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Exposure to and health effects of volatile PCBs

Abstract

Introduction: Polychlorinated biphenyls (PCBs) are persistent, lipophilic contaminants that are known to increase risk of a number of human diseases. Although ingestion of animal fats is a major route of exposure, there is increasing evidence that inhalation of vapor-phase PCBs is also important and may be as or even more important than ingestion under some circumstances.

Methods: The evidence that inhalation of PCBs may cause cancer, heart disease, hypertension, and diabetes is reviewed and presented in this report.

Results: PCBs are known human carcinogens. A husband and wife, occupationally required to 'smell' PCB-containing oils, both developed thyroid cancer, malignant melanoma/severely melanocytic dysplastic nevus (a precursor to malignant melanoma) and the husband, a non-smoker, developed and died of lung cancer. The serum of both had highly elevated concentrations of lower chlorinated, volatile PCB congeners. In other studies, residents living near PCB-containing hazardous waste sites, and thus breathing PCB-contaminated air, have elevated rates of hospitalization for cardiovascular disease, hypertension, diabetes and reduced cognitive performance, whereas other studies in defined populations show that there is an elevated risk of all of these diseases in individuals with elevated serum PCBs.

Conclusions: These results are consistent with the conclusion that inhaled PCBs can increase risk of cancer, cardiovascular disease, hypertension, diabetes and reduce cognitive function.

Keywords: cancer; cardiovascular disease; diabetes; hypertension; PCB exposure; volatile PCBs.

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Introduction

Polychlorinated biphenyls (PCBs) were manufactured in many countries from the late 1920s until they were found to be persistent and toxic in the late 1970s, when their manufacture and use was stopped in most developed countries. It is reported, however, that they are still being manufactured in North Korea, and even in the US, many transformers and capacitors that are still being used contain PCBs.

PCBs consist of mixtures of up to 209 individual congeners, which vary depending on how many chlorines are on the biphenyl rings and where they are located on the molecule. Figure 1 shows the PCB molecule and the convention for identifying different congeners based on the location of chlorines. PCBs were manufactured in many countries as commercial mixtures through the chlorination of biphenyl with anhydrous chlorine in the presence of a catalyst, usually iron. The duration of the reaction determined the average degree of chlorination. In the US, almost all PCBs were manufactured by Monsanto, who sold commercial mixtures under the trade name 'Aroclor'. Aroclor 1242 was 42% chlorine by weight, whereas Aroclor 1260 was 60% chlorine. However, all commercial products contained a variety of PCB congeners, with the exception of Aroclor 1271, which was pure PCB 209 that contained chlorine groups at all 10 sites.

Most widely used commercial PCB mixtures are oils, and the greater the degree of chlorination, the more viscous the oil. They had many useful purposes. However, they had major uses in capacitors and light ballasts given because they are relatively nonflammable and nonconductive. They were widely used as hydraulic fluids, as solvents for paints or caulking, in carbonless copy paper, and in other products requiring a lipophilic solvent.

Although all PCB congeners have some common properties, they also have significant differences in physical properties and routes of exposure to humans. In general, PCBs have low water solubility and volatility. However, those congeners containing fewer chlorines are more water soluble and more volatile than those with more chlorines (1, 2). Table 1 (3) shows vapor pressure, water solubility, log octanol/water partition coefficient (log K_{ow}), and approximate evaporation rates as a function of the number of chlorines on the PCB molecule.

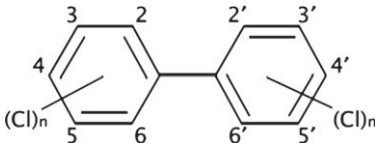

Figure 1: The structure of PCBs. There can be any number of chlorines around the biphenyl ring between one and ten. The convention for labelling the position is shown by the numbers, where the 2 and 6 positions are *ortho,* the 3 and 5 positions are *meta*, and the 4 position is *para*. The prime sign distinguishes in which ring the chlorines are located.

Table 1: Physical characteristics of PCBs by homologue groups at 25°.

PCB homologue group	Vapor pressure, Pa	Water solubility, g/m³	Log octanol/ Water coefficient	Evaporation rate, g/m³/h
Monochloro	1.1	4.0	4.7	0.25
Dichloro	0.24	1.6	5.1	0.065
Tetrachloro	0.012	0.26	5.9	4.2×10^{-3}
Hexachloro	5.8×10^{-4}	0.038	6.7	2.5×10^{-4}
Octachloro	2.8×10^{-5}	5.5×10^{-4}	7.5	1.5×10^{-5}
Decachloro	1.4×10^{-6}	7.6×10^{-4}	8.3	8.5×10^{-7}

Data from Ref (3).

Even commercial mixtures with primarily highly chlorinated congeners contain lower chlorinated congeners at low concentrations. Figure 2 shows the congener pattern of Aroclor 1260 (60% chlorine by weight) and that of PCBs in the vapor phase, resulting from blowing air over the commercial mixture. Clearly, even this highly chlorinated mixture contains lower chlorinated PCBs that volatize. There is also some volatilization of moderately chlorinated congeners, but the overall profile in the vapor phase shifts markedly to the left, indicating that lower chlorinated congeners are more volatile.

