Comments and Studies on the Use of Polychlorinated Biphenyls in Response to an Order of the United States Court of Appeals for the District of Columbia Circuit

submitted by

The Utility Solid Waste Activities Group,

The Edison Electric Institute

and

The National Rural Electric Cooperative Association

to

The United States

Environmental Protection Agency

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Volume II
Potential Health Effects in the Human from Exposure to Polychlorinated Biphenyls and Related Impurities

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XII. EQUIPMENT LIST, contd.

Closed Tanks, contd.

CT-0767 contd.

Steam traced vent to drum outdoors.
Manlid. Dipping hole with cap.
Fixed overflows at 4 levels back to diphenyl store tank CT-0748 by steam traced line with sight glass and right angle cross pieces with blank flanges.

Lower part of vessel jacketed for steam from the 70 lb. main. Angle thermometer 30" long through side of vessel. Bottom outlet to header leading to the 4 chlorinators. S. G. at each chlorinator.

CT-0768 # 3 Aroclor 1260 finished product storage tank. Made by Grever. Dwg. C-609. Horiz. steel 10' dia. x 26' long on straight side, dished heads, shell ½", heads 9/16". Test tank 60# and coil 300# Hydro. Press. Coil 2" xHy pipe with 1" xHy risers. Welded construction throughout. All inside and flg. surfaces, coils, supports, etc., to be sprayed first .005" zinc and then .003" tin. Same as CT-0769. Order B7711 on 4/17/36, Req. 69231. Chg. out $1385.00. $CaCl_2$ vent trap.

CT-0769 # 4 Aroclor 1254 Finished Product Storage Tank. Same as CT-0768.

CT-0770 Tubular heat exchanger made by Nooter. Dwg. B651, Plant A, Size 12" dia. x 5'0" lg. having 19 x 2" OD 11 ga. Monel Tubes, Monel tube sheets, Monel reducer and carbon steel jacket and back-up rings on flanges.
Order B5848 on 5/1/36. Req. 69605. Price $660.00
Above No. 1 still 8043, supported by 3rd floor steel.

Plant "B" (Krummrich Plant) continue to recommend monel for the condensers on the vacuum stills. See also item CT-01378.

Only monel in contact with the goods on the "descending" side of the condensing system.

XII. EQUIPMENT LIST, contd.

Closed Tanks, contd.

CT-0770, contd.

Mr. Thrift, December 5, 1949, raised the question of the necessity of using monel for the vacuum still condensers and subsequent vessels. Mr. Ellenburg of Anniston replied, 15th December, 1949, stating that iron contamination of the Aroclors would have a bad effect on the resistivity and the power factor of the products. Steel also hastens the darkening of Aroclors at temperatures of 80°C. or higher.

Messrs. Hodges and Barbre of the Krummrich plant replied that monel was satisfactory for the condensers and receivers but that there were no reasons to believe steel would not be satisfactory. Although General Electric Company report that steel is satisfactory for storage and treatment vessels, Krummrich plant do not care to risk the use of steel because of the high standards required by G. E. for Aroclors.

CT-0771 Monel vacuum receiver made by Nooter. Dwg. C-795. (Plant A). Size 5'6" dia. x 5'6" str. side, 3/8" shell, ½" bottom and removable head, 4 support brackets on outside of tank of steel. 2" IP size xhy Monel coil with 2" inlet and 1" outlet with Monel bars and U bolts. 3 turns 5' dia. along side and 3 turns spiral on bottom. 60# Hyd. test on tank and 300# on coil.
Order B7379 on 4/24/36, Req. 69118. Price $3240.00.
On second floor level, 12' level, Bldg. CR.
No. 1 still. Return line, for spoilt material, to the still
of the vacuum still receivers
The covers/carry the following connections:

Inlet from condensers CT-0770, 01378 via sight glasses.

The cylindrical surface of the sight glass fitting is steam jacketed and so is the pipe from the condenser to the sight glass.

Manlid with hand hole and dipping opening.

XII. EQUIPMENT LIST, contd.

Closed Tanks, contd.

CT-0771 contd.

Dial vacuum gauge and mercury U-gauge.

Thermo recorder well.

Vent cock.

Steam coil in and out. This coil goes well down into the bottom dish of the receiver.

Vacuum line to the top of coke scrubber CT-0753 and -01396.

Bottom outlet to pump P-0984 for delivery to the Sparkler press and to Blackmer pumps, P-0565, -01037, for delivery to the blending tank, CT-0779.

Electric strip heaters to drawing C-847, formerly used on these vessels have been abandoned, so no copy of the drawing has been requested for MCL. Material 1268 requires M. P. steam in the coil to keep it molten.

There is only one receiver for each vacuum still in the crude room, no fractionation being attempted.

There is no gauge glass or level indicator, only a gauging hole.* A receiver will hold a full batch from the still.

CT-0779 #1 blending tank made by Graver. Dwg. B-862. Welded steel tank 7' dia. x 7' high dished heads ¼", shell 3/8". All inside surfaces and nozzles sprayed .005 zinc then .003 tin. 2" xHy pipe coil and supports. Yoke and drive supports. Cast bronze turbine stirrer and bronze shaft. Test tank 60# and coil 300#, hydrostatic Pressure.

Order B7707 on 4/17/36, Req. 69227, Chg. out $599.00. On 2nd floor level, 12' level, Bldg. CR. Same as CT-0780

*But see page 21, section VI.

XII. EQUIPMENT LIST, contd.

Closed Tanks, contd.

CT-0779 contd.
See also CT-01399, #2 Blender and CT-0780, Filtrate Receiver.

Drawings E-862 and E-6838 are essentially the same. Drawings A-459 and A-6853 of the bearing have been requested. Drawings D-2076, 2077, show the agitator rotor and stator.

Anniston, December 15, 1949, state that their blenders are of steel, sprayed with zinc then with tin and that the agitator in one case is of Tobin bronze (stated to be 60% Cu. 39.25% Zn, 0.75 Sn), and in the other case is of steel, sprayed with zinc then with tin.

The sprayed agitator is said to be satisfactory. Plant "B", January 5, 1950, state 0.005" Zn then 0.003" Sn for the tanks, and their agitators are of bronze of unknown composition, probably "ordinary commercial bronze". Anniston and Plant "B" agree in distrusting plain steal for these vessels. Anniston suggest Aluminium.

CT-0780 #1 filtrate receiver tank. Dwg. E-862. Made by Graver. Welded steel tank 7' dia. x 7' high, dished heads ¼", shell 3/8". Same as CT-0779.

Materials 1260 and 1254 can be run from the receivers CT-0780 and 01400 to bulk store tanks. Other materials are filled off into drums.

To save time, most of the control tests are done on samples taken before filtration.

Material 1268 needs H.P. steam to keep it fluid.

