REPORT

PCBs, Dioxins, and Dibenzofurans
Historical and Current Perspectives

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december, 1985
report number 85-10

MONS 223082

PCBs, DIOXINS, AND DIBENZOFURANS
HISTORICAL AND CURRENT PERSPECTIVES

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December 1985

Report Number 85-10

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HISTORICAL AND CURRENT PERSPECTIVES

I. INTRODUCTION

Polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and to a lesser extent, non-ortho polychlorinated biphenyls, are three structurally related families of anthropogenic chemical compounds that in recent years have been shown to cause serious environmental contamination (1). Although reference to the chlorodibenzofurans and dioxins as potent ecotoxicants may seem somewhat anticlimatic today in the light of the publicity that they have received in the recent past, it is quite apparent that the hazards presented by these persistent chemicals will remain with us for years to come, especially in the form of natural products and synthetic organic compounds subjected to photolysis and thermochemical pyrolysis (2,3,4,5).

Probably the most common precursors of the chlorooibenzofurans and dioxins are tri-, tetra-, and pentachlorobenzenes; tri-, tetra-, and penta- chlorophenols; polychlorinated biphenyls; and polychlorinated biphenyl ethers. Evidence is mounting, however, that numerous non-chlorinated predioxin hydrocarbons present in waste sludges, commercial compounds, or whatever, may react thermally in the presence of chlorine (or chloride) to form chlorodibenzodioxins and chlorodibenzofurans.

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Early injudicious waste chemical dumpings and pesticide applications plus a mounting number of industrial accidents coupled with the recent development of ultra-sensitive chemical analytical procedures have stimulated a proliferation of animal toxicological studies, some of which have demonstrated about a dozen chlorodibenzodioxin and -furan congeners to be the most toxic substances made by man (5,6,7). Publication of the study data, part of which is confusing and perhaps controversial, in turn has generated strong public opinion and pressure from special groups for involved entities to control the presence and movement of these chemicals in the ecosystem. In this discussion an attempt will be made to investigate the most pertinent part of this mass of data, to summarize it, and then to present it in a clear and unbiased manner.

II. EARLY HISTORY

Although the chemical structure of polychlorinated biphenyls has been known since 1867 (15), commercial production of the compounds was not initiated until 1929 (19). At that time the Swann Chemical Company in Anniston, Alabama, began producing the material in response to the electrical industry's need for improved dielectric insulating fluids which also would increase fire resistance when used in transformers and capacitors (9). In 1935, Swann was purchased by the Monsanto Company which, being the sole producer of these compounds in the United States, began an expansion program to exploit their unique functional characteristics of fire resistance, thermal stability, low water solubility, low vapor pressure, solvency power, viscosity, etc. Polychlorinated biphenyls evolved in response to important needs by both industry and society for heat transfer liquids, hydraulic fluids, dye and pigment carriers in pressure-sensitive duplicating paper, deinkers in the paper industry, hot-melt adhesives, plasticizers, caulking compounds, paint and varnish solvents, fluorescent light ballast coolants, optical and microscopy liquids, and more. Production was at its peak in 1970 when rumors concerning the environmental hazards of PCBs convinced Monsanto to consider curtailing production of these important compounds. As verification of environmental problems surfaced, an organized voluntary phaseout was decided and finally accomplished in 1977. This decision was based on Monsanto's concern over the presence of PCBs in the environment and because of their belief that it was the right thing to do

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(9). It is estimated that between the years 1929 and 1977 about 1.2 billion pounds of PCBs were produced in the United States, and that 750 million pounds still are in use as of January 1985, nearly all in closed-system heat exchangers (10). 162 million pounds of which are associated with the electric utility industry (14).

In answer to the question of why federal regulations still permit the use of this material, the EPA has stated that "Based on the analysis presented...EPA has determined that the use of PCBs in transformers does not pose unreasonable risks to public health or the environment, provided that..."(13), and goes on to describe an organized contingency plan of siting, maintenance, record keeping, and inspection.

PCBs were not discovered in the environment until 1966 when two Swedish scientists at the Karolinska Institute investigating DDT residues in fish tissue picked up interfering peaks in a new electron capture chromatograph procedure for chlorinated pesticide residues (11, 12). PCBs remained hidden for several reasons. First, they had not been deliberately distributed about the ecosystem. Second, because of their relatively low acute toxicities, their presence was not immediately evident. Finally, they were difficult to detect analytically (12). Probably the incident creating the most publicity for PCBs was the Yusho episode in Japan (1968).

Chlorinated dioxin was first synthesized in 1872 by two German chemists who obtained octachlorodibenzo-p-dioxin by heating the potassium salt

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of pentachlorophenol. As it had no useful purpose, it was shelved at that time (8). Several incidents of occupational exposure to chlorodioxins had occurred previous to 1957 in which the symptoms of polychlorodibenzo-p-dioxin (and possibly polychlorodibenzofuran) poisoning were demonstrated, but it was not until that year that chlorodioxins were identified as contaminants in the chemicals involved (7, 8, 21). One of these early incidents involved an industrial accident in Nitro, West Virginia (1949) in which 250 workers were exposed to 2,4,5-trichlorophenol when symptoms of chlorodioxin poisoning such as chloracne were noticed.

Two occupational exposures occurred in the Federal Republic of Germany (1952) in which 60 workers involved in the manufacture of trichlorophenols in two factories developed chloracne. Another occupational exposure surfaced at another German plant manufacturing 2,4,5-trichlorophenoxyaceticacid (2,4,5-T) at Boehringer Ingeheim, near Hamburg, in which 31 cases of chloracne occurred (1953 - 1955). Two years later (1957), about 20 grams of 2,3,7,8-tetrachlorodibenzo-p-dioxin were synthesized for the first time at the University of Hamburg. The researcher who accomplished this fete developed severe chloroacne and was hospitalized at the same institution in which the Boehringer Ingeheim workers were treated earlier (21). By associating the two incidents, investigators were able to determine the cause of the illnesses and were able to demonstrate that the 2,3,7,8-tetrachlorodibenzo-p-dioxin was present as a contaminant in the 2,4,5-trichlorophenol used to prepare the 2,4,5-T at Boehringer Ingeheim.

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Probably the incident(s) generating the most publicity for chlorodioxins could be the Agent Orange episode in Vietnam (1962 - 1970) and/or the Seveso episode in Italy (1976).

Chlorinated dibenzofurans were first associated with the chlorinated cyclic hydrocarbon group of toxicants in 1957 when Hoffman, a German chemist, described the syntheses and potent chloracnegenic and hepatogenic toxicity bioassay characteristics of chlorinated dibenzofurans containing three, four, and five chlorines. The work was done in 1953 in an effort to determine the cause of chloracne and liver damage in French and German workers in 2,4,5-trichlorophenol manufacturing plants. The chlorinated dibenzofurans did not seem to be present in technical 2,4,5-trichlorophenol, however (50).