PCBs can volatilize from a variety of sources, including commercial mixtures, water, landfills, and commercial products. As lower chlorinated PCBs are more water soluble and more volatile (Table 1) they will selectively dissolve in water and then move from a soluble aqueous phase into the air. PCBs evaporate along with the water (4, 5), and this process is very temperature dependent (6). Volatile loss of PCBs from Lake Superior was calculated to be about 1900 kg per year (7). Outdoor air concentrations of PCBs near New Bedford Harbor, a highly contaminated body of water, ranged from 0.4 to 53 ng/m³ (8); these are significantly higher than those at a comparison site. PCB fluxes to air along the contaminated Hudson River ranged from 0.5 to 13 μg/m²/day (9).

The greater water solubility of lower chlorinated PCBs has implications for drinking water quality. The majority of the higher chlorinated congeners will be bound to particulates in water and then removed by standard drinking water treatments. However, those that are dissolved are more difficult to remove and may be an important route of human exposure, especially if contaminated surface water is used for municipal drinking water.

PCBs will also volatilize from contaminated soils and sediments. As from water, the PCBs volatize with water, and dry sediments lose fewer PCBs to the air as compared with wet sediments or soils (4). PCBs can also volatilize from landfills, depending upon how tightly they are covered (10). Hermanson et al. (11) studied air PCB concentrations near a Monsanto landfill in Anniston, Alabama, the site of a PCB synthesis factory, and compared results to those from a nearby site that had superficial soil PCB contamination. They found less dependence on surface temperature for PCB release to air from the landfill, and suggested that most of the sources of PCBs from the landfill site were materials buried within the landfill.

In addition to the differences in physical properties, congeners have both differences in rates of metabolism in the human body and major differences in mechanisms of action and health effects in humans. PCBs, like most chlorinated compounds, are poorly metabolized and are thus persistent. In general the half-life increases with number of chlorines but other factors like location of the chlorines around the ring also influence rates of metabolism. The half-lives in humans of several individual PCB congeners are shown in Table 2 (12). *Ortho* chlorine substitution usually increases the half-life relative to that of a PCB with the same number of chlorines but with none in the *ortho* position (13).

Many of the volatile mono-, di-, and tri-chloro congeners are metabolized within hours in rats (14). Hu et al. (15) found that labeled PCB 11 (3,3′-dichloro biphenyl) had a half-life of 12 h in male rats. Although human metabolism is generally not as rapid as in rodents, it is sufficiently rapid such that lower chlorinated congeners are rarely found at significant concentrations in human blood. Long half-life makes it convenient to determine the exposure of a person to PCBs in the past, but there is often the assumption that long half-life is indicative of greater health effect. This assumption is not necessary correct. This is because even those congeners that are more rapidly metabolized may have significant toxicity, especially if there is prolonged exposure, as would be the case if they were inhaled on a daily basis.

The major metabolism of PCBs is through cytochrome P450s in the liver and other organs (13). This results in

