motor or memory scales

Study of PCBs from food (Netherlands)

10, 21 days	⇓ reflexes, hypotonicity
3 months	⇓ psychomotor score, immunological changes
7 months	⇓ psychomotor score
18 months	⇓ psychomotor development, immunological changes
42 months	⇓ general cognitive scale, ⇓ high-level play, ⇑ non-play time, ⇑ reaction time, ⇑ withdrawn/depressed behavior, ⇑ prevalence of chicken pox, ⇓ antibodies to measles

These effects were seen at 3 ppb in blood serum

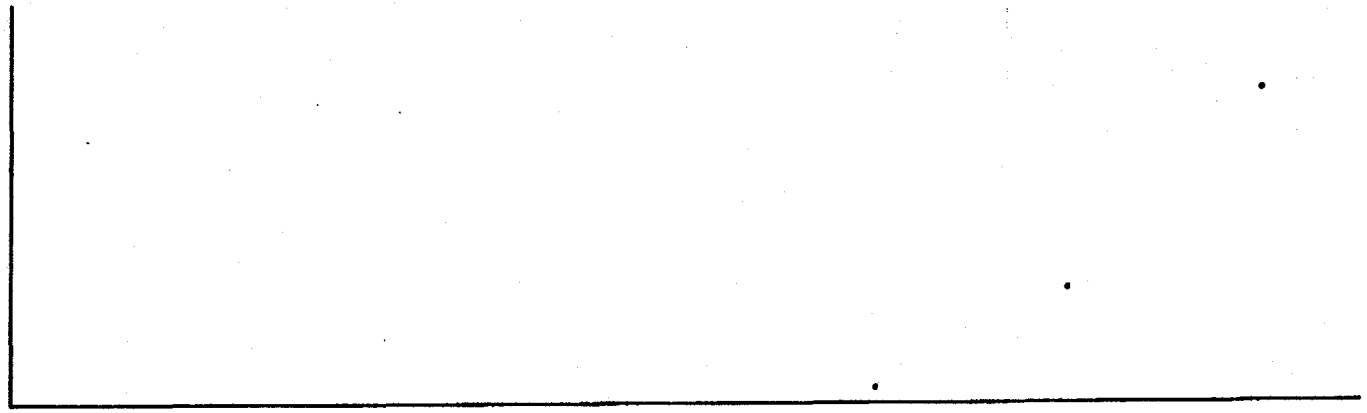
Studies of PCBs in monkeys

Independent studies in animals show that PCBs alone can cause effects analogous to those seen in the human studies, including

- ⇓ learning
- ⇓ memory
- ⇓ ability to adapt
- ⇓ ability to organize behavior
- ⇓ attention

These studies increase our confidence that the effects seen in the human studies can be attributed to PCBs

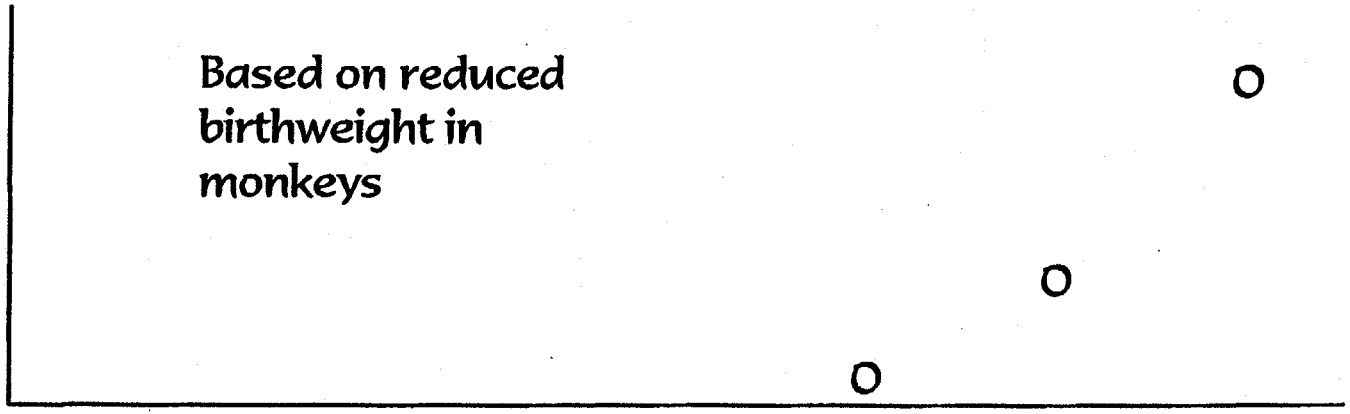
Noncancer reference dose



Human variability
Animal-to-human uncertainty
LOAEL-to-NOAEL uncertainty
Subchronic-to-chronic uncertainty
Database limitations
Modifying factor

Based on decreased antibody (IgG and IgM) response to sheep erythrocytes in monkeys				0
			0	
0.02	(300)		—	5 ug/kg-d
	10			
	3			
	3			
	3			
	—			
	—			

for Aroclor 1016



0.07	(100)	7 ug/kg-d	28 ug/kg-d
	3		
	3		
	1		
	3		
	3		

Summary

- PCB mixtures are altered in the environment — in some cases increasing the mixture's persistence and toxicity
- Principal exposures of concern are bioaccumulated PCBs and PCBs attached to soils or sediments
- Evidence is strong that environmental PCBs pose a risk of cancer
- Evidence is mounting that noncancer effects, especially learning deficits and neurological effects, have occurred from environmental PCB exposure

WHAT CAN YOU DO?

- Pay attention to fish advisories

Assessing the Cancer Risk from Environmental PCBs

Vincent James Cogliano

U.S. Environmental Protection Agency, National Center for Environmental Assessment, Washington, D.C. 20460 USA

Reprinted from:

Environmental Health perspectives

Journal of the National Institute of Environmental Health Sciences
http://ehis.niehs.nih.gov

Volume 106, Number 6
June 1998

Assessing the Cancer Risk from Environmental PCBs

Vincent James Cogliano

U.S. Environmental Protection Agency, National Center for Environmental Assessment, Washington, D.C. 20460 USA

A new approach to assessing the cancer risk from environmental polychlorinated biphenyls (PCBs) considers both toxicity and environmental processes to make distinctions among environmental mixtures. New toxicity information from a 1996 cancer study of four commercial mixtures strengthens the case that all PCB mixtures can cause cancer, although different mixtures have different potencies. Environmental processes alter PCB mixtures through partitioning, chemical transformation, and preferential bioaccumulation; these processes can increase or decrease toxicity considerably. Bioaccumulated PCBs are of greatest concern because they appear to be more toxic than commercial PCBs and more persistent in the body. The new approach uses toxicity studies of commercial mixtures to develop a range of cancer potency estimates and then considers the effect of environmental processes to choose appropriate values for representative classes of environmental mixtures. Guidance is given for assessing risks from different exposure pathways, less-than-lifetime and early-life exposures, and mixtures containing dioxinlike compounds. *Key words*: **bioaccumulation, cancer, mixtures, partitioning, PCBs, persistence, polychlorinated biphenyls, risk assessment.** *Environ Health Perspect* **106:317–323 (1998). [Online 13 May 1998]**

http://ehpnet1.niehs.nih.gov/docs/1998/106p317-323cogliano/abstract.html

Twenty years after their manufacture was halted, polychlorinated biphenyls (PCBs) remain a major environmental concern. Standards often have been based on cancer risk, yet before 1996 only commercial mixtures with 60% chlorine had been adequately tested. Different assumptions were made for other mixtures: sometimes all PCB mixtures were considered carcinogenic and sometimes only mixtures with high chlorine content. A quantitative potency estimate derived from mixtures with 60% chlorine was applied to any PCB mixture regarded as carcinogenic. The overlapping compositions of different mixtures (Table 1) show the problem with treating all mixtures the same or creating a false dichotomy of carcinogenic and noncarcinogenic mixtures.

New information is making possible a more rational approach for distinguishing among PCB mixtures. A recent study compared the cancer potential of the commercial mixtures Aroclors 1016, 1242, 1254, and 1260 (*1*). Its results strengthen the case that all PCB mixtures can cause cancer, although different mixtures have different potencies. Potency is also affected by the environmental processes that alter PCB mixtures. These processes diminish the similarity of environmental mixtures to commercial mixtures and can markedly increase or decrease a mixture's toxicity.

As the Aroclor comparisons became available, the EPA developed a new approach to assessing the cancer risk from environmental PCBs, considering both toxicity and environmental processes (*2*). A range of estimates now characterizes the potency of different mixtures, and information on environmental processes is used to choose appropriate values for representative classes of environmental mixtures. There is also guidance for assessing different exposure pathways, less-than-lifetime and early-life exposures, and mixtures containing dioxinlike compounds. The use of several kinds of information fulfills the intent of the EPA's proposed cancer guideline revisions (*3*) as well as the instruction of the EPA's mixture guidelines (*4*) to consider mixture composition. The new approach was reviewed by a panel of independent experts on the carcinogenicity of PCBs at a public peer review workshop (*5*).

Summary of Cancer Evidence for PCBs

Four commercial PCB mixtures, Aroclors 1016, 1242, 1254, and 1260, have been tested in rats for their potential to cause cancer. All mixtures induced liver tumors when fed to female rats; Aroclor 1260 also induced liver tumors in male rats (*1*). Several of these tumors were hepatocholangiomas, a rare biliary tract tumor seldom seen in control rats. These mixtures contain overlapping groups of congeners that, together, span the range of congeners most often found in environmental mixtures. Previously, lifetime dietary exposure to commercial mixtures with 60% chlorine induced liver tumors in three rat strains (*6–9*). Although many of these tumors were benign, sequential morphologic analyses have demonstrated the eventual progression of the benign liver lesions to malignant carcinomas (*8*). Commercial mixtures with 54% chlorine induced gastrointestinal tumors (*10–12*). Less-than-lifetime dietary exposure to commercial mixtures with 42–60% chlorine induced precancerous liver lesions in rats and mice (*13–18*).

Epidemiologic studies have reported similar tumor sites, although the same specific response was not seen across all studies. Capacitor manufacturing workers exposed to a series of commercial mixtures with 41–54% chlorine had increased mortality from liver, gall bladder, and biliary tract cancers (*19*), gastrointestinal tract cancers (*20*), or malignant melanoma (*21*). An analysis of these and a smaller study (*22*) found the combined results significant for liver, gall bladder, and biliary tract cancers and for malignant melanoma (*23*). Earlier, petrochemical refinery workers exposed to Aroclor 1254 and other chemicals had significantly increased mortality from malignant melanoma (*24*). More recently, electric utility workers exposed to PCBs had significantly increased mortality from malignant melanoma and brain cancer (*25*). Recent case–control studies have found a significant association between non-Hodgkin's lymphoma and PCB concentrations in adipose tissue (*26*) and serum (*27*). In a general population, dietary consumption of rice oil accidentally contaminated with PCBs and chlorinated dibenzofurans, which can be formed when PCBs are heated above 270°C (*28*), was associated with significantly increased mortality from liver cancer and lung cancer (*29*).

Mechanistic studies have demonstrated tumor-promoting activity in liver or lung

Address correspondence to V.J. Cogliano, U.S. Environmental Protection Agency, 401 M Street, SW (8623-D), Washington, DC 20460 USA.

The author gratefully acknowledges the contributions of all who commented on the EPA's assessment, including the peer review panel and many scientists in the EPA's program, regional, and research organizations. Their efforts truly improved the final product.

The views expressed in this paper are those of the author and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

Received 22 May 1997; accepted 9 February 1998.

from Aroclor 1254 and some congeners with four to six chlorines: tetrachlorobiphenyl congeners PCB-47, -49, -52, and -77 [International Union of Pure and Applied Chemistry (IUPAC) numbering]; pentachlorobiphenyl congeners PCB-105, -118, and -126; and the hexachlorobiphenyl congener PCB-153 (*30*). Toxicity of some congeners is correlated with induction of mixed-function oxidases: some congeners are phenobarbital-type inducers, some are 3-methylcholanthrene-type inducers, and some have mixed inducing properties (*31–33*). The latter two groups most resemble chlorinated dibenzo-*p*-dioxins and dibenzofurans in structure and toxicity (*33,34*). These congeners contributing to cancer induction can be present in mixtures with either high or low chlorine content (Table 1).

PCBs are absorbed through ingestion, inhalation, and dermal exposure, after which they are transported similarly through the circulation (*35*), providing a reasonable basis for expecting similar internal effects from different exposure routes. Quantitatively, dermal exposure poses lower risks because PCBs are substantially but incompletely absorbed through the skin (*36–39*).

Recent research is suggesting mechanisms by which PCBs can contribute to cancer at other sites. One experiment raises concern for PCBs of low chlorine content, finding that dihydroxy metabolites of PCBs with low chlorine content are activated to reactive intermediates that produce oxidative DNA damage (*40*). These results provide a possible mechanism to support the hypothesis that environmental PCBs may contribute to human breast cancer. Among the case–control studies of non-Hodgkin's lymphoma, one study found an association with both dioxinlike and nondioxinlike congeners (*26*), and the other found a multiplicative interaction with seropositivity for the Epstein-Barr virus early antigen (*27*). Because PCBs suppress the immune system and immunosuppression is an established risk factor for non-Hodgkin's lymphoma, immune system suppression may be a possible mechanism for PCB-induced cancer. Other research has associated both dioxinlike and nondioxinlike congeners with toxicity due to endocrine disruption (*41,42*).

Table 1. Typical composition of some commercial PCB mixtures

	Aroclor 1016	Aroclor 1242	Aroclor 1248	Aroclor 1254	Aroclor 1260
Mono-CBs	2	1	–	–	–
Di-CBs	19	13	1	–	–
Tri-CBs	57	45	21	1	–
Tetra-CBs	22	31	49	15	–
Penta-CBs	–	10	27	53	12
Hexa-CBs	–	–	2	26	42
Hepta-CBs	–	–	–	4	38
Octa-CBs	–	–	–	–	7
Nona-CBs	–	–	–	–	1
Deca-CB	–	–	–	–	–
PCDFs (ppm)	ND	0.15–4.5	NR	0.8–5.6	0.8–5.6
Chlorine content	41	42	48	54	60
Production, 1957–1977	13	52	7	16	11

Abbreviations: PCB, polychlorinated biphenyl; CBs, chlorinated biphenyls; PCDFs, polychlorinated dibenzofurans; ND, not detected; NR, not reported. Values shown are percent of weight except where noted.
Data from Silberhorn et al. (*30*), the Agency for Toxic Substances and Disease Registry (*35*), and Brown et al. (*43*).

Table 2. Reported composition of commercial mixtures tested in the 1996 rat study

	Aroclor 1016	Aroclor 1242	Aroclor 1254	Aroclor 1260
Mono-CBs	0.83	0.08	–	–
Di-CBs	17.64	14.48	0.12	0.15
Tri-CBs	54.98	42.83	0.66	0.48
Tetra-CBs	25.84	33.49	19.67	2.41
Penta-CBs	0.69	6.64	45.33	11.96
Hexa-CBs	0.01	1.70	31.38	39.28
Hepta-CBs	–	0.10	2.76	36.38
Octa-CBs	–	0.01	0.07	7.67
Nona-CBs	–	–	0.02	1.59
Deca-CB	–	–	–	0.07
PCB-77 (3,3′,4,4′-TetraCB) (ppm)	66.0	3340.0	918.0	31.0
PCB-126 (3,3′,4,4′,5-PentaCB) (ppm)	0.95	44.0	134.3	0.0
PCB-169 (3,3′,4,4′,5,5′-HexaCB) (ppm)	0.0	0.0	1.52	0.0
PCDFs (ppm)	0.05	2.2	0.13	5.5
TEQ from PCBs (ppm)	0.14	8.1	46.4	7.1
TEQ from PCDFs (ppm)	0.002	0.1	0.01	0.08

Abbreviations: CBs, chlorinated biphenyls; PCB, polychlorinated biphenyl; PCDFs, polychlorinated dibenzofurans; TEQ, toxic equivalent. Values shown are molecular percent except where noted.
Data from Brown et al. (*43*).

Differences in Cancer Potential of Commercial PCB Mixtures

The recent study comparing Aroclors 1016, 1242, 1254, and 1260 (*1*) provides the best information for distinguishing the cancer potential of different mixtures. Composition of the tested mixtures was reported by homologues, plus three dioxinlike congeners and total chlorinated dibenzofurans (Table 2; compare with Table 1). Prior to the study, the polychlorinated dibenzofurans were removed from the Aroclor 1254 fed to the rats because of "unusually high" dibenzofuran concentrations (*43*). Despite this pretreatment, the resulting mixture was reported to have double the usual dioxin toxic equivalents (*43*).

Concentrations of the three dioxinlike congeners reported lie within the historical range. One historical analysis found each of these congeners below 500 ppm in each Aroclor, except for 4500 ppm PCB-77 in Aroclor 1242 and 500 ppm PCB-169 in Aroclor 1260 (*44*). Another analysis found 2700–3300 ppm PCB-77 in Aroclor 1242, 300–2000 ppm PCB-77 in Aroclor 1254, and up to 200 ppm PCB-126 in Aroclor 1254 (*45*). In sharp contrast, however, an earlier analysis found 15,900 ppm PCB-126 in Aroclor 1260 (*35,46*). These and other variations provide evidence of significant lot-to-lot variability among similar mixtures. Striking lot-to-lot differences have been found for Aroclors 1248 and 1254, due primarily to numerous congeners with four to six chlorines being created and altered during the chlorination process by which Aroclors are manufactured, and also to differences in the chlorination processes that can be used (*45*). These lot-to-lot differences highlight the importance of characterizing and reporting mixture composition, both in toxicity testing and in environmental samples.