The filtrate receivers are like the blenders CT-0779 and 01399 except that the filtrate receivers have no agitators.

XII. EQUIPMENT LIST, contd.

Closed Tanks, contd.

CT-0785 Middle acid tank south of CR on foundation. Made by Goodrich. Dwg. C-823. "Vulcalok" lines - steel tk. 7'0" ID x 8'6", shell 5/16", dished head 5/16", bottom 7/16", 4" outlet for safety plug on bottom. 18" manhole and cover, 5 - 5" flgd. outlets in head, 3/16" Triflex lining, rubber covered float and card for measuring device. Head with 6 - 1½" couplings for railings. Order B9983 on 5/19/36, Req. 69966. Chg. out $945.65. South of CR on foundation. Same as 0784 and 0786.

CT-0786 West acid tank, same as CT-0784 and 0785.

CT-0808 Storage tank and chlorinator with stirrer and gas burner. (Gas fired chlorinator). Made by Kilpatrick and Sons Fdy. Co. Dwg. A324. Cast Iron, 6' ID x 4'11" deep inside, wall 2" thick, bottom 3" thick and dished in 3". 3" outlet at lower rim. Marked S-459, weight 12,675#. Machining outside of top flange but without holes and machining outlet in rim including drilling and tapping holes. Cost of machine work $36.00. Order B8162 on 4/24/36, Req. 69398, Cost $517.65. On 12' leval SW corner Bldg. CR. Drawing C830 gas heater on exit-line.

Subsidiary drawings:

Pr. relief door on 6'0" CI storetank	B-613
Clamp for electric strip heater	B-684
Vent for CI tank	B-686
Shear pin unit -- for drive on agitator	C-605
Brick setting	P-867
Drive for stirrer	E-888
8'3" x 10'11" steel shell for tank	E-881
Vent stack for still heater	B-689
Still heater	E-886

This gas-heated chlorinator is also called S-0459. The chlorine enters the gas-fired chlorinator through a perforated pipe ring, and there is a separate inlet pipe

XII. EQUIPMENT LIST, contd.

Closed Tanks, contd.

CT-0808, contd.
with a simple open end for use when the perforated pipe becomes choked.

The cover carries a wide neck through which material recovered from the monel catch vessel CT-01258 can be returned by means of a wide steel funnel. There is another neck, wide enough to admit a sampling bottle - also used as a gauging hole. Inlet from #1 chlorinator CT-01283 by a gas-heated gravity line or via pump P-0907 through lines with H. P. steam tracing.

9" monel duct, with cleaning flanges, rises at 45° from the chlorinator cover, then descends at 45° to the monel gas chamber CT-01258. From the monel chamber onwards the ducting to the scrubber is of steel with cleaning flanges.

Compressed air connection into the chlorine inlet for clearing (not very successful).

Agitator with water cooled stuffing box. Thermo recorder well. Bottom outlet with gas flame heating, to the retort vessels R-026 and R-027 in an adjoining lean-to building.

See Drawing E-867 for the furnace setting,
E-881 for the steel casing of the setting
E-888 for the drive
C-605 for shear pin for drive
E-613 for pressure relief door on furnace
E-886 for vent stack,
P-324 which shows a shallower vessel; the chlorinator pot is similar but is 4'11" deep.

The final chlorination to high chlorine content is more easily done in this separate chlorinator because higher temperatures are needed to keep the charge molten.

XII. EQUIPMENT LIST, contd.

Closed Tanks, contd.

CT-0808 contd.
Drawings B-684 strip heater
B-686 clamp for strip heater
B-689 vent stack for furnace

have not been requested as they are not of interest.
Strip heaters are not now used.

CT-0831 Water condenser made by Heine Boiler Company. Dwg. B483 (Plant A), used as temperature control for Aroclor condenser CT-0770. 12 tubes, 1" OD - 10 GA seamless steel tubing 10'-0½" long, 10'0" overall length of 6" std. pipe shell single pass. Order B8773 on 5/11/36, Req. 69576, Price $98.00.
Used on #1 vacuum still.
Safety valve on shell.

CT-0833 Chlorinator puchased from Leader Iron Works. Size 3' dia. x 16' made up complete including coils, inner shell, and grating. Dwg. E-880 and B-659. Order B-2813 on 2/5/37, Req. 76475 on 1/26/37, chg. out $790.00 on 3/31/37.
East chlorinator. #3 chlorinator. See CT-0744.

CT-0848 TCB stg. Tank. Made by Graver.
Tank dwg. E 4413
Coil C4412 for steam
General E4366
Tank 8' ID x 25'6" long welded. 3/8" shell, 7/16" dished heads. 13-26" and 2-24" dia. manhole openings on top.
2-1" xhy. W. S. pipe coil, 71' approx.
Order B3634 on 2/17/37, Req. 76931 on 2/12.
Price $920.00 West of CR underground. Pyranol Plant.

CT-0852 Raymond 2 stage cyclone dust collector sent to B by Anniston Plant. Each cyclone approx. 20" dia. - 21" str. section 32" depth of cone, steel construction, used with B-0105. In lean-to of building CR. No drawing.

XII. EQUIPMENT LIST, contd.

Closed Tanks, contd.

CT-0968 Scrubber liquor pump tank purchased from Hooter. Dwg. C-4616. Steel vertical jacketed, size 4'6" ID x 5'6" long with jacket.
Order B15673 on 8/2/37. Req. 81458 on 8/2/37.
Price $575.00.

CT-01013 #1A scrubber liquor pump tank made by Leader. Dwg. C-4616. Size 4'6" ID x 5'6" vertical, steel, flange quality, all welded. Jacketed.
Order B 4164 on 4/29/38, Req. 87029 on 3/9/38.
Price $582.00 On 38' level SE corner CR.

CT-01014 Scrubber tank made by Heintz. Dwg. C-4845. Steel 12" dia. std. wrought steel pipe 10'10" high, ½" dished end and other end fitted with 3/4" faced and drilled flg. with 5/8" cover plate. Steel plate, and distributor. Use 5 cu. ft. 1" CI Raschig rings pkg., Order B3933 on 3/4/38, Req. 86921 on 3/4/38. Price $139.00. On top of CT-01013, #1A scrubber.

CT-01162 Scrubber tank made by Heintz. Dwg. C5743. Welded steel scrubber, size 12" ID x 5'.
Order B19519 on 9/27/39, Req. 1977 on 9/19
Price $102.00. Vent line to CT-0848. (*)

CT-01163 Catch Tank 55 gal. steel drum.
For CT-0762. Rate to CT-01164. Chg. out $11.40. 11/27/39. (*)

(*) Both CT-01162 and CT-01163 are on vents of CT-01321 and 02621, Pyranol Plant.

CT-01164 Catch Tank. Same as CT-01163.