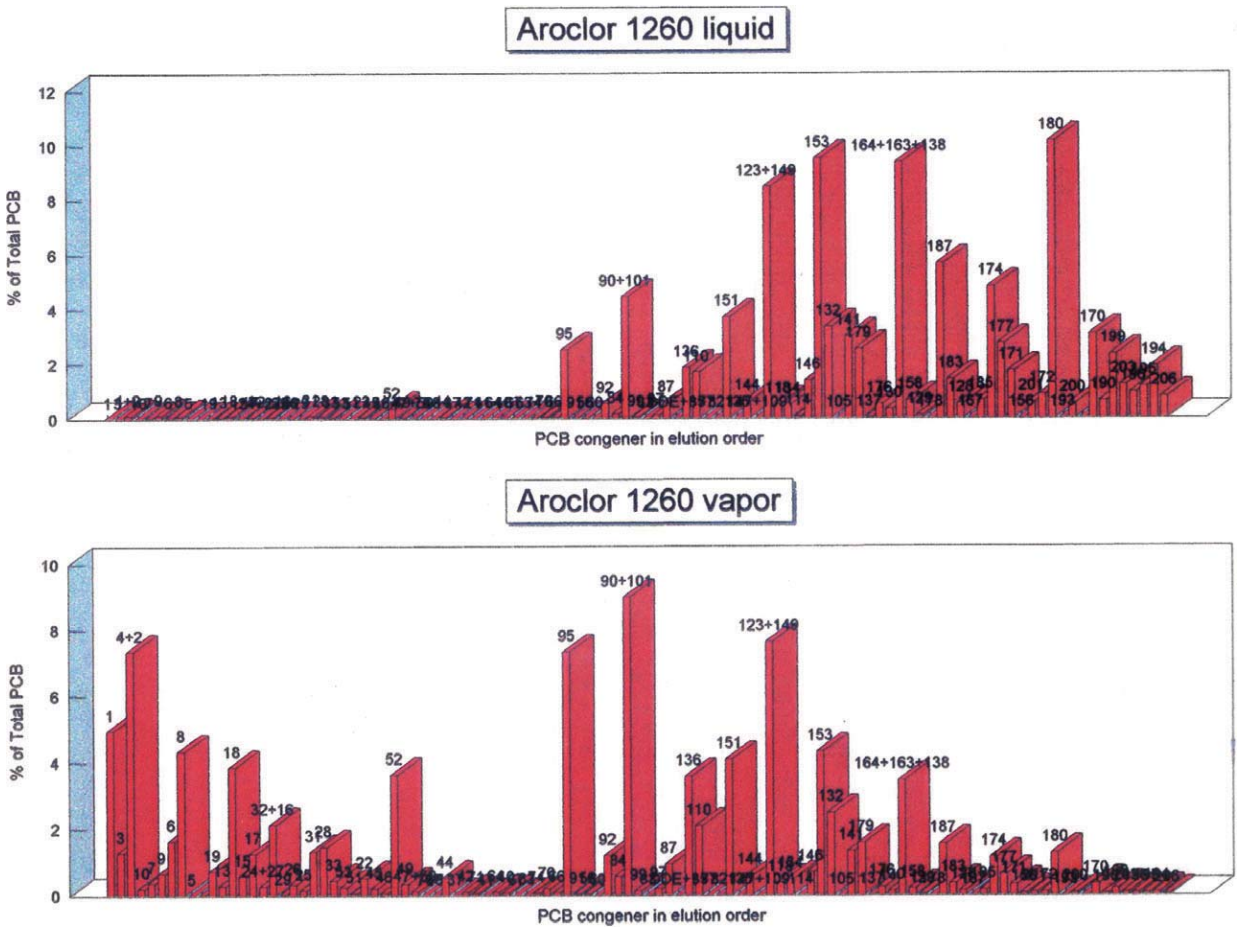

Figure 2: The congener patterns in Aroclor 1260 liquid (top) and the congener pattern seen when passing air over the liquid and collecting and analyzing the vapor-phase PCBs.
Peaks are shown in the order they elute from the column. The numbers above the peaks identify individual congeners or groups of congeners. Those peaks to the left have fewer chlorines.

Table 2: Half-lives of single PCB congeners in the human adult body.

PCB number	PCB structure	Half-life, years
28	2,4,4′ Trichlorobiphenyl	5.5
52	2,2′,5,5′ Tetrachlorobiphenyl	2.6
105	2,3,3′4,4′ Pentachlorobiphenyl	5.2
118	2,3′4,4′,5 Pentachlorobiphenyl	9.3
138	2,2′,3,4,4′,5′ Hexahlorobiphenyl	10.8
153	2,2′,4,4′,5,5′ Hexachlorobiphenyl	14.4
170	2,2′,3,3′,4,4′,5 Heptachlororbiphenyl	15.5
180	2,2′,3,4,4′,5,5′ Heptachlorobiphenyl	11.5

Data from Ref (4).

introduction of oxygen onto the molecule, which then allows for further metabolism by other transferases. Many of the hydroxylated or methyl sulfonated metabolites are somewhat persistent and have biologic activity (16). The position of the chlorines around the PCB molecule influences the rate of metabolism (17). This is why different PCB congeners with the same number of chlorines have different half-lives, as shown in Table 2. In addition, different congeners are targets of different P450s. Many studies have focused on PCB congeners that have dioxin-like activity as well as those that bind to the aryl hydrocarbon receptor, induce P4501A and then induce many different genes (18). Other congeners induce different P450s and many genes, but with a different pattern (19). To make matters even more complex, the profile of genes that are induced may vary from one tissue to another (20). Many of the adverse health effects reported in humans are likely a consequence of different patterns of gene induction.

Despite the more rapid metabolism of lower chlorinated PCBs, evidence for inhalation exposure can be obtained from serum samples. Our group has studied PCB exposure in a Native American population for many years. Many older

adults have a pattern of congeners dominated by a few highly chlorinated and persistent congeners like PCBs 138, 153, 170, and 180. However, we have been able to identify a pattern of lower chlorinated PCBs in the serum of younger Mohawks, which matched closely to the pattern of the PCB profile in air over a contaminated site (21) Figure 3. The pattern could not be observed clearly in older individuals because serum levels increase with age and the PCBs from ingestion obscure those more readily metabolized PCBs.

Herrick et al. (22) measured serum PCB levels in teachers working in a school that had elevated PCBs in indoor air, and found significantly higher concentrations of lower

