FINAL REPORT OF THE
SUBCOMMITTEE ON THE HEALTH EFFECTS
OF
POLYCHLORINATED BIPHENYLS
AND
POLYBROMINATED BIPHENYLS

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DEPARTMENT OF HEALTH, EDUCATION AND WELFARE

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about 0.2 ppm for individual foods and about 0.05 ppm for Total Diet composites. Fish from certain fresh water locations are the food most frequently and consistently found to contain PCB residues. The residues in fish are most often similar in gas chromatographic peak pattern to Aroclor 1254 but usually with higher concentrations of the late eluting (higher chlorination) chlorobiphenyl components.

E. Chlorinated Dibenzofurans

(See Appendix for structural information and definitions)

In considering the potential hazard to humans of the commercial chemical mixtures of chlorinated biphenyls called PCBs, one must consider which if any identified trace contaminant in these complex mixtures might contribute significantly to the overall hazard potential of the mixture. Although there is evidence for the presence of chlorinated napthalenes and possibly chlorinated terphenyls in PCBs, the chlorinated dibenzofuran (Cl-DBF) contaminants are regarded as a greater potential danger for several reasons. In using a chick bioassay to monitor fractionation of commercial PCB mixtrues, it was found (Vos et al., 1970) that the fraction most toxic to chicks, and far more toxic than the other fractions, contained Cl-DBFs and chlorinated naphthalenes. What limited toxicological information there is available on these halogenated naphthalenes, terphenyls and dibenzofurans suggests that only the Cl-DBFs may be more toxic than chlorinated biphenyls by orders of magnitude (Bauer et al., 1961; Moore et al., 1976).

The extremely high toxicity of some of the chlorinated-dibenzo-p-dioxins (NIEHS Conference 1973; Schwetz, et al., 1973) a class of organic chemicals very similar in structure to the Cl-DBFs, also suggests the latter are likely to be highly toxic. Knowledge of the chemistry and toxicity of various chlorinated dibenzo-p-dioxin structures and the relationship between toxicity and structure, although recently developed, is more complete than for Cl-DBFs. Therefore, findings in the chlorodioxin field provide indicators to assess the difficulties likely to be encountered in the study of Cl-DBFs.

Chlorinated dibenzofuran contaminants have been reported and confirmed in PCB mixtures manufactured in Germany and France (Vos et al., 1970; Bowes, et al., 1975a) in Japan (Roach and Pomerantz, 1974a; Nagayama, et al. 1975) and in the United States (Aroclors) (Roach and Pomerantz, 1974b; Bowes, et al., 1975a). An additional claim that a cl-DBF contaminated an Aroclor was not sufficiently supported by the evidence presented (Curley et al., 1975). In the PCBs of U.S. manufacture, the range of Cl-DBFs found was from dichloro through hexachloro (see references cited above) and sufficient evidence was obtained to show that 2,3.7,8-tetrachloro and 2,3,4,7,8,-pentachlorodibenzofuran are presen' in Aroclors (Bowes et al., 1975b). That the Cl-DBFs reported were actual contaminants and not artifacts resulting from the experimental procedures used, was considered in two instances (Roach and Pomerantz, 1974b; Nagayama et al., 1975).

Proper quantitation of the individual Cl-DBF contaminants is very difficult. It requires full structural identification of the Cl-DBF contaminant, availability of the contaminant as a highly purified reference standard for quantitation purposes and evaluation of the procedure used to concentrate and separate the Cl-DBFs, (e.g. from chlorobiphenyls) to determine the capability of the procedure to recover the specific Cl-DBFs in the PCB mixture. Reported attempts to quantitate the Cl-DBFs in PCB suggest contamination levels in the low parts per million range for total chlorinated dibenzofurans (Bowes et al., 1975a; Nagayama et al., 1975). Many of the reported values probably can be taken as minimal in the absence of recovery data.

Although the source of the Cl-DBF contaminants in commercial PCB mixtures has not been determined, several possibilities may be considered. The simplest explanation would be the likely presence of dibenzofuran (parent compound) in the technical grade biphenyl subjected to the chlorination process. From a consideration of the procedures used in the commercial synthesis of PCBs (Hubbard, 1964) various chlorinated biphenyls, if substituted in the ortho and ortho-prime positions with hydroxy groups and/or chlorine atoms, might ring close to form the furanoid ring by dehydration or dehydrochlorination.

It is important to recall that Cl-DBFs have been reported as contaminants also in other chemicals of commercial importance. Samples of pentachlorophenol (Schwetz et al., 1974) as well as

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lower chlorinated phenols (Firestone et al., 1972) and hexachlorobenzene, (Villanueva et al., 1974) have been found to contain a range of Cl-DBFs. The ppm level of Cl-DBFs in certain pentachlorophenols examined by Schwetz and co-workers (1974) was considerably higher than the highest level thus far reported in commercial PCB mixtures; the chlorine level in the reported dibenzofuran contaminants of pentachlorophenol ranged from hexa to octa.

It is now known that "PCB residues" obtained from environmental samples usually do not simply represent an easily identified original commercial PCB mixture. For example, there is evidence from the study of electron capture gas chromatograms that certain chlorinated biphenyl compounds are preferentially lost or concentrated in passing through environmental media. This has led to recent studies of the toxicity, metabolism and physiological effects of specific, individual chlorinated biphenyl compounds, synthesized by routes intended to yield a single compound of known structure. In addition to permitting the development of structure-activity correlations, these studies presumably were intended to avoid complications in interpreting results from the testing of the commercial chlorinated biphenyl mixtures (Vos and Notenboom-Ram, 1972), now known to contain toxic Cl-DBFs as contaminants. Interpretaion of results from the testing of individual chlorinated biphenyl compounds, however, may not be entirely straight forward. In the Ullmann coupling reaction of

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2,4,5-trichloroiodobenzene, it has been reported that the highly toxic 2,3,7,8-tetrachlorodibenzofuran is formed in 3% yield in addition to the expected 2,2'4,4',5,5'-hexachlorobiphenyl product (Moron, et al., 1973). This hexachlorobiphenyl is a significant constituent of PCB mixtures (Sissons and Elti, 1971; Tas and Kleipool, 1972; Jensen and Sundström, 1974) and has been singled out for biological studies by several workers (Vos and Notenboom-Ram, 1972; Johnstone et al., 1974; Hansell and Ecobichon, 1974). Careful purification and, if necessary, chemical analysis of symmetrical chlorobiphenyls prepared by the Ullmann coupling reaction (for dibenzofuran content) is suggested as a prerequisite to biological testing of the biphenyl.

There are two other aspects of the chemical relationship betwen chlorinated biphenyls and Cl-DBFs that need to be mentioned. Both deal with possible environmental alteration. Evidence has been obtained for photochemical conversion of certain chlorinated biphenyls to Cl-DBFs in very low yields (Crosby and Moilanen, 1973). Although the scope of this study was limited, formation of Cl-DBF was shown to occur under conditions of sunlight irradiation and in the laboratory using sunlight-simulating conditions. Two different ortho-chlorinated biphenyls (the 2,5-dichloro and 2,2',5,5'-tetrachloro) were claimed to produce approximately 0.2% steady-state yields of a monochloro DBF. The limited reports regarding the photochemical decomposition of Cl-DBFs (Crosby and Moilanen, 1973; Hutzinger et al., 1973) indicate relatively

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rapid destruction of the compounds may take place in the environment. Since reductive dechlorination is a major route of photochemical alteration of Cl-DBFs, the possibility of dechlorination of highly chlorinated DBFs to more toxic DBFs of lower chlorine content must be considered. The extent to which specific chlorinated biphenyls, found as major constituents of commercial PCB mixtures, can be photochemically converted to Cl-DBFs can only be determined by further experimental studies.

Analysis of the Yusho oil (the rice oil contaminated by PCB-containing heat exchange fluid implicated in the Japanese "Yusho" poisoning incident) by Nagayama et al., (1975) for Cl-DBF content, led to a value of 5 ppm Cl-DBFs. This value is about 300 times the Cl-DBF level expected in the Yusho oil if one simply assumes contamination of the oil by Cl-DBFs to be proportional to the Cl-DBF level found in unused Kanechlor 400 (the Japanese PCB mixture claimed to have been used as the heat exchange fluid) and to the level of PCB in the Yusho oil. This led Kuratsune et al., (1975) to suggest that Cl-DBF levels increased in the heat exchange fluid through use. Going a step further, these questions may be raised: Is Cl-DBF concentration increased, generally, in PCB-containing heat exchange fluids through use? Does such increase occur in PCB-containing transformer fluids or electrical capacitors through use?

A critical review is needed of the published data upon which Kuratsune's suggestion is based (Nagayama et al., 1975), particularly

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since the results from a recent analysis of a portion of Yusho oil (Trotter, 1976) raises questions about the concentration of chlorinated biphenyls in the Yusho oil. Further laboratory studies suggested by such a review and analyses of selected, used PCB-containing industrial fluids might help to answer the above questions.

Considering the Cl-DBFs as the toxicologically most significant class of chemical impurities in the PCB mixtures, the questions may be asked: what portion of the observed effects from animal and human exposure to PCB mixtures can be attributed to the Cl-DBFs? It is doubtful this question can be answered in any quantitatively explicit way. There are analytical problems in identifying and measuring accurately the amounts of chlorinated dibenzofurans in various PCB mixtures. Even though only a relatively few of the 135 possible chlorinated dibenzofurans may be identified in PCB mixtures, the toxicity of these compounds can be expected to vary with both number and ring position of chlorine atoms in the Cl-DBF molecule. Toxicity data on specific, high purity Cl-DBFs is very limited because the compounds themselves are not readily available. In addition to these, essentially chemical, difficulties, toxicological judgements would be difficult to make. To begin to evaluate the toxicological "burden" to be placed on Cl-DBF contaminants in commercial PCB mixtures, a practical approach would be to use analytical procedures that can recover and quantitate specific Cl-DBF compounds known to be highly toxic. For example, 2,3,7,8-tetrachlorodibenzofuran, already reported by Bowes (1975b) as

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present in PCBs, can serve as a measure of potential hazard until further toxicity data for Cl-DBFs become available.

To date, there have been no published, positive findings of Cl-DBFs in environmental samples or in foods. Analytical procedures to detect Cl-DBFs in such samples should be developed, tested and applied to appropriate samples. If chlorinated dibenzo-p-dioxin residue analytical findings can be taken as an indicator, procedures suitable for parts per trillion detection of Cl-DBFs will be required and quantitation will be difficult.

No clear evidence for the presence of chlorinated dibenzo-p-dioxins in commercial PCB mixtures has been reported. A recent publication suggesting the presence of such contaminants in some PCBs and in a synthesized chlorinated biphenyl (Ax and Hansen, 1975) almost certainly misinterpreted the significance of the experimental finding related to the dioxins.

III. Chemistry of Brominated Biphenyls

A. Comparison of Brominated Biphenyls with Chlorinated Biphenyls

Unlike PCBs, the chemistry and stability of PBBs have not been well studied and documented in the literature. It is difficult to assess the stability and the extent of possible chemical conversion of PBBs in the environment. PBBs can be compared chemically to the PCBs. Since both bromine and chlorine are

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