For CT-01162, Pyranol Plant

XII. EQUIPMENT LIST, contd.

Closed Tanks, contd.

CT-01258 Monel gas chamber made by Nooter. Dwg. C-5825. 4' dia. x 4' high constructed of Monel. Order B7835 on 4/3/40, Req. 8061 on 3/27/40, Req. 8061 on 3/27/40. Chg. out $867.00. On gas exit from fire heated chlorinator.

This monel vessel is at the lowest point of the gas exit line from the gas-heated chlorinator. Solid Aroclor which collects in it is removed by hand and returned to the chlorinator with a subsequent batch.

CT-01259 Cyclone Tank made by Heintz. Dwg. B5821. 2'6" dia. x 6'7" high constructed of 3/16" steel plate. Order B7345 on 4/27/40. Req. 8062 on 3/27/40. Price $92.00. Hang from roof of Bldg. on 38' level.

CT-01259,01279, 01280, 01281, 01282, cyclones on chlorinator off-gas, follow the scrubbing towers CT-0759 etc. Drain through S. G's to the return seal pipes between towers and circulation tanks. Off-gas to the main leading to the HCl absorption systems.

See drawing B-5821 (This drawing not yet found April 5, 1947). See drawing B-660.

CT-01263 Monel condenser made by Nooter. Dwg. C-6144. 42" dia. x 63" high cone bottom condenser constructed of 3/16 Monel metal welded construction throughout. Order B-8364 on 4/9/40. Req. 8198 on 4/1/40. Price $928.00

This vessel is obsolete.

CT-01279 Cyclone separator made by Nooter Dwg. 5821. 2' dia. x 6'7" high cyclone separator made of steel and welded throughout. Order B13177 on 6/12/40. Req. 10232 on 6/5/40. Chg. out $66.25. For use at CT-0968.

XII. EQUIPMENT LIST, contd.

Closed Tanks, contd.

CT-01280 Cyclone separator made by Nooter. Dwg. B-5821. 2' dia. x 6'7" high cyclone separator made of steel and welded throughout. Order B13177 on 6/12/40. Req. 10232 on 6/5/40. Price $66.25/ At CT-0762 east scrubber.

CT-01281 Cyclone separator. Same as CT-01279 and 1282. At CT-0759. 2nd from E scrubber.

CT-01282 Cyclone separator. Same as CT-01279 - 1280 - 1281. Used at CT-0760. 3rd from E scrubber.

CT-01283 Chlorinator made by Leader Iron Works, Inc. Dwg. B6209, 3' x 16' steel vertical chlor. welded const. Order B-14119 on 6/21/40, Req. 10408 on 6/11/40. Price $720.00 East of CT-0833. #4 chlorinator. See CT-0744.

CT-01310 #5 Aroclor 1260 Storage Tank made by Leader Iron Works. Dwg. C-609. Horizontal 10' OD x 26' long on str. shell, incld. coils, etc. Omitted 2 - 3" nozzles changed 18" noz. to 24" and added covers for 24" noz. Tanks, coils, coil supports, inside of noz. and manholes and manholes and noz. and inside covers must be sprayed with zinc 0.005" thick followed by a sprayed coat of 0.003" tin. Order B13240 on 6/11/40, Req. 10432 on 6/11/40 Price $2200.00. Underground S of CT-0848. Pump P-0929.

CT-01321 Pyranol Mixing Tank made by Nooter.
Drawing D6455.
14' OD x 10' high steel tank with 3/8" shell, 1/2" std. knuckle radius heads, entire interior sprayed with min. thickness of .015" tin.
42" Quadruplex turbo mixer complete including Turbo adaptor assembly -- off set from centre.

(1) Order B20976 on 9/27/40. Chg. out $2930.00
(2) Order B21762 on 10/8/41, Req. 13664, Cost $740.00

TABLE OF CONTENTS

XII. EQUIPMENT LIST, contd.

Closed Tanks, contd.

CT-01321 contd.

Driven by MSC-01288, Motor M01718.
1½" steam coil, 45 turns, 18" diameter, through the cover.
9600 Imp. gallons. Outdoors. Everdur or galvanized piping. Bronze valves.

Bottom outlet to Taber pump P-01540 delivering to filter press P-0159. Capped inlet on cover for Attapulgus Earth. Manlid. Steam coil. Dial thermo. Vent to soda-lime vent box. Heat insulation (gons).

CT-01377 Still receiver tank made by Nooter. Dwg. C-795, B-7082, like CT-0771. PA #145. 5'6" x 5'6" Monel metal receiver, complete with cover, coil, etc. Glass wool insulation 2" and ½" finished coat.
Order B4137 on 6/27/41, Req. 18315 on 2/17/41.
Price $3295.00. NE corner of 12' level platform in Bldg. CR. Is used on #2 still S-062.

CT-01378 Condenser tank made by Nooter. Dwg. B651.
12" ID x 5' long Monel metal.
Order B4137 on 10/20/41. Req. 18315 on 2/17/41.
Price $650.00 W of CT-01413 on 20'6" level platform, Bldg. CR. Like CT-0770. Used on #2 still.

CT-01396 Vacuum scrubber purchased from Combustion Engineering Co.
Drawing C-807. 3' ID x 10' high, steel construction including grating and screen.
Order B8360 on 4/4/41, Req. 19989 on 4/4/41
Price $260.00. N one on 29' platform.
Like CT-0753. On #2 still, coke scrubber.

CT-01397 Water heat exchanger made by Leader Iron Works.
Dwg. B-483. 6" dia. x 10' long, 12 tube.
Order B8324 on 4/4/41, Req. 19993, Price $119.00
North of CT-0831. On #2 still. Spare.

XII. EQUIPMENT LIST, contd.

Closed Tanks, contd.

CT-01398 Cooler tank made by Leader. Dwg. B644.
2'6" ID x 3' high steel cooler tank complete with coil.
Order B8324 on 4/4/41, Req. 19993. Price $152.00
South one on 29' platform
Used on #2 still. Vented.

CT-01399 #2 blending tank made by Nooter. Dwg./D-10290, general arrangement. 7' ID x 7' high, complete with coil, agitator, and drive support, zinc and tin lined, seams to be chipped and ground smooth.
E-6839 and
Order B8325 on 4/4/41, Req. 19990 on 4/4/41
Chg. out $950.00. Driven by M-02170. Middle one of 3, north end of 12' level platform.
Vertical bearing for agitator shaft, A-6853.
Compare CT-0779.
Newport experience shows the need for adequate heating and agitation in blending higher Aroclors.

CT-01400 #2 filtrate receiver, made by Nooter.
7' ID x 7' high incl. coil and supporting legs.
Inside of tank zinc sprayed, all seams chipped and ground. 1" glass wool insulations 2½" fin. coat.
Order B8323 on 4/4/41, Req. 19992, Price $925.00
West one of 3 north end of 12' level platform, CR.
Dwg. C-6863. See CT-0780.