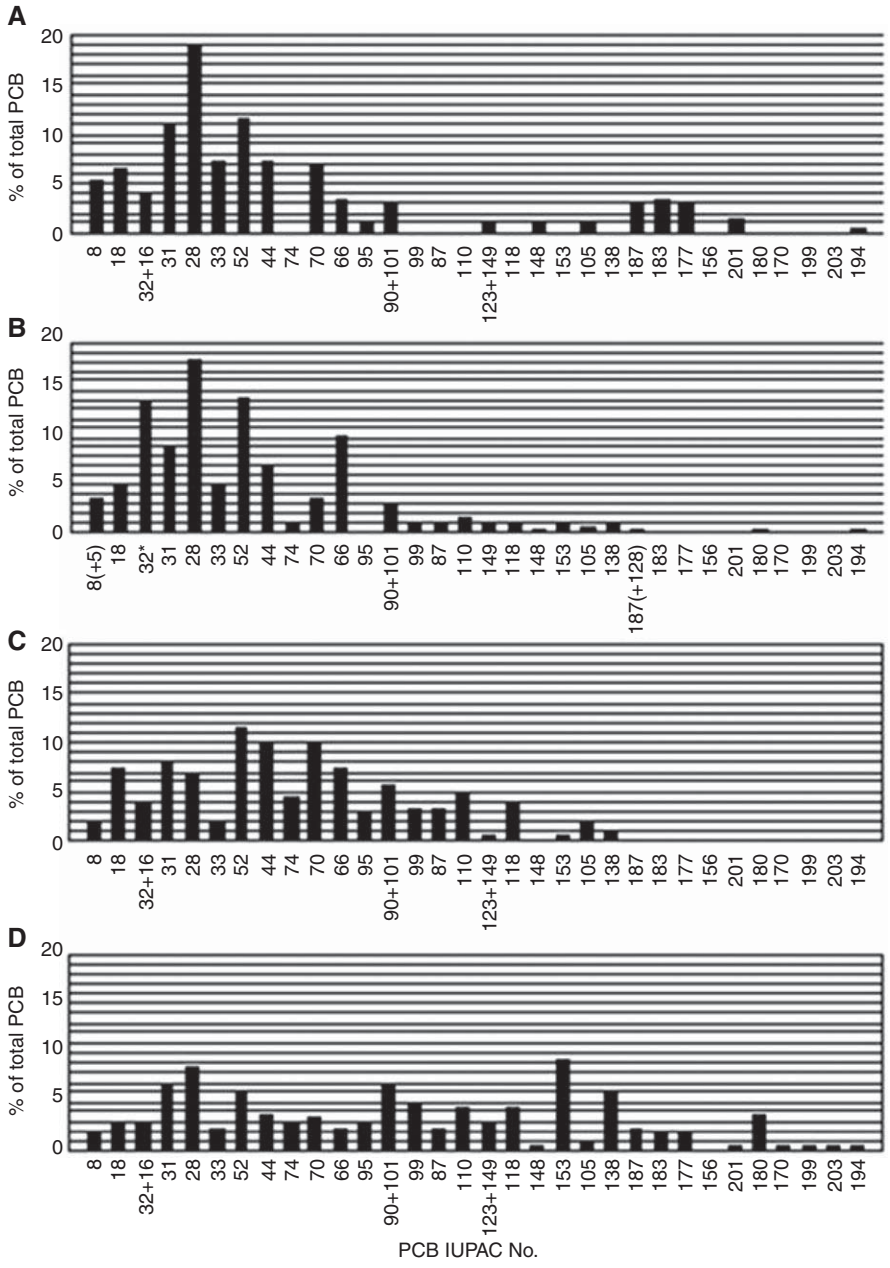

Figure 3: Congener compositions of (A) End-member (EM)-1 as determined by polytopic vector analysis (PVA) of serum PCB congener data for 702 adult Mohawks, (B) air sampled above "Contaminant Cove" at the western boundary of Akwesasne in summer 1993,[17] (C) native commercial A1248 liquid, and (D) serum from the subject with the highest proportion (46.2%) of EM-1. For profiles not generated in the authors' laboratory (i.e., B), the same congener elution order as that in the other samples is presented to facilitate comparisons. Differences in congener coelutions between samples are indicated by brackets; congeners analyzed in the authors' laboratory but not by others are shown in italics. For brevity, CB 138 is listed alone although it coelutes with CBs 163 and 164 for all samples. In addition, CB 32 coelutes with CBs 11, 12, and 13 for the sample shown in (B). *Reprinted from DeCaprio et al.[21] with permission from Elsevier B.V.*

chlorinated congeners (PCBs 6–74) than those found in unexposed teachers. Meyer et al. (23) obtained serum PCB measurements from 134 residents of a flat with high concentrations of PCBs in the indoor air, and compared levels to those of 139 unexposed persons. Levels of 27 congeners, especially lower chlorinated congeners, were found to be four times higher in the serum of the exposed individuals.

The goal of this paper is to review the evidence that the inhalation of PCBs can lead to adverse health effects in humans. The paper will focus on a few specific diseases for which evidence exists to support the conclusion that inhalation is an important route of exposure. The problem is that most scientists who are investigating health effects of PCBs use serum PCB concentration as their exposure assessment measure. Given that most of the more volatile congeners are rapidly metabolized, they are not present in high concentrations in serum samples and, thus, they are usually not considered. However, the typical source of inhaled PCBs is indoor air in homes, schools and offices, places where people spend many hours a day. Under these circumstances, people may be more or less continuously exposed and affected by the lower chlorinated congeners.

Cancer

PCBs have been identified as Group 1, known human carcinogens, by the International Agency for Research on Cancer (24). The specific cancer with the strongest evidence is malignant melanoma. There are, however, many of types of cancer for which strong associations with serum PCB levels have been found (25). However, there is little direct evidence for cancer in humans resulting from inhalation exposure to PCBs.