Probably the incidents creating the most publicity for polychlorinated dibenzofurans were the Yusho episode (Japan, 1968) and the Yu-Cheng episode in Taiwan (1979).

Like the terms Dioxin and Dibenzofuran, the term PCB is used rather loosely in both language and literature. Although theoretically PCBs can consist of different mixtures of a possible 209 different chlorobiphenyl congeners presenting varying chlorine content and chlorine position, each industrial PCB (Aroclor, U.S.) consists of about six to eight different homologs, each of which again may consist of up to about eight different isomers. As a result, a single Aroclor may contain about 40 to 70 different chlorinated biphenyl congeners (15). These congeners usually average about three to five chlorine atoms per molecule (42 percent to 54 percent chlorine) (17).

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At least 25 different international trade names have been established by 17 different companies in nine different countries (16, 20). The generic name most familiar in the United States is askarel and the manufactured product most familiar is Aroclor. This latter material has been produced in the United States in at least 13 different grades (nine of which are biphenyls in the 1000 and 1200 series, Monsanto) and released under at least 16 different domestic trade names (15, 16, 18, 20).

A list of trade names follows, some of which may contain Aroclors in the 2500, 4400, or 5400 series (Monsanto) which consist partially at least of polychlorinated terphenyls.

	Trade Name	Manufacturer
1.	Aroclor series	Monsanto
2.	Therminol	Monsanto
3.	Pyroclor	Monsanto
4.	Santoval	Monsanto
5.	Pydraul	Monsanto
6.	Turbinol	Monsanto
7.	Pyranol	General Electric
8.	Inerteen	Westinghouse
9.	Hyvol	Aerovox
10.	Chlorextol	Allis-Chalmers
11.	Abestol	American Corp.
12.	DyKanol	Cornell Dubilier
13.	Saf-T-Kuhl	Kuhlman Electric
14.	Elemex	McGraw Edison
15.	Diaclor	Sangamo Electric
16.	Noflamol	Wagner Electric

Askarel is a generic term applied to a "broad class of fire resistant synthetic chlorinated hydrocarbons used as dielectric fluids" (17). Usually they are composed of mixed PCB congeners, at a concentration of about 60 to 65 percent, dissolved in trichlorobenzene and/or lesser

quantities of tetrachloro- and pentachlorobenzene if needed or if present inadvertently (these are the Aroclors). The askarels can consist, however, of any concentration of any designated chlorocarbon with or without chlorinated biphenyl.

During the last 20 years, considerable PCB compounds have been produced in Europe and in Japan, part of which has been exported to the United States. A few import figures are available. In the period 1973 to 1976, about 400,000 pounds of Fenlor DK were imported annually from Italy, and about 50,000 pounds of Pyralene were imported annually from France. In addition, during 1975 the importation of a large number of foreign transformers involved about 300,000 pounds of PCB coolant (20). A list of foreign trade names follows.

	Trade Name	Country of Origin
1.	Kanec lor	Japan
2.	Santotherm	Japan
3.	Fenc lor	Italy
4.	Aspirolio	Italy
5.	Clophen	Germany (G.F.R.)
6.	Pyralene	France
7.	Phenoclor	France
8.	Delor	Czechoslovakia
9.	Sovol	U.S.S.R.
	--	Great Britain
	--	Austria

III. CHEMISTRY AND FORMATION OF THE PCBs, CDDs, and CDFs

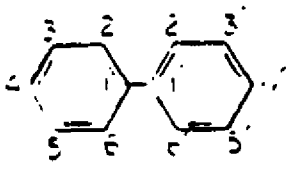
Hutzinger describes 23 different procedures for synthesizing chlorobiphenyls (18). In many of these, the yielded congener species may be predicted if the conditions of preparation are controlled carefully. Industrial PCBs have been prepared by the direct chlorination of molten biphenyl in the presence of iron filings or ferric chloride as a catalyst, with a final purification step. Although the mass yield is relatively high by this method (19), congener species cannot be controlled precisely. It is for this reason that the Aroclors are composed of mixed congeners, nearly all of which, incidentally, appear to be ortho-substituted. Inadvertent contaminants found in certain commercial PCBs have been chlorinated dibenzofurans and chlorinated naphthalenes (11).

As will be explained more fully later, the toxicities of PCBs, chlorodibenzodioxins, and chlorodibenzofurans vary widely not only according to animal species involved but also according to chemical structure of the specific congener(s). For this reason it will be necessary to present a few rules for numbering the ring systems in reference to chlorine substitution. The numbering system for PCBs differs slightly from that of the chlorodioxins and the chlorofurans. The following rules for PCB numbering are taken from Hutzinger (18).

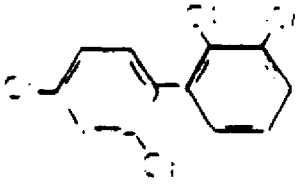
1. An unprimed locant is of lower order (preferred) than its corresponding primed locant.

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2. Locants as low as possible should be given to all substituents, ignoring primes at this stage.
3. As few primed locants as possible should be used.
4. When the number of chlorine substituents in each ring is the same, the ring with the lower numbered substituents receives the unprimed numbers. If everything else is equal, the locant cited first is unprimed.



Biphenyl ring numbering scheme



2,2',3,4'-tetrachlorobiphenyl

From the above it can be seen that numbering each of the two rings may proceed in any direction according to the rules stated. When discussing a series of isomers, it is standard practice to demonstrate a model scheme to which all isomers conform that are being presented in the discussion. Ortho substitution would be in the 2 and 6 positions in each ring. Several entities have analyzed the Aroclors for isomer specificity and have demonstrated ortho chlorine substitution in every meaningful congener component. For reasons to be discussed later, ortho substitution increases the tendency of the chlorobiphenyl molecule to become non-planar which in turn decreases its toxicity potential.

At this point, however, it is necessary to state that toxicity of the PCBs, chlorodibenzofurans, and chlorodibenzodioxins is associated with

their measured activity as cellular receptor excitors in halogenated aryl hydrocarbon enzyme induction systems. Enzyme induction activity procedures are used to indicate chemical toxicities because they can be demonstrated at less than actual toxicity levels. The most active PCB congeners in AHH induction are presented below (22).

1. 3,3',4,4'-tetrachlorobiphenyl
2. 3,4,4',5-tetrachlorobiphenyl
3. 3,3',4,4',5-pentachlorobiphenyl
4. 3,3',4,4',5,5'-hexachlorobiphenyl

The lack of ortho substitution in the above four PCB congeners decreases their tendency to become non-planar and thus increases their activity in the cell protein receptor mechanism.

The phenomenon of variable planarity does not affect chlorodibenzodioxin and chlorodibenzofuran biological cellular activity because each of the two phenyl groups is connected by double bonds which prevents ortho-oriented repulsive twisting which occurs quite easily on the single-bonded pivot of the PCB molecule.