In the recent cancer study (*1*), groups of 50 male or female Sprague-Dawley rats were fed diets with 50, 100, or 200 ppm Aroclor 1016; 50 or 100 ppm Aroclor 1242; or 25, 50, or 100 ppm Aroclor 1254

or 1260. There were 100 controls of each sex. Exposure began when the rats were 6–9 weeks old, and the animals were killed 104 weeks later. Complete histopathologic evaluations were done for control and high-dose groups; for low- and mid-dose groups, evaluations were done for liver, brain, mammary gland, and male thyroid gland. Statistically significant increased incidences of liver tumors were found in female rats for all Aroclors and in male rats for Aroclor 1260 (Table 3). Fewer than a quarter of the tumors were malignant, but the proportion of tumors that were malignant increased with dose. In female rats, Aroclor 1254 appeared most potent, followed by Aroclors 1260 and 1242, with Aroclor 1016 markedly less potent. In male rats, only Aroclor 1260 caused liver tumors.

To investigate tumor progression after exposure stops, this same study exposed groups of 24 female rats for 52 weeks; exposure was then discontinued for an additional 52 weeks before the rats were killed. For 52 weeks exposure to Aroclors 1242 or 1254, tumor incidences were approximately half those for 104 weeks exposure, that is, nearly proportional to exposure duration. In contrast, there were no tumors from 52 weeks exposure to Aroclor 1016, while for Aroclor 1260 incidences were generally greater than half those for 104 weeks exposure (Table 4). For 100 ppm Aroclor 1260, the incidence from 52 weeks exposure was greater than that from 104 weeks, 71 and 48%, respectively.

Different patterns may hold for other cancers. In the study just described (*1*), thyroid gland follicular cell adenomas or carcinomas were increased in males for all Aroclors, and statistically significant trends were noted for Aroclors 1242 and 1254. The increases did not continue proportionately above the lowest dose, and no thyroid trends were apparent in females.

Modeling Results for Commercial PCB Mixtures

Under the EPA's proposed cancer guideline revisions (*3*), dose–response assessment first considers developing a biologically based model, that is, one whose mathematical structure reflects the ascertained mode of action and whose parameters are experimentally measured. Few PCB congeners or mixtures, however, have been tested to measure the rate parameters that would be used in a biologically based model. Consequently, the information available at this time is more suited to empirical modeling, in which a flexible default model—allowing either linearity or nonlinearity—is fitted to describe tumor incidence as a function of dose in the experimental range.

The EPA's new assessment (*2*) fitted a linear-quadratic dose–response model [that is, a model of the form $P(d) = 1-\exp(-q_1 d - q_2 d^2)$, where $P(d)$ is the probability of response at dose d, and q_1 and q_2 are parameters] to the liver tumor incidences in female Sprague-Dawley rats fed Aroclors 1016, 1242, 1254, or 1260 (Table 3). Dose was expressed as a lifetime daily average, calculated from weekly body weight measurements and food consumption estimates. Doses were scaled to humans using a factor based on the three-fourths power of relative body weight (*3*). Response was taken as the incidence of hepatocellular adenomas or carcinomas. Combining adenomas and carcinomas reflects the guidance of the National Toxicology Program (*47*) and the progression of hepatocellular adenomas to carcinomas in female Sprague-Dawley rats (*8*). To reflect lot-to-lot variability among similar mixtures, the EPA also modeled earlier results in female Sprague-Dawley rats fed from a different lot of Aroclor 1260 (Table 5).

In the experimental range, the EPA described the cancer potency of each mixture by an estimated dose associated with 10% increased incidence (ED_{10}) and its 95% lower confidence bound (LED_{10}), expressed as equivalent human doses (Table 6). ED_{10}s have been used both for potency ranking and as a starting point for low-dose extrapolation (*48,49*). The EPA recently proposed using an LED_{10} for these purposes, while inviting public comment on the alternative of using 1% for tumor responses (*3*).

To gauge the potential risk at environmental exposure levels, the EPA extrapolates to doses below the experimental range. Extrapolation considers both linear and nonlinear approaches, with a linear default if there is not sufficient information to support a sublinear model (*3*). This policy rests, in part, on some general considerations. Low-dose linear models are appropriate when a carcinogen acts in concert with other exposures and processes leading to a background incidence of cancer (*50,51*).

Table 3. Liver tumor[a] incidences from the 1996 rat study

Mixture	Dose (ppm)	Females	Males
Aroclor 1260	Control[b]	1/85 (1%)*	7/98 (7%)*
	25	10/49 (20%)	3/50 (6%)
	50	11/45 (24%)	6/49 (12%)
	100	24/50 (48%)	10/49 (20%)
Aroclor 1254	Control[b]	1/85 (1%)*	7/98 (7%)
	25	19/45 (42%)	4/48 (8%)
	50	28/49 (57%)	4/49 (8%)
	100	28/49 (57%)	6/47 (13%)
Aroclor 1242	Control[b]	1/85 (1%)*	7/98 (7%)
	50	11/49 (24%)	1/50 (2%)
	100	15/45 (33%)	4/46 (9%)
Aroclor 1016	Control[b]	1/85 (1%)*	7/98 (7%)
	50	1/48 (2%)	2/48 (4%)
	100	6/45 (13%)	2/50 (4%)
	200	5/50 (10%)	4/49 (8%)

Data from Brunner et al. (*1*), and reported by the EPA (*2*).
[a]Hepatocellular adenomas, carcinomas, cholangiomas, or cholangiocarcinomas in rats alive when the first tumor was observed.
[b]One control group supported all experiments.
*Statistically significant ($p<0.05$) by Cochran-Armitage trend test.

Table 4. Liver tumor[a] incidences in female rats from less-than-lifetime exposure

Mixture	Dose (ppm)	Less-than-lifetime[b] exposure	Lifetime[c] exposure
Aroclor 1260	Control[d]	1/85 (1%)*	1/85 (1%)*
	25	4/24 (17%)	10/49 (20%)
	50	3/24 (12%)	11/45 (24%)
	100	17/24 (71%)	24/50 (48%)
Aroclor 1254	Control[d]	1/85 (1%)*	1/85 (1%)*
	25	5/24 (21%)	19/45 (42%)
	50	7/24 (29%)	28/49 (57%)
	100	6/24 (25%)	28/49 (57%)
Aroclor 1242	Control[d]	1/85 (1%)*	1/85 (1%)*
	50	3/24 (12%)	11/49 (22%)
	100	6/24 (25%)	15/45 (33%)
Aroclor 1016	Control[d]	1/85 (1%)	1/85 (1%)*
	50	0/24 (0%)	1/48 (2%)
	100	0/24 (0%)	6/45 (13%)
	200	0/24 (0%)	5/50 (10%)

Data from Brunner et al. (*1*), and reported by the EPA (*2*).
[a]Hepatocellular adenomas, carcinomas, cholangiomas, or cholangiocarcinomas.
[b]Dosed for 52 weeks and killed after 104 weeks.
[c]Dosed for and killed after 104 weeks (from Table 3).
[d]One control group supported all experiments.
*Statistically significant ($p<0.05$) by Cochran-Armitage trend test.

Table 5. Liver tumor[a] incidences from the Norback rat study

Mixture	Dose	Females	Males
Aroclor 1260	Control	1/45 (2%)*	0/31 (0%)
	100/50/0 ppm[b]	41/46 (89%)	5/40 (12%)

Data from Norback and Weltman (*8*), reevaluated by Moore et al. (*9*).
[a]Hepatocellular adenomas or carcinomas.
[b]Dosing was decreased after 16 and 24 months.
*Statistically significant ($p<0.05$) by Fisher exact test.

Table 6. Human potency estimates (mg/kg/day) derived from liver tumors in female Sprague-Dawley rats

Mixture	ED_{10}	LED_{10}	Reference
1016	2.4	1.4	(1)
1242	0.38	0.27	(1)
1254	0.086	0.067	(1)
1260	0.24	0.19	(1)
1260	0.062	0.046	(8)

Abbreviations: ED_{10}, estimated dose associated with 10% increased incidence; LED_{10}, 95% lower confidence bound on an ED_{10}.
Data from the EPA (2).

Moreover, even when the mode of action indicates a nonlinear dose–response curve in homogeneous animal populations, the presence of genetic and lifestyle factors in a heterogeneous human population tends to make the population dose–response curve more linear (51). This is because genetic and lifestyle factors contribute to a wider spread of human variability, which extends and straightens the dose–response curve over a wider range. Although these considerations provide a reasonable argument for a model that is linear at low doses, the relation of the low-dose slope to one from the experimental range is uncertain, an uncertainty that increases with distance below the experimental range.

For PCBs, genetic activity testing is generally negative (35), raising the possibility of a sublinear dose–response curve. At the low end of the experimental range (25–50 ppm), however, dose–response curves are not sublinear for Aroclors 1242, 1254, and 1260 (Table 3). Below the experimental range, some PCB congeners add to the considerable background of human exposure to dioxinlike compounds and augment processes associated with dioxin toxicity, providing a linear component to the dose–response curve. There is also considerable background exposure to nondioxinlike congeners, so additional PCB exposure can augment other carcinogenic processes that may be operating. Lacking a dose range in which a sublinear dose–response curve has been observed, the information available at this time is more suited to linear extrapolation.

Extrapolation below the ED_{10} follows a line with slope $0.10/ED_{10}$. An upper bound on the slope is $0.10/LED_{10}$. (Note that slopes are inversely proportional to ED_{10}s; high potency is indicated by high slopes but low ED_{10}s.) Slope estimates can be multiplied by lifetime average daily dose estimates (in milligrams per kilogram body weight per day) to obtain a plausible upper bound on the increased cancer risk. The slope estimates (Table 7) reflect experimental uncertainty and lot-to-lot variability of commercial mixtures, but not human heterogeneity or differences between commercial and environmental mixtures. Environmental processes have profound effects that can increase or decrease toxicity, so an Aroclor tested in the laboratory is not necessarily the best surrogate for assessing that Aroclor as altered in the environment.

Table 7. Human slope estimates (per mg/kg/day)

Mixture	Central slope	Upper-bound slope	Reference
1016	0.04	0.07	(1)
1242	0.3	0.4	(1)
1254	1.2	1.5	(1)
1260	0.4	0.5	(1)
1260	1.6	2.2	(8)

Data from the EPA (2).

Environmental Alteration of PCB mixtures

In the environment, PCBs occur as mixtures whose compositions differ from the commercial mixtures. This is because after release into the environment, mixture composition changes over time through partitioning, chemical transformation, and preferential bioaccumulation.

Partitioning refers to processes by which different fractions of a mixture separate into air, water, sediment, and soil. PCBs adsorb to organic materials, sediments, and soils; adsorption tends to increase with chlorine content of the PCBs and organic content of the other material (52). PCBs can volatilize or disperse as aerosols, providing an effective means of transport in the environment (52). Congeners with low chlorine content tend to be more volatile and also more soluble in water (52). Vaporization rates and water solubility of different Aroclors and individual congeners vary over several orders of magnitude (53,54).

Chemical transformation can occur through biodegradation of PCB mixtures in the environment. Anaerobic bacteria in sediments can selectively remove chlorines from *meta* and *para* positions, appearing to reduce the toxicity and bioaccumulation potential of residues; the occurrence and extent of these dechlorinations can be limited by sediment PCB concentrations (55–57). Dechlorination is not synonymous with detoxication, as congeners having carcinogenic activity can be formed through dechlorination. Aerobic bacteria can remove chlorines from PCBs with low chlorine content and break open the carbon rings through oxidation (55). PCBs with higher chlorine content are extremely resistant to oxidation and hydrolysis (52). Photolysis can slowly break down congeners with high chlorine content (52). Overall, however, dechlorination processes are slow, and altered PCB mixtures persist in the environment for many years.

Preferential bioaccumulation occurs in living organisms. PCBs are highly soluble in lipids and are absorbed by fish and other animals. Rates of metabolism and elimination are slow and vary by congener (58). Each species in the food chain retains persistent congeners that prove resistant to metabolism and elimination (59). Bioaccumulation through the food chain tends to concentrate congeners of higher chlorine content, producing residues that are considerably different from the original Aroclors (59–61). PCB residues in fish and turtles, changed through environmental or metabolic alteration, cannot be characterized by Aroclor 1242, 1248, 1254, or 1260 standards (60). Congener distributions in several species, including humans, do not resemble any Aroclor (33).

In humans, too, bioaccumulated PCBs also appear to be more persistent in the body (62). This is significant because in animals bioaccumulated PCBs appear to be more toxic than Aroclors (63). A study comparing mink fed a given quantity of Aroclor 1254 with mink fed Great Lakes fish contaminated with one-third that quantity of bioaccumulated PCBs (plus other chemicals) found similar liver and reproductive toxicity (64).

Assessing Risks from Environmental PCBs

Consensus has emerged on the fallacy of assessing environmental PCBs as if they were Aroclors. Safe (34) wrote, "Regulatory agencies and environmental scientists have recognized that the composition of PCBs in most environmental extracts does not resemble the composition of the commercial products." When assessing risks from environmental PCBs, the EPA now considers how environmental processes alter mixture composition (2).

Through partitioning, different portions of a PCB mixture are encountered through each exposure pathway. The mixture fraction that adsorbs to sediment or soil tends to be higher in chlorine content and persistence than the original mixture; it also tends to be less inclined to metabolism and elimination and, thus, higher in persistence and toxicity. (Persistence is not synonymous with toxicity; however, in the absence of testing of most congeners, it is reasonable to assume some correlation between persistence and toxicity.) Consequently, ingesting contaminated sediment or soil or inhaling contaminated dust can pose relatively high risks. On the

10.10950

other hand, the mixture fraction that dissolves in water or evaporates into air tends to be lower in chlorine content and persistence, so risks from ingesting water-soluble congeners or inhaling evaporated congeners would tend to be lower, in the absence of contaminated sediment or dust.

Preferential bioaccumulation can have even more pronounced effects, as each species in the food chain retains persistent congeners that prove resistant to metabolism and elimination. Bioaccumulated PCBs appear to be more toxic than Aroclors and more persistent in the body. The Aroclors tested in laboratory animals were not subject to prior selective retention of persistent congeners through the food chain. For exposure through the food chain, therefore, risks can be higher than those estimated in this assessment.

To reflect these environmental processes, the EPA now provides a tiered approach that considers how partitioning and bioaccumulation affect each exposure pathway or situation. Three tiers are provided:

- High risk and persistence (upper-bound slope, 2 per mg/kg/day; central-estimate slope, 1 per mg/kg/day). The highest slope from Table 7 is used for pathways in which environmental processes tend to increase risk: food chain exposure, sediment or soil ingestion, dust or aerosol inhalation, exposure to dioxinlike, tumor-promoting, or persistent congeners, and early-life exposure (all pathways and mixtures).
- Low risk and persistence (upper-bound slope, 0.4 per mg/kg/day; central-estimate slope, 0.3 per mg/kg/day). A lower slope is appropriate for pathways in which environmental processes tend to decrease risk: ingestion of water-soluble congeners and inhalation of evaporated congeners. Dermal exposure is also included because PCBs are incompletely absorbed through the skin; however, if an internal dose has been calculated by applying an absorption factor to reduce the external dose, then the highest slope would be used with the internal dose estimate.
- Lowest risk and persistence (upper-bound slope, 0.07 per mg/kg/day; central-estimate slope, 0.04 per mg/kg/day). The lowest slope from Table 7 is used when congener or homologue analyses verify that congeners with more than four chlorines comprise less than one-half percent of total PCBs.

The key finding supporting the lowest tier is the lower potency of Aroclor 1016 compared with 1242 (Table 3). Though these mixtures have similar chlorine content, Aroclor 1016 has virtually no congeners with more than four chlorines (Table 2). Thus, the lowest slope, derived from the Aroclor 1016 study, is appropriate only for mixtures free of congeners with more than four chlorines.

The key assumption supporting lower-tier risks for water-soluble or evaporated congeners is that partitioning has reached equilibrium. Congener or homologue analysis of environmental samples can verify whether equilibrium has been achieved. For example, if water samples contain congeners of high chlorine content, this could indicate a continuing release into the environment, a recent release without sufficient time to partition as expected, a past release with high chlorine content, or the presence of stirred-up sediment with adsorbed congeners of high chlorine content. Judgment should be used to choose a higher slope in these situations.

Because the potency range for Aroclors (Tables 6 and 7) can underestimate the range for environmental mixtures, congener analysis can be an important tool in risk assessment, providing information on the presence in environmental samples of specific congeners that contribute to cancer induction. When concentrations of dioxinlike congeners are available, risk estimates can be refined using toxic equivalency factors developed for dioxinlike PCB congeners (*65*); the EPA provides an example of this (*2*). Congener analysis can also reveal composition changes for persistent or tumor-promoting congeners that are not dioxinlike. Among these, PCB-153 (2,2′,4,4′,5,5′-hexachlorobiphenyl) is of particular interest, as it shows tumor promoting activity, is highly persistent, and comprises 12 and 21% of PCBs in human milk and fat, respectively (*33*).