Until the recent IARC identification of all PCBs being carcinogenic, there was a widespread belief that only dioxin-like PCBs had carcinogenic activity. This is despite clear evidence presented by van der Plas et al. (26). They reported that majority (about 80%) of the tumor-promoting activity of PCBs can be found the in 2–4 *ortho*-substituted congener groups, which have little or no dioxin-like activity. Sandal et al. (27) compared the genotoxic activities of PCB 52 (2,2′,5,5′tetrachloro biphenyl, a non-dioxin-like congener) and PCB 77 (3,3′,4,4′ tetrachlorobiphenyl, a dioxin-like congener) on cultured human lymphocytes. They found that both congeners caused DNA damage as monitored by the comet assay, but that PCB 52 is significantly more potent. Both PCB 9 (2,5 dichlorobiphenyl) (28) and PCB 11 (29) generate reactive oxygen species, known to be a risk factor for cell damage and death. Ludewig et al. (30) found that PCB 3 (4-monochlorobiphenyl) and/or its metabolites increase mutations in rat liver. Tan et al. (31) found that PCBs 8 (2,4 dichlorobiphenyl), 28, 47 (2,2′4,4′-tetrachlorobiphenyl), and 52 are cytotoxic to both neurons and thymocytes, but the dioxin-like congeners PCBs 77, 80 (3,3′,5,5′-tetrachlorobiphenyl) and 81 (3,4,4′,5-tetrachlorobiphenyl) are not. Although not all of these effects are necessarily directly related to cancer, they clearly demonstrate toxicity of lower chlorinated, non-dioxin-like congeners.

Case study

Company X was an analytic services laboratory that provided analysis of fluids from electric transformers. Up until 1977, when their manufacture and new use was outlawed by the US Environmental Protection Agency (EPA) due to their persistence and toxicity, most electric transformers were filled with commercial mixtures of PCBs. However, old transformers that have not been serviced still contain PCBs. Now EPA requires that the fluid from transformers being serviced or discarded be tested to determine whether PCBs are present; if they are, then the EPA requires that the fluid be removed and the transformer cleaned and filled with a non-toxic substitute. All PCB-containing fluids at concentrations <50 ppm are to be treated as hazardous waste, and rules have been established to regulate disposal of oils containing PCBs at concentrations between 2 and 50 ppm.

JM, a relatively dark-skinned Hispanic, was employed by company X between 1994 and 2003 as a laboratory technician. His job was to analyze 100–150 transformer oil samples per day to determine whether they contained PCBs. It was known that 10%–20% of those samples would have PCBs at concentrations ranging from 50 to 499 ppm, and another 10% would have even higher concentrations, some being 100% commercial PCBs. JM was told to smell the fluid to determine whether or not it contained high concentrations of PCBs. PCBs have a subtle but distinctive odor. The reason for smelling the fluids before analyzing them was that running a sample with a high PCB concentration in the gas chromatograph would result in contamination that would then take time to wash out. Thus, if samples with high concentrations could be identified before being run, they could be serially diluted to the point that they would not require extra time to be taken to wash out the gas chromatograph.

JM was born in 1967 and did not smoke nor drink to excess. His medical history was unremarkable except for hypertension, and elevated LDL with a slightly low HDL. On December 14, 2001 he was found to have a greatly

reduced thyroid stimulating hormone (TSH) level, and highly elevated thyroxine (T4) level. On February 28, 2003 he was treated with radioactive ^{131}I, which resulted in a decrease in his TSH level. On March 3, 2003 a large papillary thyroid carcinoma was removed in a subtotal thyroidectomy. The tumor surrounded the vagus nerve and it was difficult to remove. On August 26, 2003 he was found to still have an abnormally elevated uptake of ^{131}I, which was suggestive of recurrent disease. Although he continued to work at company X after his surgery, he was no longer required to analyze for PCBs. In March, 2011 JM had a malignant melanoma removed from his back. In March, 2013 JM was diagnosed with lung cancer, which on biopsy, proved to be a poorly differentiated adenocarcinoma, not a metastasis from the melanoma. JM died later in 2013 with massive hemorrhagic brain metastases.

GM, wife of JM, was born in 1968 and hired by company X in 1996. Her job was to dump oils that were in the GC sampling vials that had been analyzed into 55 gallon drums, separating those with and without high concentrations of PCBs, and ensure that any liquids containing PCBs were not allowed down the drain. She also was required to wash the glassware. She worked in a 50 sq ft room with a hood and waste basin but without windows or air conditioning, and was told to keep the door closed. When the oils were to be dumped, she was told to sniff each sample in order to determine which 55 gallon drum the material should be placed in. If it smelled like PCBs, it would go into one drum, but if not then it should go into the other. The glassware contaminated with PCBs was to be washed with toluene and acetone, followed by soap and water. She was never provided with a lab coat, gloves, or a mask.

GM was also diagnosed with thyroid cancer in May of 2003, after which she stopped working at company X. She had a total thyroidectomy in July, 2003. She completed a course of 100 mC ^{131}I on September, 2003. She had some abnormal uptake of the isotope on August 26, 2003, but there was no evidence of recurrent disease by March, 2004. In 2011, she was diagnosed with a compound melanocytic dysplastic nevus, a highly dangerous mole that is a precursor to melanoma. This was removed. She also had abnormal liver function tests, perhaps a fatty liver, diabetes, and hypertension. She does not drink and does not have hepatitis.

Serum samples were obtained in the late summer and fall of 2005 for measurement of PCBs, and analysis was done by ERGO Forschungsgesellschaft mbH in Hamburg, Germany. The results for six PCB congeners are shown in Table 3.

Table 3: PCB concentrations (μg/kg or ppb wet weight) in serum samples from JM and GM.