As prepared industrially, most of the mixed PCB congener components of the Aroclor compounds were solids at room temperature (18). When dissolved in the second chlorobenzene component in order to form the respective Aroclor, they became mobile oils (Aroclors 1221, 1232, 1016, 1242, and 1248), viscous liquids (Aroclor 1254), or sticky resins (Aroclors

1260 and 1262) (18). Approximate water solubilities and specific gravities of selected Aroclors are presented below (18). The percent chlorine is represented by the last two digits of the series number. The exception is Aroclor 1016 which is a distillation product of 1042 in which nearly all of the penta-, hexa-, and hepta- chlorobiphenyls have been removed. The chlorine content of 1016 is about 41 percent.

Aroclor	Water Solubility mg/L at 25°C	Vapor Pressure (mm Hg at 100°F)	Specific Gravity Corrected to 15°C
1221			1.19
1232		0.005	1.28
1016			1.38
1242	0.2	0.001	1.39
1248	0.1	0.00037	1.41
1254	0.04	0.00006	1.50
1260	0.025	0.00004	1.56
1262			1.58

It can be seen that the solubilities of the Aroclors are very low and that they decrease further as chlorine content increases. Exact solubilities for the Aroclors are difficult to assign in the environment for several reasons: (1) the solubilities of different isomers within homologs vary, (2) the congener content of each Aroclor cannot be controlled uniformly, and (3) individual chlorobiphenyls (congeners) are adsorbed strongly onto solid surfaces such as silt, sand, shells, wood, chars, plastic, glass, etc. The solubilities can be increased, however, by the addition of nonionic surfactants such as Solar NP, Tween 80, Tergitol NP, Triton series, etc.

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The approximate distribution of PCB homologs in several Aroclors follows (18).

Chlorobipnenyl	Percent Chlorine	Presence in Aroclor w/w % 1221	1016	1242	1254
$C_{12}H_{10}$	0	11	<0.1	<0.1	<0.1
$C_{12}H_9Cl$	18.8	51	1	1	<0.1
$C_{12}H_8Cl_2$	31.8	32	20	16	0.5
$C_{12}H_7Cl_3$	41.3	4	57	49	1
$C_{12}H_6Cl_4$	48.6	2	21	25	21
$C_{12}H_5Cl_5$	54.3	<0.5	1	8	48
$C_{12}H_4Cl_6$	58.9	N.D.	<0.1	1	23
$C_{12}H_3Cl_7$	62.8	N.D.	N.D.	<0.1	6
$C_{12}H_2Cl_8$	66.0	N.D.	N.D.	N.D.	N.D.

PCBs were constructed to be chemically inert. As a result, transformations by oxidation, reduction, dechlorination, nitration, isomerization, cyclization, etc. are not expected to occur in the environment without the addition of some form of energy. The two most obvious natural forms are light and heat, and these forms have been shown to convert PCBs, CDDs, and CDFs into different compounds, both in the laboratory and in the environment (18, 23). In addition, the photochemical reactivity of chlorine has been demonstrated to be historically characteristic of this element. Photolysis is a very expedient process and has been receiving considerable attention in relation to the removal of these chemicals from the environment by way of dehalogenation.

The photochemical dechlorination of the chlorodibenzodioxins and chlorodibenzofurans allegedly occurs more easily and more completely than that of the chlorobiphenyls; however, under proper conditions photodechlorination of PCBs progresses at least to the monochloro compound with the

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more highly chlorinated compounds reacting faster and more completely than the less chlorinated ones (18). At least three conditions are necessary for photodechlorination to occur here: (1) a hydrogen-donating solvent must be present, (2) ultra-violet (UV) light of the appropriate wavelength must impinge on the solution, and (3) the light must be absorbed (18, 23).

Although UV light penetrates water quite readily, it will not initiate chlorocarbon dechlorination unless the chlorocarbon and the hydrogen-donating solvent are in intimate contact as would be the case with an organic polar solvent such as an alcohol or a ketone or perhaps aided by a surfactant. Available natural UV energy for the photoreduction of these particular compounds drops off abruptly below 310 nanometers and becomes negligible below 290 nm (23). Fortunately, dechlorination occurs quite readily between 290 nm and 310 nm for these compounds.

Due to the variable congener content of industrial PCBs, it could be difficult to demonstrate an optimum wavelength for them in relation to molar absorptivity, but values have been demonstrated for a few dioxins: 2,3,7,8-TCDD (λ max 308 nm, ϵ = 6050) (24); 1,2,3,4,6,7,8,9-OCDD (λ max 318 nm, ϵ = 4000) (23); and 2,3,7-Tri-CDD (λ max 304 nm, ϵ = 3500) (23). There are indications that chlorodibenzofurans are formed from the photochemical transformation of PCBs, but the CDFs themselves are photolabile; thus an assessment concerning the environmental accumulation of CDFs this way could be somewhat difficult without more investigation (18).

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possibly the greatest hazard presented by PCBs as an environmental toxicant is the low temperature (300°C) thermochemical oxidation to chlorodibenzofurans (and chlorodibenzodioxins indirectly through the production of chlorobenzenes) (3). In this connection, the chlorobenzenes present in askarels also are a source of CDDs and CDFs by way of thermochemical transformation. The most notorious source of chlorodioxins, especially the ?,3,7,8-tetra isomer, was as a contaminate by way of the high temperature (230°C), high pressure alkaline hydrolysis of 2,4,5-trichlorophenol in 2,4,5-T, Silvex, and hexachlorophene production. 2,4,5-trichlorophenate also is used in the production of several other pesticides (Ronnel, Erbon, Sesone).

Several methods for the industrial production of 2,4,5-trichlorophenol have been tried, all of which are variations of the alkaline batch hydrolysis of 1,2,4,5-tetrachlorobenzene at temperatures between 160 and 180°C and followed by purification and neutralization steps. The reaction rate is greatest (less than 2 hours) and yield is highest (90 percent or more) with water as the only solvent (6), but the temperature and pressure are very difficult to control and the tendency for the inadvertent dimerization of the 2,4,5-trichlorophenate to 2,3,7,8-TCDD also is greatest in this case. The use of monohydric or polyhydric alcohols as the reaction solvent and employing lower temperatures and pressures reduces (but does not eliminate) the inadvertent production of 2,3,7,8-TCDD. A purification step is accomplished by mixing with toluene and consequent phase separation. The aqueous chlorophenate phase is neutralized with hydrochloric acid to 2,4,5-trichlorophenol and

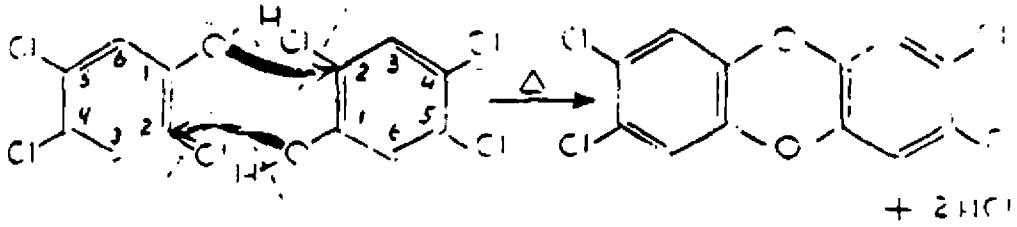
the toluene phase containing the impurities is redistilled for recycling. The greatest concentration of inadvertent 2,3,7,8-TCDD would be present in toluene distillation still bottoms, but some 2,3,7,8-TCDD (due to its low solubility in any solvent) would be carried over with the purified 2,4,5-trichlorophenol. Toluene still bottoms and 2,4,5-TCP wastes are reported to be the source of the 2,3,7,8-TCDD contamination at Love Canal, NY, and Times Beach, MO (6). Heat (180°C) is used to initiate the hydrolysis, but the reaction can become exothermic at about 230°C and thus requires cooling coils for temperature and pressure control after the reaction has started. An aging step also is included here. These are the two steps that went out of control at Seveso.