CT-01413 Separator tank made by Heintz Steel. Used on #2 still.
Dwg. C6957. 3' ID x 6' high tangential separator with integral vapor pipe complete.
Order B10722 on 5/9/41, Req. 20429 on 5/1/41.
Chg. out $382.50. North one on 29' level platform Bldg. CR.

CT-01432 5th chlorinator. See CT-0744. Nooter. Drawing B6209.

CT-01491 Heat exchanger tank made by Leader Iron. Dwg. B483, CABI #217. 6" dia. x 10' long, all steel, 12 tubes
Order B21479 on 9/19/41, Req. 24894 on 9/19/41.
Chg. out $140.00. Used on #2 vacuum still system.

XII. EQUIPMENT LIST, contd.

Closed Tanks, contd.

CT-02086 Air blowing tank. Like CT-0750.

CT-02404 This store tank has been set up outdoors to hold the tri-tetra-chloro benzene mixture, which is bought in rail cars and unloaded by pump P-01111. The tank is a vertical cylindrical vessel 13'0" ID, 20'0" high on straight side with dome top and bottom.
Total capacity 20,000 U.S. gallons. It has a bottom outlet, with a strainer box, to pump P-02077 delivering to either of the Pyranol blending tanks. The tank has a Varec depth indicator with stainless steel exposed parts, a vent pipe, a dip pipe for air blowing, an internal steam coil, and external heat insulation.

NOTE: Mr. Barbre, 1947, said that a batch tank to hold filtered Pyranols, pending final approval, would be a convenience.

CT-02621 An additional blender, CT-02621 has been installed outdoors for making Pyranols. It is a vertical cyclindrical steel tank 10'6" ID 23'0" high with flat top and bottom. Total capacity 14,800 U.S. gallons. The bottom slopes 2" to the bottom outlet, which leads through a strainer box to a Taber pump P-02179, delivering to the filter press, P-0172.

The tank has a 7½ H.P. Lightnin mixer installed horizontally low down through the straight side, the exposed parts of the mixer being metallized with 0.015" of aluminium. The vessel also has a Varec depth gauge with stainless steel float etc, a vent pipe to a soda lime vent box, an internal steam coil with T.I.C., item I-01894, set at 50°C. (tin-sprayed thermo well), and external heat insulation. There is also a dip pipe through which dry air from the Lectrodryer PC-046 can be blown by a hose connection with Corty coupling to agitate and dry the contents of the tank. Attapulgus earth is introduced through a funnel fitted to an opening (with screw cap) in the top of the tank.

XII. EQUIPMENT LIST, contd.

Note: In MCC manuals the CT and OT items of equipment are listed under "T", e. g. Closed Tanks and Open Tanks.

XII. EQUIPMENT LIST, contd.

Dryers

D-012 Flaker, Devine, 48" dia. x 30" long, drum 5/8" thick, rolled steel, machined and polished. Housing to be of #16 ga. monel.
Order B 7378 on 4/14/36, Req. 69124 on 4/14/36.
Price $1668.00 quot. 3/17/36.
In lean-to on floor on found. of concrete.
Driven by M-0827 - 3 HP Wagner motor thru MSC-0639.
Jones Speed Reducer. The pan is heated by gas flames.

Sketch showing drum side-knife, dip pan and essential dimensions on 48" diam. x 30" long steel drum, monel hood flaker -- drg. B-675, chutes for finished product. Drg. D-518.

See drawing B-374. General arrangement, and C-827, weighing truck.

Dryer for Attapulgus Earth.

In 1946 a vertical steel tank with internal steam coils was installed at the Krummrich plant. It was still the only equipment for drying earth at the Krummrich plant in 1955, but reliance was placed mainly on supplies drawn from Anniston. With the Krummrich plant dryer, the earth was fed in through a hand-hole in the cover, and withdrawn, as required, by means of a twin damper arrangement on the wide bottom outlet.

See hand sketch sent to MCL April 1947.

At Anniston the earth is screened, 20 mesh, then dried in trays about 3" deep, place in an electrically heated cupboard. Each tray contains a weighed amount, so that the correct charge of earth can be put into the treatment tank directly from the dryer.

XII. EQUIPMENT LIST, contd.

Dryers, contd.

Dryer for Attaplugus Earth, contd.

In 1947 at the Krummrich plant the Attapulgus earth was being dried in a vertical cylindrical steel vessel, with cone bottom, and an internal steam coil. The earth was fed in through a hand hole in the cover and withdrawn as wanted through twin dampers in the bottom. See the sketch sent to MCL with the drawings collected in 1947.

The cover of this dryer had a vapour vent, but there was no positive movement of air through the vessel, and the electrically heated shelf dryer used at Anniston (see page 5 of the report "Notes on the Anniston Aroclor plant" Havercroft and Mather, September 1947), would appear more likely to give thorough drying. The steam heated dryer was still in use at the Krummrich plant March 31, 1954. The reference of Schwarting and others, November 12, 1953, page 10, to an electrically heated dryer refers to a still earlier unit which had been abandoned.

XII. EQUIPMENT LIST, contd.

Filters

F-0106 Steel filter purchased from Nooter. Dwg. C-3775, Size 12" dia. x 3'10-3/4" high. Leg supports, glass wool packing. Order B3511 on 2/19/36. Req. 67729 on 2/14/36. Price $56.00 quot. 2/5/36.

Formerly used on chlorine gas, but used in 1946 to filter out iron etc. impurities from the HCl gas coming from other departments through a long steel line.

F-0113 Sperry 24" bronze filter press. Cover for electric oven heater for press --- Drg. B-685. Replaced by Sparkler press F-0172.

Steel support and pan for Sperry filter B-7121. 3/4" pipe coil for filter catch pan -- A-7136.

F-0159 General Electric Filter Press. Serial #6186968. Type FF30. Accessories included. 3 HP motor and 4 compartment drying oven. Form G, Cap. 25/30 gal. per min. Size 12", 20 chambers. Heated and insulated steel cover* with pullies, cable, counter weight and strip heaters, Pyranol plant.

Order B18935 on 9/21/39. Req. 1991 on 2/20/39. Chg. out $984.00 on 11/30/39.

F-0172 Sparkler filter. Serial 484. Model 18-d12 all bronze construction with improved Scavenger plate, plates to be arranged so entire set can be removed. Steam tracing inside the lagging, then a metal shield over all. Steel legs and floor flanges for bolting to floor. Served by pump P-0984. Order B10302 on 4/2/41, Req. 20430 on 4/30/41. Price $830.00 per quot. 3/19/41. On ground floor center of Bldg. CR.

Installed for Aroclors, but later transferred to use on Pyranols. Chain hoist, MSC-01495, provided for lifting out the nest of plates.