Early-life exposure is treated with special concern because of the potential for higher exposure during pregnancy and nursing (*66,67*) and the possibility of greater perinatal sensitivity. Metabolic pathways are not fully developed in human infants; for example, some nursing infants receive a steroid in human milk that inhibits the activity of glucuronyl transferase, reducing PCB metabolism and elimination (*68*). In animals, Aroclor 1260 induced high incidences of liver tumors when exposure began early in life and lasted a short time (*18*). Perinatal exposure to polybrominated biphenyls enhanced susceptibility to liver tumors in female rats also exposed as adults and in male and female mice not further exposed (*69*). It is, therefore, important to assess early-life exposure through human milk and other pathways.

For less-than-lifetime exposure, current practice typically assumes that effects are proportional to exposure duration, yet there is evidence that cancer risks can be higher for persistent mixtures. Tumor incidences in rats from 52 weeks exposure to Aroclor 1260 were comparable to those from lifetime exposure (Table 4). This confirms earlier findings that some PCBs persist in the body and retain biological activity after exposure stops (*70*). Thus, current practice can underestimate risks from persistent mixtures.

Some Implications and Research Needs

The EPA's new approach highlights how environmental processes—partitioning, chemical transformation, and preferential bioaccumulation—alter the cancer potential of environmental mixtures. Bioaccumulated mixtures are of greatest concern because they appear to be more toxic than commercial mixtures and more persistent in the body. Two highly exposed populations are exposed to bioaccumulated mixtures. One is nursing infants, for whom average intake of total PCBs was estimated at 1.5–27 μg/kg/day (*35*), 3–11 μg/kg/day (*46*), or 2.1 μg/kg/day (*71*), compared to 0.2 μg/kg/day estimated for adults (*46,71*). Dietary intake varies widely, often depending on proximity to where PCBs were released into the environment (*35,46*). This gives rise to another highly exposed population: people who derive much of their diet from local sources that happen to be contaminated, for example, subsistence anglers and their families who frequently eat fish from a contaminated source.

One prominent research need is a cancer study comparing commercial and bioaccumulated mixtures. The EPA's assessment warns that risks from exposure through contaminated food can be underestimated, but the extent is not quantified. Also needed is a method for using lifetime studies to assess risks from less-than-lifetime exposure to persistent agents. The EPA's assessment warns that assuming risk and exposure duration are proportional can underestimate risks from persistent mixtures, but the extent is not quantified. For persistent agents, delivered dose might be a better dose metric than the lifetime average daily dose.

The next question is how environmental processes alter the potential for noncancer toxicity and adverse ecological effects. This requires a separate analysis, as different sets of congeners may be associated with cancer and other effects. Characterizing the effects of environmental processes can improve assessments of these other effects. The same may be true when assessing complex environmental mixtures other than PCBs.

Additionally, the new assessment may change the way analytical laboratories characterize environmental samples. The prevailing practice has been to describe environmental

samples in terms of Aroclors, even though environmental processes make the composition of environmental mixtures considerably different from Aroclor mixtures. Congener and homologue analysis may become preferred for the ability to estimate the dioxin toxic equivalence of an environmental mixture or verify whether PCBs found in water or air are, as expected, of low chlorine content and persistence. In particular, analysis of dioxinlike congeners may be warranted for exposure through contaminated food; recently, PCB–126 (3,3′,4,4′,5-pentachlorobiphenyl), the PCB congener with the highest dioxin toxic equivalency factor (*65*), was found in all of 63 samples of beef back fat (*72*).

Finally, the EPA's assessment proves that good research can indeed improve risk assessments. The recent study of four Aroclors strengthened the case that all PCB mixtures can cause cancer, resolving questions about the cancer hazard from different PCB mixtures and providing key information that now enables risk assessors to quantify differences in cancer potency.

References and Notes

1. Brunner MJ, Sullivan TM, Singer AW, Ryan MJ, Toft JD II, Menton RS, Graves SW, Peters AC. An Assessment of the Chronic Toxicity and Oncogenicity of Aroclor-1016, Aroclor-1242, Aroclor-1254, and Aroclor-1260 Administered in Diet to Rats. Battelle Study No SC920192. Columbus, OH:Battelle, 1996.
2. U.S. EPA. PCBs: Cancer Dose–Response Assessment and Application to Environmental Mixtures. EPA/600/P–96/001F. Washington, DC:U.S. Environmental Protection Agency, 1996.
3. U.S. EPA. Proposed guidelines for carcinogen risk assessment; notice. Fed Reg 61(79):17960–18011 (1996).
4. U.S. EPA. Guidelines for the health risk assessment of chemical mixtures. Fed Reg 51(185):34014–34025 (1986).
5. U.S. EPA. Report on Peer Review Workshop on PCBs: Cancer Dose–Response Assessment and Application to Environmental Mixtures. Washington:U.S. Environmental Protection Agency, 1996.
6. Kimbrough RD, Squire RA, Linder RE, Strandberg JD, Montali RJ, Burse VW. Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyl Aroclor 1260. J Natl Cancer Inst 55:1453–1459 (1975).
7. Schaeffer E, Greim H, Goessner W. Pathology of chronic polychlorinated biphenyl (PCB) feeding in rats. Toxicol Appl Pharmacol 75:278–288 (1984).
8. Norback DH, Weltman RH. Polychlorinated biphenyl induction of hepatocellular carcinoma in the Sprague-Dawley rat. Environ Health Perspect 60:97–105 (1985).
9. Moore JA, Hardisty JF, Banas DA, Smith MA. A comparison of liver tumor diagnoses from seven PCB studies in rats. Regul Toxicol Pharmacol 20:362–370 (1994).
10. National Cancer Institute. Bioassay of Aroclor 1254 for Possible Carcinogenicity. Carcinogenesis Technical Report Series 38. Washington, DC:National Cancer Institute, 1978.
11. Morgan RW, Ward JM, Hartman PE. Aroclor 1254-induced intestinal metaplasia and adenocarcinoma in the glandular stomach of F344 rats. Cancer Res 41:5052–5059 (1981).
12. Ward JM. Proliferative lesions of the glandular stomach and liver in F344 rats fed diets containing Aroclor 1254. Environ Health Perspect 60:89–95 (1985).
13. Kimbrough RD, Linder RE, Gaines TB. Morphological changes in livers of rats fed polychlorinated biphenyls: light microscopy and ultrastructure. Arch Environ Health 25:354–364 (1972).
14. Kimbrough RD, Linder RE. Induction of adenofibrosis and hepatomas of the liver in BALB/cJ mice by polychlorinated biphenyls (Aroclor 1254). J Natl Cancer Inst 53(2):547–552 (1974).
15. Kimura NT, Baba T. Neoplastic changes in the rat liver induced by polychlorinated biphenyl. Gann 64:105–108 (1973).
16. Ito N, Nagasaki H, Arai M, Makiura S, Sugihara S, Hirao K. Histopathologic studies on liver tumorigenesis induced in mice by technical polychlorinated biphenyls and its promoting effect on liver tumors induced by benzene hexachloride. J Natl Cancer Inst 51(5):1637–1646 (1973).
17. Ito N, Nagasaki H, Makiura S, Arai M. Histopathological studies on liver tumorigenesis in rats treated with polychlorinated biphenyls. Gann 65:545–549 (1974).
18. Rao CV, Banerji AS. Induction of liver tumors in male Wistar rats by feeding polychlorinated biphenyls (Aroclor 1260). Cancer Lett 39:59–67 (1988).
19. Brown DP. Mortality of workers exposed to polychlorinated biphenyls—an update. Arch Environ Health 42(6):333–339 (1987).
20. Bertazzi PA, Riboldi L, Pesatori A, Radice L, Zocchetti C. Cancer mortality of capacitor manufacturing workers. Am J Ind Med 11:165–176 (1987).
21. Sinks T, Steele G, Smith AB, Watkins K, Shults RA. Mortality among workers exposed to polychlorinated biphenyls. Am J Epidemiol 136(4):389–398 (1992).
22. Gustavsson P, Hogstedt C, Rappe C. Short-term mortality and cancer incidence in capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Am J Ind Med 10:341–344 (1986).
23. Nicholson WJ, Landrigan PJ. Human health effects of polychlorinated biphenyls. In: Dioxins and Health (Schecter A, ed). New York:Plenum, 1994;487–524.
24. Bahn AK, Rosenwaike I, Herrmann N, Grover P, Stellman J, O'Leary K. Melanoma after exposure to PCBs (letter). N Engl J Med 295:450 (1976).
25. Loomis D, Browning SR, Schenck AP, Gregory E, Savitz DA. Cancer mortality among electric utility workers exposed to polychlorinated biphenyls. Occup Environ Med 54:720–728 (1997).
26. Hardell L, van Bavel B, Lindström G, Fredrikson M, Hagberg H, Liljegren G, Nordström M, Johansson B. Higher concentrations of specific polychlorinated biphenyl congeners in adipose tissue from non-Hodgkin's lymphoma patients compared with controls without a malignant disease. Int J Oncol 9:603–608 (1996).
27. Rothman N, Cantor KP, Blair A, Bush D, Brock JW, Helzlsouer K, Zahm SH, Needham LL, Pearson GR, Hoover RN, et al. A nested case–control study of non-Hodgkin lymphoma and serum organochlorine residues. Lancet 350:240–244 (1997).
28. Morita M, Nakagawa J, Rappe C. Polychlorinated dibenzofuran (PCDF) formation from PCB mixture by heat and oxygen. Bull Environ Contam Toxicol 19:665–670 (1978).
29. Masuda Y. The Yusho rice oil poisoning incident. In: Dioxins and Health (Schecter A, ed). New York:Plenum, 1994;633–659.
30. Silberhorn EM, Glauert HP, Robertson LW. Carcinogenicity of polyhalogenated biphenyls: PCBs and PBBs. Crit Rev Toxicol 20(6):439–496 (1990).
31. Buchmann A, Kunz W, Wolf CR, Oesch F, Robertson LW. Polychlorinated biphenyls, classified as either phenobarbital- or 3-methylcholanthrene-type inducers of cytochrome P-450, are both hepatic tumor promoters in diethylnitrosamine-initiated rats. Cancer Lett 32:243–253 (1986).
32. Buchmann A, Ziegler S, Wolf A, Robertson LW, Durham SK, Schwarz M. Effects of polychlorinated biphenyls in rat liver: correlation between primary subcellular effects and promoting activity. Toxicol Appl Pharmacol 111:454–468 (1991).
33. McFarland VA, Clarke JU. Environmental occurrence, abundance, and potential toxicity of polychlorinated biphenyl congeners: considerations for a congener-specific analysis. Environ Health Perspect 81:225–239 (1989).
34. Safe S. Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment. Crit Rev Toxicol 24(2):87–149 (1994).
35. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Polychlorinated Biphenyls. Atlanta,GA:Agency for Toxic Substances and Disease Registry, 1997.
36. Wester RC, Bucks DAW, Maibach HI, Anderson J. Polychlorinated biphenyls (PCBs): dermal absorption, systemic elimination, and dermal wash efficiency. J Toxicol Environ Health 12:511–519 (1983).
37. Wester RC, Mobayen M, Maibach HI. *In vivo* and *in vitro* absorption and binding to powdered stratum corneum as methods to evaluate skin absorption of environmental chemical contaminants from ground and surface water. J Toxicol Environ Health 21:367–374 (1987).
38. Wester RC, Maibach HI, Bucks DAW, McMaster J, Mobayen M. Percutaneous absorption and skin decontamination of PCBs: *in vitro* studies with human skin and *in vivo* studies in the rhesus monkey. J Toxicol Environ Health 31:235–246 (1990).
39. Wester RC, Maibach HI, Sedik L, Melendres J, Wade M. Percutaneous absorption of PCBs from soil: *in vivo* rhesus monkey, *in vitro* human skin, and binding to powdered human stratum corneum. J Toxicol Environ Health 39:375–382 (1993).
40. Oakley GG, Devanaboyina U, Robertson LW, Gupta RC. Oxidative DNA damage induced by activation of polychlorinated biphenyls (PCBs): implications for PCB-induced oxidative stress in breast cancer. Chem Res Toxicol 9(8):1285–1292 (1996).
41. Birnbaum LS. Endocrine effects of prenatal exposure to PCBs, dioxins, and other xenobiotics: implications for policy and future research. Environ Health Perspect 102(8):676–679 (1994).
42. Birnbaum LS, DeVito MJ. Use of toxic equivalency factors for risk assessment for dioxins and related compounds. Toxicology 105(2-3):391–401 (1995).
43. Brown JF Jr, Silkworth JB, Mayes BA. Characterization of PCB Composition, Tissue Accumulation, and Correlations with Tumorigenicity in Chronically Dosed Male and Female Sprague-Dawley Rats. Battelle Study No SC920192. Columbus, OH:Battelle, 1997.
44. Schulz DE, Petrick G, Duinker JC. Complete characterization of polychlorinated biphenyl congeners in commercial Aroclor and Clophen mixtures by multidimensional gas chromatography-electron capture detection. Environ Sci Technol 23(7):852–859 (1989).
45. Frame GM, Cochran JW, Bøwadt SS. Complete PCB congener distributions for 17 Aroclor mixtures determined by 3 HRGC systems optimized for comprehensive, quantitative, congener-specific analysis. J High Resolut Chromatogr 19:657–668 (1996).
46. WHO. Polychlorinated Biphenyls and Terphenyls. 2nd ed. Environmental Health Criteria 140. Geneva:World Health Organization, 1993.
47. McConnell EE, Solleveld HA, Swenberg JA, Boorman GA. Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J Natl Cancer Inst 76(2):283–289 (1986).
48. Cogliano VJ. The U.S. EPA's methodology for adjusting the reportable quantities of potential carcinogens. In: Proceedings of the 7th National Conference on Management of Uncontrolled Hazardous Wastes (Superfund '86), December 1986, Washington, DC. Washington, DC:Hazardous Materials Control Research Institute, 1986; 182–185.
49. National Research Council. Issues in Risk Assessment. Washington, DC:National Academy Press, 1993.
50. Crump KS, Hoel DG, Langley CH, Peto R. Fundamental carcinogenic processes and their implications for low dose risk assessment. Cancer Res 36:2973–2979 (1976).
51. Lutz WK. Dose–response relationship and low dose extrapolation in chemical carcinogenesis. Carcinogenesis 11(8):1243–1247 (1990).
52. Callahan MA, Slimak MW, Gabel NW, May IP, Fowler CF, Freed JR, Jennings P, Durfee RL, Whitmore FC, Maestri B, et al. Water-related Environmental Fate of 129 Priority Pollutants, Vol 1. EPA–440/4–79–029a. Washington,DC:U.S. Environmental Protection Agency, 1979.
53. Hutzinger O, Safe S, Zitko V. The Chemistry of PCB's. Boca Raton, FL:CRC Press, 1974.
54. Erickson MD. Analytical Chemistry of PCBs. Boston, MA:Butterworth, 1986.

10.10952

55. Abramowicz DA. Aerobic and anaerobic biodegradation of PCBs: a review. Biotechnology 10(3):241–251 (1990).
56. Brown JF Jr, Wagner RE. PCB movement, dechlorination, and detoxication in the Acushnet Estuary. Environ Toxicol Chem 9:1215–1233 (1990).
57. Lake JL, Pruell RJ, Osterman FA. An examination of dechlorination processes and pathways in New Bedford Harbor sediments. Marine Environ Res 33:31–47 (1992).
58. Matthews HB, Anderson MW. Effect of chlorination on the distribution and excretion of polychlorinated biphenyls. Drug Metab Dispos 3(5):371–380 (1975).
59. Oliver BG, Niimi AJ. Trophodynamic analysis of polychlorinated biphenyl congeners and other chlorinated hydrocarbons in the Lake Ontario ecosystem. Environ Sci Technol 22:388–397 (1988).
60. Schwartz TR, Stalling DL, Rice CL. Are polychlorinated biphenyl residues adequately described by Aroclor mixture equivalents? Isomer-specific principal components analysis of such residues in fish and turtles. Environ Sci Technol 21:72–76 (1987).
61. Lake JL, McKinney R, Lake CA, Osterman FA, Heltshe J. Comparisons of patterns of polychlorinated biphenyl congeners in water, sediment, and indigenous organisms from New Bedford Harbor, Massachusetts. Arch Contam Toxicol 29:207–220 (1995).
62. Hovinga ME, Sowers M, Humphrey HEB. Historical changes in serum PCB and DDT levels in an environmentally-exposed cohort. Arch Environ Contam Toxicol 22:362–366 (1992).
63. Aulerich RJ, Ringer RK, Safronoff J. Assessment of primary vs. secondary toxicity of Aroclor 1254 to mink. Arch Environ Contam Toxicol 15:393–399 (1986).
64. Hornshaw TC, Aulerich RJ, Johnson HE. Feeding Great Lakes fish to mink: effects on mink and accumulation and elimination of PCBs by mink. J Toxicol Environ Health 11:933–946 (1983).
65. Ahlborg UG, Becking GC, Birnbaum LS, Brouwer A, Derks HJGM, Feeley M, Golor G, Hanberg A, Larsen JC, Liem AKD, et al. Toxic equivalency factors for dioxin-like PCBs. Chemosphere 28(6):1049–1067 (1994).
66. Dewailly É, Weber J-P, Gingras S, Laliberté C. Coplanar PCBs in human milk in the province of Québec, Canada: are they more toxic than dioxin for breast fed infants? Bull Environ Contam Toxicol 47:491–498 (1991).
67. Dewailly É, Ryan JJ, Laliberté C, Bruneau S, Weber J-P, Gingras S, Carrier G. Exposure of remote maritime populations to coplanar PCBs. Environ Health Perspect 102(suppl 1):205–209 (1994).
68. Calabrese EJ, Sorenson AJ. The health effects of PCBs with particular emphasis on human high risk groups. Rev Environ Health 2:285–304 (1977).
69. National Toxicology Program. Toxicology and Carcinogenesis Studies of Polybrominated Biphenyls (CAS No. 67774–32–7) (Firemaster FF–1) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies). TR 398. Research Triangle Park, NC:National Toxicology Program, 1993.
70. Anderson LM, Fox SD, Dixon D, Beebe LE, Issaq HJ. Long-term persistence of polychlorinated biphenyl congeners in blood and liver and elevation of liver aminopyrine demethylase activity after a single high dose of Aroclor 1254 to mice. Environ Toxicol Chem 10:681–690 (1991).
71. Kimbrough RD. Polychlorinated biphenyls (PCBs) and human health: an update. Crit Rev Toxicol 25(2): 133–163 (1995).
72. Winters D, Cleverly D, Lorber M, Meier K, Dupuy A, Byrne C, Deyrup C, Ellis R, Ferrario J, Leese W, et al. Coplanar polychlorinated biphenyls (PCBs) in a national sample of beef in the United States: preliminary results. Organohalogen Compounds 28:350–354 (1996).

