THE LANCET

Polybrominated Biphenyls, Polychlorinated Biphenyls, Pentachlorophenyl —and All That

As the uses of plastics and synthetic fibres continue to increase, the flammability of synthetic polymers has become a source of concern. In an effort to reduce the fire risks, intensive research has been directed at finding chemical additives to improve the fire-resistant properties of these products. Early in 1972, toxicologists from the E. I. du Pont de Nemours Company reported that decabromobiphenyl, which had excellent fire-retardant properties, did not exhibit overt toxicity in short-term, high-dose toxicity tests. However, they noted that the compound was very stable and had a long biological half-life. In view of the potential for bioaccumulation and the consequent environmental hazards associated with the use of such an agent, the compound was deemed unsuitable for marketing.[1] However, the Michigan Chemical Company was already manufacturing a similar chemical, BP-6, which was incorporated in a product tradenamed 'Firemaster FF-1'. This agent is a mixture of polybrominated biphenyls (P.B.B.), principally hexabromobiphenyls.* Production of BP-6 which started at 20 000 lb (9000 kg) in 1970, had already reached 2·3 million lb by 1972.[2]

The major application of BP-6 was as a flame retardant for high impact plastics, used in making cases for electrical office and business machines. Under normal circumstances, BP-6 was not expected to pose an environmental problem, because obsolete equipment was usually buried and BP-6 was unlikely to be leached out of the plastic composition. Unfortunately, normal circumstances did not prevail. As a result of a series of untoward events,[3] an amount of BP-6 between 500 and 1000 lb, or perhaps more, was inadvertently incorporated in animal feeds during May, 1973. The contaminated feeds were distributed throughout Michigan's lower peninsula. The effects of the contaminated feeds were apparent immediately. In a herd of 400 cows fed rations subsequently thought to contain up to 3000 p.p.m. P.B.B., early effects were anorexia, decreased milk production, increased frequency of urination, and lacrimation. After 16 days the feed was changed to a non-contaminated batch; although food intake and milk production improved, they did not return to normal. In subsequent months, hæmatomas were observed which developed into abscesses. Despite restored appetite, high-producing cows continued to lose weight. Disturbances in the œstrus cycle were noted, along with abnormal hoof, skin, and hair growth. Prolonged gestation, dystocia, and stillbirths were common among cows that had received the contaminated diet during the first trimester.[3,4]

A year passed before the poison was identified. To a large extent, this delay is a measure of the insensitivity of some of the responsible State and Federal agencies. It is also a reflection of the analytical problems associated with the identification of totally unexpected pollutants of this type. The outcome of the delay was the contamination of large numbers of farm animals and large amounts of farm produce with P.B.B.[5,6] Despite the destruction of over 20 000 cattle, sheep, and pigs, as well as 1·5 million chickens,[6] the ultimate consequence of these events was the consumption by the local Michigan population of farm and dairy produce contaminated with levels of P.B.B. ranging from barely detectable trace amounts to several hundred p.p.m. A cycle of secondary contamination with P.B.B. was initiated by the incorporation into protein supplements fed to livestock of the carcasses of many animals that had died of unknown causes.

Few data were or are available with which the consequences of such human exposure to P.B.B. may be predicted. However, the polychlorinated biphenyls (P.C.B.), a group of compounds chemically similar to P.B.B., have been studied extensively.[8,9] Several well-documented instances of human exposure to P.C.B. have been recorded, mostly in the work environment. The most extensively studied incident resulted from the accidental contamination with P.C.B. of domestic rice-oil in Japan, giving rise to "yusho", a disease characterised by various dermal, gastrointestinal, and neurological manifestations.[10] There is no clear evidence that P.C.B. are teratogenic in man or animals, although transplacental transfer of P.C.B. has been demonstrated. Equally, there is no evidence that P.C.B. are human carcinogens, although in rodents

*The principal component is 2,4,5,2',4'5'-hexabromobiphenyl, and the second most prevalent is 2,3,4,5,2',4',5'-heptabromobiphenyl.