* MSC-02108.

XII. EQUIPMENT LIST, contd.

Filters, contd.

F-0172, contd.

Samples of filter paper for the Sparkler press F-0172, which was then being used on Aroclors, bought under the reference "#21-18 Filter paper", $2.755 per 100 sheets, Sparkler Mfg. Co. Mundelein, were sent to London, April 9, 1947.

F-0172 was moved to the Pyranol department and repleced by a 33" Sparkler. See Operating Instructions 8/10/54, and Mr. Harden's notes of August 1950.

F-0238 Sparkler Filter, 33D-12 cell type, 304 Stainless Steel, with jacket for 30 psig.

33" Sparkler press for Aroclors installed in place of F-0172, F-0172 being used for Pyranols.

F-0239 Sweetland, Size 10 RH, 54 leaves. 523 sq.ft. C.I. body, lined with thick nickel. Nickel valves and outlet line, with pump F-01757. Out of use in 1955. (Pyranol plant).

XII. EQUIPMENT LIST, contd.

Furnaces

PC-045 Gas heater for No. 1 still. Steel shell 3/16" x 3'9" dia. x 4'10½" long, lined with insulating fire brick, etc. 1 coil 2" xHy pipe, 12 turns formed into a 2' dia coil with spare blocks and legs. Drawing B-886. Req. 69859 on 5/14/36, Order B9665 on 5/29/36. Used to heat material in S-043, pumped thru coil by P-0593.

Vent stack drawing B-689 (could not be found in 1946.) Piping details, drawing C-815, was sent to London April 24, 1947.

At plant B in 1946, there were two natural gas burners aimed tangentially into the bottom of each furnace, and there was some evidence of damage due to overheating of the lowest part of the coil. The central "dummy" inside the coil was made as a solid cylinder of firebrick and plastic refractory material built up on a circular plate suspended on a central steel lifting bar. Head room and a suspension hook are required over each furnace, for maintenance work.

The material from the still is pumped downwards through the coil in the furnace of the new still, but upwards in the old still. The main reason for this is that this arrangement enables the coil of the deep still to be on the same level as that of the shallow one.

At Anniston the material is pumped upwards because this puts the coldest Aroclor in at the bottom where the coil is most in danger of overheating. This can have little advantage, except towards the end of the run, when the temperature spread between the inlet and the outlet is greater.

There is a thermo-recorder pocket in the inlet of each coil, and another in the outlet. There are valves on the circulation lines, by which the coil can be sucked empty. See Section VI, page 18. These also help in locating any blockage in the circulation system.

XII. EQUIPMENT LIST, contd.

Furnaces, contd.

PC-045 contd.
Mr. Purzey reported, December 5, 1951, that the coils last about 12 months, but may require cleaning every 3 or 4 months to remove plugs.

At Newport the still coil is interchangeable with that of the diphenyl department still.

A temperature difference recorder controller was installed on the heater coil at Newport, and a CO_2 connection made to the furnace for emergency use.

At Anniston there is a 12-point Micromax temperature recorder on the chlorination system, and one for each of the two vacuum stills.

PC-046 Electric, Air Drying Furnace purchased from Lectrodryer Corp. Serial 270, Size BWC-250, dual-absorber type. 40# pressure. 440 volts, single phase, 60 cy. 4-8 hours operation. 300 amp. heater on each side thermostatically controlled, at 270°F. See T-014. Order B7403 on 4/14/36, Req. 69119 on 4/14/36.
Price $1,350.00 on 6/30/36. Has blower with Motor M-01486 for scavenging. Serves the air-blowing tanks CT-0750 and CT-02086, and the melter CT-0763, in the latter case at pressure enough to blow the charge to the chlorinator. Brings the dew point of the air to between - 10°F. and + 10°F.

Lyles, Soffrenko and Miller (Pyranol report March 24, 1947, page 60) state that the dry air should be checked twice a month for its moisture content, and that the alumina needs renewal about once a year.

PC-066 Steel Heater Furnace for No. 2 still. Drawing C-3479. Brick lining, coil, burners and stack. S. W. corner of the 20'6" level platform, Bldg. CR.
Generally like PC-045.
Drawing C-3479 (missing April 1946).

EXECUTIVE SUMMARY

The present study on the potential health effects in human populations from exposure to commercial polychlorinated biphenyl (PCB) mixtures under occupational or other environmental conditions was conducted by a team of specialists in the medical, toxicological, and epidemiological sciences designated as the Category I team. Draft material for the study report was reviewed by a second group of specialists designated as the Category II team, and other scientists, leading to comments and suggestions for improvement which were incorporated into the draft report. The available body of scientific literature on health effects of PCBs in humans and in test animal systems was reviewed and analyzed with emphasis on the relationships linking exposure, dosage to the biological target, and occurrence of specific health effects in the animal or human. Both the toxicological and epidemiological data from acute and chronic animal and human exposures were considered in generating assessments of the probability of occurrence of any specific health effect in humans. The results of these assessments are summarized below, separately itemized under each major health effect. It should be noted that each assessment applies to the potential for development of that effect under the type and level of human exposures actually encountered in the U.S. during the past decades, with the most intensive integrated exposures having occurred in manufacturing operations that were terminated in this country in 1977.

XII. EQUIPMENT LIST, contd.

Instruments

I-016 Taylor Temperature Controller. Drawing D4417, Size 1, #36JR323. Direct acting, self acting, with std. double seated valve incl. steam strainer. Range 110°F. to 170°F., Set 122°, 25' tubing 3/4" union hub connection placed 7' from bulb end.
Order B3443 on 3/10/37, Req. 76979 on 2/15/37.
Chg. out 3/31/31, $76.57.
On CT-0848, Pyranol blender.

I-0108 Rotameter Instrument purchased from Economy Equipment Co. Serial #10166. For scrubber TW-0182. No. 6, Fig. 25 bronze with stainless steel float calibrated for max. cap. of 300 gph water.
Order B19959 on 11/10/37, Req. 83079. Price $66.70

I-0204 Foxboro. DP cell. Stainless Steel body. Ni diaphragm.

I-0244 TIC, L & N.
2 point Micromax. Range changed to 0-600°C. Used to replace MSC-0668.

I-0381 Palmer Supercar Dial Thermometer, 8" cone Mercury actuated. Range 0-150°C., 25' stainless steel connecting tubing with adj. clamp, flg. to be located 9' from end of bulb.
Order B18385 on 8/23/40, Req. 12533 on 8/23/40.
On 1269 stg. tk. CT-01310. Price $56.50

I-0398 Fulton Sulphon Temperature regulator #931 with 6A bulb and 20' of capillary - Bronze body stainless steel trim, to be used on steam at 65# pressure. Range No. 76K-190F. to 250°F. Size 1, press N. G. on CT-0748 diphenyl stg. tk. Order B23310 on 10/28/40, Req. 14583 on 10/28/40. Price $69.05

I-0441 L & N 6 point temperature recorder. Serial #389329, #40352M, Model S, micromax strip chart temperature recorder. Type DC potentiometer - multi point curve printing, record numbered and color dot for each

XII. EQUIPMENT LIST, contd.

Instruments, contd.