10.10953

Save Energy

PREVENT AIR POLLUTION

PROTECT OUR HEALTH

SAFEGUARD OUR ENVIRONMENT

SAVE MONEY

Protection of the environment is an integral part of health promotion and disease prevention. Increasing energy efficiency results in the reduction of sulfur dioxide (respiratory irritant and component of acid rain), nitrogen oxide (contributor to smog and component of acid rain), and carbon dioxide (implicated in global climate change).

Simple efforts to reduce energy bills also can significantly reduce facility operating costs. Energy efficiency upgrades (e.g., lighting, office equipment, heating, ventilation, and air conditioning) in offices, clinics and research facilities can save 30 to 40 percent on energy costs, with payback for investment within three years and continuous savings thereafter.

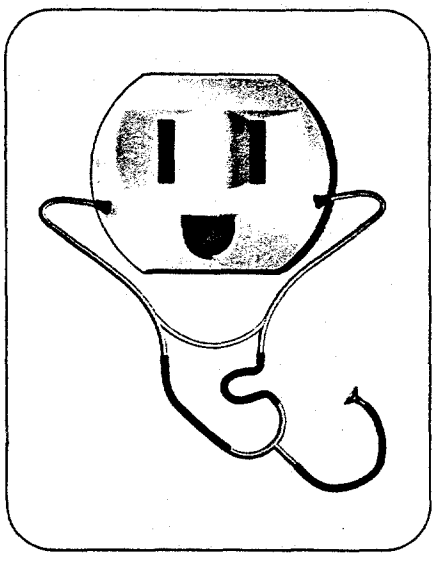
The National Association of Physicians for the Environment (NAPE), in cooperation with the U.S. Environmental Protection Agency, has developed an information assistance program designed especially to help healthcare and biomedical research facilities of less than 100,000 square feet become more energy efficient.

The EPA's ENERGY STAR® programs offer expert technical assistance, financial information, and public relations assistance. More than 2,000 organizations already participating in the programs are saving millions of dollars and preventing many tons of air pollutants from being released. All programs are voluntary!

Participation in energy efficiency programs demonstrates a commitment to protecting the environment; money is saved at the same time. Materials (brochures, posters, news releases) are provided to inform the public of your environmental contribution to keeping people healthy.

For more information, visit NAPE's homepage:
http://www.intr.net/napenet.

EPA DOE
SAVING THE EARTH. SAVING YOUR MONEY.



Socket Doc says:
"Pollution prevention is disease prevention."

Socket Doc posters and draft news releases are available at no charge.

NATIONAL ASSOCIATION OF PHYSICIANS FOR THE ENVIRONMENT

FAX THIS FORM TO 301-530-8910

Energy Efficiency in Healthcare and Research

☐ Yes, please send me more information. I understand there is no obligation.

☐ We already have made energy efficient upgrades (e.g., lighting, HVAC, office equipment). *NAPE wants to know about your facility's successes (large or small), so that we may inform your colleagues. Please contact us.*

Name _____

Title _____

Organization _____

Address _____

_____

Phone _____ Fax _____

e-mail _____

National Association of Physicians for the Environment
6410 Rockledge Drive, Suite 412
Bethesda, MD 20817
Fax 301-530-8910 Ph 301-571-9790
e-mail nape@ix.netcom.com

Mortality in Male and Female Capacitor Workers Exposed to Polychlorinated Biphenyls

Renate D. Kimbrough, MD
Martha L. Doemland, PhD
Maurice E. LeVois, PhD

A mortality study was conducted in workers with at least 90 days' exposure to polychlorinated biphenyls (PCBs) between 1946 and 1977. Vital status was established for 98.7% of the 7075 workers studied. In hourly male workers, the mortality from all cancers was significantly below expected (standardized mortality ratio [SMR] = 81; 95% confidence interval [CI], = 68 to 97) and comparable to expected (SMR = 110; 95% CI, 93 to 129) in hourly female workers. No significant elevations in mortality for any site-specific cause were found in the hourly cohort. All-cancer mortality was significantly below expected in salaried males (SMR = 69; 95% CI, 52 to 90) and comparable to expected in salaried females (SMR = 75; 95% CI, 45 to 118). No significant elevations were seen in the most highly exposed workers, nor did SMRs increase with length of cumulative employment and latency. None of the previously reported specific excesses in cancer mortality were seen. This is the largest cohort of male and female workers exposed to PCBs. The lack of any significant elevations in the site-specific cancer mortality of the production workers adds important information about human health effects of PCBs.

Polychlorinated biphenyls (PCBs) are complex mixtures of 209 different chlorinated biphenyl congeners. They were used extensively in the United States from the 1930s through 1977 in a variety of industrial applications. PCB mixtures have several chemical and physical properties that made them extremely versatile, including resistance to acids and bases as well as oxidation and reduction; compatibility with organic materials; and thermal stability and nonflammability. The major volume usage of PCBs was in capacitors and transformers as dielectric fluids, but they were also used as lubricants and sealants; as additives in paint, plastics, newspaper print, and dyes; as extenders in pesticides; and as heat transfer and hydraulic fluids. More than 95% of the liquid-filled electrical capacitors and transformers produced before the early 1970s contained PCBs. PCBs are persistent chemicals and have bioaccumulated in the environment. They continue to be detected in air, soil, water, and sediment. Trace amounts are also present in the tissues of wildlife, domestic animals, and humans;[1] however, the levels of PCBs in the environment are declining.

The potential for adverse human health effects of PCB exposure has been a concern since the early 1970s and resulted in the Environmental Protection Agency's ban of the production of PCBs in 1978. Current knowledge regarding the human health effects of PCBs is limited, inconsistent, and difficult to interpret. Occupational mortality studies of capacitor workers have reported

From the Institute for Evaluating Health Risks, Washington, DC.
Portions of this study were presented in poster form at the 1997 North American Congress of Clinical Toxicology Annual Meeting, September 11–16, 1997.
Address correspondence to: Renate D. Kimbrough, MD, Institute for Evaluating Health Risks, Suite 302, 1629 K Street, NW, Washington, DC 20006.

higher than expected rates of melanoma[2] and cancer of the liver,[3,4] rectum,[3] gastrointestinal tract,[5] brain,[2] and hematopoietic system.[5] The site-specific elevations, however, have not been observed consistently across studies. More importantly, many of the elevated cause-specific standardized mortality ratios (SMRs) reported in the various studies were not correlated with higher and/or longer exposures to PCBs or longer latency periods, which would be suggestive of a dose-response relationship.

We conducted a retrospective cohort mortality study of 7075 workers exposed to PCBs during the capacitor manufacturing process. The cohort represents all hourly and salaried workers from two plants in upstate New York who were employed for 90 days or more from 1946, when capacitor manufacturing began, through June 15, 1977, when PCB use was completely phased out. A cohort of the same workforce was previously assembled by other investigators[6,7] but was incomplete because it did not include approximately 850 workers. A portion of the highly exposed male workers in this study were also included in the cohort assembled by Brown and Jones.[3]

Methods

Study Purpose

The purpose of this study was to further explore previously reported excesses in cancer-specific mortality in capacitor workers exposed to PCBs. Six a priori cancers that were previously reported as being elevated were the primary focus of this study (melanoma, liver, rectum, gastrointestinal tract, brain, and hematopoietic cancers).

Study Population

All hourly and salaried workers employed for at least 90 days between January 1, 1946, and June 15, 1977, in two capacitor manufacturing plants in upstate New York were included in the cohort. Salaried personnel were included in the cohort because they were often involved in the manufacturing process and all personnel were housed in the same building. Personal identifiers, including Social Security number, demographics, and each worker's job history information, were abstracted from employment records that had been microfilmed by the company. Completeness of the cohort was established by our reviewing all available company records, such as pension rosters and the quarterly earning reports of the Social Security Administration (SSA, 941 forms; the complete payroll record for every employee that was ever paid by the company, by plant and location).

Vital Status Determination

The National Death Index and the Equifax Nationwide Death Search tapes were matched against our cohort to identify deceased cohort members through December 31, 1993. A match was considered to exist when at least six digits of the Social Security number, the date of birth, and the first and last name for men and first name for women matched. Death certificates were obtained from the state where death occurred and were coded by a certified nosologist. The underlying cause of death was coded using the International Classification of Diseases (ICD) revision in force at the time of death.[8]

Significant effort went into establishing the vital status of workers not identified as deceased, working, or receiving a pension. Company files were used to identify workers still employed in 1994 and retired workers receiving a pension. The locating services of Equifax were used to establish "alive" status for cohort members that were separated from employment at the time of vital status determination. This was done primarily through the identification of cohort members involved in activities such as insurance underwriting and claims and financial transactions, such as mortgage applications. Computerized county voter registration lists and annual R.L. Polk and Haines City Directories were also used and matched against the cohort list to establish alive status. When employees could not be identified as alive by the above sources, direct contact with neighbors or relatives was attempted to verify vital status. A private investigator was employed to locate difficult-to-find former employees. Long-term workers who were currently employed also assisted us in locating former employees. Workers with unknown vital statuses were considered to be "lost-to-follow-up" and were observed through their last date of employment.

Exposure Assessment

Capacitors were produced by assembling the capacitor canisters, filling them with PCBs, heating them to achieve better impregnation, and closing, soldering, and cleaning them. Capacitors were also repaired, which entailed removing the cover, draining the PCBs, repairing the unit, and re-constructing the capacitor.

From 1946 through 1971, the Aroclor™ mixtures (the tradename for Monsanto [St. Louis, MO] PCB products) 1254 and 1242 were predominantly used. Aroclor 1254 was phased out after 1954, and Aroclor 1242 was used until 1971. From 1971 until 1977, Aroclor 1016 was used. Aroclor 1016 was similar to Aroclor 1242 but with lower environmental persistence, which was accomplished by the removal of higher chlorinated homologs.

All jobs were classified according to their levels of PCB exposure prior to the determination of vital status. Jobs with direct PCB contact (dermal contact and/or inhalation exposure to high PCB air levels) experienced while filling, impregnating, repairing, or moving PCB-filled capacitors were classified as high-exposure jobs. In the areas of filling and impregnating, air levels ranged from 227 to 1500 $\mu g/m^3$ in 1975,[9] and in

the spring of 1977, when PCB use had declined substantially, air levels ranged from 170 to 576 μg/m³.[10] Work operations in which no PCBs were used, such as the winding, can, and cover manufacture and the assembly and shipping department, were tested in the spring of 1977, and air levels ranged from 3 to 50 μg/m³.[10] These jobs were classified as low exposure, and workers in these areas primarily had inhalation exposure to the background levels of PCBs in the plant. There were jobs for which the PCB exposure of the worker varied depending on the location where the individual was performing the task. Insufficient information was provided in the worker history records to determine the location of these jobs, and it was therefore not possible to assign exposure classifications for them. These jobs were classified as undefinable.

Between 1976 and 1979, the general population had average serum PCB levels on a wet-weight basis of approximately 5 to 7 parts per billion (ppb; measured in ng/mL), with levels ranging from nondetectable to 20 ppb (ng/mL),[1] with occasional higher levels.[11] In a population of 290 self-selected employees from this plant, the PCB levels measured in serum on a wet-weight basis ranged from 6 to 2530 ppb (ng/mL) for the lower chlorinated compounds and ranged from 1 to 546 ppb (ng/mL) for the higher chlorinated PCBs.[12] In 1976, Lawton et al[13,14] found similar high levels in a group of 190 workers who had been selected because of their estimated high exposures, establishing the extensive exposure to PCBs.

Exposure to other chemicals in these plants was limited. A small number of workers were exposed to low concentrations of toluene in the painting area, with air levels from nondetectable to 21.4 μg/m³ (time-weighted average = 188 mg/m³). Trichloroethylene levels in the degreasing area ranged from 3.7 to 321 μg/m³ (time-weighted average = 269 mg/m³). Low air levels of lead, aluminum, and iron were also reported in the soldering area.[10]

Statistical Analyses

The mortality experience of the cohort is expressed as the SMR (number of observed deaths in the cohort divided by the number of expected deaths derived from the comparison population). Age-, sex-, race-, and calendar-specific mortality rates for the US population and the regional population from the eight counties surrounding the plants (Franklin, Essex, Warren, Saratoga, Washington, Hamilton, Clinton, and Herkimer counties) were used to calculate the expected number of deaths. The US mortality rate tables were provided by the National Institute of Occupational Safety and Health and comprised 92 causes of death for the years 1946 through 1993 for white and nonwhite males and females in 5-year age and calendar time periods.[15] The regional mortality rate tables were obtained from the Mortality and Population Data System[16] and comprised 62 causes of death for the years 1950 through 1989 for malignant neoplasms and the years 1962 through 1989 for nonmalignant causes. The regional rates were also provided for white and nonwhite males and females in 5-year age and calendar time periods. Person-years were accumulated beginning on the 91st day of employment and continued to December 31, 1993, or the date of death, whichever came first. Person-years for workers lost to follow-up were calculated through the last date they were known to be alive, which was typically their last date of employment. Person-years were combined into 5-year age-, sex-, race-, and calendar-specific categories and multiplied by the corresponding age-, sex-, race-, and calendar-specific US mortality rates (or regional rates) to yield the expected numbers. Calculations were performed using OCMAP (Occupational Cohort Mortality Analysis Program).[17] The statistical significance of the differences between the observed and expected numbers was tested assuming a Poisson distribution for the observed deaths, using a two-sided test of significance.[18] SMRs were calculated for all 92 underlying causes of death; however, only selected causes of death, including all causes, all cancers, all site-specific cancers, the major cardiovascular diseases, diabetes, cirrhosis of the liver, and accidental causes are shown.

Presentation of the exposure-specific analysis is confined to those workers who had the greatest potential for exposure, which was defined in three ways: (1) all hourly workers who ever worked in a high-exposure job; (2) all hourly workers who had worked for at least 6 months in a high-exposure job; and (3) all hourly workers who worked for at least 1 year in a high-exposure job. Only 112 male and 12 female workers were exclusively employed in high-exposure jobs, thereby restricting our ability to analyze them as a separate group.

In addition to the overall SMRs, the impact of PCB exposure on mortality in both the total cohort and the high-exposure cohort was examined by categories of cumulative length of employment (<1 year, 1 to <5 years, 5 to <10 years, and ≥10 years) and years of latency. Two latency categories were defined: one as less than or equal to 20 years since first exposure, and the other as greater than 20 years since first exposure. SMRs were calculated for each category of cumulative length of employment by latency for all-causes, all-cancers, and specific causes for which there was an elevated total SMR with two or more observed deaths and for which the lower boundary of the 95% confidence interval (CI) was 90 or above. This analysis examined the trend across categories of increasing length of employment and latency. The purpose was to determine whether the SMRs increased over the length of employment and latency

TABLE 1
Demographic Characteristics of 4,062 Male and 3,013 Female Workers

Characteristic	Hourly Workers		Salaried Workers		Total (mean)
	Male	Female	Male	Female	
Number of workers	2,984	2,544	1,078	469	7,075
Number of person-years	85,991	75,674	34,755	16,358	212,778
Number of deaths	586	380	177	52	1,195
Number of missing death certificates	20	4	9	4	37
Number lost to follow-up	33	52	7	3	95
Mean age started work	26	29	29	25	(27)
Mean time employed, years	6.2	5.8	5.7	4.8	(5.6)
Mean age stopped working	33	35	35	31	(34)
Mean age at death	61	64	62	61	(62)
Mean age for workers alive on December 31, 1993	53	57	60	59	(57)
Mean follow-up time, years	28	30	32	34	(31)
Percentage who attended college	15	7	73	26	(30)

categories, which would suggest a trend consistent with a dose-response effect.

The individual category-specific SMRs are not particularly relevant, and, because of the small number of deaths, the rates are unstable. Trend analysis using the Mantel-Cox chi-square test[19] with one degree of freedom was done to determine the significance of the trend among the observed over the expected rates within the subpopulation of women who died of intestinal cancer.

