THE CARCINOGENIC AND OTHER CHRONIC EFFECTS OF PERSISTENT HALOGENATED ORGANIC COMPOUNDS

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A number of persistent halogenated organic compounds have been shown to produce liver tumors in rodents such as DDT, dieldrin, mirex, Kepone®, hexachlorobenzene, polychlorinated and polybrominated biphenyls (PCBs and PBBs) and now also 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) as well as hexachlorodibenzodioxin. TCDD also induced tumors of the lungs, hard palate or nasal turbinates in rats. It is possible that other isomers of the halogenated dibenzodioxins are also carcinogenic. Representatives of other groups of compounds in this category, the halogenated dibenzofurans, naphthalenes and terphenyls have not been tested for a carcinogenic effect. Most of the chemicals mentioned are persistent in mammals once they have been absorbed. They are also poorly degraded in the environment. For this class of compounds it is generally assumed that not the chemicals themselves but their metabolites are the proximate carcinogens. TCDD may be an exception. While most of the chemical compounds mentioned are commercial products, the halogenated dibenzodioxins and dibenzofurans are contaminants of a number of technical products. Some of these products that may theoretically be contaminated are listed in Table 1.

The persistent halogenated organic compounds under discussion induce mixed function oxidases and cause hepatomegaly in rodents and other mammals. The hepatomegaly is the result of the hypertrophy of individual hepatocytes. Some hyperplasia also occurs and increased mitotic activity can be noted. The hepatocytes may accumulate lipid in their cytoplasm. At the ultrastructural level the enlarged hepatocytes show an increase in smooth endoplasmic reticulum and inclusions within the cytoplasm which appear like concentric whorls surrounding lipid vacuoles. Morphologic changes in the mitochondria have also been described (Grimes *et al.*[1], Kimbrough *et al.*[2]). In addition to these alterations the PCBs, PBBs, some isomers of the halogenated dibenzodioxins as well as hexachlorobenzene induce experimental hepatic porphyria. In the rat experimental hepatic porphyria only occurs in the female, but in other species it can be induced in both sexes. On microscopic examination an increase in macrophages and pronounced Kupffer cells containing brown ceroid pigment and necrobiosis of liver cells is prominent. Lipid accumulates in the cytoplasm of hepatocytes resulting in clumps in hepatocytes with foamy cytoplasm. Similarly lipid accumulation, lipofuscinin (ceroid pigment) have also been reported in livers of humans suffering from porphyria cutanea tarda (Blomgren *et al.*[3]).

Adenofibrosis (cholangiofibrosis) (Kimbrough *et al.*[4]) has been observed in rats fed PCBs and technical but not pure pentachlorophenol (Kimbrough and Linder[5]). The PCBs were contaminated with trace amounts of chlorinated dibenzofurans and the pentachlorophenol with chlorinated dibenzodioxins and dibenzofurans. The significance of adenofibrosis and its relationship to the development of hepatocellular carcinomas is presently not understood. It usually occurs concomitantly with

[illegible] carcinogenic in rodents (Kimbrough and Linder; Kimbrough[illegible]) has [illegible] been described in rats exposed to other [illegible] [illegible] [illegible] [illegible]enzene (Edwards and White). Although hepatocellular tumors have been reported in rodents after exposure to DDT, dieldrin, mirex and Kepone, [illegible] compounds do not produce the same type of liver pathology [illegible] [illegible] [illegible] possible that PCBs, PBBs and related compounds cause lipid peroxidation [illegible] mirex, Kepone, DDT and dieldrin do not. Whether the experimental hepatic porphyria produced by these compounds is in any way related to the induction of hepatocellular carcinoma is presently not known. A study reported by [illegible] Sweeney[illegible] is interesting in this regard. These authors treated [illegible] (DBA/2J) or nonresponsive (DBA/2J) mice to the induction of [illegible] hydroxylase with TCDD. [illegible] nonresponsive [illegible] [illegible] [illegible] [illegible] [illegible] uroporphyrinogen decarboxylase activity, while it was decreased in the [illegible] [illegible] uroporphyrin excretion was increased in this group. In the study [illegible] presented in this volume, only the female rats showed hepatic porphyria [illegible] developed hepatocellular carcinomas while the male rats had neither. [illegible] explored whether an effect on certain enzymes related to porphyrin [illegible] coupled with an effect on enzymes somehow related to the induction of [illegible]

TABLE 1

EXAMPLES OF COMMERCIAL PRODUCTS THAT MAY BE CONTAMINATED WITH HALOGENATED DIBENZODIOXINS OR DIBENZOFURANS

2,4,5-Trichlorophenol	[illegible]
Pentachlorophenol	Erbon
Hexachlorobenzene	[illegible]
2,4-Dichlorophenyl p-nitrophenyl ether (TOK)	Hexachlorophene
2,4,5-Trichlorophenoxyacetic acid	[illegible] ether [illegible]
Fenoprop (Silvex)	[illegible]

carcinomas or whether hepatic porphyria and hepatocellular carcinoma [illegible] [illegible]

Hepatic porphyria (porphyria cutanea tarda) has also been reported [illegible] following occupational exposure to some of these chemicals and porphyrin [illegible] should be screened for carefully in such cases in the future. The sex difference [illegible] induction of hepatic porphyria found in rats does not exist in humans. [illegible] TCDD and perhaps also the PBBs affect reproduction. The reduction [illegible] dependent tumors in the study by Kociba *et al.* may be indicative of [illegible] these compounds on steroids. Other halogenated persistent organic compounds [illegible] affect endocrine glands. Kepone has been shown to cause hyperplasia of the [illegible] cortex in rats (Cannon and Kimbrough) and in quail (Eroschenko and Wilson). High doses of technical hexachlorobenzene also caused hyperplasia of the [illegible] cortex in rats (Kimbrough and Linder).

All of the halogenated organic compounds that I have mentioned [illegible] in biologic systems. Certain isomers of PBBs and PCBs seem to be retained indefinitely (Kimbrough *et al.*). If a single high dose of a mixture of PBBs is given to [illegible] rats, hepatocellular tumors can be induced. It is therefore not necessary to conduct 2 year feeding studies with these compounds to show that they are carcinogenic. A single high dose at least of the PBBs will have the same effect. When rats [illegible]

[illegible] about 6 months after dosing (Kimbrough *et al.*[illegible]). It was also found that PBB levels in the liver did not regress. It is presently not known whether the isomers that persist are the ones that are carcinogenic. If the persistent isomers prove to be carcinogenic, then the tumor induction would be due to the continuous internal exposure of the target organ to these isomers.

Neoplastic nodules are considered to represent part of the spectrum of response elicited by hepatocarcinogens in rodents. First, areas of alteration will develop; some of these will become neoplastic nodules and some of the neoplastic nodules will in time transform into hepatocellular carcinomas (Squire and Levitt[?]). A number of carcinogens [illegible] produced this same spectrum of response and there is no difference in the response whether the chemical producing it is a carcinogen of long standing or whether it is one of the halogenated compounds discussed here. Although it has been shown many times that the neoplastic nodules are part of the carcinogenic response, they are not always included in the statistical evaluation of bioassays, which may lead to erroneously interpreted results, particularly when they are classified as hyperplastic nodules or nodular hyperplasia and when the number of animals studied was small (Carcinogenesis Testing Program, 1977[?]).

Since all of these compounds are also inducers of mixed function oxidases and could enhance the metabolism of other xenobiotics, they may, depending on the circumstances, prevent or enhance the tumor induction by other chemicals. Yet, metabolites would have to be formed for many of the halogenated compounds, tetrachlorodibenzo-*p*-dioxin perhaps being an exception. The dermal application of these compounds that have to be activated would therefore not necessarily result in tumor formation. Further studies will have to be done to elucidate these problems. The question of skin carcinogenesis is particularly important in workers that have had occupational dermal exposure to TCDD, PCBs or chlorinated naphthalenes as evidenced by chloracne.

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