I-0441 contd.
thermocouple. Time cycle - 30 sec. normal for each point.
Order B13260 on 6/18/41, Req. 21072 on 6/17/41.
Price $395.00.
In second floor control room, Bldg. CR.

I-0443 Watt hour meter instrument purchased from General Electric.
Serial 21-220-743. #85 x 905. Type V3A, 220 to 5 CT use.
Order B 9118 on 4/15/41.
Req. 20313 on 4/14/41. Chg. out $51.40 on 6/30/41.
In cabinet outside E wall Bldg. CR.

I-0537 Palmer Dial Thermometer. CABI #217, Range 0-150°C.
in Pyranol Mixing Tank CT-01321. 15 ft. stainless steel
special armor flexible tubing plain bulb. Order B20438
on 12/1/41, Req. 24425 on 9/9/41.
Chg. out $49.59 on 12/27/41.

I-0835 Bailey Integrating and Recording Flow Steam Flowmeter.
Serial #13996R. Order B11589 on 9/25/45, Req. 67905 on
5/11/45. Price $348.00
In control room E wall. For steam from the 200 lb. main.
Supplies the ejectors, the high pressure coils in the
air-blowing tanks, and melter. See MSC-0682 for the low
pressure steam metsr.

Taylor Fullscope recording controller on the No. 1 still
vacuum system.

Chlorine flow recorder controller on No. 5 chlorinator.

See also MSC-0663, page 61.
0668, page 61.
0675, page 61.
0682, page 63.
0705, page 63.

I-01118 Foxboro steam flow controller, 0 - 2000 lbs. per hour.

XII. EQUIPMENT LIST, contd.

Instruments, contd.

I-01547 Taylor PR, 2 pen, with alarm and shut off valve. Chlorine lines. 0 - 100 psig.

I-01894 Taylor Pulscope TI C. 0-150°C. working at 50°C. Tin-sprayed thermo well. On blender CT-02621. Controls Fisher diaphragm valve on steam to coil in CT-02621. Pyranol blender.

I-01941 Foxboro. D.P. cell for chlorine liquid in store tank.

I-02019 Taylor Pulscope LRC.

I-02045 Worthington meter, gallons, well water.

See also MSC - 0663
0668
0675
0682
0705
0770
01393

XII. EQUIPMENT LIST, contd.

Elevators

L-031 Bucket elevator from General Conveyor & Mfg. Co. Drawing E-870. Lg. to be 22'4-11/16" OA c to c take up shafts and 20'6" casing and head section 3/16" and boot 1/4". 6" belting, 4 ply R covered pinched 10-7/32" for buckets of 4½" x 3" chrome steel. Order B10455 on 5/15/36, Req. 70140 on 5/25/36. Price $491.20. Driven by M-0854. Drive drawing B-661. Solid Aroclors (dismantled 1952).

See also V44, 45, 46 conveyors from flaker D-012 to elevator L-031, and chain hoist MSC-01495 over the Sparkler filter E-0172, and electric hoist MSC-0655 for solid Aroclors.

A chain hoist is used also to lift bags of lime to the still operating platform.

XII. EQUIPMENT LIST, contd.

Motors

Note: The motors are changed to other duties from time to time, but the following details will serve to indicate the types of motors used.

M-0790 Westinghouse Motor 3 HP-1750 RPM. Serial 7435. Type CS, sq. cage induction motor, horiz., frame W225, 220/440 V. 3 ph., 60 cy., 8/4 amp., 55°C. temp., rise, style 801068Y, class 1, total enclosed, ball bearing. Rec'd. 8/20/35. (#6058-5077) $78.96. On pump P-0346.

M-0827 Motor 3 HP 1200 RPM from Wagner Electric Co. Serial #1718199, horizontal induction motor, totally enclosed, fan cooled, ball bearing, 3 ph, 60 cy, 220/440 volts, 8.2/4.1 amp., type CPI, frame 254, model W425198. Order B8184 on 4/23/36, Req. 69376 on 4/23/36. Chg. out $94.16 Also drives V-046 thru second chain on link belt; drives D-012 flaker thru MSC-0639 speed reducer and chain.

M-0830 Motor 2 HP 1800 purchased from General Electric. Serial HK-1407, Horizontal induction, totally enclosed, fan cooled ball bearing, frame 225, 2HP 1740 RPM, 220/440 volts, 5.61/2.81 amp., type K, 3 ph., 60 cy., model SK-225-A715. Order B8169 on 4/23/36, Req. 69377 on 4/23/36. Chg. out $73.84 on 6/30/36. Drives P-0565.

M-0832 Motor 3 HP 1200 RPM purchased from Wagner Electric. Serial 1714954. Horizontal induction, totally enclosed, fan cooled, ball bearing, 220/440 volts, frame 254, 3 ph., 60 cy., type CPI, model W42J198, 8.2/4.1 amp. Order B8178 on 4/23/36, Req. 69378 on 4/23/36. Chg. out $94.16 on 6/30/36. On blower B-094.

M-0834 Geared head motor 2 HP 1200 RPM purchased from Master Electric Co. Serial ME-975, air jacketed, totally enclosed, fan cooled, 1140 to 220 RPM single reduction parallel geared head, 220/440 volts, 3 ph., frame 254, type PA, style 47476, 55° cont. rating, 6.2/3.1 amp. Drives L-031. Order B8156 on 4/24/36. Req. 69373. Chg. out $109.14.

XII. EQUIPMENT LIST, contd.

Motors, contd.

M-0835 Reeves vertical motodrive 1½ HP 1800 RPM purchased from Bates Co. Motor serial 1914691, motodrive unit serial MD-1136. Size 4253-E-18, model V 34J223, 3ph, 60 cy., 1.9 amp., frame 224, 4 to 1 speed variation and 50 to 1 gear reduction, hand chain control and chain in place of standard hand wheel.
Order B 7376 on 4/14/36, Req. 69123.
Charged out $300.96. Drives V-044.

M-0836 Reeves vertical motodrive, same as M-0835. Drives V-045.

M-0841 Geared head vertical mounted motor 5 HP purchased from Master Electric Co. Serial ME-988. 220, 440 volts, 3 ph., 60 cy., totally enclosed, fan cooled, ball bearing, type PA, frame 11230 # 254 DP - 1725 to 80.2 RPM
Style 47478 - cont. 55°C.
Order B 8155 on 4/24/36, Req. 69375 on 4/23/36.
Chg. out $211.84 on 6/30.
Drives stirrer in blending tank CT-0779.