Results

Description of the Cohort

The cohort consisted of 2984 hourly white male, 2544 hourly white female, 1078 salaried white male, and 469 white salaried female workers (Table 1). Hourly male and female workers contributed 85,991 and 75,674 person-years of observation, respectively, and salaried male and female workers contributed 34,755 and 16,358 person-years. Only 1.1% of the hourly male, 2% of the hourly female, and less than 1% of the salaried workers were lost to follow-up. The average age at entry for the different groups, the mean time employed, and the mean follow-up time are also shown in Table 1. The mean age at the end of employment for the four subgroups ranged from 31 to 35 years. The mean age of the 5880 cohort members alive at the end of the follow-up period was 57 years, while the mean age at death was 62 (Table 1). Among the salaried male cohort, 73% ever attended college, while in the hourly male cohort only 15% ever attended college. Among salaried female workers, 26% ever attended college, and among the hourly female workers, 7% ever attended college.

There were 586 deaths among the hourly male workers, and 380 deaths among hourly female workers. There were 177 deaths among the salaried male workers and 52 deaths among the salaried female workers. For 38 workers, the cause of death was not known, either because the death certificate could not be located or because the cause of death was not provided on the death certificate.

In Table 2 the length of employment and years of follow-up for the cohort are shown. Over one third of hourly male and female workers and nearly one third of the salaried male cohort worked less than 1 year, and nearly one third of hourly and salaried male and female employees worked 5 years or more. The distribution of follow-up time for the cohort is also presented and indicates that follow-up time for the majority of the cohort exceeded 25 years. The distribution of length of employment by years of follow-up (not shown) illustrated that follow-up time was longest for the long-term workers (ie, those with the longest overall exposure times were observed for the longest period of time).

In Table 3 the distribution of exposure type by gender and pay status is presented. Females primarily held jobs with low exposures (97% of women); they were engaged in the winding operation, which was done in a separate "clean" room, or they held clerical salaried jobs. The distribution of exposure type presented in Table 3 indicates that workers, especially hourly male workers, experienced different exposures throughout their employment. For example, in the hourly male cohort, 27% of men had jobs with high, low, and undefinable exposures during their employment (not shown), and 66% of the male hourly cohort held a job with undefinable exposure sometime during their employment.

The observed deaths, expected deaths, SMRs, and their 95% CIs for selected causes of death for the cohort by subgroup are presented in Table 4. All malignant neoplasms, the major cardiovascular diseases, diabetes, cirrhosis of the liver, and accidental causes of death are presented. Causes with only one death are not presented, nor are irrelevant causes with small numbers of deaths (ie, mental disorders). The expected numbers were calculated from the

10.10958

TABLE 2
Length of Employment and Follow-Up Time

Characteristic	Hourly Workers (%)		Salaried Workers (%)	
	Male	Female	Male	Female
Length of employment, years				
<1	1066 (35.7)	842 (33.1)	343 (31.8)	106 (22.6)
1 to <5	864 (29.0)	902 (35.5)	341 (31.6)	216 (46.1)
5 to <10	381 (12.8)	251 (9.9)	177 (16.4)	83 (17.7)
10 to <15	212 (7.1)	208 (8.2)	87 (8.1)	130 (5.8)
≥15	461 (15.4)	341 (13.4)	130 (12.1)	37 (7.9)
Years of follow-up				
<10	61 (2.0)	28 (1.1)	11 (1.0)	0
10 to <20	383 (12.8)	333 (13.1)	67 (6.2)	32 (6.8)
20 to <25	656 (22.0)	626 (24.6)	156 (14.5)	33 (7.0)
25 to <30	830 (27.8)	487 (19.1)	206 (19.1)	72 (15.4)
30 to <35	267 (8.9)	240 (9.4)	159 (14.7)	51 (10.9)
≥35	787 (26.4)	830 (32.6)	479 (44.4)	281 (59.9)

TABLE 3
Distribution of Exposure Types

Characteristic	Hourly Workers		Salaried Workers	
	Male	Female	Male	Female
Number ever highly exposed (%)	1268 (42.4)	352 (13.8)	87 (8.0)	10 (2.1)
Median years in high exposure	1.7	1.6	3.2	2.0
Number ever undefinably exposed (%)	1984 (66.4)	379 (14.8)	407 (37.7)	15 (3.1)
Median years in undefinable exposure	1.8	1.5	2.4	1.4
Number ever low exposed (%)	2343 (78.5)	2468 (97.0)	831 (77.0)	459 (97.8)
Median years in low exposure	6.5	6.5	5.0	4.9

mortality rates of the US population. Among the hourly workers, the all-causes mortality was significantly lower than that of the US population (SMR = 84, 95% CI, 77 to 91 for males; SMR = 90, 95% CI, 82 to 100 for females). The all-cancers mortality was also significantly lower than that of the US population in hourly male workers (SMR = 81; 95% CI, 68 to 97). In hourly female workers, the all-cancers mortality rate was comparable to the US rate (SMR = 110; 95% CI, 93 to 129).

In the male hourly cohort no significant elevations in the six a priori cancers of interest (cancers of the rectum, liver, gastrointestinal tract, melanoma, brain, and hematopoietic system) were noted. Several causes of death had SMRs above 100; however, none of them were significantly elevated (Table 4).

In the hourly female cohort, there were no significantly elevated SMRs for any of the six a priori cancers of interest. SMRs for several other cancer sites were elevated, although none were significantly elevated (Table 4).

SMRs for deaths from diseases other than cancer were also not significantly elevated in either hourly male or female workers. The SMR for diabetes, however, was significantly lower than expected in hourly male workers (four observed and 10.5 expected; SMR = 38; 95% CI, 10 to 97).

Overall, among salaried male workers, a striking healthy worker effect was observed (Table 4). The all-causes SMR for salaried male workers was 54 (177 observed and 328 expected; 95% CI, 46 to 62) and the all-cancers SMR was 69 (56 observed and 81 expected; 95% CI, 52 to 90). None of the a priori cancers of interest were elevated in the salaried male workers. The lung cancer rate was significantly lower than expected, with an SMR of 41 (12 observed and 29.6 expected; 95% CI, 21 to 71), as was ischemic heart disease, with an SMR of 45 (44 observed and 97.5 expected; 95% CI, 33 to 61), and cerebrovascular disease, with an SMR of 20 (three observed and 15.2 expected; 95% CI, 4 to 58).

The female salaried workers (Table 4) also demonstrated a marked healthy worker effect, with an all-causes SMR of 69 (52 observed and 75 expected; 95% CI, 52 to 91) and an all-cancers SMR of 75 (19 observed and 25 expected; 95% CI, 45 to 118). The only significant finding in the salaried female workers was that for cancer of the connective tissue, with an SMR of 1290 (two observed and 0.2 expected; 95% CI, 156 to 4659). However, one of the connective tissue tumors was a pericytoma, a lesion of borderline malignancy.

The age-, sex-, race-, and calendar-specific mortality rates for the hourly workers, compared with the regional population (eight counties surrounding the plants), were similar to the SMRs calculated using the US rate tables (not shown). None of the a priori cancers of interest in either males or females were significantly different than expected.

SMRs by Length of Employment and Latency Categories

There was no trend of increasing SMRs over length of employment and latency categories for all causes or all cancers in either male or female hourly workers. The data for all cancers are presented in Tables 5 and 6.

The only site-specific cause of death that met the a priori criteria for analysis by cumulative length of employment and latency (ie, greater than two observed cases and CIs with a lower boundary >90) was intestinal cancer in female hourly workers. As listed in Table 6, the

TABLE 4

Observed and Expected Deaths[a] in 2984 Hourly Male Workers,[b] 2544 Hourly Female Workers,[c] 1078 Salaried Male Workers,[d] and 469 Salaried Female Workers[e]

	Hourly Workers[f]				Salaried Workers[f]			
	Males		Females		Males		Females	
Cause of Death	Obs/Exp	SMR (95% CI)	Obs/Exp	SMR (95% CI)	Obs/Exp	SMR (95% CI)	Obs/Exp	SMR (95% CI)
All causes	586/699	84** (77–91)	380/420	90* (82–100)	177/328	54** (46–62)	52/75	69.0** (52–91)
All cancers	128/158	81* (68–97)	150/136	110 (93–129)	56/81	69* (52–90)	19/25	75 (45–118)
MN[g] of tongue	1/0.9	103 (3–576)	2/0.4	483 (59–1745)	0/0.1	—	1/0.07	1346 (34–7498)
MN of buccal cavity	2/1.1	178 (22–642)	2/0.5	365 (44–1317)	0/0.5	—	1/0.1	1021 (26–5690)
MN of pharynx	4/2.0	199 (54–509)	2/0.8	253 (31–915)	0/1.0	—	0/0.1	—
MN of esophagus	5/3.8	131 (42–304)	1/1.1	87 (2–482)	1/2.0	49 (1–272)	0/0.2	—
MN of stomach	4/5.9	68 (18–173)	4/3.0	132 (36–339)	1/2.7	36 (0.9–200)	0/0.5	—
MN of intestine	8/14.0	57 (25–112)	20/12.7	157 (96–242)	7/7.1	98 (40–203)	1/2.2	44 (1–247)
MN of rectum	3/3.4	87 (18–255)	4/2.3	169 (46–434)	3/1.6	185 (38–540)	0/0.4	—
MN of biliary passages and liver	2/2.5	80 (10–289)	2/2.2	89 (11–321)	1/1.2	79 (2–439)	0/0.3	—
MN of pancreas	9/7.8	115 (53–219)	7/5.9	117 (47–241)	6/3.9	150 (55–327)	0/1.1	—
MN of larynx	3/2.0	147 (30–428)	1/0.4	215 (5–1198)	0/1.0	—	0/0.1	—
MN of trachea, bronchus and lung	42/54.5	77 (56–104)	32/25.2	127 (87–179)	12/29.6	41** (21–71)	5/4.7	104 (34–244)
MN of breast	—	—	25/30	82 (53–121)	—	—	6/5.7	104 (38–226)
MN of cervix uteri	—	—	6/4.7	126 (47–277)	—	—	1/0.9	112 (3–622)
MN of other parts of uterus	—	—	5/3.8	130 (43–305)	—	—	0/0.6	—
MN of ovary, tube and broad ligament	—	—	8/9.3	85 (37–168)	—	—	2/1.7	115 (14–415)
MN of prostate	12/10.9	110 (57–192)	—	—	3/5.3	56 (5–136)	—	—
MN of kidney	3/4	75 (15–219)	2/2.1	94 (11–341)	0/2.1	—	—	—
MN of bladder and other urinary tract	3/3.8	77 (16–226)	2/1.3	151 (18–545)	1/1.8	54 (1–299)	0/0.2	—
MN of skin (melomonas)	5/3.8	130 (42–303)	3/2.0	144 (30–421)	4/1.9	210 (57–538)	0/0.4	—
MN of brain and nervous system	2/5.1	39 (5–140)	2/3.7	53 (6–192)	4/2.5	156 (42–398)	0/0.7	—
MN of connective tissue	0/0.9	—	1/0.8	125 (3–694)	1/0.4	229 (6–1275)	2/0.2	1290* (156–4659)
Other and unspecified cancer	6/10.3	58 (21–126)	3/8.6	35 (7–101)	3/5.4	55 (11–161)	0/1.5	—
Lymphosarcoma	2/2.1	92 (11–331)	1/1.5	65 (2–364)	0/1.0	—	0/0.2	—
Leukemia and aleukemia	4/6.3	63 (17–162)	4/4.3	93 (25–238)	5/3.0	166 (54–387)	0/0.8	—
Other lymphatic and hematopoietic	5/5.7	87 (28–202)	5/4.7	105 (34–245)	4/3.0	131 (36–336)	0/0.8	—
Cirrhosis of the liver	13/18	72 (39–124)	6/9.2	65 (24–142)	3/9.1	33* (7–96)	1/1.7	57 (1–318)
Diabetes	4/10.5	38* (10–97)	9/10.3	87 (40–165)	5/5.1	97 (32–226)	0/1.8	—
Ischemic heart disease	182/205	89 (76–103)	71/87	81 (64–103)	44/97.5	45** (33–61)	8/14.3	56 (24–110)
Hypertension with heart disease	5/5.8	86 (28–201)	2/4.4	45 (6–164)	0/2.5	—	0/0.7	—
Other diseases of the heart	34/34.7	98 (68–137)	18/21.4	84 (50–133)	16/18.2	88 (50–143)	1/3.8	26 (0.7–146)
Cerebrovascular disease	26/34.9	74 (49–109)	27/30	89 (59–130)	3/15.2	20** (4–58)	6/5	120 (44–260)
Arteries, veins, pulmonary circulation	19/17.0	112 (67–174)	10/11	95 (46–175)	4/8.0	50 (14–128)	1/1.8	56 (1–310)
Transportation accidents	29/34.7	84 (56–120)	14/9.1	153 (84–257)	3/12.6	24** (5–69)	3/1.9	156 (32–455)
Other accidents	10/14.4	69 (33–127)	5/3.1	158 (51–369)	3/5.9	51 (11–148)	1/0.6	159 (4–886)
Suicide	14/21.3	66 (36–110)	3/6.8	44 (9–128)	2/8.6	23* (3–84)	2/1.4	140 (17–507)
Homicide	3/8.4	36 (7–104)	2/2	96 (12–345)	0/3.0	—	0/0.4	—

* Significant at $P < 0.05$.

** Significant at $P < 0.01$.

[a] Expected numbers for selected causes of death based on age-, sex-, race-, and time-specific US rates coded according to the rules of the International Classification of Diseases coding in force at the time of death. ICD code groupings are shown as listed in Steenland et al.[15]

[b] 85,991 Person-years of observation.

[c] 75,674 Person-years of observation.

[d] 34,755 Person-years of observation.

[e] 16,358 Person-years of observation.

[f] Obs/Exp, observed/expected; SMR, standardized mortality ratio; CI, confidence interval.

[g] MN, malignant neoplasms.

TABLE 5
Mortality by Length of Employment and Latency from All-Cancers for Hourly Male Workers

	Length of Employment (years)									
	<1		1 to <5		5 to <10		≥10		Total	
Cause/Latency	No. of Deaths Observed	SMR	No. of Deaths Observed	SMR	No. of Deaths Observed	SMR	No. of Deaths Observed	SMR	No. of Deaths Observed	SMR
All cancers, *n*										
<20	8	81	8	79	9	105	10	89	35	89
≥20	19	74	14	59*	12	108	48	78*	93	78*
Total	27	76	22	65*	21	107	58	81*	128	81*

* $P < 0.05$.

TABLE 6
Mortality by Length of Employment and Latency from All-Cancers and Intestinal Cancer for Hourly Female Workers

	Length of Employment (years)									
	<1		1 to <5		5 to <10		≥10		Total	
Cause/Latency	No. of Deaths Observed	SMR	No. of Deaths Observed	SMR	No. of Deaths Observed	SMR	No. of Deaths Observed	SMR	No. of Deaths Observed	SMR
All cancers, *n*										
<20	9	84	13	90	8	106	8	107	38	95
≥20	31	145	30	117	13	120	38	100	112	96
Total	40	124	43	107	21	114	46	101	150	110
Intestinal cancer, *n*										
<20	0	—	0	—	1	154	1	147	2	62
≥20	4	198	5	208	5	458*	4	100	18	189*
Total	4	142	5	143	6	345*	5	106	20	157

* $P < 0.05$.

intestinal cancer SMRs occurred primarily in women with greater than 20 years of latency; however, the deaths distributed evenly through the length-of-employment categories. While some of the category-specific SMRs for intestinal cancer were significantly elevated in and of themselves, they were calculated using small numbers and were therefore unstable.

To further evaluate any increased risk of mortality from intestinal cancer with increasing length of employment, an internal analysis for trend was calculated. The observed over the expected rates calculated by length of employment and the associated trend were tested for statistical significance using the Mantel-Cox chi-square test for trend. The observed over expected rates for employment time of less than 1 year, 1 to less than 5 years, 5 to less than 10 years, and 10 years or greater were 5.07, 1.27, 2.26, and 0.40, respectively. The chi-square was significant at $P < 0.001$; however, the trend of the observed over the expected rates did not increase but rather decreased with length of employment.

Exposure-Specific SMRs

Mortality in the 1268 hourly male and 362 hourly female workers who worked for at least 1 day in a high-exposure job was compared to the mortality experience of the US population. The 1268 ever-high-exposed hourly male workers contributed 37,739 person-years of observation. The all-causes SMR was significantly lower than expected (SMR = 82; 95% CI, 72 to 93), and the all-cancers SMR was 77 (95% CI, 57 to 101). The 362 ever-high-exposed hourly female workers contributed 10,584 person-years of observation. Both all-causes and all-cancers mortality in the ever-high-exposed hourly female workers did not deviate from that expected (all-causes SMR = 96, 95% CI, 75 to 123; all-cancers SMR = 100, 95% CI, 63 to 152). There were no significant differences in any of the site-specific SMRs for either male or female ever-high-exposed hourly workers.