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standard, long-term, high-dose bioassays produce hepatic carcinomas.[11,12]

Existing data support the hypothesis that the toxicity of P.B.B. is similar to that of the P.C.B. The P.B.B. at high doses cause enlargement of the liver, and liver cells are abnormal by light and electron microscopy.[1,14,15] Some workers purport to have shown that P.B.B. are teratogenic;[15] however, this conclusion depends on incorporation of control animals from a different laboratory. The effects of P.B.B. on the hepatic microsomal mixed-function oxidase system have been studied extensively; both acute and prolonged administration of P.B.B. result in persistent stimulation of this system.[16,17] Enzyme induction was observed when pregnant and nursing rats were fed P.B.B., and induction in the young resulted from exposure transplacentally and through the mothers' milk.[18,19]

Although brominated naphthalenes have been identified as constituents of P.B.B., there is no evidence of the presence of brominated dibenzofurans or dibenzo-*p*-dioxins.[2] Moreover, halo-acne has not been reported in exposed populations, especially in the manufacture of P.B.B., an indication that any contamination of P.B.B. with brominated dibenzofurans or dioxins is probably at a very low level. In contrast, P.C.B. have been found to contain chlorinated derivatives of dibenzodioxin, dibenzofurans, naphthalene, and terphenyl.[8] What is more, the levels of these trace contaminants vary with the country of origin; in general, American P.C.B. contain less than those from Japanese or European sources. In fact, victims of yusho have detectable levels of persisting polychlorinated dibenzofurans (almost exclusively pentachloro and hexachloro derivatives) in liver and adipose tissue—presumably derived from the 5 p.p.m. present in rice-oil at the time of the tragedy.[20] It is possible that some of the toxic effects of P.C.B., in both animals and man, may result from these trace contaminants. Thus, although the toxicities of "pure" P.C.B. and P.B.B. may be similar, the observed toxicity of commercial products may differ according to the amounts and contribution of the often highly toxic trace contaminants.

The human health effects of P.B.B. have only lately come under scrutiny. After an extended delay, Dr I. J. SELIKOFF and a team from the City University of New York were given permission to undertake a clinical field survey of potentially exposed persons in Michigan. The final report of this study is not yet available. These investigators themselves acknowledge that the selection of the interview sample was, as a result of the delay in initiation of the study and the nature of the problem, less than perfect. Some subjects were referred by physicians and others by lawyers, who may possibly be involved in litigation. Yet other people simply volunteered by telephone. Another criticism, and one which highlights a general problem in situations such as this, is the role and effect of news-media coverage: the Press reported symptoms of exposure, both before the study and throughout its course. However, the report does indicate that adverse health effects may have resulted from exposure to P.B.B. The health effects observed may include abnormalities of the nervous, musculoskeletal, and gastrointestinal systems, along with dermatological effects. The report serves to highlight the great need for continued and greatly extended research into the P.B.B. problem as it relates to human health.

The question arises—How can an objective assessment be made of the effects of an incident of this nature? We badly need criteria that are less readily biased—for example, liver and other organ function tests, neurological evaluation and, in this instance, tests to measure the activity of the mixed-function oxidase system in liver and other organs. The extent of human exposure can be assessed by analysing tissue contents of P.B.B. A sampling of human breast milk revealed detectable levels of P.B.B. in 51 out of 53 women surveyed.[21] In the light of a recent report that P.B.B. cause changes in the mixed-function oxidase activity in rat mammary glands,[22] the presence of P.B.B. in human milk points to possible human health effects. Alterations in the capacity of the mammary gland to metabolise xenobiotics could lead to both qualitative and quantitative changes in the transfer of such compounds from mother to young in the milk, and may result in abnormal toxic responses in the infant. Also, such alterations may modify the susceptibility of the mammary gland to the toxicity of other chemicals. The Michigan incident highlights the need for more toxicological data about P.B.B.

