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The Human Health Effects of Polychlorinated Biphenyls

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Polychlorinated biphenyls (PCBs) are 209 closely related chemical compounds—chlorinated biphenyls—that differ only in the number and location of chlorine atoms on the molecule. The stability and biological properties of these chemicals vary according to the number and position of the chlorine atoms on the molecule. As a group, PCBs are soluble in fat and, unlike many other chemicals, tend to accumulate in body tissues.

PCBs do not occur naturally in the environment. They were first produced commercially in the 1920s, and their use increased greatly in the 1950s. About 1.3 billion pounds of PCBs were produced and consumed in the United States between 1930 and 1975. They were used, for example, in capacitor, hydraulic, and transformer fluids, in carbonless copying paper, and as plasticizers in paint. In the United States, the Monsanto Chemical Company was the sole producer of commercial mixtures of PCBs.

As a result of these varied uses, PCBs have entered the environment and accumulated in the food chain. While their concentrations in urban areas are usually higher than in rural and remote areas, PCBs may be transported for long distances by air, and traces of PCBs are found even in remote areas (Kimbrough and Jensen 1989).

Once in the environment, the fate of a PCB molecule varies with its chemical composition. Isomers (chemical variants) with few chlorine atoms are metabolized and eliminated more easily by living organisms, and also are more easily broken down in the environment. Thus, the composition of a commercial mixture of PCBs changes after release into the environment. Some of the more toxic PCB isomers either were not present in commercial PCB mixtures manufactured in the United States or were present at very low concentrations. However, they may to some extent be preferentially concentrated in the environment; low levels of some these isomers have occasionally been found in human tissues. It is

not clear whether they originated from commercial PCB mixtures or whether other sources exist.

In 1966, Jensen identified PCBs in wildlife. When better methods became available to detect them, scientists soon identified PCB residues in fish. birds, meat, and human tissues, usually at higher concentrations in fatty tissues. Today, a major source of human exposure to PCBs comes from eating some kinds of fish from polluted waters.

Scientists initially considered PCBs to be "safe" because single doses, even very large ones, did not promptly kill test animals. But these studies were designed to detect only acute toxic effects, and involved short-term observation of animals (usually for two weeks).

However, more sophisticated studies later uncovered toxic effects in test animals given daily doses of PCBs over much longer periods of time. Now, cumulative toxicity from low-level exposures to PCBs is the principal concern of scientists and the center of much legal and regulatory concern.

Much of the public concern about potential health effects of PCBs can be traced to the late 1960s and 1970s, with reports of illness in Japan in 1968 and in Taiwan in 1979 after people consumed rice oil contaminated with PCBs and other chemicals for a period of time. Initially, the illnesses were reported as having been caused by PCBs; investigators later found that the rice oil had also been contaminated with chlorinated dibenzofurans, polychlorinated quarterphenyls, chlorinated dibenzodioxins, and chlorinated napthalenes. The illness that these people suffered has been called *yusho* in Japan and *yu-cheng* in Taiwan (Lee and Chang 1985; Kuratsune 1989). These illnesses were not caused by PCBs but by other contaminants.

The mechanisms of PCB toxicity are complex. At very low doses, even cumulative exposures will not reach toxic levels in the body over a lifetime. The body eliminates PCBs in various ways, and the substances will reach an equilibrium concentration in the body even if there is daily intake. Some PCBs are eliminated or metabolized more easily than others; thus the mixture of PCBs in the body will change with time and may be quite different from that to which the organism was initially exposed.

Responding to health and environmental concerns about PCBs, government and industry have taken steps to reduce the use of these chemicals. Monsanto, the sole U.S. producer, voluntarily ceased production of many PCBs in 1971 and stopped marketing PCBs for open-ended use. Previously, it had marketed a range of PCBs, including more highly chlorinated biphenyl mixtures such as Aroclor 1248, 1254, and

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1260; thereafter it produced only lower chlorinated biphenyls (Fed. Reg. 1982). In 1977, Monsanto stopped producing PCBs entirely.

The United States and other industrial nations have since taken further steps to limit the flow of PCBs into the environment. Although PCBs are no longer produced commercially in the United States (Fed. Reg. 1982), they remain present in many capacitors and transformers and in waste dumps, and their containment is still of concern. The removal of PCBs from the environment has proved difficult and expensive, and the effectiveness of various cleanup attempts is unclear, since no useful inventory of PCBs and their locations is available.