PCB congener	JM	GM
28	1.82	3.47
52	1.22	1.60
101	nd	0.33
138	nd	0.22
153	0.17	0.23
180	0.16	0.44
Sum	3.37	6.28

nd, not detected.

There are several remarkable findings in this tragic story. For two persons who are not blood relatives to both develop two relatively rare cancers of the same type (thyroid and melanoma) by chance is extraordinarily unlikely. Malignant melanoma is the cancer for which there is the strongest evidence for causation by PCBs. This is reflected in the recent report from the International Agency for Research on Cancer, which declared PCBs to be Group 1, known human carcinogen, based primarily of occupational studies (24). Although the route of occupational exposure is uncertain in these reports, inhalation is certainly a major component.

Thyroid cancer has been reported in rats exposed to commercial PCB mixtures (32, 33). An elevation in lung cancer has been reported in one occupational cohort after control for other factors (34). Animal studies have shown that exposure of mice to Kanechlor-400 (a Japanese PCB product) resulted in various kinds of lung neoplasms (35). JM was a non-smoker living in an area where radon is not a major problem, and it is likely that his lung cancer was also a consequence of inhaling PCBs.

The pattern of PCB congeners found in the serum sample is striking. In the general population, PCB 153, 138, and 180 are found at much higher concentrations than PCBs 28 and 52. However because PCBs 28 and 52 have fewer chlorines, are much more volatile. In the 2003–04 NHANES, mean concentrations of PCB 28 in adults over 20 was 0.031 and the 95th percentile was 0.067 ppb. For PCB 52, the mean concentration was 0.016 and the 95th percentile was 0.043 ppb. Hence, the concentrations of both congeners are two orders of magnitude higher in both JM and GM. For PCB 153, the levels in both JM and GM are within the background concentrations found among the individuals in the 2003–2004 NHANES (mean, 0.148 ppb, 95th percentile, 0.671 ppb). This pattern of PCBs in serum alone is convincing evidence that the major route of exposure for both JM and GM was inhalation of volatile PCBs.

There is other evidence consistent with the conclusion that lower chlorinated, more volatile PCBs are

carcinogenic. Although those congeners with fewer chlorines are more rapidly metabolized, they generate hydroxylated and other metabolic progeny that exhibit genotoxicity (36) and oxidative stress (29). Maddox et al. (37) demonstrated a non-significant two-fold increase in spontaneous mutations induced by PCB 3 (4 monochloro biphenyl) and 4-OH-PCB 3 in rat lung. Xie et al. (38) showed that PCB 3 is converted to quinones which are very efficient in inducing gene mutations and chromosomal breaks.

Studies using hospitalization diagnoses to assess diseases from inhalation of PCBs

My colleagues and I have performed a series of studies using New York State (NYS) hospitalization data to examine residences near hazardous waste sites containing identified chemicals, particularly PCBs. In NYS, the diseases diagnosed in every patient admitted as an inpatient to a state-regulated hospital (all except federal hospitals like Veterans' Administration and Indian Health Services) must be reported to the Department of Health upon discharge. The data available to us include sex, age, race, method of payment and zip code of residence, as well as up to 15 different disease diagnoses. The data are limited in that we do not know names or street addresses, and do not have any information about personal habits. We do have access to behavioral characteristics by county from the Behavioral Risk Factor Surveillance System (BRFSS), and we have information on median household income and population density by zip code from the US Census. We have matched rates of hospitalization for specific diseases to residence in zip codes that either contain or do not contain a hazardous waste site. The Department of Environmental Conservation lists 814 such sites in NYS and identifies those containing PCBs. Our hypothesis behind these studies is that living near a PCB-contaminated site increases exposure, and that such exposure must be primarily by inhalation. There is no reason to assume that dietary exposure would be different depending upon where you live, and it is unlikely that most people are going to have significant dermal exposure.

There are some important limitations in ecologic studies of this sort, particularly with regards socioeconomic status (SES). Poverty is well known to be an important risk for disease, but we adjust for this the best we can using the BRFSS, which provides some information on personal habits in the locale and census data, from which we can obtain median household income in the zip code. The exposure assessment is also very limited, being only the zip code of residence. We cannot distinguish multiple hospitalizations by one person from those of different individuals. However, despite these limitations, there are some other major strengths. For example, there are 2.5 million hospitalizations each year in NYS, and we have data from 1993 through 2008. We have used results of these studies to generate hypotheses, which we then tested in smaller populations wherein we have better exposure assessment.

Cardiovascular disease

Sergeev and Carpenter (39) examined rates of hospitalization for coronary heart disease and myocardial infarction in NYS residents living in a zip code wherein a PCB hazardous waste site was located, and compared these rates with those living in a zip code without any hazardous waste site after adjustment for age, sex, race, income, and health insurance coverage. They found an odds ratio (OR) of 1.15 (95% confidence interval=1.03–1.29) for coronary heart disease and an OR of 1.20 (1.03–1.39) for myocardial infarction. They then examined a sub-set of the PCB zip codes, that being those along the 200 miles of the contaminated Hudson River. Average income is higher in these zip codes, and BRFSS data show more exercise, less smoking, and greater consumption of fruits and vegetables in these counties than in the rest of NYS. Despite living a healthier life style, the ORs for coronary heart disease and myocardial infarction in these zip codes were 1.36 (1.19–1.56) and OR=1.39 (1.19–1.63), respectively. Thus, living in a zip code containing a PCB hazardous waste site (either a landfill or a contaminated body of water) is associated with an increased risk of coronary heart disease and myocardial infarction, and this is unlikely due to inadequate adjustment for socio-economic status because the elevations in ORs are even higher along the Hudson.

Strokes ('brain attacks') are closely related to myocardial infarctions ('heart attacks'). Shcherbatykh et al. (40) used the same hospitalization records for stroke. They found significant elevations for ischemic stroke for individuals living in PCB-contaminated zip code (OR=1.17, 1.04–1.39) and a slightly greater elevation for individuals living along the Hudson River (OR=1.20, 1.10–1.32) as compared with zip codes without any hazardous waste site.

The above ecologic studies support the hypothesis that exposure to PCBs increases the risk of cardiovascular disease. In order to test this hypothesis, we performed

studies in two PCB-exposed populations where we have measured serum PCB concentrations. We suspect that the route of exposure for those individuals living near PCB hazardous waste sites is inhalation of lower chlorine congeners which are not very persistent. Hence, it is not clear whether the associations seen with measurement of total serum PCBs will give exactly the same results.

Goncharov et al. (41) determined self-reported rates of cardiovascular disease among the Mohawks at Akwesasne, a Native American group living at the US-Canadian border, in relation to measured serum PCBs and serum lipids. They found significantly elevated risk of self-reported cardiovascular disease, but found this to be an indirect effect via an elevation in serum cholesterol and triglycerides. Aminov et al. (42) investigated these same relationships in 575 residents of Anniston, Alabama who live near the Monsanto plant that manufactured PCBs. They also found that increased total serum PCB concentrations was significantly associated with elevated concentrations of total cholesterol and triglycerides, but found no effect on HDL or LDL cholesterol. Thus, there is a clear association between elevation in serum lipids, a major risk factor for cardiovascular disease, and more highly chlorinated PCBs, whereas the ecologic results support the conclusion that the lower chlorinated congeners are also important. At present, the relative importance of lower and higher chlorinated congeners on cardiovascular disease remains to be fully determined. Hennig et al. (43) have demonstrated pro-inflammatory changes induced by PCBs on endothelial cells, which may combine with elevations in serum lipids to increase the risk of cardiovascular disease. Ha et al. (44) have reported that there is a dose-dependent relationship between serum PCB concentrations and cardiovascular disease using data from the National Health and Nutrition Examination Survey (NHANES).

Hypertension

Hypertension is not usually considered to be an environmental disease. However, using the hospitalization data set, Huang et al. (45) reported a significantly elevated OR=1.19 (1.09–1.31) for hospitalization diagnosis of hypertension among individuals living in a zip code with a PCB hazardous waste site. They also found elevated hospitalization for hypertension (OR=1.14; 1.05–1.23) for residents living along the Hudson River.

We have determined the associations between serum PCB levels and blood pressure in 351 residents of Anniston who were not on anti-hypertensive medication. Three measurements of blood pressure were taken in individuals where serum PCBs levels had been measured. We found striking associations between rates of hypertension and serum PCB concentrations (46). After adjustment was age, sex, BMI, serum lipids, smoking and exercise the OR for lowest to highest tertile of PCB concentration was 4.09 (1.3–12.7) for clinical hypertension and 5.28 (1.0–25.8) for both systolic and diastolic hypertension. Even within the normotensive range of blood pressure, there were significant associations with total PCB concentration (47). Serum PCB concentration showed a stronger association than any other factor but age, including BMI, total lipids, sex, race, smoking, and exercise. Associations between serum PCBs and hypertension have also been reported using NHANES data (48, 49).

Diabetes

Kouznetsova et al. (50) analyzed NYS hospitalization data for adult inpatient admissions for diabetes in relation to residence in a zip code containing a PCB-contaminated waste site. Living in a PCB-contaminated zip code was associated with a 23% elevated chance of hospitalization for diabetes as compared with rates for individuals living in a zip code that did not contain a hazardous waste site (OR=1.23; 1.15–1.32), after adjustment for age, race, sex, median household income, and urban/rural residence. Living along the Hudson River was associated with an even greater elevation (OR=1.36; 1.25–1.42). As with the above diseases, the most likely exposure must have come from inhalation.

We have examined rates of physician-diagnosed diabetes in relation to serum PCB concentrations in the Mohawk population at Akwesasne. In a preliminary study, Codru et al. (51) reported that after adjustment for sex, age, BMI and smoking, individuals in the top tertile PCB concentration had a significant 3.9-fold elevated risk of diabetes (95% CI=1.5–10.6). Only two individual congeners were reported, PCBs 74 (2,4,4′,5-tetrachlorobiphenyl) and 153. When adjusted for all other contaminants in addition to the factors listed above, only PCB 74 showed a significant association. We have followed-up on this study (52) with a more complete single congener analysis and with adjustment for all other contaminants but the one under investigation. These results indicate that the only significant association with diabetes is with non- or mono-*ortho* PCB congeners that do not have dioxin-like activity. This is an important observation because these are the lower-chlorinated, volatile congeners. This provides strong support for the hypothesis developed from the hospitalization studies (50), which concluded that

the association between diabetes and living near a PCB-contaminated site is secondary to inhalation of lower chlorinated PCBs.

Discussion and conclusions

These results are consistent with the conclusion that inhalation of PCBs is not only an important route of exposure, but that it can also result in serious disease. PCB exposure is well documented to increase the risk of the diseases reviewed here, namely, cancer, cardiovascular disease, hypertension and diabetes, based on documentation that incidence of these diseases increased with serum concentrations of PCBs. However, the majority of the PCBs found in serum are the more persistent congeners, often with half-lives of a decade or more. These are the congeners found in the higher chlorinated commercial mixtures, and are the ones commonly found in animal fats, which is an important route of exposure to humans. From the point of view of research, the persistence of these higher chlorinated congeners is helpful for establishing associations because a blood sample will provide information about PCB exposure after many years have passed.

This review has focused on only four diseases, chosen because of at least some evidence for elevated risk coming from inhalation exposure. However, these are certainly not the only diseases for which exposure to PCBs is known to increase risk. PCBs are known to cause deficits in learning and memory (53, 54), and there is evidence from animal studies indicating that lowered chlorinated congeners are more neurotoxic than more highly chlorinated congeners (55). Fitzgerald et al. (56) reported decrements of verbal learning and an increase in depressive symptoms in adults living near the contaminated Hudson River, but serum concentrations are not significantly different from those in a comparison population (57). This finding is consistent with inhalation of lower chlorinated, more rapidly metabolized PCBs as the critical factor. PCBs are structurally somewhat similar to T4, and exposure has been shown to suppress thyroid function (58). PCBs also alter sex hormone function, with many congeners and hydroxylated metabolites having estrogenic activity (59). Elevated PCB exposure results in earlier puberty in girls (60) and a reduction in testosterone levels in men and boys (61, 62). PCBs suppress the immune system, leading to increased respiratory infections in children (63, 64) and elevations in cases of asthma (64, 65). PCB exposure to mothers is associated with lower birth weight of infants (66, 67). The relative role of inhalation of lower chlorinated PCBs, to date, has not been studied with regards these diseases and effects.

The PCB congeners that volatilize easily are less highly chlorinated, and most of them are much more rapidly metabolized in the human body. Some, like PCBs 28 and 52, are somewhat more persistent than others, and are frequently found at low concentrations in human serum, although the majority of those congeners with four of fewer chlorines are often not present at detectable concentrations. However, just because they are more rapidly metabolized and do not accumulate does not mean that they do not have adverse health effects. This is particularly the case if the concentrations of these lower chlorinated congeners in air are significant in places where people spend long periods of time (e.g., at home, school, or work). Under these circumstances exposure can be almost continuous, but would not be reflected in high levels of PCBs. Although the specific mechanisms whereby serum PCBs cause neurotoxicity are still uncertain, animal studies have shown that PCB, like lead, are effective in reducing long-term potentiation, an electrophysiologic marker of learning and memory (68).

The most extreme demonstration of the hazards of inhalation of PCBs is the cases of JM and GM, workers occupationally instructed to inhale PCB vapors. Both developed multiple cancers of the same type, and JM died of cancer. Their serum contained elevated concentrations of the lower chlorinated, more volatile PCBs, and only background concentrations of more highly chlorinated congeners that are less volatile.

The ecologic studies showing elevations of cardiovascular disease, hypertension, and diabetes in relation to residences near PCB-contaminated waste sites strongly suggest that inhalation is the route of exposure. However, there are significant limitations to ecologic studies, and they must be viewed as being hypothesis generating. Therefore, we have performed other investigations in defined populations where we have good exposure assessment (albeit with the limitations discussed above for lower chlorinated congeners), as well as access to medical and clinical chemistry information. These studies confirm the hypothesis that PCB exposure is associated with elevated risks of all three diseases. Thus, these studies provide support for the conclusion that inhalation of PCBs is the major cause of the elevated rates of hospitalization.

The implications of these studies are significant for several reasons. First, these results suggest that living near a PCB-contaminated waste site poses risk to health, and by extrapolation this applies also to attending a school with elevated PCBs in the air due to PCB-containing light ballasts or caulk (69–73), working in a contaminated building

(74, 75), working as a fireman around certain house fires (76), and living downwind of sewage sludge drying plants (77). Lower chlorinated PCBs are found in current retail paints, and would be expected to volatilize into room air (78). Urban areas are likely to have more hot spots with higher concentrations than in rural areas, as has been demonstrated in Chicago and Cleveland (79). Thus, many people are being unknowingly exposed to these sources via inhalation. Scientists from the USEPA have recently published a report calling for greater evaluation of health risks from inhaled PCBs (80).

PCBs are dangerous chemicals, but the danger is not restricted to dioxin-like congeners or persistent congeners. These findings reinforce the conclusion that it is imperative to find ways of removing these contaminants from the environment. Furthermore, it is important that risk assessment methodologies no longer rely only on measurement of serum PCB levels and their associations with various diseases, but rather consider air concentrations and the evidence that even low concentrations of PCBs in air constitute an important route of exposure and disease, especially if the exposure is prolonged.

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