The tale of woe is not complete. Earlier this year, the herd of cattle of one of the Michigan farmers previously affected by P.B.B. was the victim of a new affliction traced, mainly by the Press, to pentachlorophenol (P.C.P.) used as a wood preservative for barns and feed-bins as well as other timber on the farm. P.C.P. has been detected at levels as high as 1000 p.p.m. in the blood from eight herds (out of the 1000 herds previously conta-

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minated with P.B.B.). In the case of P.C.P., the problem was initially attributed to the hexa-, hepta-, and octachlorinated dibenzodioxin impurities (different from the tetradioxin in 2,4,5-T) present in P.C.P. products at levels ranging from less than 1 p.p.m. to 1000 p.p.m. No reference has been made to dibenzofurans, but dioxins are indisputably present in cow and calf livers, the latter probably contaminated through milk, since dioxins are readily secreted into milk. In fact, contaminated milk from affected herds now poses serious disposal problems. Returning to the issue of P.C.P., if this material—even with greatly reduced levels of dioxins—presents a toxic hazard, there is a national problem stemming from the wide use of P.C.P.-treated wood in livestock areas. The substitution for P.C.P. of products containing arsenic, cadmium, or creosote hardly represents an escape to safety. The dilemmas in the realm of toxic substances are mounting day by day.

What do such incidents portend for industrialised countries? In the case of P.B.B., the exposure was limited and controllable, since the product was manufactured in only one place for a limited time and the contamination was confined to a small area. Thus conditions were ideal for study and containment of the effects of an environmental pollutant. The same has not been the case with P.C.B., which has had many sources and uses. In view of the succession of environmental incidents of this sort, plans are afoot in the U.S. for the creation of a "Chemical Emergency Response Team" as part of the proposed amendments to the Toxic Substances Control Act. It is questionable whether the superposition of yet another Government group upon the multitude of existing strata will achieve its objective. The best advice for hacking through the bureaucratic jungle was provided by the witch who called upon Macbeth to "Be bloody, bold and resolute . . ."

Poliomyelitis Vaccines

PARALYTIC poliomyelitis has been practically eliminated from the United Kingdom and many other countries by means of live, attenuated vaccines given simply by mouth, usually on a lump of sugar. In Finland, Holland, and Sweden the same result has been secured with killed, injected vaccines, which elsewhere have been little used since about 1962, when Sabin's live vaccine became generally available. The question has recently been raised in the U.S.A., notably by Dr JONAS SALK by whom it was first developed: is killed, injected poliovaccine (I.P.V.) now a better choice and should it be reintroduced?[1,2] After careful examination of these questions, an American report concludes that live, oral poliovaccine (O.P.V.) is still preferable for general use.[3]

The main claim of the supporters of I.P.V. is that it is safer than O.P.V. There is little doubt that O.P.V. may on rare occasions actually cause paralytic poliomyelitis in recipients of the vaccine or their contacts. However, the risk has been quantified in a number of countries, including the United Kingdom, and provided that manufacture of the vaccine is carefully controlled the risk is very low.[4,5] For every five million doses of vaccine given, about one case of paralysis may be expected in a recipient and about two cases in contacts of vaccinated persons (such as an unvaccinated parent or older sibling of a baby receiving routine immunisation). Killed vaccine, properly prepared, cannot cause poliomyelitis, although if the killing process is incomplete the consequences are liable to be serious, as in the Cutter incident of 1955 in which the type-1 component of incompletely inactivated vaccine caused an estimated 60 cases in recipients of vaccine and 89 cases in family contacts, together with other cases in the areas concerned.[6] The process of laboratory inactivation of poliovirus is now well understood, and the safety tests that are made should ensure that killed poliovaccine cannot contain any live poliovirus particles. But killed vaccines given by injection may have other rare side-effects—for example, anaphylaxis or neurological illness.[7] Thus an association of Guillain-Barré syndrome with influenza vaccine in the U.S.A. was revealed in 1976 only as a result of the nationwide swine influenza vaccination campaign in which over 40 million people were immunised.[8] The risk, if any, of such serious side-effects from I.P.V. is undoubtedly extremely low, but the possibility cannot be discounted that large-scale use of I.P.V. could reveal undesirable complications.

An important advantage that has been claimed for oral poliovaccine is that it gives rise to a herd immunity as a consequence of the local intestinal immunity which, in addition to serum antibody, arises in vaccinated people after the growth of poliovirus in gut cells. Since the human intestine is its natural home, the wild virus may therefore be unable to survive in a population once a sufficient proportion of people have been vaccinated. Moreover, spread of the vaccine viruses by natural means to non-vaccinated contacts should potentiate the herd immunity. In general, this expectation has been realised and, where O.P.V. has been used widely, poliomyelitis has become rare even in non-

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