One complication in discussing the health risks of PCBs is that they are sometimes contaminated with another group of chemicals, polychlorinated dibenzofurans (PCDFs), some of which are far more toxic than PCBs. In the commercial mixtures produced by Monsanto, PCDFs were usually present in only trace amounts or not at all. However, they are formed when PCBs are heated to temperatures between 200 and 600°C (Morita et al. 1978). They may have caused some of the toxic effects attributed to PCBs in various animals and humans, and were definitely responsible for the incidents of *yusho* and *yu-cheng*.

Toxicity in Animals

Over the years, scientists have studied the toxicity of PCBs in various animals. Different animals apparently respond very differently to PCBs. The subhuman primates, guinea pigs, and mink, for example, appear to be more sensitive to PCBs than dogs, rats, mice, and rabbits. Also, the target organs (the organs that are principally affected by the chemicals) vary with species. For these reasons, it is unclear which species of animal is best for assessing the toxic effects of PCBs in humans.

I will briefly review the acute and chronic toxic effects of PCBs, and the organs that are primarily affected; more detailed reviews are available elsewhere (Kimbrough and Jensen 1989, Kimbrough 1987). In the rat and the mouse, and to some extent the rabbit, the primary target organ is the liver. For example, highly chlorinated mixtures of PCBs such as Aroclor 1260 produce liver tumors in rats and mice (for exposure levels, see Table 9.1A). By contrast, hormone-dependent tumors (such as tumors of the pituitary and the mammary glands) occur less frequently in rats fed PCBs than in controls without exposure to PCBs. However, lower chlorinated PCB mixtures do not produce the same increase in tumors in rodents at similar doses. PCBs can also produce skin lesions in rabbits and hairless mice.

PCBs produce other biological effects in addition to cancer. In chickens, PCBs cause fluid to accumulate in tissue underneath the skin, the sac around the heart, the chest cavity, and the abdominal cavity. In subhuman primates, PCBs do not particularly affect the liver but cause alterations in the lining of the stomach, and cause skin lesions of the type referred to in humans as chloracne. Some PCBs affect the reproduction in rats and mice and (at much lower doses) in subhuman primates (Table 9.1A).

PCBs and associated chemicals can affect the immune system. In animals, PCBs, particularly those containing appreciable amounts of PCDFs, suppress the immune system[1] (Vos and Luster 1989) at doses similar to those leading to reproductive effects. In humans, suppression of the immune system has been reported only in patients acutely poisoned by exposure at high levels to mixed PCDFs, PCBs, and chlorinated quarterphenyls. (It appears that in humans PCDFs were the culprit, not PCBs.) Reported immunological changes include depression of serum immunoglobulin, delayed-type hypersensitivity reactions, and enhanced in vitro proliferation of T-lymphocytes (Vos and Luster 1989).

It is difficult to judge the significance of such immunological changes to the health of the animal or of humans. Many laboratory tests of immune function, for example, yield abnormal responses for all sorts of reasons that have nothing to do with PCB exposure, which have no clear relation to clinical illness (Peter 1989).

The interpretation of the animal studies is also complicated by the fact that different PCB isomers have very different biological effects. Commercial PCBs consist of complex mixtures that have different effects on different organs, and require different doses to cause similar toxic effects in different animals. In one study (see Table 9.1A), investigators found that Aroclor 1260 required a dose 25 times higher than for Aroclor 1254 to produce the same reproductive effects in the same strain of rats. In another study, a German PCB mixture, Clophen A-30 (with a comparatively high concentration of lower chlorinated biphenyls), caused no increase in liver tumors in rats (Schaeffer et al. 1984, as reviewed in Institute for Evaluating Health Risks 1991). But a different mixture, Clophen A-60 (composed primarily of more highly chlorinated biphenyls), at the same dose, produced a pronounced increase in liver tumors in the rats.

The PCB mixtures with a great amount of chlorine are associated with the production of liver tumors in animals. In addition to Clophen A-60, Aroclor 1260 (a highly chlorinated biphenyl mixture produced in the United States) led to a statistically significant increase in liver tumors

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in rats. However, data are limited. Both mixtures were studied at only one dietary level (100 mg of PCBs per kg of body weight), and some commercial mixtures containing lower chlorinated biphenyls, such as Aroclor 1242 and Aroclor 1016, were not tested for carcinogenicity. In addition, scientists do not know which chemical component in the Aroclor 1260 and Clophen A-60 mixtures was responsible for the liver tumors in the rats.

Human Health Effects

PCBs are persistent and ubiquitous in the environment, and are found in the food chain and, at low concentrations, in the air. Thus it is often impossible to determine how, or in what amounts, a person has been exposed to PCBs. This is particularly true for the general population, whose members tend to have low body burdens of the chemicals. The general population has been, and will continue to be, exposed to trace amounts of PCBs, particularly in industrialized countries.

The accurate determination of exposure is a recurrent problem in assessing the health effects of PCBs and other environmental chemicals. Environmental sampling—measuring chemical concentrations in the soil or air—cannot accurately predict a person's actual exposure to and uptake of PCBs. Ten out of 12 recent investigations of sites contaminated with very high PCB concentrations in the soil (up to 13 percent PCB concentration by weight), or in material oozing into surface water (up to 0.002 percent), found no excess proportion of nearby residents with PCB levels in the blood serum above those found in the general population (greater than 20 parts per billion or ppb) (Stehr-Green et al. 1988). In other words, these "highly exposed" people did not have much higher body burdens of PCBs than other members of the general population. In the two studies that did report increases in serum levels of PCBs, the individuals had also been exposed to PCBs through their occupations or by eating PCB-contaminated fish.

In short, mere proximity to a PCB-contaminated site often does not lead to greater exposure. With persistent chemicals like PCBs, a person's exposure is best determined by measuring the levels of the chemical in the blood serum or body fat. These levels must be compared with those in the general population, to determine whether a person has had an increased exposure to PCBs.

Some people in the United States have been exposed to high levels of PCBs, particularly in the workplace. Workers who repair transformers or handle toxic waste may have high exposures (Kimbrough

1985). Because of their exposures, workers who produced PCBs, and PCB-filled transformers or capacitors, retain higher body burdens of PCBs than the general population. Nonoccupational sources of exposure include eating fish from contaminated waters. In the past, some farm families, and to a lesser extent the general population, were exposed to PCBs from some dairy products and meat.

PCBs are soluble in fat, and for this reason are primarily stored in fatty tissue. They are also present, to a lesser degree, in blood serum, other tissues, and human milk, in levels that are related roughly to the fat contents of these materials. The PCB concentration of human milk averages a few parts per million or less on a fat basis, that is, a few milligrams or less of PCBs per kilogram of fat in the milk (Kimbrough and Jensen 1989). Occasionally higher concentrations of PCBs are found in a person's tissues or blood despite the apparent lack of unusual exposure. Newborn babies may have measurable levels of PCBs, transferred from the mother through the placenta.

Scientists and public health officials have attempted to determine the health significance of body burdens of PCBs. One communitywide study in Triana, Alabama, examined 458 persons who had eaten a great deal of DDT-contaminated fish from a local river; among other things, the investigators measured levels of PCBs in the residents' blood serum (Kreiss et al. 1981). Most persons had serum PCB levels similar to those typically found in the general population; but in some the levels were higher. On the average, higher serum PCB levels were found in older residents and in males. The levels in these people tended to increase with higher alcohol consumption and with higher levels of serum cholesterol.

In the Triana study, Kreiss et al. attempted to relate serum PCB levels to the health of the residents. The Triana residents in general had a much higher prevalence of high blood pressure than expected from national rates, taking into account the distribution of sex, age, and race. Based on their initial analysis of the data, the investigators suggested that the increased serum PCB levels were associated with high blood pressure in these residents.

In another study, Lawton et al. (1985) examined workers who had been exposed to the commercial mixtures Aroclor 1016, 1242, and/or 1254. The serum PCB levels of these workers considerably exceeded those of the Triana residents, those reported in other community studies, or in the general population. Lawton et al. reported that increased PCB blood levels were positively associated with serum cholesterol, abnormal liver function, and hypertension (high blood pressure) in the subjects. However, when PCB whole-serum levels were adjusted to account for

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the amount of fat present in serum, these positive associations disappeared. It thus appears that the important variable was the fat content of serum rather than PCB levels: more fat will contain more PCBs and is also associated with more serum cholesterol and with altered liver function. Thus, in these two studies the increased body burdens of PCBs had not caused the increased serum cholesterol and hypertension. Rather, because these people had higher serum cholesterol, their whole-serum PCB levels were increased.

Other reported correlations between PCBs and health were spurious as well. Kreiss et al. (1981), for example, also reported a connection between PCB exposure and hypertension and abnormal liver function. But liver function and blood pressure are affected by many lifestyle factors, including consumption of alcohol; Mathews (1976) suggested that in developed countries, heavy drinking could account for 30 percent of all cases of hypertension. This makes it difficult to establish a correlation between these health conditions and a single variable such as PCB exposure.

Another problem is the variability in results of liver function tests. A recent study found that 2–3 percent of potential blood donors had sufficiently elevated liver function tests to require the blood banks to discard their blood (Saxena et al. 1989). Possible causes of this variability might include high intake of sucrose or alcohol, normal day to day variations in a person, obesity, ethnic origin, and measurement error if the serum contains a great deal of lipid.

Thus, before linking abnormal liver function with PCB exposure, an investigator must consider and rule out many other possible factors. That in turn requires the investigator to evaluate each subject in a study individually. An epidemiologic study that is based on simplistic interpretations of laboratory tests, without the clinical evaluation of individual subjects, cannot be analyzed completely enough to lead to useful conclusions for individuals.

Another problem is statistical. An investigator who performs many different tests on a group say of people living near a toxic waste site, and defines a "normal" result for each test as one that lies within two or three standard deviations of the mean for the entire population, will surely find some "abnormal" results. Such findings might arise from sampling errors, and are known in the jargon of statistics as "false positive" errors.

Indeed, using the statistical criteria commonly employed in science, a single test applied to a normal population will result in an "abnormal" finding 5 percent of the time: 10 tests will yield at least 1 "abnormal" finding 40 percent of the time; and 50 tests will yield at least 1 "abnor-

mal" result 92 percent of the time (Galen and Gambino 1975). Thus an "abnormal" finding may or may not have clinical significance. If biologically plausible, it would warrant further investigation to determine whether it was a false positive result or a truly abnormal finding.

Diverse health problems have been reported in workers exposed to high concentrations of airborne PCBs, including upper respiratory irritation, skin irritation, and abnormal pulmonary function. When PCBs were first produced, some workers in plants manufacturing the chemicals developed a skin disease called chloracne that may have resulted from exposure to PCBs or other chemicals, such as PCDFs (Kimbrough 1987) that may have been present as contaminants.[2] Skin irritation and respiratory problems have been reported among workers exposed to other chemicals as well as PCBs, and it is not clear whether the PCBs were responsible for these complaints.

Other health problems that have sometimes been attributed to PCBs include fatigue, headaches, and nausea. Such problems, however, have many causes, and frequently occur in the general population for reasons that have nothing to do with PCB exposure. In one study of polybrominated biphenyls, a related class of chemicals, such complaints were more frequent among people with lower exposures who insisted on being examined than in more highly exposed people who had been invited into the studies (Landrigan et al. 1979). A cardinal axiom of toxicology is that real effects tend to increase with increasing dosage; thus more highly exposed individuals should exhibit more symptoms, even though individual members of the group may vary in their susceptibility (Cannon et al. 1978).

Reproductive Effects

PCBs have reproductive effects in animals (Table 9.1A), but no such effects have been conclusively demonstrated in humans. Taylor et al. (1989) surveyed female workers in a capacitor plant, and reported a small decrease (30 grams) in the average birth weights of their children, after accounting for other risk factors including cigarette smoking, alcohol consumption, and use of drugs by the mother; twinning; genetic factors; sex of the child; height of the mother; and illness of the mother during pregnancy. The workers had much higher exposure to PCBs than the general population and (as the investigators pointed out) the clinical significance of this small difference in the birth weight is unclear.

Rogan et al. (1986), in a follow-up study of 856 breast-fed infants, reported that higher exposure to PCBs in utero was associated with lower muscle tone and less well developed reflexes in the child. Again,

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Animal tests using P

Aroclors tested	D n
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Table 9.1B
Human exposures

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Table 9.1A
Animal tests using PCB mixtures

Aroclors tested	Daily dose mg/kg	Total dose mg/kg	Effect	Reference
Aroclors[1]	Single dose given in stomach	1,000–10,000	Kills half of test animals	Kimbrough et al. 1978
Aroclor 1260[2]	about 25	4,650[5]	Some reproductive effects	Linder et al. 1974
Aroclor 1254[3]	about 1	186[5]	Some reproductive effects	Linder et al. 1974
Aroclor 1260[4]	about 5[6]	3,500	Cancer of the liver	Kimbrough et al. 1975

1. The lower chlorinated mixtures are generally more acutely toxic.
2. Highly chlorinated mixture.
3. Less chlorinated mixture.
4. Only mixtures with 60 percent chlorination caused cancer in the test animals.
5. Lower doses of PCBs produce reproductive effects in subhuman primates. However, some of these primates were exposed to other chemicals, making the interpretation of the results of this study uncertain.
6. This was the only dietary dose tested.

Table 9.1B
Human exposures to PCB mixtures[1]

Population	Daily dose mg/kg	Total or lifetime dose mg/kg	Reference
General population	0.00001 to 0.0003	less than 0.7[2]	World Health Organization 1988
Workers	Varied	195–260	Lawton et al. 1985

1. PCBs only; the accidental exposure leading to yusho-yucheng syndrome (from contaminated food) is excluded.
2. Mostly from dietary exposure.

the health significance of these findings is unclear. Their interpretation is further complicated by the fact that higher PCB levels were found in older women and women who regularly consumed alcohol—factors that might be related to the condition of the child. PCB levels were also higher in women bearing their first child (Rogan and Gladen 1982). Further follow-up of these children at ages three, four, and five showed that the deficits reported earlier were no longer apparent (Gladen and Rogan 1991).

Several investigators (Schwartz et al. 1983; Jacobson et al. 1984; Fein et al. 1984; Jacobson et al. 1983) reported changes in behavior or reduced gestation period in newborns associated with the mother's consumption of fish or exposure to PCBs. The investigators suggested that PCB exposure of the fetus during pregnancy may lead to behavioral abnormalities in the infant.

The significance of these findings is difficult to judge. The tests the investigators employed have not been widely used for predicting behavioral abnormalities of children. Obvious limitations of threshold studies included uncertainties in the exposure of the subjects to PCBs and lack of a clear relation between the extent of exposure and magnitude of the changes reported in the children. Other factors, such as exposure to heavy metals, the mother's lifestyle and well-being, and her genetic makeup may also have affected the results. This was also reviewed by Paneth (1991). In short, these observations warrant further study. Compared with other variables, we can conclude that PCB exposure has at most a minor or negligible influence on the birth weight, growth, and development of children.

Immunotoxicity

Immunotoxicity occurs when chemical agents or other factors adversely affect the immune system. No immunotoxic effects have been reported in people exposed only to elevated levels of PCBs. Such effects were reported in the victims of the rice-oil poisoning episodes in Japan and Taiwan, but contaminants other than PCBs were responsible.

Tests of the immune system might, for many reasons, yield abnormal results unrelated to chemical exposure. (Peter 1989). These include bacterial or viral infections during testing, drug treatment, some poorly understood diseases such as Sjögren's syndrome, systemic lupus erythematosus, motor neurone disease, recent surgery with general anesthesia, stress, aging, malnutrition, cancer, uremia, and extensive burns. Some immune-system tests yield a wide range of "normal" results in individ-

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An example of the difficulty of interpreting tests of the immune system is found in a study done by the Centers for Disease Control on individuals exposed to dioxin (specifically 2,3,7,8-tetrachlorodibenzo-p-dioxin). The study reported abnormal results of immune function tests in some individuals. But these initial findings could not be verified in a follow-up study. Moreover, none of the subjects showed clinical signs of disease from deficiencies of the immune system (Hoffman and Stehr-Green 1989). By themselves, many tests of the immune system are not useful for diagnosis of disease, and their interpretation requires the clinical evaluation of the subjects or patients in the study.

Cancer

Several investigators have studied cancer risk from PCBs by comparing tissue levels of PCBs in patients dying of cancer with those in patients dying from other causes. Some of these studies reported higher levels of PCBs in the adipose tissue of the cancer patients, suggesting higher cancer risk from PCBs. For instance, Unger and Olsen (1980) reported mean level of PCBs in adipose tissue of about 9 ppm (mg of PCBs per kg of tissue) in male and female cancer patients, 6 ppm in male noncancer patients and 4.5 ppm in female noncancer patients. While these differences were statistically significant, all of the PCB levels were within the range normally found in the general population at the time the study was done. Such small differences might have been caused by weight loss in the cancer patients, impairment of liver metabolism, or the effects of cancer treatment. In short, these differences—which were found in patients after their disease had developed—do not point to a cause-effect relationship between PCBs and cancer.

Numerous studies have attempted to measure the cancer incidence rates in groups of workers exposed to PCBs. Most of these studies compared the causes of death (as listed on death certificates) of the exposed workers with those of the general population, after taking into account any differences in sex and age at death in the groups being compared. Other studies used different comparison populations—such as other workers in the same factory who were not exposed to PCBs, or the population of the same geographic area.

One early, preliminary study (Bahn et al. 1976) reported 3 melanocarcinomas and 2 carcinomas of the pancreas among 92 workers who had been exposed to PCBs between 1949 and 1957, significantly more

than expected. However, in this small group the calculated cancer rates are uncertain; the workers had also been exposed to other chemicals.

Other studies did not confirm these results. For example, Brown and Jones (1981) studied 2,567 present and former workers in two capacitor plants, of whom 163 had died. If the data from both work sites were combined, the workers had slightly more than the expected number of deaths from liver and rectal cancer, and cirrhosis of the liver; but these increases were not statistically significant. However, females at one of the work sites did exhibit a statistically significant elevation in incidence of cancer of the rectum. In a follow-up study, Brown (1987) found no additional cancers of the rectum among these workers, and the total number of cancers of the rectum was not nearly as elevated, compared with the controls, as previously reported. The follow-up study, however, observed two additional cancers of the liver and biliary tract, for a total of five such cases based on entries on death certificates.

A review of the medical records of these subjects, however, raised several questions. One autopsy report listed the cause of death as hepatic coma due to metastatic disease, with the primary site unknown (i.e., the cancer did not originate in the liver). Malignant tumors (cancers) commonly spread to the liver in advanced stages, and should not be counted as primary liver cancers in epidemiologic studies. In another case, the death certificate listed a primary cancer of the bile ducts as cause of death; the hospital pathology report, however, classified this tumor as an adenocarcinoma that probably originated in the bile ducts, and noted that the patient had a history of cancer of the uterus. This cancer might have originated in the uterus and spread to the bile ducts. It is also debatable whether a tumor originating in the bile ducts should be counted with tumors that originated from parenchymal liver cells. In a third case, the cancer may have originated in the gall bladder rather than the liver. Thus, a detailed examination of the workers' records does not make a strong case for a relation between PCB exposure and liver cancer. Moreover, in these workers the incidence of cancer did not seem to be related to dose, length of exposure, or time between exposure and development of the tumor—which further weakens the case that PCB exposure caused the tumors.

Bertazzi et al. (1981) surveyed 290 male and 1,020 female workers in an Italian capacitor plant. The investigators compared the number of cancer deaths among the workers with the expected rates, based on national mortality figures. Among the men, there were more cancer deaths than expected, particularly from neoplasms of the digestive system, the lining of the cavity that contains the digestive system, and the lymphatic

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and blood-forming tissues. Six men had died from cancers of the gastrointestinal tract; the expected number was 1.5.[3] Of these, however, one was a liver cancer and another a cancer of the biliary tract, an entirely different disease. Three men had died from cancers of the lymphatic and blood-forming systems; only one such death was expected. The female workers had a higher overall death rate than expected from national mortality figures. Four had died from cancers of the hemopoietic system (including three cases of Hodgkin's disease), whereas only 1.5 such deaths were expected.

We can, however, draw no firm conclusions from this study. The total number of deaths was small, which makes any comparison of death rates very uncertain. Other problems include uncertainties about the workers' exposure to PCBs, and their exposure to other chemicals. The workers had a higher overall death rate than expected for the general population. By contrast, most epidemiologic studies on workers show lower death rates than for the general population, the "healthy worker effect." *Something* might have damaged the workers' health, unrelated to PCB exposure. Also, the cancers that were increased in this study were different from the cancers that were increased in other studies. This raises further questions about the role that PCBs played in all of this.

Cancer, like other chronic diseases, results from a complex series of events. And cancer risk is related to many factors, such as genetic predisposition, nutrition, lifestyle, and environment. These factors, and a host of other technical difficulties, greatly complicate the interpretation of mortality studies.

For example, consider the difficulties in the use of death certificates to study cancer mortality rates. Between 20 percent and 50 percent of death certificates disagree with autopsy reports in the cause of death (Cottreau et al. 1989). The cause of death (from death certificates) is coded for entry into computers by specialists in the classification of disease (nosologists), using the International Classification of Disease system (ICD), which for cancer is based on the site where the tumor originates. But nosologists are not physicians or pathologists, and may introduce errors of interpretation. For instance, a soft tissue sarcoma may be coded according to the organ site where it was found or as a malignant neoplasm of soft and connective tissue. A tumor may be misdiagnosed, particularly if rare, and misclassified (Brown et al. 1987). Such errors can have a major impact, particularly when the total number of tumors in the subjects of a study is small (Percy et al. 1981). To what extent the studies described above are affected by such problems is difficult to determine.

Sinks et al. (1990) reported a retrospective mortality study of workers at a capacitor plant. The investigators noted an excess mortality from malignant melanocarcinomas (two females, seven males) and brain cancer (five males, two females). For most of the brain cancer cases, the investigators could not confirm the diagnosis through medical records or pathology reports. Moreover, one brain cancer death occurred in an individual with less than six months' employment; in another, melanocarcinoma had been diagnosed before the employee had been hired (which suggests that the diseases were not connected with employment at the plant). In two of the other cases of melanocarcinoma, the date of diagnosis and the date of death coincided; in a third case these dates were only two months apart. Thus, in at least two of the cases, the primary cause of death does not appear to have been melanocarcinoma, and the number of reported cases does not represent true mortality rates. Furthermore, the workers' exposure to PCBs was not well defined, and no excess of these cancers was reported in any of the other studies. Further investigation is needed to elucidate these findings.

Conclusion

Relating a person's exposure to a chemical to health problems is difficult. Many diseases have unknown cause; scientists understand the health effects of few environmental chemicals; and exposure to a chemical may be associated with a disease without causing it. Thus, we need to assess cautiously all claims of an association between an environmental agent and a particular disease. Our final conclusion will depend on the overall weight of the evidence that has been accumulated and critically reviewed according to well-accepted criteria.

Hill's criteria are most often cited (they are summarized in chapter 1). By these criteria, the epidemiologic studies discussed above do not make a strong case that PCBs, at typical environmental levels, or even at high occupational exposures, cause cancer or other health problems.

Certainly, PCBs are toxic to animals, at relatively high levels of exposure; some PCB isomers and PCDFs and other substances commonly associated with PCBs are quite toxic. While not discussed in this chapter, ecological effects of these chemicals have also been reported in the literature. Outlawing the commercial uses of PCBs was a justified and prudent action.

By contrast, claims of association, based on epidemiologic studies, of chronic health effects such as cancer and trace exposure to environmental levels of PCBs are unjustified. One highly chlorinated mixture

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of PCBs does cause cancer in laboratory animals (Tables 9.1A and 9.1B)—but at levels that vastly exceed any to which the general population is exposed. People have overreacted to possible hazards from PCBs at typical environmental levels.

Notes

1. A suppressed immune system is less effective in fighting off infection or preventing the development of cancer (see chapter 16).

2. Chloracne has also been reported among workers exposed to some chlorinated dibenzo-p-dioxins (see chapter 11). The *yusho* and *yu-cheng* instances of human poisoning also resulted in chloracne which, in these cases, was caused by chlorinated dibenzofurans.

3. The reader might ask what is meant by "1.5 deaths." Death, like pregnancy, is an all-or-none phenomenon. For any group (e.g., the 290 Italian workers in this study) a statistician might apply national mortality rates and predict 1.5 deaths from a particular cancer. Because of chance (sampling effects) zero, one, or two (or even six) members of the group might succumb to the cancer, even though their risk might be the same as for the population at large. How to decide whether an unexpectedly high number of deaths in a group arises from sampling error or a real increase in risk is a crucial but sometimes difficult questions.—The Editors.

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Biographical Sketch

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10

Trichloroethylene: T
A Critical Review of

Rudolph J. Jaeger and Arlen

Introduction

Pollution that drifts visibly regulate than that which se taminant of groundwater t in scientific, regulatory, a chloroethylene (TCE). Wh mans at environmental exp

The answer offered i chronic low-level exposur factors is sparse. Direct te cal. Scientists have therefc overexposures, mostly in form such extrapolations a mechanistic understandi

Background

TCE is a colorless, highl temperature it smells swe natural sources of TCE.

Most of the TCE pr ing fabricated metal part is either exported or us industrial painting syste time, TCE was commor and degreasing products sumer products, includi and paint strippers, adh fluids for rugs, and met