As mentioned earlier, commercial 2,4,5-trichlorophenol or the sodium salt are used as feedstocks in producing several other pesticides, but it is doubtful that additional inadvertent 2,3,7,8-TCDD normally would be formed in these procedures as the reaction temperatures are all below 150°C. The possibility of a formation site, however, has been suggested at the steam coil interface of reactor vessels (6). Under certain conditions, hydrolysis of these compounds has been shown to produce tetra isomers of both dioxins and furans.

The following schematic will demonstrate that the formation of 2,3,7,8-tetrachlorodibenzo-p-dioxin from 2,4,5-trichlorophenol is very selective and requires site-specific occupancy of hydroxyl and chlorine groups on the reacting aromatic rings. Due to the effect of proximate energy relation, the reaction is analagous to simple metathesis in that the products can be predicted if the numerical configuration of the reactants

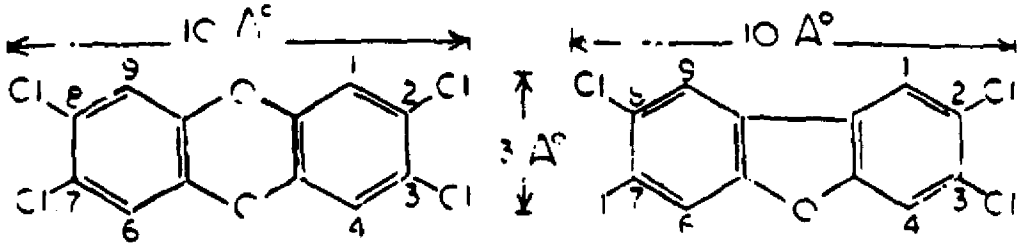
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is known. The temperature required to drive the reaction is about 200 to 400°C (25) or >180°C (20).



2(2,4,5-TCP) 2,3,7,8-TCDD (4)

All CDD and CDF congeners have one numbering system:



2,3,7,8-tetrachlorodibenzo-p-dioxin 2,3,7,8-tetrachlorodibenzofuran

Although a total of 75 chlorodibenzodioxin congeners are possible, about five are considered to be the most toxic. Toxicity is related to the 2,3,7,8 chlorine substitution with increasing ortho substitution (positions 1, 4, 6, 9), gradually decreasing the toxicity of the respective congener. Molecular structural requirements for chemical toxicity have been introduced by Kende and Wade as follows (6):

1. Halogen substituents at positions 2, 3, and 7 are minimum structural requirements.

2. Bromine as a substituent is more active toxicologically than chlorine which is more active than fluorine.
3. At least one hydrogen atom must remain on the dibenzo-p-dioxin nucleus.

Acute toxicities of selected chlorodioxins are presented below (6):

Substitution with Chlorine	30 D. LD_{50} (hg/kg) oral	
	Guinea Pigs	Mice
None		>50 x 10^3 (I.P.)
2,8	>300,000	
2,3,7	29,444	>3000.0
2,3,7,8	0.6 - 2.0	283.7
1,2,3,7,8	3.1	337.5
1,2,4,7,8	1,125	>5000.0
1,2,3,4,7,8	72.5	825.0
1,2,3,6,7,8	70 - 100	1,250.0
1,2,3,7,8,9	60 - 100	>1,440.0
1,2,3,4,6,7,8	>600:7180	
1,2,3,4,6,7,8,9		4 x 10^6

The toxicity pattern of the chlorodibenzofurans presents the same variability in relation to chlorine number and position except the hazard could be nearly ten-fold less than the chlorodibenzodioxins (11). A total of 135 dibenzofuran congeners are possible, but about three are considered to be most highly toxic. These are 2,3,7,8-tetra, 1,2,3,7,8-, and 2,3,4,7,8-pentachlorodibenzofurans (3).

The production of pentachlorophenol (PCP) also has been shown to be an inadvertent source of chlorodioxins (6). Although the manufacturing process differs in that PCP is produced by the direct catalytic chlorination of phenol forming a mixture of congeners varying in chlorine

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substitution, dimerization still occurs to produce hexa-, hepta-, and octachlorodioxins (6). It also is believed that pentachlorodioxins have been produced inadvertently from tetrachlorophenol which is one of the mixed congeners obtained in commercial pentachlorophenol production. Innumerable methods have been presented in the literature for the laboratory production of chlorodioxins and chlorofurans, mostly based on alkaline condensation and dimerization reactions, but the above chlorophenol condensations remain as proved inadvertent commercial sources of these two chemical toxicants.

At the present time, considerable attention is being directed toward thermal formation as a major source of chlorodioxins and chlorofurans detected in the environment. Thermal formation includes but is not confined to combustion and hydrolysis, as it is possible for clean Aroclors (or Kaneclors) to produce CDDs and CDFs in closed heat-exchange systems when heated to temperatures below the ignition point for extended periods. There is evidence that this occurred at Kyusho (Yusho) and Taiwan (Yu-Cheng). Transformers and capacitors that contain PCBs and chlorobenzenes, and that have been in service for a while, also may form CDDs and CDFs as thermal degradation products. As mentioned earlier, the most obvious chemical precursors are chlorophenols and chloroorganic pesticides as well as the PCBs and chlorobenzenes, but an immense number of chemically unrelated organic materials have been shown to synthesize CDDs and CDFs in combustion processes (3). The accompanying diagram from Choudhry and Hutzinger will illustrate combustion recycling. The temperature range necessary for combustion synthesis is believed to be