In the 723 hourly male workers, with 22,217 person-years of observation, who were engaged in a high-exposure job for at least 180 days, the all-causes SMR was 87 (95% CI, 74 to 102) and the all-cancers SMR was 82 (95% CI, 58 to 114). In the 184 hourly female workers, with 5783 person-years of observation, the all-causes SMR was 92 (95% CI, 65 to

TABLE 7
Mortality by Length of Employment and Latency from All-Cancers for Hourly Male and Female Workers Highly Exposed for 180 Days or More

	Length of Employment (years)									
	<1		1 to <5		5 to <10		≥10		Total	
Cause/Latency	No. of Deaths Observed	SMR	No. of Deaths Observed	SMR	No. of Deaths Observed	SMR	No. of Deaths Observed	SMR	No. of Deaths Observed	SMR
Males										
All cancers, *n*										
<20	1	116	4	164	3	121	5	140	13	140
≥20	1	45	6	108	2	53	14	67	23	67
Total	2	64	10	125	5	80	19	82	36	82
Females										
All cancers, *n*										
<20	0	—	2	193	1	98	0	—	3	86
≥20	0	—	1	102	1	110	6	82	8	87
Total	0	—	3	149	2	103	6	70	11	87

TABLE 8
Mortality by Length of Employment and Latency from All-Cancers for Hourly Male and Female Workers Highly Exposed for 1 Year or More

	Length of Employment (years)							
	1 to <5		5 to <10		≥10		Total	
Cause/Latency	No. of Deaths Observed	SMR	No. of Deaths Observed	SMR	No. of Deaths Observed	SMR	No. of Deaths Observed	SMR
Males								
All cancers, *n*								
<20	0	—	3	146	4	143	7	107
≥20	4	121	1	30	11	60	16	64
Total	4	83	4	75	15	71	23	73
Females								
All cancers, *n*								
<20	1	170	0	—	0	—	1	40
≥20	1	213	0	—	4	65	5	69
Total	2	189	0	—	4	56	6	61

127) and the all-cancers SMR was 88 (95% CI, 43 to 155). There were no elevated site-specific SMRs above the expected number.

The all-causes SMR for the 479 hourly male workers who had worked for at least 1 year in a high-exposure job was 89 (95% CI, 74 to 107; 15,181 person-years of observation) and the all-cancers SMR was 73 (95% CI, 46 to 109). In the 122 hourly female workers who worked in a high-exposure job for at least 1 year, the all-causes SMR was 81 (95% CI, 53 to 119; 4047 person-years of observation) and the all-cancers SMR was 61 (95% CI, 23–134). No site-specific elevations were seen in either males or females.

In Tables 7 and 8, the results of the SMR analysis by length of employment and latency are presented for all-cancers for hourly male and female workers highly exposed for at least 180 days (Table 7) or for at least 1 year (Table 8). Because of the small number of site-specific cancers, analysis by cumulative length of employment and latency category was not feasible. There was no consistent trend across the length-of-employment categories and/or latency categories in either males or females that would suggest an association between PCB exposure and increased mortality (Tables 7 and 8).

Comment

The lower-than-expected mortality seen in this cohort has been reported in other PCB mortality studies[2–6] and is consistent with the healthy worker effect often observed in employed populations.[20] The lower all-cancers SMR seen in hourly male

workers is, however, unusual and raises the question of whether cancer deaths have been sufficiently ascertained in this cohort. This discrepancy was not seen in the female cohort, and a systematic underascertainment or ICD coding problem related to gender is unlikely.

The excess cancer mortality related to PCB exposure that has been reported previously in the literature was not replicated in this study. However, the capacitor workers in prior studies were exposed to the same mixtures of PCBs at similar concentrations, since the production process in different plants was the same. The significant excess of liver cancer reported by Brown[4] was not observed in this cohort. SMRs for liver cancer for both males and females in our cohort were similar to those of the US population, with SMRs below 100 (SMR = 89 for hourly female and SMR = 80 for hourly male workers). Brown and Jones[3] also reported a significant increase in mortality from rectal cancer women, with three observed aths and 0.50 expected; however, the excess was no longer significant in Brown's follow-up study of the same cohort.[4] Among hourly female workers in our cohort, there were four observed deaths from rectal cancer and 2.3 expected, a nonsignificant increase (SMR = 169; 95% CI, 46 to 434). All four women who died of rectal cancer held only low-exposure jobs during their employment. Length of employment in the four women ranged from 6 to 22 years, with a mean of 10 years. Years since first exposure in three of the deaths exceeded 20. Known risk factors for rectal cancer include smoking[21] and family history.[22] Occupational risk for rectal cancer in females has been reported for women involved in the furniture-making industry, with an SMR of 3.2 (95% CI, 1.3 to 4.5).[23] Occupational history before and after employment at the capacitor plants was not available for members of our cohort and could not be evaluated.

In the Bertazzi et al[5] cohort of 2100 workers, a significant excess of total cancers and cancers of the gastrointestinal tract (ICD codes 150 to 159) among males was reported (six observed vs 1.7 expected, SMR = 346; 95% CI, 141 to 721). In contrast to the Bertazzi et al[5] cohort, hourly male workers in our cohort had lower than expected numbers of both intestinal and rectal cancers, although not significantly lower (cancer of the intestine SMR = 57, 95% CI, 25 to 112; cancer of the rectum SMR = 87, 95% CI, 18 to 225). Hourly female workers in our cohort had nonsignificantly elevated SMRs for intestinal and rectal cancer (cancer of the intestine SMR = 157, 95% CI, 96 to 242; cancer of the rectum SMR = 169, 95% CI, 46 to 434). In the Bertazzi et al[5] cohort, the numbers of lung cancer and hematological neoplasms were also elevated in males, but the excesses were not statistically significant. In our cohort, neither the numbers of lung cancer nor neoplasms of the hematopoietic system were elevated.

The 1556 females in the Bertazzi et al[5] cohort experienced higher than expected all-causes mortality, when compared with the Italian national population, and significantly higher than expected all-cancers mortality and mortality related to hematological neoplasms, when compared with the local population. In our cohort the all-causes mortality in females was significantly lower, the all-cancers mortality in females was comparable to the expected number, and no elevation in hematological neoplasms was observed.

In the cohort of 3588 male and female capacitor workers examined by Sinks et al,[2] a significant increase in mortality from melanoma and a nonsignificant increase in mortality from cancers of the brain and nervous system was observed. In our cohort the numbers of cancers of the brain and nervous system were lower than expected for both males and females. Mortality from melanoma was similar to the expected number in both males and females (five observed and 3.8 expected deaths in males, and three observed and 2.08 expected deaths in females). None of the five males with melanoma had worked for longer than 2 years at the plants, and two of them had less than 20 years of latency. Of the three women with melanoma, one had worked for 1 year, one for 3.4 years, and one for 12 years at the plants; all three held only low-exposure jobs. Exposure to the sun is the major risk factor for melanoma and accounts for 65% of melanomas worldwide[24]; melanomas represent almost all fatal skin cancers.

In our cohort the SMR for intestinal cancer (large and small intestine) in hourly female workers was elevated and approached statistical significance (SMR = 157; 95% CI, 96 to 242). There were 20 observed deaths and 12.7 expected, using the US rate data. One of the intestinal cancers was a carcinoid originating from endocrine argentaffin cells, representing a tumor with a different etiology but one grouped with intestinal carcinomas in the ICD coding system. In contrast, there were eight observed deaths and 14 expected deaths in the hourly male cohort (SMR = 57; 95% CI, 25 to 113). The SMR for cancer of the large intestine in hourly female workers, using the regional population as the comparison population, was lower (SMR = 120; 95% CI, 74 to 186), with 16.6 deaths expected. Since the incidence of intestinal cancer is greatly influenced by ethnicity and since higher rates are observed among the white population of the northeastern part of the United States, the regional comparison is more representative.[25] The majority of intestinal cancers occurred in women with 20 or more years of latency; however, the cancers were evenly distributed across the length of employment. All of the women worked exclusively in sedentary, low-exposure jobs during their employment. Trend analysis did not reveal any increase but rather a decrease in the observed over the ex-

pected rates by the category length of employment. Known risk factors for intestinal cancer include tobacco use,[26,27] dietary factors,[28] family history,[29] and lack of physical activity.[25] Known occupational risks for intestinal cancer in women are few.[23,30]

The low SMRs in the male salaried cohort may represent a socioeconomic effect. The salaried male workers comprised mostly professional staff, with 73% (792) having attended at least some college and 71% of these 792 employees having graduated from college. In contrast, only 15% of hourly male workers had some college education, and only 13% of them completed 4 years of college.

Overall, the salaried women demonstrated a larger healthy worker effect than did their hourly counterparts. Again, this may reflect a socioeconomic effect, including better education, as 26% (n = 120) of the salaried women ever attended college and 30% of those completed 4 years (n = 36). Low SMRs in salaried employees have been reported in other occupational cohorts.[31] The disparity in mortality between socioeconomic groups has been increasing, and the differences in SMRs between the hourly and salaried workers may reflect this disparity.[32,33]

The exposure-specific analysis for this cohort was limited by the lack of individual dosimetry data. The only available industrial hygiene data consisted of PCB air levels measured in various production areas in 1975 and in 1977.[9,10] Because of the persistence of PCBs and the length of time that a worker had repeated exposures, length of employment was a useful proxy of cumulative exposure. Hourly workers employed in high-exposure jobs represented the most highly exposed group of workers and were grouped by their cumulative time in high-exposure jobs into three groups. None of the six a priori cancer sites of interest, all-cancers mortality, or any site-specific mortality were elevated in either males or females for any of the three groupings of high-exposed workers. There was no consistent trend in any of the tables illustrating SMRs by length of employment and latency for any of the groupings. The number of workers employed in high-exposure jobs for long time periods was small and limited the extent of the analysis; however, the consistent lack of any significant elevation in mortality in any of the groups in either males or females is worth noting. Reliance on categorical exposure assessment may result in misclassification. However, jobs that involved direct dermal and inhalation exposure to PCBs were clearly identified by job code in the worker history records, and the PCB exposure in these jobs was substantial, as indicated by the air-monitoring data and PCB serum and adipose tissue levels measured in selected workers.

While not an a priori consideration, the large cohort of women in this study provided an opportunity to examine the relationship between breast cancer and occupational exposure to PCBs. In our study, mortality from breast cancer among hourly and salaried female workers was not increased over the expected number. Additionally, we had the opportunity to examine a cohort of women, albeit small, who experienced high exposure to PCBs.

In the past, capacitor workers as an occupational group had the highest exposures to PCBs, through the inhalation of PCB vapors and the dermal absorption of PCB liquid. Since PCBs were heated, their volatility was increased, resulting in high air levels. The worker groups such as electric utility workers[34] had poorly defined and definitely lower exposures than the capacitor workers. Such workers did not inhale vapors from heated PCBs nor did they have daily dermal contact with liquid PCBs.

The potential for bias in any observational study is always a concern and must be considered in the study design as well as in the examination of results. Both selection and information bias can be prevented if disease and/or vital statuses are not known when exposure assignments are made. In this study, exposure was assigned on the basis of the historical information related to PCB exposure that was contained in the job codes. The exposure assignment was done before the vital status determination.

In conclusion, this is the largest cohort of workers directly exposed to PCBs that was assembled specifically for the examination of the association between exposure and increased cancer mortality. Extensive effort went into assembling a complete cohort and obtaining vital statuses from over 98% of the cohort. Despite the fact that the cohort is relatively young, 85% of the cohort was observed for at least 20 years, with a mean follow-up time of 31 years. Neither overall cancer mortality nor numbers of any of the a priori cancers of interest previously reported as being elevated were elevated in this cohort. With the exception of intestinal cancer in the hourly female workers, there were few cancer sites whose numbers were elevated, with few cases and wide CIs, and these sites have not been reported in other studies, suggesting that our results were chance findings.

Because of the inherent limitations in any retrospective cohort mortality study, the best way to evaluate the validity of a reported association is to replicate the study in similarly exposed populations. To date none of the reported elevations in cancer mortality have been successfully replicated, even within individual cohorts (eg, Brown[4]). Notwithstanding the bias inherent in retrospective occupational cohort studies, the lack of consistent findings with respect to occupational PCB exposure and mortality in studies conducted to date would suggest a lack of an association.

Acknowledgments

This study was funded by the General Electric Company. The assistance of Mr Long-Gon Chon in developing our database is appreciated. Dr Kyle Steenland of the National Institute for Occupational Safety and Health provided the US mortality rate tables. We thank the members of our advisory panel: Arthur C. Upton, MD, John E. Vena, PhD, Jack S. Mandel, PhD, Roy E. Shore, PhD, and Gilbert W. Beebe, PhD, for their helpful suggestions and support throughout the study.

References

1. Kimbrough RD. Polychlorinated biphenyls (PCBs) and human health: an update. *Crit Rev Toxicol.* 1995;25:133–163.
2. Sinks T, Steele G, Smith A, Watkins A, Shults R. Mortality among workers exposed to polychlorinated biphenyls. *Am J Epidemiol.* 1992;136:389–398.
3. Brown DP, Jones J. Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. *Arch Environ Health.* 1981;36:120–129.
4. Brown DP. Mortality of workers exposed to polychlorinated biphenyls: an update. *Arch Environ Health.* 1987;42:333–339.
5. Bertazzi PA, Riboldi L, Pesatori A, Radice L, Zocchetti C. Cancer mortality of capacitor manufacturing workers. *Am J Ind Med.* 1987;11:165–176.
6. Taylor PR. *The Health Effects of Polychlorinated Biphenyls* [doctoral thesis]. Boston, MA: Harvard School of Public Health; 1988.
7. Taylor PR, Reilly AA, Stelma J, Lawrence CE. Estimating serum polychlorinated biphenyl levels in highly exposed workers: an empirical model. *J Toxicol Environ Health.* 1991;34:413–422.
8. World Health Organization. *International Classification of Diseases: Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death.* Geneva: World Health Organization; Revisions 5–9, 1940–1993.
9. Lawton RW, Sack BT, Ross MR, Feingold J. *Studies of Employees Occupationally Exposed to PCBs, a Progress Report.* September 18, 1981 (General Electric Report submitted to the US Environmental Protection Agency).
10. Jones M. *Industrial Hygiene Survey.* Washington, DC: National Institute for Occupational Safety and Health; 1983. NIOSH publication 83–137224. Reprinted by the National Technical Information Service.
11. Kreiss K. Studies on populations exposed to polychlorinated biphenyls. *Environ Health Perspect.* 1985;60:193–199.
12. Wolff MS, Fischbein A, Thornton J, Rice C, Lilis R, Selikoff IJ. Body burden of polychlorinated biphenyls among persons employed in capacitor manufacturing. *Int Arch Occup Environ Health.* 1982;49:199–208.
13. Lawton RW, Ross MR, Feingold J, Brown JF Jr. Effects of PCB exposure on biochemical and hematological findings in capacitor workers. *Environ Health Perspect.* 1985;60:165–184.
14. Lawton RW, Brown JF, Jr, Ross MR, Feingold J. Comparability and precision of serum PCB measurements. *Arch Environ Health.* 1985;40:29–37.
15. Steenland K, Beaumont J, Spaeth S, Brown D, Okun A, Jurcenko L. New developments in the NIOSH life table analysis system. *J Occup Med.* 1990;32:1091–1098.
16. Marsh GM, Ehland J, Sefcik S. *Mortality and Population Data System (MPDS)* [technical report]. Pittsburgh, PA: University of Pittsburgh, Department of Biostatistics; 1987.
17. Marsh GM, Preininger M, Ehland JJ. *OCMAP PC: A User-Oriented Occupational Mortality Cohort Analysis Program for the IBM PC.* Pittsburgh, PA: University of Pittsburgh; 1989.
18. Bailar JC, Ederer F. Significance factors for the ratio of a Poisson variable to its expectation. *Biometrics.* 1964;20:639–643.
19. Dixon WJ, ed. *BMDP Statistical Software Manual.* Berkeley: University of California Press; 1992.
20. Monson RR. Observations on the healthy worker effect. *J Occup Med.* 1986;28:425–433.
21. Heineman EF, Zahm SH, McLaughlin JK, Vaught JB. Increased risk of colorectal cancer among smokers: results of a 26-year follow-up of US veterans and a review. *Int J Cancer.* 1994;59:728–738.
22. Burt RW. Familial risk and colorectal cancer. *Gastroenterol Clin North Am.* 1996;25:793–803.
23. Miller BA, Blair A, Reed EJ. Extended mortality follow-up among men and women in a U.S. furniture workers union. *Am J Ind Med.* 1994;25:537–549.
24. Armstrong BK, Kricker A. Skin cancer. *Dermatol Clin.* 1995;13:583–594.
25. Schottenfeld D, Winawer SJ. Cancers of the large intestine. In: Schottenfeld D, Fraumeni JF, eds. *Cancer Epidemiology and Prevention,* 2nd ed. New York: Oxford University Press; 1996:813–840.
26. Slattery ML, Potter JD, Friedman GD, Ma KN, Edward S. Tobacco use and colon cancer. *Int J Cancer.* 1997;70:259–264.
27. Newcomb PA, Storer BE, Marcus PM. Cigarette smoking in relation to risk of large bowel cancer in women. *Cancer Res.* 1995;55:4906–4909.
28. Giovannucci E, Willett WC. Dietary factors and risk of colon cancer. *Ann Med.* 1994;26:443–452.
29. Burt RW. Familial risk and colon cancer. *Int J Cancer.* 1996;69:44–46.
30. Ruder AM, Ward EM, Brown DP. Cancer mortality in female and male drycleaning workers. *Am J Epidemiol.* 1992;136:389–398.
31. Teta MJ, Ott MG. Mortality in a research engineering and metal fabrication facility in Western New York State. *Am J Epidemiol.* 1988;127:540–551.
32. Pappas G, Queen S, Hadden W, Fisher G. The increasing disparity in mortality between socioeconomic groups in the United States, 1960 and 1986. *N Engl J Med.* 1993;329:103–109.
33. Sorlie PD, Backlund E, Keiler JB. US mortality by economic, demographic, and social characteristics: the National Longitudinal Mortality Study. *Am J Public Health.* 1995;85:949–956.
34. Loomis D, Browning SR, Schenk AP, et al. Cancer mortality among electrical workers exposed to polychlorinated biphenyls. *Occup Environ Med.* 1997;54:720–728.