M-0846 Vertical mounted induction motor. 1 HP 1800 purchased from General Electric. Serial EP-2773. Totally enclosed fan cooled, ball bearing, thrust type with ring base and drip cover, 3 ph., 60 cy., 220/440 volts, 1720 RPM.
Model 5K204A1550. Frame 204Y.
Order B 8175 on 4/23/36, Req. 69371.
Chg. out $55.44. Drives P-0573.

M-0847 Vertical mounted induction motor 1 Hp 1800 purchased from General Electric Co. Serial EP-2779. Totally enclosed, fan cooled, ball bearing, etc. same as M-0846.
Drives P-0909.

M-0848 Vertical mounted induction motor 1 HP 1800 purchased from General Electric Co. Serial EP-2777. Totally enclosed, fan cooled, ball bearing, thrust type with ring base and drip cover, 3 ph., 60 cy. 220/440 volts, 1720 RPM, model 5K204A1550, frame 204Y.
Order B8175 on 4/23/36, Req. 69371. Chg. out $55.44
Drives P-0674.

XII. EQUIPMENT LIST, contd.

Motors, contd.

M-0849 Wagner horiz. induction motor 5 HP 1800 Serial #1714362, totally enclosed, fan cooled, ball bearing, type CPI, frame 254, model W-30J195, 3 ph., 60 cy., 220/440 volts 1750 RPM, 12.6/6.3 amp.
Order B-8177, Req. 69372, chg. out $97.08 6/30/36
Drives P-0578. On pump P-0578, on No. 2 chlorinator.

M-0850 Horizontal induction Wagner motor 5 HP 1800 Serial 1718376. Same as M-0849 and 0851. Drives P-0579. On pump P-0579 on #3 chlorinator.

M-0851 Motor same as M-0849 and 0850. Serial 1718377.

M-0853 Vertical mounted induction motor 3 HP 1800 G. E. Makers. Serial FP-1104. Totally enclosed, fan cooled, ball bearing, thrust type with ring base and drip cover, 3 ph., 60 cy., 220/440 volts, 1730 RPM, model 5K225A2430, 8.54/4.27 amp.,frame 225Y, type K.
Order B 8174 on 4/23/36, Req. 69367.
Chg. out $95.92. Drives P-0583

M-0854 Motor Serial FP-3898 same as M-0852 and 3, on CT-0768.

M-0856 Vertical mounted induction motor 3 HP 1800. Made by G. E. Serial FP-2457. Thrust type and drip cover, ring base, class 1, group d, underwriters #5474727. Explosion proof, ball bearing, 1720 RPM, 3 ph., 60 cy., model 5K225A2446, 220/440 volts, 8.42/4.21 amp., frame 225Y, type K
Order B8172 on 6/26/36, Req. 69368 on 4/23/36.
Chg. out $115.58 on 7/13/36. Drives P-0585.

M-0871 Vertical induction motor 5 HP - 1750 RPM from G. E. Serial FP-3177. Totally enclosed, fan cooled, ball bearing, thrust type with ring base and drip cover. 220/440 volts, 13.9/6.95 amp., frame 254 Y, type K, 60 cy., 3 ph., model 5K254B1930.
Order B8173 on 4/23/36, Req. 69369. Chg. out $124.21 on 7/31/36. Still pump drive, drives P-0593.

XII. EQUIPMENT LIST, contd.

Motors, contd.

M-0873 Vertical mounted induction motor 5 HP - 1750 RPM. Purchased from G. E. Serial FP-3107. 220/440 volt, 60 cy., 3 ph., totally enclosed, fan cooled, ball bearing, thrust type with ring base and drip cover. Model 5K254B1930, 13.9/6.95 amp., frame 254Y, type K. Order B8176 on 4/23/36, Req. 69370. Chg. out $124.21 on 7/31/36. Drives P-0592 in tank outside.

M-0875 Horizontal induction motor 1 HP 1200 made by G. E. Serial DP-5227, Totally enclosed, fan cooled, 60 cy., 1130 RPM, model 5K204A1036, 220/440 v., 3.45/1.73 amp., frame 204, type K, 3 phase. Order B13188 on 7/2/36, Req. 71152, chg. out 7/21. Drives P-0595.

M-0885 Vertical mounted induction motor 1 HP 1800 purchased from Continental Equipment Co. Serial 50498. Totally enclosed, fan cooled, ball bearing, thrust type with ring base and drip cover. 2.9 amp. 3 ph., 60 cy., 220/440 v., 1750 RPM, type NCU20. Ordered for spare. Drives P-0604. Price $48.00. Order B-13196, Req. 71147 on 7/1/36.

M-0904 Motor 3 HP - 1200 purchased from Continental Electric Co. Serial 51704. Totally enclosed, fan cooled, normal starting current, squirrel cage induction motor, 3 ph., 60 cy., 220/440 volts, 1150 RPM, 55° cont. rise, type NP 254, 8.4/4.2 amp. Order B17431 on 9/1/36, Req. 72637, Chg. out $90.40 on 10/24. Drives B-0105 in Bldg. CR.

M-0914 Blackmer motor 7½ HP 1800 made by Louis Allis. Serial 217543. Totally enclosed, fan cooled, type JX, 3 ph, 60 cy., 220/440 volts, 1750 RPM, frame 284, class 53d, form B, 18.4/9.2 amp. Order B21241 on 10/22/36, Req. 74034, Chg. out $133.12 Drives Naphthalene pump P-0617 for CT-0347.

XII. EQUIPMENT LIST, contd.

Motors, contd.

M-0955 Portable "Lightnin-Mixer" 1/4 HP 1725 purchased from Mixing Equipment Co. Mixer Serial 37108, Motor Serial ME-4536. CARI 106/1936. Model C-4, 3" folding monel metal propeller monel shaft, 4/2 amp., 110/220 volts, single phase, 60 cy., class 1, group d, explosion proof, underwriters P-519372, extension cord and attachment plug.
Order B1340 on 1/19/37, Req. 76212 on 1/18.
Chg. out $109.42 on 2/27/37. Used for drum shipments.

M-0975 Motor 5 HP 1800 purchased from Wagner Electric Co. Serial 1725358. Totally enclosed, fan cooled, ball bearing, induction motor, type CPI, frame 254, model W30J247, 3 ph, 60 cy. 220/440 volts, 12.6/6.3 amp. cont. rating 55°C.
Order B2834 on 2/9/37, Req. 76765 on 2/5/37.
Cost $95.61. On P-0629. On No. 1 chlorinator pump P-0629.