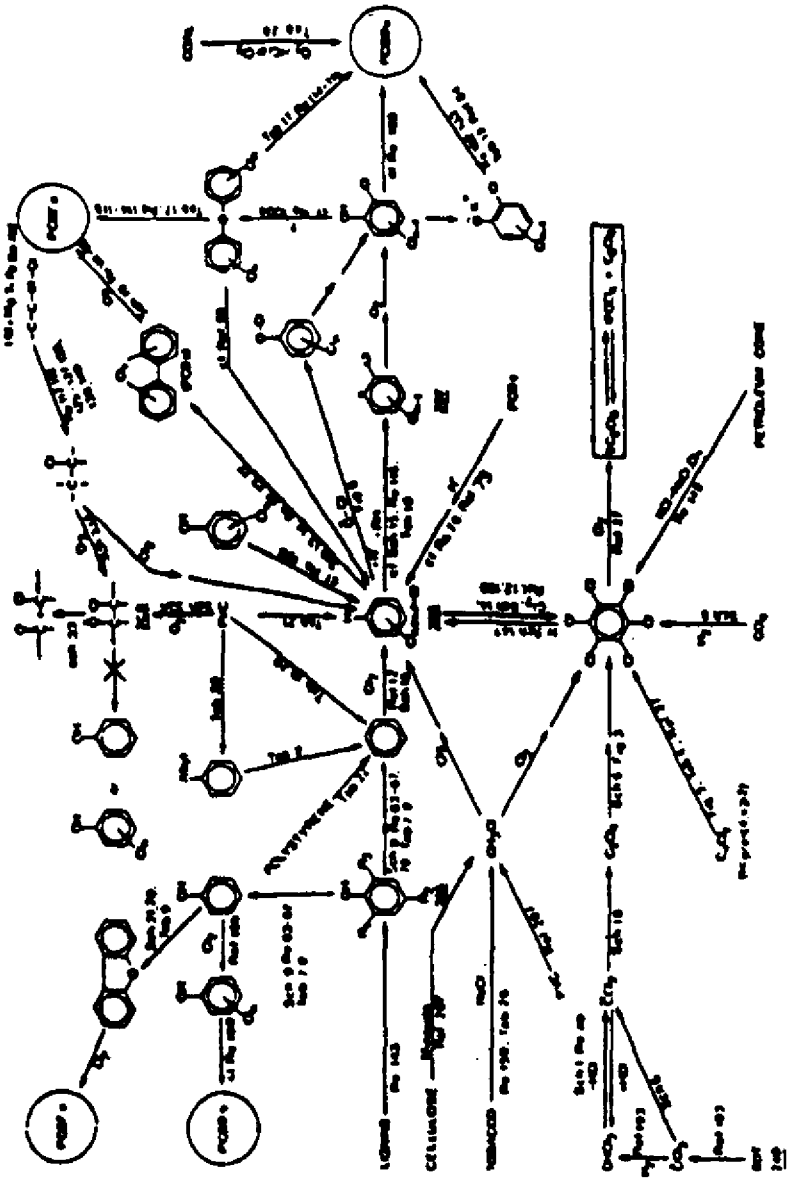


FIGURE 10 Complex array of syntheses of polychlorinated dibenzofurans (PCDFs) and polychlorinated dibenzo-p-dioxins (PCDDs) from chemically unrelated organic matter *i.e. de novo* syntheses of PCDFs and PCDDs. (Re. = Reaction, Ref. = References, Sch. = Scheme, and Tab. = Table)

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between 270°C and 500°C which, because of the lesser contact time involved, is somewhat higher than that required for industrial chemical batch process synthesis.

In open burning, chlorodioxins (and perhaps chlorofurans) begin to volatilize at about 500°C, part of which condenses on smoke particles and fly ash and part of which drifts off into the atmosphere to condense on dust particles. Combustible waste facilities operating at the normal low temperature below 800°C have been shown to produce CDDs and CDFs at concentrations ranging between 10 and 180 ng/g of fly ash (TCDDs between 2 and 10 ng/g) (4). An industrial heating facility burning waste oil in Switzerland was found to produce 100 ng/g of TCDDs in the fly ash (4).

The most obvious combustion sources of CDDs and CDFs are municipal waste incinerators, industrial waste incinerators, burning landfil dump sites, and transformer reclamation wastes burned below 800°C; but chemists at Dow Chemical have presented data indicating that chlorodioxins can result from the "thermal synthesis of inorganic chlorine and organic material...that chlorinated dioxins may occur in particulate matter from the combustion of most types of organic material," and they have "suggested the hypothesis that chlorinated dioxins result from trace chemical reactions occurring in fire." (26). They also have stated that normal commercial and domestic combustion processes are inadequate to eliminate the production of chlorodioxins from the combustion recycling of organic chemicals. Dow scientists believe that combustion efficiency

CO_2 ÷ (CO_2 + CO) must be 99.9 percent to reduce dioxin combustion source from 1 part per million to 1 part per billion. Dow analysts have found parts per trillion concentrations of 2,3,7,8-TCDD in urban soil, in metropolitan dust, in commercial sludge fertilizer, in fly ash from a municipal incinerator, in a diesel truck muffler, and in a home electrostatic precipitator (26). Also there is evidence that the thermal generation of chlorodioxins is catalyzed by copper and that of chlorodibenzofurans by stainless steel and nickel (5,7).

The water solubility of 2,3,7,8-TCDD is reported as 19.3 ppt (71). Its biodegradability is considered to be negligible (27). It binds very tightly to particulate matter such as soil, fly ash, and organic material. It has a half-life of about 1 year in an environment exposed to light and oxygen but up to 10 years in an unexposed environment. Thus it is reasonable to assume that 2,3,7,8-TCDD and its congeners as well as the TCDFs would have an extensive residence time in the environment.

A series of core studies have been made from sediment taken from Saginaw Bay, Michigan, and from southern Lake Huron. The samples were analyzed for PCDDs and PCDFs and dated by way of the cesium-lead technique. The workers concluded that although measurable PCDDs and PCDFs have been present in the sediment in the years preceding 1940, it was about that time that an abrupt increase in concentrations occurred. The workers associated this buildup with the substantial increase in the industrial production of chlorinated organic compounds which also began about then, and they concluded that the input of dioxins and dibenzofurans probably

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resulted from the combustion of chlorinated organic precursors in waste products (27). They demonstrated similar analytical profiles between sediment and combustion effluents, in reference to congener content, as well as coincidences in industrial chemical production profiles for that period to support their conclusions. Obviously an important source of PCDDs and PCDFs in soil and sediments would be the uncontrolled burning of PCBs and chlorobenzenes. Perhaps the most notorious episode of combustion-generated dioxins and dibenzofurans would be the accidental transformer fire at the Binghamton, NY, state office building in 1981.

Due to similarities in physical characteristics of the PCBs, PCDDs, and PCDFs such as low solubilities, low vapor pressures, high boiling points, adsorption onto soils, chemical inertness, etc., their environmental transport characteristics are similar also. Vertical leaching in soil has been demonstrated to be less than nine inches and horizontal leaching is reported to be nil, especially in clay soils (11). A midnight dump site in Pierce County, Washington, however, allegedly has demonstrated a vertical penetration by Aroclors in rocky loam to a depth of at least 10 feet (39). If released into a water column, they would adhere either to suspended soils or accumulate in the surface sediment. Degradation by microorganisms, plankton, and fish in the lower trophic levels would not occur, but bioconcentration can occur and eventually could reach the higher trophic levels. Although accumulation occurs in liver, muscle, and fat tissues, there is doubt as to just which tissue should be used for bioconcentration calculations (11).