Letters to the Editor

Readers are invited to submit letters for publication in this department. Submit them to: The Editor, Journal of Occupational and Environmental Medicine, PO Box 370, Bryn Mawr, PA 19010. Letters should be typewritten and double spaced and should be designated "For Publication."

Evidence of Excess Cancer Mortality in a Cohort of Workers Exposed to Polychlorinated Biphenyls

To the Editor: To further explore previously reported excesses in cancer-specific mortality in workers who have been occupationally exposed to polychlorinated biphenyls (PCBs), Kimbrough et al[1] reported a retrospective cohort mortality study of 7075 male and female workers exposed to PCBs during the capacitor-manufacturing process at two General Electric (GE) plants in upstate New York. Kimbrough et al concluded that the study results failed to show any association between occupational PCB exposure and cancer-related mortality. We interpret their study findings differently. Although limitations in the study approach (outlined below) tend to dilute any excesses in cancer mortality resulting from PCB exposure, the findings *still* suggest a relationship between PCB exposures and excess cancer in humans.

First, this study demonstrated once again that modern industrial workers are healthier than the general population. Known as the "healthy worker effect" (HWE), this bias results in standardized mortality ratios (SMRs) that are considerably less than expected (eg, SMR < 90) for all mortality and cancer mortality[2-4] when workers are compared with a general population. Consistent with the HWE bias, Kimbrough et al found that all cancer mortality was significantly below that expected in male hourly workers (SMR = 81), male salaried workers (SMR = 69), and female salaried workers (SMR = 75). However, despite the HWE, female hourly workers had elevated SMRs for all cancer mortality (SMR = 110) and for three (intestinal [SMR = 157], rectal [SMR = 169], and melanoma [SMR = 144]) of the six cancers of a priori interest. Melanoma mortality was also elevated for male hourly workers (SMR = 130). Although the elevations in cancer-specific SMRs did not achieve statistical significance, they were consistent with elevations found in other studies of PCB-exposed workers.[4-6] Given the HWE, these elevations are particularly noteworthy.

Second, when looking at cancer mortality rates, it is customary to include a latency period to adjust for the time lag between exposure and clinical evidence of disease (or, in this study, cancer death).[7] However, Kimbrough et al included a latency period only for all cancer mortality and for intestinal cancer mortality among female hourly workers. When female hourly workers with at least 20 years of follow-up were evaluated (ie, with a sufficient latency period), the SMR for all cancers increased from 110 to 117* ($P = 0.058$). The SMR for intestinal cancers increased from 157 to 189, thus becoming statistically significant ($P < 0.05$).

Third, proper assessment of exposure should have accounted for the dates (calendar years) of employment, the intensity of exposure for each type of job, and the specific Aroclor PCB used. For example, in the earlier years of plant operation (1946 to 1954), any exposures would have been to Aroclor 1254, whereas exposures in the 1970s would have been to the less toxic Aroclor 1016.[8,9] Industrial hygiene procedures at the plant probably improved over time as well. Therefore, length of employment alone was an inadequate surrogate of exposure and a likely source of exposure misclassification bias that could have led to an underestimate of effect and distortion of exposure-response relationships.

Kimbrough et al assembled the largest cohort of hourly PCB workers studied to date, including a large number of female workers. However, most of the hourly workers had exposures that were comparable with exposures among the general US population. From the data provided, it appears that approximately one fourth of the person-years contributed by male hourly workers, and approximately 10% of the person-years contributed by female hourly workers, were contributed by workers who had been employed for at least 6 months in high-exposure jobs. Only 112 (3.8%) male hourly workers and 12 (0.5%) female hourly workers were employed exclusively in high-exposure jobs. The majority of the hourly workers never worked in high-exposure jobs. Only a small percentage of hourly workers had evidence of PCB exposure that was appreciably greater than that of the US population. Therefore, relatively small elevations in cancer mortality would be expected for this group, even if PCB cancer potency were alarmingly high.

Fourth, although one of the goals of this study was to evaluate six specific cancers of a priori interest (ie, melanoma, liver, rectal, gastrointestinal tract, brain, and hematopoietic cancers), the study focused almost entirely on all cancer mortality. In planning the study, the researchers should have realized that the size and age distribution of the hourly work-

*Note: There is an error in Table 6 of the study report. The SMR for "all cancers" in female hourly workers with ≥20 years' latency over all lengths of employment should be "117," not "96" as reported.

TABLE 1
Calculations of Statistical Power to Detect Varying Standardized Mortality Ratios (SMRs) for the Six Cancers of A Priori Interest

Cancer	Expected Number	SMR = 150	SMR = 200	SMR = 300
Male hourly workers				
Melanoma	3.8	12%	35%	80%
Liver	2.5	9%	24%	62%
Rectum	3.4	14%	37%	80%
GI*	14.0	36%	85%	100%
Brain	5.1	15%	44%	89%
Blood	14.1	37%	86%	100%
Female hourly workers				
Melanoma	2.0	8%	22%	55%
Liver	2.2	12%	28%	65%
Rectum	1.6	10%	22%	52%
GI*	12.7	36%	83%	100%
Brain	3.7	11%	32%	78%
Blood	10.5	32%	77%	100%

* GI, Gastrointestinal tract.

force would result in poor statistical power to evaluate the cancers of a priori interest. Table 1 shows the expected number of deaths for each of these cancers for male and female hourly workers and the resulting statistical power for SMRs from 150 to 300, using the study's method for determining statistical significance (ie, the 95% confidence interval). Because of the biases in the study and the low percentage of highly exposed workers, an SMR of 150 might be as high as would be expected for these cancers. As seen in Table 1, for an SMR of 150, the study had less than a one in five chance of obtaining a statistically significant result for four of the six cancers. Given the sample size and the numbers of expected cancers, the study did not have sufficient statistical power (>80%) to detect an SMR of 300 for most of the cancers of interest.

Kimbrough et al examined and reported SMRs for categories of increasing length of employment and years of latency only when "... there was an elevated total SMR with two or more observed deaths and for which the lower boundary of the 95% confidence interval (CI) was 90 or above."[1] The impact of this decision can be seen in Table 2. Given

TABLE 2
Number of Observed Deaths and the SMR Required for ≥90 as the Lower Limit of the 95% Confidence Interval

No. of Deaths	SMR
2	744
3	437
4	331
5	278
6	245
7	224
8	209
9	197
10	188
11	180
12	174
13	169
14	165
15	161
16	157
17	154
18	152
19	150

the biases mentioned previously, it is understandable that just one of the six a priori cancers met these requirements. Furthermore, accounting for a latency period should be a prerequisite for calculating any adult cancer SMR. Otherwise, the SMR is biased toward or below 100. For all six cancers of a priori interest, analyses accounting for latency and for length of employment should have been done and presented, allowing the reader to decide whether or not the results were meaningful.

In summary, the Kimbrough et al study suffered from HWE bias, failure to account for latency, exposure misclassification, potentially insufficient dosage differences between exposed and comparison groups, and poor statistical power. Nevertheless, the study did find excesses in three of the six cancers of interest. Future research should include analyses made with internal comparisons (to minimize biases from HWE) of sufficient numbers of highly exposed workers, as well as analyses accounting for cancer latency periods. This might require an additional decade or more of follow-up on this cohort and the addition of exposed workers from other PCB plants (eg, workers at the Massachusetts plant included in Brown[5]), before a definitive statement about the association between PCB exposure and specific cancers can be made.

Frank J. Bove, ScD
Barbara A. Slade, MD
Richard A. Canady, PhD
Agency for Toxic Substances and Disease Registry
Division of Health Studies/ Division of Health Assessment and Consultation
Atlanta, GA

References

1. Kimbrough RD, Doemland ML, LeVois ME. Mortality in male and female capacitor workers exposed to polychlorinated biphenyls. *J Occup Environ Med.* 1999; 41:161–171.
2. Checkoway H, Pearce NE, Crawford-Brown DJ. *Research Methods in Occupational Epidemiology.* New York: Oxford University Press; 1989:78–79.
3. Park RM, Maizlish NA, Punnett L, Moure-Eraso R, Silverstein MA. A comparison of PMRs and SMRs as estimators of occupational mortality. *Epidemiology.* 1991;2:49–59.
4. Loomis D, Browning SR, Schenck AP, Gregory I, Savitz DA. Cancer mortality among electric utility workers exposed to polychlorinated biphenyls. *Occup Environ Med.* 1997;54:720–728.
5. Brown DP. Mortality of workers exposed

to polychlorinated biphenyls: an update. *Arch Environ Health.* 1987;42:333–339.
6. Sinks T, Steele G, Smith AB, Watkins K, Shults RA. Mortality among workers exposed to polychlorinated biphenyls. *Am J Epidemiol.* 1992;136:389–398.
7. Checkoway H, Pearce N, Hickey JLS, Dement JM. Latency analysis in occupational epidemiology. *Arch Environ Health.* 1990;45:95–100.
8. Cogliano VJ. Assessing the cancer risk from environmental PCBs. *Environ Health Perspect.* 1998;106:317–323.
9. Mayes BA, McConnel EE, Neal BH, et al. Comparative carcinogenicity in Sprague-Dawley rats of the polychlorinated biphenyl mixtures Aroclors 1016, 1242, 1254, and 1260. *Toxicol Sci.* 1998; 41:62–76.

To the Editor: We were glad to see the recent article on mortality among workers exposed to polychlorinated biphenyls.[1] At a time when fewer and fewer companies are funding occupational epidemiological studies, we commend the sponsor, General Electric, for this initiative. The completeness of case ascertainment was outstanding. In addition, this report was a model of clear writing and clear display of results.

However, two issues, sample size and exposure, raise significant concern. First, the study population was very small. Over 7000 workers contributed over 200,000 person-years of observation, more than in prior PCB mortality studies. But when attention is restricted to those workers with high exposure, moderate- to long-duration employment, and adequate person-time after a latency period, the numbers are dramatically reduced. For example, only one third of the cohort worked for longer than 5 years. (We note in passing that Table 2, the source of these data, shows 7178 workers in the upper panel and 7075 workers in the lower panel, a disparity the authors do not explain.) Similarly, less than one fourth of the cohort was classified as highly exposed, and the median period of high exposure was less than 2 years. Although data are not presented to support exact calculations, it appears that fewer than 10 cancers of any type, and more typically fewer than three, were expected in any sex-salary stratum with high exposure, more than a year of employment, and more than 20 years of latency. Could this be why the article is conspicuously silent on the issue of statistical power?

The problem of small number could have been addressed. A company as large as GE presumably had other capacitor plants and could have supported a multisite study. Alternatively, an industry-wide study would have been informative, as we have seen in the semiconductor, rubber, petrochemical, automobile, and other industries. Indeed, we wonder why restricting a cancer mortality study to only two plants should not be viewed as a willful effort to avoid a positive finding.

The second major concern lies with exposure assessment. As with many historical cohort studies, the authors created a matrix to characterize each individual's exposure. If the designated "high exposure" jobs did not actually entail high exposure, then misclassification occurred and could have introduced substantial bias toward the null. Were the exposures accurately assessed?

The article makes reference to a readily available way to validate the exposure assessment: serum PCB levels obtained during the 1970s on a sample of several hundred cohort members. Where are these measurements? Did the authors check their exposure assignments against the past serum measurements? If not, why not? If so, why was this comparison not reported?

Another difficulty with exposure in this article is the admixture of various types of PCBs. More carcinogenic forms, such as Aroclor 1254, were used in the early years, and less carcinogenic forms, such as Aroclor 1016, were used later. By combining the two rather than focusing on the early exposures, the authors may have obscured a true effect.

Overall, these concerns significantly limit the conclusions that can be drawn from the study. The authors conclude that their results "would suggest a lack of an association." This conclusion is overstated. These results do offer some evidence that PCBs are not highly potent carcinogens causing relative risks above 10 or 20, a conclusion that was already fairly well established. But they provide little reassurance that PCBs do not double or triple the risk of some cancers after significant exposure.

For this reason, we were especially concerned that the results of the study were not interpreted and presented more carefully. The authors might have noted, in their conclusion, that PCBs are serious health hazards irrespective of carcinogenicity,[2] with effects that include decreased birth weight,[3] neurodevelopmental abnormalities,[4–8] and interference with both estrogen[9] and thyroid[10] hormone function. Accordingly, even negative findings in a cancer study would not reassure us of safety. That omission in the *JOEM* article, in turn, may have contributed to overtly misleading journalistic coverage, such as the *New York Times* headline: "Study Finds Little Risks [sic] From PCB's."[11]

The authors of this study note that our knowledge of PCB health effects is "limited." On the path to a more complete understanding, the current study results represent a great leap sideways.

Howard Frumkin, MD, DrPH
Department of Environmental and Occupational Health
Rollins School of Public Health of Emory University
Atlanta, GA

Peter Orris, MD, MPH
Division of Occupational Medicine
Cook County Hospital
Chicago, IL

References

1. Kimbrough RD, Doemland ML, LeVois ME. Mortality in male and female capac-

itor workers exposed to polychlorinated biphenyls. *J Occup Environ Med.* 1999; 41:161–171.
2. Carpenter DO. Polychlorinated biphenyls and human health. *Int J Occup Med Environ Health.* 1998;11:291–303.
3. Patandin S, Koopman-Esseboom C, de Ridder MA, Weisglas-Kuperus N, Sauer PJ. Effects of environmental exposure to polychlorinated biphenyls and dioxins on birth size and growth in Dutch children. *Pediatr Res.* 1998;44:538–545.
4. Rylander L, Stromberg U, Dyremark E, Ostman C, Nilsson-Ehle P, Hagmar L. Polychlorinated biphenyls in blood plasma among Swedish female fish consumers in relation to low birth weight. *Am J Epidemiol.* 1998;147:493–502.
5. Winneke G, Bucholski A, Heinzow B, et al. Developmental neurotoxicity of polychlorinated biphenyls (PCBS): cognitive and psychomotor functions in 7-month old children. *Toxicol Lett.* 1998;102–103: 423–428.
6. Patandin S, Lanting CI, Mulder PG, et al. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. *J Pediatr.* 1999;134:33–41.
7. Tilson HA, Kodavanti PR. The neurotoxicity of polychlorinated biphenyls. *Neurotoxicology.* 1998;19:517–525.
8. Jacobson JL, Jacobson SW. Evidence for PCBs as neurodevelopmental toxicants in humans. *Neurotoxicology.* 1997;18:415–424.
9. Connor K, Ramamoorthy K, Moore M, et al. Hydroxylated polychlorinated biphenyls (PCBs) as estrogens and antiestrogens: structure-activity relationships. *Toxicol Appl Pharmacol.* 1997;145:111–123.
10. Porterfield SP, Hendry LB. Impact of PCBs on thyroid hormone directed brain development. *Toxicol Ind Health.* 1998; 14:103–120.
11. Cushman JH. Study finds little risks from PCB's. *New York Times.* March 10, 1999.

The Authors Reply: Thank you for giving us the opportunity to reply to the letters by Bove et al and Frumkin and Oris commenting on our mortality study of PCB-exposed capacitor workers.[1] We disagree with the statement by Bove et al that "... limitations in the study approach tend to dilute any excesses in cancer mortality resulting from PCB exposure. . . . " These assertions are speculative and not supported by the data. Although some degree of misclassification in observational studies is unavoidable, it is usually not possible to determine whether this misclassification is differential or non-differential. Furthermore, non-differential misclassification does not always result in bias toward the null hypothesis. Neither the type nor the effect of the misclassification can be determined by Bove et al. In our article, we do, however, discuss at length the measures taken to limit misclassification, and we feel strongly that we were successful in doing so.

Bove et al assert that the healthy worker effect (HWE) results are an underestimate of the SMRs for all-causes mortality and cancer mortality. This is partially true. The HWE is most pronounced for cardiovascular deaths and thus affects all-causes mortality.[2] It has much less of an effect on cancer deaths.[3]

The presentation by Bove et al of the all-cancers SMRs and selected cancer-specific SMRs without confidence intervals (CIs) gives incomplete information and is misleading. Had the confidence intervals been reported, the lack of significance for these SMRs would have been immediately obvious to the reader. Bove et al selected the female hourly employees' all-cancers SMR of 110 (95% CI, 93 to 129), intestinal cancer (SMR = 157; 95% CI, 96 to 242), rectal cancer (SMR = 169; 95% CI, 46 to 434), melanomas (SMR = 144; 95% CI, 30 to 421), and melanomas in male hourly employees (SMR = 130; 95% CI, 42 to 303). Notably absent from this list of SMRs considered by Bove et al are the male hourly SMRs for intestinal and rectal cancer (SMR = 57; 95% CI, 25 to 112; and SMR = 87; 95% CI, 18 to 255, respectively).

Bove et al suggest that the male all-cancers SMRs of 81 (hourly employees; 95% CI, 68 to 97) and 69 (salaried employees, 95% CI, 52 to 90) are largely due to the HWE. A careful examination of Table 4 in our article suggests that the statistically significantly low all-cancers SMRs in both the hourly and salaried males result primarily from the lower than expected lung cancer SMR (for hourly workers: 42 observed/54.5 expected; SMR = 77; 95% CI, 56 to 104; and for salaried workers: 12 observed/29.6 expected; SMR = 41; 95% CI, 21 to 71).

The statement by Bove et al that these elevations were consistent with elevations found in other studies of PCB-exposed workers is not correct.[4–6] In addition to the three studies cited by Bove et al, there is the Bertazzi cohort and its update by Bertazzi et al[7] and Tironi et al.[8] The results of the Brown[4] and Sinks et al[5] studies are inconsistent with each other. The Loomis et al[6] study of utility workers, not capacitor workers, did report an elevation in melanomas in some subsets of the cohort that were presumed to have had exposure to PCBs while working outdoors. Exposure to sunlight was not adequately accounted for by Loomis et al.[6] Brown and Jones[9] and Brown[4] found an excess of liver and rectal cancers. Neither Sinks et al[5] nor Loomis et al[6] reported such increases. Sinks et al[5] reported a nonsignificant elevation in brain and nervous system cancers. Neither Brown and Jones,[9] Brown,[4] Bertazzi et al,[7] or Tironi et al[8] found an elevation in brain cancer. These inconsistencies were discussed in our article.

Bove et al state that we only included a latency-period analysis for all cancers and for intestinal cancer. This was done primarily because of space limitations. Cumulative exposure and latency tables were computed and evaluated for many other causes of death, including all of the cancers of interest. The interpretation by Bove et al that the intestinal cancer SMR increases to a significant level for women with ≥20 years of latency ignores the importance of examining the trend associated with latency and length of employment. Furthermore, it might be worth noting that for women employed for 10

years or longer with a latency period ≥20 years, the SMR was 100. The individual category–specific SMRs cannot be interpreted as meaningful without examination of the trend across cumulative exposure categories. Although the intestinal cancer SMR for latency ≥20 years was significantly elevated, there was no significant trend indicating an increase in risk with cumulative exposure or latency, as discussed in our article. Furthermore, comparison with the regional population resulted in a much-reduced SMR (SMR = 120; 95% CI, 74 to 186) for intestinal cancer in female hourly workers. The regional comparison is more representative because higher rates of intestinal cancer are observed among the white population of the northeastern part of the United States.

Bove et al raise concerns about our exposure assessment. Several factors need to be recognized when assessing the propriety of our exposure assessment and our use of length of employment as a surrogate of exposure. Workers accumulate PCB body burdens over time, which persist for many years even after their occupational PCB exposure is discontinued. To suggest that PCB body burdens among capacitor workers were comparable to those found in the general population is unjustified and is not supported by previously published data.[10–13] The fact that workers in capacitor plants had significantly higher body burdens than the general population has been demonstrated in other capacitor plants.[14] As reported in our article, average serum PCB levels in the general population between 1976 and 1979 were 5 to 7 parts per billion (ppb; μg/L).[14] Geometric mean serum PCB levels in GE workers in 1979 (2 years after PCBs were no longer used) were 277 ppb (μg/L) reported as Aroclor 1242 and 55 ppb (μg/L) reported as Aroclor 1254. In 1983, 5 years after termination of the use of PCBs, geometric mean serum levels were 116 ppb (μg/L) for Aroclor 1242 and 34 ppb (μg/L) for Aroclor 1254. In 1988, the geometric mean serum PCB levels were 90 ppb (μg/L) quantitated as Aroclor 1242 and 32 ppb (μg/L) quantitated as Aroclor 1254.[15] Workers preferentially retained the more persistent congeners so that the gas chromatographic pattern of their body burden gradually approached that observed in the general population, with primary retention of the more highly chlorinated, poorly metabolized congeners.[12] The half-lives of the major PCB congeners retained in these workers were as follows: for 2,4,4′ trichlorobiphenyl, 1.4 years; for 2,4,4′5 tetrachlorobiphenyl, 3.2 years; for 2,3′,4,4′,5 pentachlorobiphenyl, 5.8 years; and for 2,2′,4,4′,5,5′ hexachlorobiphenyl, 12.4 years.[16] Even though different commercial mixtures of PCBs were used in the capacitor plants, the congeneric composition on a qualitative basis is similar.[17] Production began in 1946 with the highly chlorinated Aroclor 1254, and small amounts of Aroclor 1254 were used in the plant at least through 1971.

The statement that length of employment alone was an inadequate surrogate for exposure and a likely source of exposure misclassification bias leading to an underestimation of the effect and a distortion of the exposure-response relationship is not supported by the toxicokinetics of PCBs, nor is it an accurate representation of the data analyses conducted on our cohort and reported in the article.

Bove et al report that the majority of hourly workers never worked in a high-exposure job, when in fact 1268 of the 2984 male hourly employees (42.4%) did work in a high-exposure job. Only 13.8% of the female hourly employees worked in a high-exposure job, not an uncommon occurrence in an industrial setting. To suggest that the remaining portion of the cohort experienced PCB exposure similar to that of the general population is not an accurate representation of the facts. This is presented in the exposure-assessment section of our article.

Bove et al state in the opening sentence that although the goal of the study was to evaluate six specific cancers, we focused almost entirely on all-cancers mortality. Table 4 in the article presents SMRs and 95% CIs not only for the six cancers of interest but for 32 other causes of death, including 15 additional cancers. The issue of statistical power is raised by Bove et al and two tables were provided. These tables were not properly referenced nor was the methodology used to generate these calculations explained. It is unclear why an SMR of 150 should be considered the "highest expected" for these cancers, when previous publications on smaller cohorts reported statistically significant SMRs well above 150. Our study was an attempt to evaluate these earlier observations in a larger study with a longer follow-up period.

Bove et al question the decision to limit the latency by length of employment calculations to cancers with more than two observed cases and a lower boundary of the 95% CI of 90 or above. This decision was made by the investigators to limit the multiple comparison problem and to provide more meaningful data, rather than to obscure data. Additionally, the lack of presentation of data should not be interpreted as the data not having been analyzed. All six a priori cancers of concern were examined carefully; however, publication space is limited and presenting a table of latency by cumulative exposure for liver cancer, for instance, with two deaths was deemed unwarranted.

In their summary statement, Bove et al dismiss our study findings because of the HWE effect, failure to account for latency, exposure misclassification, potentially insufficient dosage differences between exposed and comparison groups, and poor statistical power, yet they still insist that we did find excess cancer risk for three of the six a priori cancers of interest and give credence to those findings. It is inconceivable to the

investigators of this study how Bove et al, given this litany of problems, were able to differentiate the impact and direction of these biases with such certainty and specificity.

The authors take exception to the tone of the letter by Frumkin and Orris and find statements such as "conspicuously silent" and "willful effort to avoid a positive finding" inflammatory and suggest that such statements do little to advance the understanding of PCBs and cancer risk.

Most of the issues raised by Frumkin and Orris have been addressed earlier. Their suggestion to include more capacitor plants to increase power has merit, however. The General Electric Company had only the two facilities in upstate New York (Hudson Falls and Fort Edward) where capacitors were made using PCBs.

Frumkin and Orris question whether high-exposure jobs actually entailed high exposure and raise concerns about misclassification. The exposure misclassification suggested by Frumkin and Orris is highly improbable, given the distinction between jobs with direct dermal and inhalation exposure and those with only inhalation exposure to PCB air levels in the plant, as explained and referenced in our article. Additionally, the characterization of this bias as substantial is unwarranted and is an overstatement of the potential effect. Assignment of exposure for specific job categories was done before determination of vital status. At both plants, workers were located in the same building, and the same air-ventilating system served the entire building. We verified the physical layout by conducting a walk through the building and by talking to present and former employees. Many workers had different jobs in the different exposure categories (high, undefinable, and low). All workers, including those in low-exposure jobs, had significantly higher exposures than the general population, on the basis of PCB serum levels reported by Lawton et al,[11] Brown et al[15,16] and Brown.[18]

The PCB blood levels (from 194 and 290 workers) mentioned by Frumkin and Orris were of limited value in validating an exposure job matrix for 7075 workers. Although the job histories and the exposure assignment did confirm that workers in high-exposure jobs had high PCB blood levels, these workers were selected either because of their known high-exposure job[11] or they were self-selected.[10] The high-exposure jobs were readily identified by plant personnel and were confirmed by PCB air-level readings and PCB blood levels. Misclassification of jobs into the high-exposure category or misclassifying high-exposure jobs as lower-level exposure jobs was extremely unlikely.

Frumkin and Orris suggested that PCBs are serious health hazards, irrespective of carcinogenicity, with effects that include decreased birth weight, neurodevelopmental effects, and interference with thyroid and estrogen hormone function. It has not been shown that PCBs interfere with estrogen-hormone function in humans. Studies conducted to examine the effects of PCBs in infants and children have been critically reviewed[19–25] or could not be supported.[26] Results from thyroid function tests performed in infants were within the normal range. Furthermore, Koopman-Esseboom et al[27] stated, "The mean dioxin-like PCB toxic equivalent levels and the mean total PCB and dioxin toxic equivalent levels of the neurological normal infants were significantly higher ($p = 0.04$ for both) compared with the levels of the neurologically (mildly or definitely) abnormal infants. There was no relationship between the TT3 (serum total triiodothyronine), TT4 (serum total thyroxine), FT4 (free thyroxine), and TSH (thyroid stimulating hormone) levels in maternal, umbilical, or infant plasma (collected in the second week after birth) and the results of the neonatal neurological examinations. We conclude that overt abnormalities found in the neonatal period are not caused by either direct effects of PCB or dioxin exposure or lowered thyroid hormone levels." According to the National Center for Health Statistics,[28] birth weight is affected by education of the mother, mother's age, birth order, interval between births, gender, inadequate prenatal nutrition, alcohol consumption, smoking, lack of prenatal care, incidence of elective induction, contraceptive utilization, out-of-wedlock births, metropolitan areas (lower), and race. The body size of the parents and maternal illnesses such as diabetes also play a role. These many variables exemplify the difficulties of appropriately designing studies to examine a single factor affecting birth weight. Given these uncertainties and the published criticisms of studies reporting "other health effects of PCBs," it has not been conclusively shown that PCBs cause other "serious" health problems in humans.

We disagree with the final comment by Frumkin and Orris that this study was a great leap sideways on the path to a more complete understanding of the health effects of PCBs. The issue of PCBs and potential health effects has been a significant public health concern for more than 30 years. The lack of consistent findings in the previous cohort studies was assumed to have resulted from small cohort sizes and short follow-up periods. Given the disparate findings in these smaller capacitor cohorts, the appropriate next step was to assemble a larger cohort of PCB-exposed workers and examine them throughout a longer follow-up period. The fact that we were unable to confirm any of the previously reported findings is important and adds to the knowledge about PCBs and health effects. The assumption that a negative study does not provide valuable information imposes significant restrictions on the scientific process and the ability to ade-

quately and objectively assess all data.

Errata: The correct number of female salaried workers with a length of employment of 10 to <15 years in Table 2 is 27; 5.8% is the correct percentage. In Table 6, line 2, last column, total SMR for ≥20 years of latency should be 117. The total number of workers in the upper panel of Table 2 should be 7075.

Renate D. Kimbrough, MD
Martha L. Doemland, PhD
Maurice E. LeVois, PhD
Institute for Evaluating Health Risks
Washington, DC

References

1. Kimbrough RD, Doemland ML, LeVois ME. Mortality in male and female capacitor workers exposed to polychlorinated biphenyls. *J Occup Environ Med.* 1999; 41:161–171.
2. McMichael AJ. Standardized mortality ratios and the "healthy worker effect': scratching beneath the surface. *J Occup Med.* 1976;18:165–168.
3. Checkoway H, Pearce NE, Crawford-Brown DJ. Issues of study design and analysis. In: *Research Methods in Occupational Epidemiology.* New York: Oxford University Press; 1989:78–79.
4. Brown DP. Mortality of workers exposed to poylchlorinated biphenyls: an update. *Arch Environ Health.* 1987;42:333–339.
5. Sinks T, Steele G, Smith AB, et al. Mortality among workers exposed to polychlorinated biphenyls. *Am J Epidemiol.* 1992;136:389–398.
6. Loomis D, Browning SR, Schenk AP, et al. Cancer mortality among electrical workers exposed to polychlorinated biphenyls. *Occup Environ Med.* 1997;54: 720–728.
7. Bertazzi PA, Riboldi L Pesatori A, et al. Cancer mortality of capacitor manufacturing workers. *Am J Ind Med.* 1987;11: 165–176.
8. Tironi A, Presatori A, Consonei D, et al. The mortality of female workers exposed to PCBs. *Epidemiol Prev.* 1996;20:200–202.
9. Brown DP, Jones J. Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. *Arch Environ Health.* 1981;36:120–129.
10. Wolff MS, Fischbein A, Thornton J, Rise C, Lilis R, Selikoff IJ. Body burden of polychlorinated biphenyls among persons employed in capacitor manufacturing. *Int Arch Occup Environ Health.* 1982;49: 199–208.
11. Lawton RW, Ross MR, Feingold J, Brown JF Jr. Effects of PCB exposure on biochemical and hematological findings in capacitor workers. *Environ Health Perspect.* 1985;60:165–184.
12. Lawton RW, Brown JF, Ross MR, Feingold J. Comparability and precision of serum PCB measurements. *Arch Environ Health.* 1985;40:29–37.
13. Taylor PR, Reilly AA, Stelma J, Lawrence CE. Estimating serum polychlorinated biphenyl levels in highly exposed workers: an empirical model. *J Toxicol Environ Health.* 1991;34:413–422.
14. Kimbrough RD. Polychlorinated biphenyls (PCBs) and human health: an update. *Crit Rev Toxicol.* 1995;25:133–163.
15. Brown JF Jr, Lawton RW, Ross MR, Feingold J. Assessing the human health effects of PCBs. *Chemosphere.* 1991;23: 1811–1815.
16. Brown JF Jr, Lawton RW, Ross MR, et al. Persistence of PCB congeners in capacitor workers and Yusho patients. *Chemosphere.* 1989;19:829–834.
17. Mayes BA, McConnell EE, Neal BH. Comparative carcinogenicity in Sprague-Dawley rats of the polychlorinated biphenyl mixtures Aroclors 1016, 1242, 1254, and 1260. *Toxicol Sci.* 1998;41:62–76.
18. Brown JF Jr. Determination of PCB metabolic, excretion, and accumulation rates for use as indicators of biological response and relative risk. *Environ Sci Technol.* 1994;28:2295–2305.
19. Paneth N. Human reproduction after eating PCB-contaminated fish. *Health Environ Digest.* 1991;5:4–8.
20. Paneth N. Adopting a public health approach to developmental neurotoxicity. *Neurotoxicol Teratol.* 1996;18:233–234.
21. Buck GM. Epidemiologic perspective of the developmental neurotoxicity in PCBs in humans. *Neurotoxicol Teratol.* 1996; 18:239–241.
22. Guo YL, Yu M-LM, Ryan JJ. Different congeners of PCBs/PCDFs may have contributed to different health outcomes in the Yu-Cheng cohort. *Neurotoxicol Teratol.* 1996;18:255–256.
23. Schantz SL. Developmental neurotoxicity of PCBs in humans: what do we know and where do we go from here? *Neurotoxicol Teratol.* 1996;18:217–227.
24. Schantz SL. Response to commentaries. *Neurotoxicol Teratol.* 1996;18:271–276.
25. Borak J, Israel L. Does *in utero* exposure to PCBs cause developmental toxicity? The occupational and environmental medicine report. *J Occup Environ Med.* 1997;11:13–18.
26. Grandjean P, Weihe P, White RF, et al. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol Teratol.* 1997;19: 417–428.
27. Koopman-Esseboom C, Huisman M, Touwen BC, et al. Newborn infants diagnosed as neurologically abnormal with relation to PCB and dioxin exposure and their thyroid hormone status. *Dev Med Child Neurol.* 1997;39:785.
28. NCHS. *Trends in Low Birth Weight in the United States 1975–1985.* Washington, DC: Department of Health and Human Services, CDC National Center for Health Statistics; October 1989. National Center for Health Statistics Series 21, No. 48.

Investigation of Elevated Urine Beta-2-Microglobulin in a Cohort of Cadmium Workers

To the Editor: Prior to the issuance of the 1993 Occupational Safety and Health Administration Cadmium Standard, urine testing for beta-2-microglobulin (β_2m) was not frequently performed. Testing for β_2m was an esoteric laboratory test performed only on workers whose cadmium levels had been found to be elevated. The Cadmium Standard mandated that all employees exposed to greater than 2.5 $\mu g/m^3$ cadmium dust or fumes be tested at least annually for urine β_2m, as well as for blood cadmium (CdB) and urine cadmium (CdU). At a nickel-cadmium battery manufacturing facility, approximately 1000 employees, some of whom had been exposed to cadmium and some of whom had not, were evaluated for β_2m levels, most for the first time.

Elevated β_2m was defined as a β_2m level higher than 300 $\mu g/g$ creatinine[1]; expectations were that approximately 10% of workers with cadmium levels higher than 10 $\mu g/L$ blood or 10 $\mu g/g$ creatinine would also show an elevated β_2m level.[2,3] Because 54 employees had such elevated cadmium levels in 1993, it was expected that approximately five or six would also show elevated β_2m levels. It was not known how many employees with other conditions