M-0985 Wagner Vertical Motor 7½ HP - 1800 RPM. Serial #1728961. Totally enclosed, fan cooled, ball bearing, type CP-2, frame 234Y, 440V, 60 cy., 3 ph., 18.4/9.2 amp. 1750 RPM, model W40V143.
Order B3323 on 2/12/ 37 and Req. 76927.
Chg. out $133.98. Inst. to drive submerged pump in TCB stg. tank CT-0848. On P-0346.

M-01229 Vertical mounted induction motor 1 HP 1800 purchased from Louis Allis. Serial 269797. Totally encl. fan cooled, ball bearing, thrust type with ring base and drip cover, weatherproof conduit connection box, type IS, frame 204V, class L, form B. 220/440 volts, 3 ph, 60 cy., 3/1.5 amp. cont. 55°C., 1730 RPM. Order B3853 on 3/4/38, Req. 86889 on 3/3/38.
Chg. out $55.20 on 4/29/38.
On pump P-0731.

XII. EQUIPMENT LIST, contd.

Motors, contd.

M-01377 G. E. Motor 2 HP - 1800 RPM. Serial MR-8969. Totally enclosed, fan cooled, sq. cage, induction motor, type K, ball bearing, 220/440 V, 60 cy., 3 ph., frame 254, 1760 RPM, model 5K254B91. 5.44/272 amp. Order B15955 on 9/26/38, Req. 91711, Chg. out $75.00. On P-01111.

M-01456 Westinghouse horizontal motor 3/4 HP 1200 Serial 4139. Totally encl. fan cooled, low starting current, 440 volts, 3 ph., 60 cy., 1160 RPM. Type CS, frame 204, 2.6/1.3 amp., style 1707136. 55°C. rise, Chg. out mach. $41.03 on 12/29/39 Order B17367 on 12/18/39. Req. 1357 on 8/31/39 on Blower B-0148.

M-01469 G. E. Motor 3 HP-1200. Serial #KT-10671. Totally encl. fan cooled, model 5K254A1024, frame 254, type K, 220/440V, 3 ph., 60 cy., 1165 RPM, 9.06/4.53 amp., cent. 55°C. rise, Order B18935 on 9/21/39, Req. 1991 on 9/20/39. Chg. out $72.47 on 11/30/39. On gear pump to P-0159.

M-01486 General Electric Motor 1/4 HP 1800, totally encl., model 5 KH47AB984, type KH, 110 volts, single phase, 3.4 amp., 55° Cont. Order B17923 on 10/17/39, Req. 1531 on 9/8/39. Cost $24.25. On Lectrodyer FC-046.

M-01501 Replaced by M-01706.

M-01573 Motorized car spotter 5 HP 1640 RPM purchased from Link Belt Co. motor serial 307939, spotter serial 5252. 220/440 volts, 60 cy., 3 ph, type IK, frame 225 VY, class 3, form B, 17.2/8.6 amp. 55°C. Order B26741 on 12/29/39, Req. 5128 on 12/29/39. Chg. out $373.86. On track 11 at load dock.

Yusho Disease

Separate consideration was devoted to the Yusho episode recognizing the special character of the human exposures to high concentrations of mixtures of PCBs and their thermal degradation products, polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs). Several conclusions reached by the Category I team are of importance: (a) it is impossible to stipulate whether any of the health effects observed is causally related to PCB exposure, since the other halogenated compounds are also biologically active; (b) the dosage patterns experienced by Yusho patients and U.S. industrial workers (PCB-exposed) are not at all comparable; the latter group experienced low level, long time period exposures primarily via inhalation and skin contact, with only minimal oral ingestion; (c) the similar health effects seen in Yusho patients from the Japanese and Taiwanese episodes of exposure to contaminated cooking oils point to the same type of toxic mixtures resulting from thermal heat exchanger action in the two events; (d) because of points (a)-(c) above, and the fact that at least the PCDFs in the Yusho oils are potentially more toxic than the PCBs on the basis of animal data, it is not possible to extrapolate the Yusho experience to prediction of acute and sub-chronic effects of commercial PCB mixtures in the human; (e) finally, with respect to predictions of human carcinogenesis from the Yusho type of exposure the data are so incomplete that conclusions regarding any types and amounts of excess cancers attributable to those exposures have to await further definitive study.

XII. EQUIPMENT LIST, contd.

Motors, contd.

M-01622 General Electric motor 7½ HP, 3600 RPM, Serial BU7108. Totally enclosed fan cooled, type KF, model 5KF254C25, frame 254, 220/440 v., 3 ph., 60 cy., 3435 RPM, Drives ML-045. Order B4118 on 2/20/40, Req. 6737 on 2/20. Chg. out $114.96.

M-01629 Vertical motor 7½ HP purchased from Turbo. Made by Westinghouse. Serial 2640. Totally enclosed, fan cooled, frame 284, class 1, RPM at full load 1735, cont. rating at full load 55°C. rise, 220/440 volts. 3 ph, 60 cy., 18.8/9.4 amp., style 1071192. Order B8337 on 5/20/40, Req. 8441 on 4/9/40, chg. out $112.66. On MSC-01205. Driving agitator in CT-0808, final chlorinator.

M-01650 Louis Allis motor ½ HP, serial 258334, 1750 RPM, type JS, frame 254, class 43N, form B, 220/440 v., 3 ph, 60 cy., 13/6.5 amp., full load 55°C. cont.
Order B26263, Req. 85432 on 12/24/37.
On Sparkler press pump.

M-01656 Wagner Electric Motor 5 HP 1800 RPM Serial 1758959. Horizontal totally enclosed, fan cooled, ball bearing, less base and pulley, type CPI, frame 254, 220/440 v., 3 ph., 60 cy., 1750 RPM, cont. rating 55°CP, model 1B8J247B, 13.2/6.6 amp. Order B12802 on 7/8/40, Req. 10231 on 6/5/40, chg. out $87.92.
Drives P-01056 Taber Horizontal pump.

M-01660 General Electric Motor 1 HP 1800 RPM purchased from Taber Serial GU1902. Totally enclosed, fan cooled, vertical mounted, ball bearing, thrust type, with ring base and drip cover, 3 ph, 60 cy., 220/440 volts, 1720 RPM, model 5K204A1550, frame 204Y, type K, 3.11/1.56 amp., cont. 55°C. rise
Order B13111 on 6/10/40, Req. on 6/10/40, chg. out $50.19. Drives new Taber sub. pump P-0909.

XII. EQUIPMENT LIST, contd.

Motors, contd.

M-01697 Motor made by Wagner 1/3 HP, CABI 169, 30" dia. type S-60WS, style 1249-4622 portable circulating fan, single ph., 60 cy., 115 volts, complete with guards, floor column, and cord. B16528 on 7/26/40. Req. 11797 on 7/26/40. Chg. out $60.58. Used on operating platform near chlorinator.

M-01706 Vertical mounted induction motor 3 HP 1800 made by G. E. serial JU3498. