

Chlorinated biphenyls range from liquid to solid, depending upon the degree of chlorination. On the basis of single dose animal tests commonly used to identify and label hazardous materials, they would be considered to be relatively harmless substances. Monsanto has conducted such acute toxicity and irritation tests on several chlorinated biphenyls over the years⁽¹⁾.

Questions have been raised in four areas of possible health effects of chlorinated biphenyls. These have been related to 1) skin (reddening, chloracne); 2) systemic effects (liver damage, respiratory effects); 3) environmental exposure, and 4) potential carcinogenicity.

A review of the literature from the 1930's and 1940's on the health effects of chlorinated biphenyls contains statements such as "Much of the literature that refers to chlorinated diphenyls is referring to the mixture of chlorinated diphenyl with chlorinated naphthalene." and "A number of the references recorded under chlorinated naphthalenes also discussed chlorinated diphenyl. It is difficult to determine the role played by the chlorinated diphenyls, as, in most instances, they were mixed with chlorinated naphthalene"⁽²⁾. A parallel situation occurred during the late 1960's when reports of the detection of polychlorinated biphenyls in the environment began to appear. There was confusion and disagreement as to whether polychlorinated biphenyls or other halogenated hydrocarbons such as DDT were being measured, since the latter had already been identified as environmental contaminants.

Skin

Sometime before 1934, Swann Chemical Co. observed dermatological symptoms in workers exposed to chlorinated biphenyls. In May, 1934, Swann Research, Inc., requested Dr. F. B. Flinn of Columbia University's College of Physicians and Surgeons to conduct an investigation "to determine whether or not the various chlorinated diphenyl compounds submitted or some impurities contained therein might be the causative agent producing the dermatitis which had developed among some of the workmen in the plant." He commented on these studies as follows:

"One is impressed with the fact that each of the Aroclors giving a positive reaction were of a fluid nature. Attempts were made to expose the animals to vapors but observations made us conclude that the only difference was that the animal would be exposed to the hot material and it was well-known that the reaction where such an exposure is given is more severe.

"One cannot but feel that any styrene compound which may be found to be present as an impurity is the cause of your trouble. I was rather surprised that more of the compounds submitted did not show or give reactions with the skin. It has been shown in some investigations that chlorine did not produce a dermatitis when metallic electrodes were used but did if the metallic electrodes were replaced by carbon electrodes. The theory was advanced that some organic chlorine compounds were produced in the latter case.

"I would suggest that you study your ventilation system in places where fumes are given off. That means be provided for the men to take a bath with soap and water if they come in contact with the type of material found to be positive. By this I mean if a leak or spillage occurs. The immediate bathing under these circumstances should be insisted on. I found that where I had gotten the material on my hands if I washed them thoroughly no trouble arose."

In his transmittal letter to Dr. J. N. Carothers of Swann Research, Inc., Anniston, Alabama, Dr. Flinn stated:

"It may interest you to know that the dermatitis which was produced by your materials in the case of rabbits cleared up in a couple of weeks, indicating that unless there are repeated exposures the effects are only of a temporary nature. As I said before, I believe that if washing facilities are present and the men are instructed to use them it will do much to supplement the increased ventilation which you have installed."⁽³⁾

In the published literature, "the first observations on the development of acne-like lesions among workers in the United States coming in contact with chloronaphthalenes and chlorodiphenyls as well as acute yellow atrophy of the liver occurring among such workers were reported in 1935"⁽⁴⁾. Results of Swann studies were published in 1936⁽⁵⁾.

There is a letter report dated December 22, 1949, to Dr. R. E. Kelly (Monsanto) from Dr. L. K. Halpern of the Barnard Free Skin and Cancer Hospital (St. Louis) describing a human patch study. This consisted of applying film treated with 11.5 percent AROCLOR and gauze moistened with 100 percent AROCLOR to skin of the upper arm of 218 volunteers using the technique developed by Dr. Louis Schwartz, Medical Director of the United States Public Health Service. Dr. Halpern reported "If the procedure recommended by the United States Public Health Service is sufficient to distinguish between chemical compounds that are innocuous when applied to the skin and other compounds that are primary irritants or sensitizers, then it would seem that Aroclor has no primary irritant effect nor is it a sensitizer of high potency."⁽⁶⁾ Monsanto records show that this study was conducted with AROCLOR 1254.

In 1963, Monsanto received reports of subacute rabbit dermal studies it had sponsored on several chlorinated diphenyls. Salient features of these studies, conducted according to then-currently acceptable procedures, are summarized below⁽¹⁾.

AROCLOR	1221	1242	1248	1254	1268
No effect level*	150	50	10	10	500
LD ₅₀ **	250	75	50	75	1250
Local skin effects	none	none	none	yes	yes
Systemic injury	none	none	liver injury	liver injury	liver injury

*All dosages in mg/kg/day

**Based on 20-day dosing and 14-day observation periods

These studies showed that repeated and prolonged skin contact with the higher chlorinated biphenyls could produce skin irritation and that harmful amounts could be absorbed under such conditions. They also demonstrated that there was a safe level of exposure for each material, and that they could be handled safely if the earlier precautions to avoid excessive skin contact were observed.

Systemic Effects

On June 30, 1937, a symposium on systemic effects resulting from inhalation of chlorinated hydrocarbons was held at the Harvard School of Public Health. Dr. R. E. Kelly of Monsanto participated in the sessions at which results of investigations requested by manufacturers of chlorinated hydrocarbons were presented. Subsequently, three papers summarizing the results of those studies appeared in the scientific literature^(7, 8, 9). With respect to chlorodiphenyls, the Harvard group concluded that "... it appears safe and it is certainly easily attained, to ventilate so that the air breathed does not contain more than 0.5 mgm. per cu.m. of any of these compounds ...". In a separate unpublished report to Monsanto Company⁽¹⁰⁾ Dr. C. E. Drinker of Harvard described the results of inhalation studies conducted with compound #1268, having a chlorine content of 68 percent. He concluded, "#1268, if handled with ordinary precautions as to ventilation, should be entirely harmless to workmen."

Monsanto sponsored a study at the University of Cincinnati's Kettering Laboratory on "The Toxicity of the Vapors of AROCLOR 1242[®] and AROCLOR 1254[®]." A report of those studies⁽¹¹⁾, presented at the 1956 meeting of the American Industrial Hygiene Association, stated that the investigation "... was undertaken because in the earlier literature dealing with the toxic effects of Aroclors, no distinction has been drawn between the toxic effects of chlorinated biphenyls and those of chlorinated naphthalenes ...".

No injury was observed after prolonged intermittent exposure of several species of animals to AROCLOR 1242 at air concentrations of 1.90 to 8.63 micrograms per liter. Animals subjected to comparable exposures of AROCLOR 1254 showed signs of apparently reversible liver cell injury. The authors concluded their observations by saying "It should be noted that it was necessary to heat these Aroclors in order to increase the rate of volatilization sufficiently to attain the concentrations maintained in these experiments. To the extent that their industrial usage is carried out at ordinary temperatures, the hazard of their inhalation may well be slight or entirely absent."

These studies confirmed earlier work which indicated that no harmful effects were to be expected if these materials were used with adequate ventilation since it was necessary to heat the substances to generate sufficiently high air concentrations to injure the test animals.

Prior to 1956, the American Conference of Governmental Industrial Hygienists (ACGIH) had established a Threshold Limit Value (TLV) of 1 mg/m³ for chlorodiphenyl. In 1956, the listing was changed to read chlorodiphenyl (42% chlorine) as 1 mg/m³. The 1957 list showed chlorodiphenyl (42% chlorine) as 1 mg/m³ and an added TLV of 0.5 mg/m³ for chlorodiphenyl (54% chlorine). The latter two values have been unchanged since then⁽¹²⁾. Results of the Monsanto-sponsored study⁽¹¹⁾ contributed to the decision of the ACGIH to lower the TLV for the more highly chlorinated biphenyls⁽¹³⁾.

Environmental Exposure

In response to reports of the presence of some PCBs in the environment, Monsanto, in 1969, initiated preliminary toxicity studies which led to a series of long-term tests. These tests, on the three predominant commercial polychlorinated biphenyls (AROCLOR 1242, AROCLOR 1254, AROCLOR 1260), consisted of 2-year (lifetime) feeding to rats, 2-year feeding to dogs, 3-generation rat reproduction studies with 2 litters cast per generation, rat teratology studies and dominant lethal mutagenic studies in mice. Toxicity and reproduction studies in chickens were performed to evaluate

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possible untoward effects in birds such as decreases in eggshell thickness. This series of studies⁽¹¹⁾ represented the most comprehensive safety tests of the time, and was similar to the tests required for food additives, although Monsanto certainly had no intention of applying for a food additive permit.

The highest dietary level (100 ppm) in the lifetime rat feeding studies produced a weight depression at 24 months in females fed AROCLOR 1254 and liver weight increases in all groups except males fed AROCLOR 1242. As with other halogenated hydrocarbons, the important histopathologic changes were present in the livers of animals sacrificed at the end of the study. These consisted of hepatocellular (liver) alternations such as focal hypertrophy (localized enlargement), cytoplasmic lipid changes and in some animals from the 100 ppm groups, hepatomas or cholangiohepatomas (benign tumors). There was no evidence of hepatocellular carcinogenicity with any of the AROCLOR products.

In the dog 2-year studies, some slight decreases in body weight gain were noted. At the highest feeding level (100 ppm) or AROCLOR 1260, there was evidence of gastrointestinal inflammatory lesions and ulcerations.

In the rat reproduction studies, none of the AROCLOR products produced adverse effects in the 2 litters of the first generation. In the second and third generations, there was a reduction in the mating index and a decrease in the incidence of pregnancy at the 2 highest feeding levels (10 ppm and 100 ppm). The ability of females to carry pups to delivery, once conception had occurred, and to successfully nourish the young was not affected by the three AROCLOR products. No changes were produced in the reproductive tracts of either male or female rats by any of the 3 AROCLOR products.

There was no evidence of teratogenic or mutagenic changes with any of the chlorinated biphenyls at maximally tolerated dose levels in rats and mice.

In the chicken toxicity/reproduction study, AROCLOR 1260 was without effect at all test levels. AROCLOR 1242 and AROCLOR 1254 at 100 ppm in the diet decreased egg hatchability. Poor hatchability of eggs was found from hens fed 8 ppm of AROCLOR 1242. AROCLOR 1242 at 10 and 100 ppm and AROCLOR 1254 at 100 ppm were associated with reduced eggshell thickness. Chick viability was affected by both substances at a dietary level of 10 ppm.

Data developed by Monsanto and information gained from the Yusho incident in Japan were cited by the Food and Drug Administration (FDA) as a basis for establishing tolerances for chlorinated biphenyls in various foods in 1973⁽¹⁴⁾. Subsequently, the FDA proposed a reduction in those tolerances⁽¹⁵⁾.

In 1976 it was reported that AROCLOR 1248 in the diet of monkeys, at or below FDA tolerance levels for chlorinated biphenyls, adversely affected reproduction⁽¹⁶⁾. FDA limits on PCBs in the human diet are related to a safe level of 1 $\mu\text{g/kg}$ body weight/day⁽¹⁴⁾. The studies carried out by Allen and co-workers⁽¹⁶⁾ were at dosage levels of approximately 89 and 183 $\mu\text{g/kg/day}$. Their work suggested that there could be a previously unknown effect on reproduction in primates and they failed to define a no-effect level. Monsanto, therefore, undertook a detailed monkey reproduction study with carefully administered dosages at and below those previously studied.

In the Monsanto study, 32 female and 16 male rhesus monkeys, divided into 4 groups each consisting of 8 females and 4 males, were given daily dosages of 0, 5 $\mu\text{g/kg}$, 25 $\mu\text{g/kg}$ or 100 $\mu\text{g/kg}$ of AROCLOR 1254. The in-life portion of that study, which lasted about 14 months, has been completed.

At Monsanto's highest dosage (100 $\mu\text{g/kg/day}$), which corresponded to the low level in the Allen study, we find that AROCLOR 1254 has similar effects to those reported earlier for AROCLOR 1248. The results at the lower levels are not completely evaluated.

Potential Carcinogenicity—Animal Studies

In 1975, Dr. Renate Kimbrough reported the induction of liver carcinomas in female rats fed AROCLOR 1260 for two years⁽¹⁷⁾. The same lot of AROCLOR 1260 was used in her study as in Monsanto's earlier test. Monsanto's study showed that AROCLOR 1260 as well as AROCLOR 1242 and AROCLOR 1254, produced liver injury, but no cancers. Therefore, an extensive reevaluation was made of the original liver slides from the Monsanto studies as well as additional liver sections from all rats in the Monsanto two-year feeding studies. These slides were examined independently by Dr. D. Gordon of Industrial BIO-TEST Laboratories, by Professor W. Richter of the University of Chicago and by Professor Parvis Pour of the Eppley Institute for Research in Cancer. In addition, Dr. Pour evaluated sections of liver from rats in Dr. Kimbrough's study. No carcinomas were seen in the livers of rats from the Monsanto studies, and Dr. Pour did not concur with Dr. Kimbrough's diagnosis of liver cancer in rats from her study⁽¹⁸⁾. The different criteria by which pathologists diagnose cancer, and the reported findings of cancer induced by polychlorinated biphenyls in various animal species, have been discussed by Dr. J. C. Calandra⁽¹⁹⁾.

In 1977, the National Cancer Institute reported results of a bioassay for possible carcinogenicity of AROCLOR 1254. That report stated that AROCLOR 1254 was not carcinogenic under the test conditions⁽²⁰⁾.

Human Epidemiology Studies

The toxicity testing described above has provided a foundation for understanding the potential effects of chlorinated biphenyls. However, firm conclusions cannot be drawn without human epidemiological data drawn from exposed populations.

"The view that human health risks resulting from exposure to chemicals may be determined experimentally by testing laboratory animals is one that is widely accepted in the scientific community and has been adopted by EPA. Because experimentation on human beings raises ethical questions and because epidemiological studies often provide incomplete information, toxicology studies on laboratory animals are often necessary. However, because the extrapolation from animals to man is subject to some uncertainty, corroboration of laboratory test data with sound epidemiological information is desirable." (U.S. EPA, Support Document/Draft Voluntary Environmental Impact Statement for Polychlorinated Biphenyls, 1978). Such epidemiological data on PCBs is now becoming available.

Monsanto is aware of seven epidemiological studies done in the U.S. of persons exposed to PCBs. They include persons with occupational as well as community exposure, and the effects studied range from deviations in biological parameters, through reported symptoms and illnesses, to the occurrence of death from various causes.

Selikoff and colleagues studied 326 volunteers who were occupationally exposed to PCBs. They report the percentage of those workers with various dermatological, gastrointestinal, neurological and other symptoms, as well as the percentage with abnormal values of clinical chemistry parameters and of pulmonary function. They concluded that reported symptoms and abnormal findings in

physical examinations were not related to duration of employment or level of PCBs in the blood, except for abnormal dermatological findings and abnormal levels of some indicators of liver function. Although the authors claim to have found an unusual impairment of pulmonary function in their study population, no effort was apparently made to determine whether this impairment was related to the other findings. In spite of a correlation of some liver function parameters with PCB exposure, the prevalence of abnormal liver function was low. The authors state, "*The paucity of other abnormalities on physical examination was striking*;" this included a very low prevalence of abnormal liver findings." (emphasis in original).

The Center for Disease Control examined liver function and blood levels of chlorinated biphenyls in a sample of PCB workers, their families, and exposed persons in the community, in Bloomington, Indiana. This study found very mild liver dysfunction (increased levels of the enzyme GGTP) and increased blood levels of a cholesterol-like substance in persons with higher blood levels of PCBs. It is not clear if these findings have any relationship to actual illness.

The Michigan Department of Public Health conducted a study of 182 persons who regularly consumed sports fish, a source of PCB, and classified as "exposed," "intermediate" and "controls" according to the amount of fish consumed. A direct relationship was found between the amount of fish consumed and blood level of PCB. However, no significant difference was found between the controls and the exposed in the incidence of 18 health conditions, many of which described the symptoms reported for Yusho disease. Furthermore, in 12 of the 18 conditions, people with the condition had lower blood PCB levels than those without the condition. The authors conclude, "As a group, the exposed participants had no health problems or medical conditions that could be correlated with PCB levels, exposure to Lake Michigan fish, or known symptoms of PCB poisoning."

NIOSH has completed a study of mortality rates in workers in a transformer plant where there was exposure to PCBs, but Monsanto is unable to comment because a report of the study is not yet available.

The South Carolina State Department of Health and Environmental Control recently completed a study of 32 workers in a capacitor plant, 10 of whom were regularly exposed to PCBs. Details of the study available to Monsanto are limited to those contained in newspaper reports, but the study apparently involved a medical examination and a determination of blood PCB level. The authors state that the study "clearly shows that at present there is no evidence of physical harm resulting from working with PCBs."

These four recent studies appear to constitute the most extensive epidemiological work yet done on chlorinated biphenyls. They each indicate an absence of morbidity (ill health) associated with significant exposure to PCBs.

The Mobil Corporation carried out a study of the occurrence of cases of cancer in a population exposed for varying lengths of time between 1949 and 1957. Plant medical records were used to determine the occurrence of cancer in this group between 1958 and 1975. However, records were not available for about 20 percent of the eligible study group. The 41 men who were actually studied differed from the populations described above in that they were employed in a chemical plant which manufactured a number of different materials to which they might have been exposed during their working careers. The study found an excess of skin cancer (melanoma) based on three cases. After a preliminary report of these findings was made, the Mobil Corporation informed NIOSH that there

had been "a substantial change" in the definition of the cohort, and that an analysis of the changed cohort might show quite different results. As far as Monsanto is aware, that analysis has not yet been completed.

In 1975, independent of the Mobil effort, Monsanto began to gather information for a mortality study of employees exposed to PCBs at its W. G. Krummrich plant in Sauget, Illinois. Because the plant had manufactured a number of chemicals, those persons exposed to PCBs typically had a mixed exposure to other substances as they moved from job to job. Because the work histories of past employees were not computerized, it would have been necessary to identify those who had worked with PCBs by a manual search through 6,000 records. A preliminary identification was made of 50 deaths from various causes among past workers with PCB exposure, and a review of these suggested a possible excess of lung cancer, but not of skin or pancreatic cancer. This preliminary finding was announced in 1976.

A further attempt to identify a cohort yielded 89 men who had been exposed for at least six months in the period 1945-1965, who were then followed to determine their vital status as of the end of 1977. There were no excess deaths from pancreatic cancer, but 4 lung cancer deaths were found where about 1.5 would be expected. Smoking histories were not available. The accuracy of the determination of this cohort was limited by the necessity of conducting a manual search of the records.

At the present time, computerization of the Krummrich work histories is underway, and should be completed early in 1980. At that time it may be possible to better define the exposed population, and to better determine the other substances to which the population was exposed. However, because of the mixed nature of exposures in a chemical plant, it is unlikely that the Monsanto study can ever be as specifically related to PCBs as those conducted by Dr. Selikoff, CDC, the Michigan DOH, and the South Carolina DOH.