IV. ECOTOXICITY

Many well-controlled, small, animal and primate studies have produced values for acute and chronic toxicity levels of PCB, PCDD, and PCDF exposures. Although the studies have shown some of the compounds in these groups to be perhaps the most toxic chemicals for certain animals that man has synthesized, they also have shown a very wide sensitivity variance among species tested, as demonstrated below (7):

Animal	2,3,7,8-TCDD 30-day oral LC_{50} (ug/kg body wt)
Guinea pig	1
Rat (male)	22
Rat (female)	45
Monkey	<70
Rabbit	115
Mouse	114
Dog	>300
Bullfrog	>500
Hamster	5,000

This point is brought out in order to demonstrate the difficulty in extrapolating chlorodibenzo toxicity data from one taxon to another, even with such closely related ones as hamsters and guinea pigs (order Rodentia) which differ by a factor of 5,000. Tissue examinations also have demonstrated different efects with different taxa (7). Again in contrast, the acute oral toxicities of pure PCBs have been reported as follows: LD_{50} rat - 8.65 Gm/Kg for 42 percent chlorinated and 11.9 Gm/Kg for 54 percent chlorinated (17). These are single doses and not 30-day feeding concentrations.

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Although laboratory toxicity data may demonstrate the potential hazard of a chemical toxicant, applicability to the environment is somewhat invalid without ecological risk assessment information. This is especially important with toxicants such as the chlorodibenzo compounds which posssess such varied metabolic and toxicological patterns, transportability characteristics, and formation and transformation possibilities. The very low water solubilities of these compounds and their high lipophilic properties do not permit reliable short-term LC_{50}s or EC_{50}s for aquatic life. In this respect, it might be advisable to begin aquatic toxicological studies with the primary food source as the point which initiates exposure, and place greater emphasis on food pathways and bioconcentration, bioaccumulation, and biomagnification.

PCB toxicity values and bioconcentration factors for selected plant and animal species appear below (29).

Organism	Aroclor	Effect	Concentration (ug/L)
Anizosiphonia setiger (salt water alga)	1254	reduced growth	0.1
Monochrysis lutheri (salt water alga)	1254	reduced cell division	10
Dunaliella tertiolecta (salt water alga)	1254	increased cell division	10
Euglena gracilis (freshwater algal	1242	reduced cell division	10,000
Daphnia magna (freshwater cladoceran)	1254	lethal	1.2 to 24
Gammarus pseudolimnaeus (freshwater scud)	1254	lethal	2.2 to 8.7
Tantytarsus dissimilis (midge)	1254	lethal	0.5 to 1.2
Salvelinus fontinalis (brook trout)	1254	lethal	0.7 to 1.5
Crassostrea virginica (eastern oyster)	1016	reduced growth	10.2

Organism	Aroclor	Bioconcentration Factor
Cylindrotheca closterium (saltwater alga)	1242	1000
Dunaliella sp. (saltwater alga)	1254	30,000
Daphnia magna (freshwater cladoceran)	1254	1,800
Tetrahymena pyriformis (saltwater protozoa)	1254	50
Brachionus plicatil (saltwater rotifer)	1254	51,000
Culex tarsalis (mosquito)	1254	1,500
Crassostrea virginicus (Eastern oyster)	1254	8,100
Salmo gerdneri (Rainbow trout)	1254	46,000
Engraulis mordax (Northern anchovy)	1254	1,030,000

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The maximum allowable concentration of PCBs in fish and shellfish tissue as regulated by the U.S. Food and Drug Administration is 5.0 mg/kg (29).

As mentioned earlier, each Aroclor is composed of many different PCB congeners, and each seems to possess its own bioconcentration characteristics. Storage of the congeners within tissue also is dependent upon metabolic activity and upon excretory capability. Extensive and complex studies have been made on many types of animal tissue concerning specific assimilation rates and retention times of PCBs, but in the interest of simplifiction a few generalizations can be made. PCB metabolism depends upon the degree of chlorination and upon the chlorine substitution pattern. Assimilation and excretion rates decrease with increased chlorine content (18, 20). The less planar (ortho substituted chlorines) are less soluble in fatty tissue (30). Congeners which possess unsubstituted vicinal (adjacent) carbon atoms are more rapidly eliminated (20).

Many reports have been presented describing the on-site hazards of PCBs relative to plants and subprimate animals, but because the presence and effects of interfering substances has not been ruled out in these cases, PCB hazard cannot be verified. In an effort to overcome this deficiency, the Health and Environmental Review Division of the EPA's Office of Toxic Substances has assembled data concerning controlled laboratory studies with pure substances (30). A few segments of this report are presented below:

- o PCBs decrease the rate of photosynthesis in different species of algae, affecting production and phytoplankton communities.

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- The no-effect concentration of pure PCB congeners to ciliated protozoa appears to be about 100 ug/L or greater.

- Toxicity to aquatic invertebrates increases with increased chlorination and reaches a maximum with the tetrachlorobiphenyls in the range of 30 to 700 ug/L. PCBs can result in reproductive failure of aquatic invertebrates.

- Toxicity to fish increases with increased chlorination up through the hexachlorobiphenyls and appears to increase an order of magnitude with each added chlorine. Experimental data have demonstrated that PCBs can reduce spawning, hatching, and survival of many species of freshwater fish.

- Laboratory studies have demonstrated that 10 mg/kg in the diet of doves and pheasants caused early embryonic mortality and reduced egg production. High PCB residues have been found in certain aquatic birds which have shown population declines, but no cause-and-effect relationship has been determined.

- Dietary exposure of mink to 5 mg/kg PCBs has caused reduction in the number of kits, and reduced the survival of kits.

Dermal studies with rabbits using commercial Clophen A 60, Phenoclor DP6, and Aroclor 1260 rather than pure PCB congeners demonstrated fairly severe skin lesions including hyperplasia and hyperkeratinosis of the

epidermal and follicular epithelium as well as pathological changes in the liver and kidneys from exposure to the Clophen and Phenoclor. Although exposure to the Aroclor demonstrates a similar pathological picture, the symptoms were much less severe (11, 29). Additional studies on chick embryos using the same chemical products demonstrated high mortalities from the Clophen and Phenoclor, but no mortalities from the Aroclor. Chemical analysis of polar fractions from all three products demonstrated the presence of tetra- and pentachlorodibenzofurans as well as chlorinated naphthalenes in the Clophen and Phenoclor but none in the Aroclor (11). The investigators calculated 5 mg/kg of chlorinated dibenzofurans to be present in the Clophen and 20 mg/kg in the Phenoclor. They concluded that the chlorinated dibenzofurans mainly were responsible for the toxicity of the products and that the chlorinated dibenzofurans were about one order of magnitude less toxic than chlorinated dibenzodioxins (11).

Laboratory studies on non-human primates using Aroclors rather than pure biphenyl congeners have demonstrated these subjects (especially Rhesus) to be quite sensitive to the Aroclors (29). With male Rhesus monkeys fed 300 ppm of Aroclor 1248 in their diet for three months, effects began appearing within one month which included hair loss, subcutaneous edema, purulent eye discharges, acne-form eruptions, liver hypertrophy, and invasion of gastric sub-mucosa by proliferating mucosal epithelium.

The above toxicity data have been selected as representative of the great number of studies involving PCBs. They are being presented in an

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effort to emphasize the chronic (long-term) effect of PCBs versus the acute (short-term) effect. In fact, many workers seem to believe that the acute toxicity of PCBs is no greater than other chlorinated aromatic compounds. One unbiased worker has stated that "all studies of PCBs in animals indicate that acute toxicity is not a significant factor" (12). Perhaps part of this could be due to the demonstrated pathological reversability of short-term effects of the products as well as their resistance to metabolism. It is the slow buildup in the living system until their concentrations reach a toxic level that chronic effects become evident (12).

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V. HUMAN TOXICITY

Of great concern, naturally, are the human effects of the PCBs, CDDs, and CDFs. It is at this stage in this discussion that a transition occurs from animal studies to human toxicities. In animal surrogate protocol, the subjects are exposed to absolute quantities of pure substances under standard conditions and the effects noted then confirmed, perhaps by other workers in other species. Interferences are ruled out. Commercial PCBs are not pure substances. Metabolism, tissue storage, and physiological effects appear inconsistent even in the same species. It is not really known if the chemical itself or a metabolite is the toxicant. The half-life of stored material in fat tissue is affected by exposure time, concentration, and congener ratio. Effects are not specific nor clearly reproducible. The symptoms of these products, including chloracne, are traditional chloroaromatic exposure responses. In relation to human toxicity, several researchers have expressed opinions:

- "Clearly, there is preferential elimination and retention of specific PCB isomers and congeners; this fact, coupled with the limited knowledge of the structures of the individual components and their toxicity, has made the quantitation and health hazard assessment of human PCB levels a difficult if not impossible task" (20).

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- "Therefore, it appears that PCBs are not a remarkable toxicant, but a chemical which requires high doses to produce harmful effects and one which clearly represents minimal or no risk to humans because of the limited nature of anticipated human exposure. While PCBs can be toxic, and their toxicity can be dramatically increased by high levels of dibenzofuran contamination, the mammalian toxicity data suggest that, in general, PCB mixtures can be tolerated under most real-world conditions" (31).

- "...the Yusho exposures (Japan, 1968, and Taiwan, 1979) have served to emphasize two points made in the 1982 report. First, it appears that elevated PCDF levels in the cooking oils may have been a principle (sic) cause of the enhanced toxicity of those oils over that of the parent commercial PCB mixtures originally charged into the heat exchangers. Second, because of the mixed PCB:PCDF:PCQ content of those oils, the Yusho episodes are not appropriate models for prediction of human health effects from exposure to commercial PCB mixtures" (32).

- Two NIOSH workers have stated, 1) "The (study) results showed no significant excess in total mortality from cancer, cardiovascular disease, neurological manifestations, or any other cause. The overall mortality was low; overall cancer death was lower than that of the general population. <u>If PCBs are carcinogenic, they are weak agents in humans</u>" (33). The foregoing study involved 2,500 PCBs-exposed workers from two capacitor manufacturing

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plants, 50 percent of whom were exposed on the job from 20 to 40 years. 2) "None of the published occupational and epidemiological studies (including our own) have shown that occupational exposure to PCBs is associated with an adverse health outcome, except for the occurence (sic) of chloracne during the early years of its manufacture and use, and possibly during current times as well, depending upon circumstances of its use and exposure" (33). This study involved workers from a capacitor plant and two electrical utility plants that loaded transformers with PCBs.

Today, interest in the environmental exposure of askarels and chlorophenoxy pesticides is being focused upon spills and upon thermal degradation products rather than upon occupatinal exposure to the commercial products. This change more or less emphasizes the role of chlorinated dibenzodioxins and -furans as the main toxicants. Due to the extreme toxicity of these two isostereomers on researchers as well as test animals, controlled exposure and effect data are somewhat difficult to assemble. Two methods of overcoming this problem are by demonstrating body enzyme response to minute exposure and by case histories of past accidental exposures.

During the past few years, considerable emphasis has beenm placed upon enzyme induction studies in relation to the potency of chlorodibenzodioxins and -furans as chemical toxicants. "The most important observation from these studies, however, is that for chlorinated dibenzo-p-dioxin congeners there is an excellent correlation between their potency

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to induce Aryl Aromatic Hydroxylase activity and their potency as a chemical toxicant. Subsequent studies have noted a similar correlation for congeners from other classes (chlorodibenzofurans) of halogenated aromatic hydrocarbons" (37).

3-Methylcholanthrene (3MC) is the hydrocarbon prototype normally used in cytochrome P_1450 induction studies; TCDD checked out as approximately 30,000 times as potent as 3MC, and caused the enzyme to remain in the tissue five times as long (37).

The geometry of the substrate affects the ease with which it will combine with the "pocket-type" receptor-inducer. It needs to be a generally planar, wafer-thin parallelpiped sized to fill a rectangle 10 angstroms long and 3 angstroms wide; halogen atoms occupy at least three, and for maximal potency, four, of the outer corners of the molecule; at least one ring position is unsubstituted (37).

A simplified version of the enzyme induction process used in these studies can be described as follows: Upon entrance of the aromatic hydrocarbon into the body cell, it is intercepted (and pocketed) by an aryl hydrocarbon binding receptor protein present in the cytosol which translocates it into the nucleus where a DNA molecule unwinds slightly to expose a sited gene or system of several genes, the Ah locus, which attracts the receptor-bound substrate, then alerts a messenger RNA molecule to transcribe a signal to the microsomal monooxegenase system present in the outer endoplasmic reticulum of the nuclear membrane to

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induce the synthesis of a special cytochrome P1450 enzyme to catalyze AHH activity upon the remaining hydrocarbon species present in the cytoplasm. A reactive intermediate is then produced which can form an inoccuous product for excretion, or possibly become a toxic compound targeted for other body cells with toxic consequences.

The detoxication of halogenated hydrocarbons normally occurs in liver tissue and this is where the Ah receptors and Ah locus usually are located; however, they also have been demonstrated in the cytosol fraction of rat lung, thymus, and kidney tissue as well as lower concentrations in testis, brain, and skeletal muscle (37). The Ah locus also has been found in mouse, guinea pig, hamster, rabbit, chicken, and monkey liver tissue. The Ah receptor has been demonstrated in human tissue and thus is available to mediate the toxic effects of halogenated dioxins (40).

Although the "pocket" theory for substrate binding seems to be in general acceptance, it cannot account for Ah receptor binding in certain substrates with obvious structural differences. A second theory, the "stacking" or layering of effector (substrate) molecules upon the receptor molecules, is emerging. This hypothesis is based upon molecular polarizaiton and equilibrium separation between effector and receptor and does not depend on substrate geometry for binding. The theory is still quite hypothetical, in fact a second receptor is being proposed for its implementation (38).

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VI. CONTAMINATION EPISODES

The introduction of chlorodibenzodioxins and -furans into the environment by any inadvertent sources has been and is being investigated and documented. A few of the sources are municipal incinerators, industrial plant waste streams, transformer and capacitor reclaimers, waste disposal sites, photochemical cyclization of predioxins, etc. Numerous accidents, however, have occurred throughout the world in which the chlorodibenzo toxicants have been released, some with disastrous results. A few case histories have been selected which represent episode types and consequences.

Chick Edema

Chick edema disease is an accumulation of fluid in the pericardial sac, the peritoneum, and subcutaneous tissue of fowl. It was first described in 1957 in the southeastern United States following the incorporation of toxic fat supplement into the feed of broiler chickens. The fats later were identified as commercial oleic and stearic acids produced from inedible tallow recovered from fresh animal hides. Trichlorophenol and pentachlorophenol had been used in curing the hides. Nearly eight years after discovery, the processing chemicals were analyzed and toxic levels of tetra-CDD were detected in the trichlorophenol, and toxic levels of hexa-CDD were detected in the pentachlorophenol. The acute symptoms were dyspnea, stunting, and paleness of comb; often times sudden death occurred.

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Tissue examination revealed hydropericardium, subcutaneous edema, and liver necrosis. A single episode in North Carolina resulted in the destruction of more than one million chicks. Additional outbreaks have occurred in different areas of the United States and in Japan.

Vietnam

Although small-scale tactical applications of herbicides had been practiced by the Armed Forces since 1944, the first large-scale trial application occurred at Fort Drum, New York, in 1959 and demonstrated the feasibility for large-scale defoliation trials in tropical Southeast Asia. On January 9, 1962, the first shipment of several types of herbicides arrived in Vietnam for aerial field evaluation. This tactical military evaluation and application procedure, termed Operation Ranch Hand, eventually selected the phenoxy herbicides and picloram as most suitable for defensive and offensive strategies, and began large-scale aerial applications in 1965 which were to last for six more years. The defensive role was defoliation and the offensive role was food crop denial (25).

In the late sixties, however, non-military scientific studies indicated that 2,4,5-T was a teratogen in certain animals. This prompted the Secretaries of Agriculture; of Health, Education, and Welfare; and of the Interior jointly in April 1970 to announce the suspension of certain uses of 2,4,5-T. Subsequent studies revealed that the teratogenic effects were caused by an inadvertent contaminant identified as 2,3,7,8-tetrachlorodibenzo-p-dioxin. As a result, the Department of Defense

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suspended the use of Herbicide Orange in February 1971. This herbicide was one of about 15 different formulations evaluated and used by the U.S. Armed Forces in Vietnam since January 1962; eventually Herbicide Orange had replaced all but Herbicide White and had become the most widely used defoliant in South Vietnam (25).

Herbicide White did not contain 2,4,5-T, but was a one-to-four mixture (active ingredients) of picloram and 2,4-D. Herbicide Orange was a 50:50 mixture of the n-butyl esters of 2,4,-D and 2,4,5-T dissolved in diesel oil. The butyl esters were used in order to take advantage of their volatile characteristics and ability to penetrate the forest canopy during the aerial spraying. Three other herbicides (Purple, Pink, and Green) containing 2,4,5-T also were used to a limited extent during this operation. A total of 44,232,600 pounds of 2,4,5-T were estimated to have been disseminated in South Vietnam from January 1962 through February 1971. The mean TCDD concentration in Herbicide Orange was estimated at 1.98 ppm; in Herbicide Purple, 32.8 ppm; and in Herbicides Pink and Green, 65.6 ppm. A total of 368 pounds of TCDD are estimated to have been applied to about three million acres in South Vietnam during Operation Ranch Hand (25). In September 1971, the Department of Defense directed that all remaining stocks of Herbicide Orange be consolidated for disposal. A total of 1.37 million gallons were transported from South Vietnam to Johnston Island in the North Pacific Ocean for dedruming and staging. An additional 850,000 gallons were transferred from Gulfport, Mississipi, to a designated site in the North Pacific where the Dutch-owned ship M/T Vulcanus contracted to receive and incinerate the entire 2.22 million gallons of product.

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While Operation Ranch Hand was in progress, several evaluations were performed by civilian groups in cooperation with the Department of Defense concerning the ecological effects of the herbicide applications. Very briefly, a few conclusions include:

1. The end result of the use of herbicides from an ecological standpoint is that the ecosystem is set back to an earlier sere; i.e., an earlier stage of plant succession.

2. The defoliation program has caused ecological changes. These changes are not irreversible but complete recovery may take a long time.

3. The effects of defoliation on animals is not known, but it does not appear to have been extreme. There is no evidence to suggest that the herbicide used in Vietnam will cause toxicity problems to man or animals.

4. ...it is difficult to predict effects on wildlife with any accuracy (25).

In the last week of June 1969, however, the first reports of human birth defects allegedly attributed to Herbicide Orange began to appear in Vietnamese newspapers. The public and scientific furor caused by these reports resulted in two surveys of hospital records as well as a few population studies concerning the human hazards associated with these

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herbicides. During the next four years, investigations, surveys, charges, and countercharges were made, but due to the after-the-fact limitations of the investigations and reporting, no valid conclusions could be made. In 1974, the National Academy of Sciences (NAS) announced the results of studies conducted in South Vietnam in 1972 and 1973. The NAS committee could find no conclusive evidence of association between exposure to herbicides and birth defects in humans (41).

Yusho and Yu-Cheng

Yusho and Yu-Cheng are English terms for two mass food poisoning incidents caused by the igestion of commercial deodorized rice-bran oils contaminated accidentally with polychlorinated biphenyls, polychlorinated dibenzofurans, and polychlorinated quaterphenyls during the manufacturing process. The rice oil was used mainly to prepare tempura in the home. In all respects the two incidents were very similar except the Yusho incident occurred in southwestern Japan, mainly in Fukuoka and Nagasaki Prefectures in 1968, while the Yu-Cheng incident occurred 11 years later in west-central Taiwan, mainly in Tai-Chung and Chang-Hua Counties.

In the commercial deodorization process, the rice-bran oil was heated to about 230°C in a tubular heat exchanger for a prolonged period under vacuum. Kanechlor 400 allegedly was used as the heat-exchange medium in both cases. This material contained 48 percent chlorine by weight, which demonstrates pure PCB. Comparative analyses of the Yusho Kanechlor before and after the heat exchange showed a 250-fold increase of

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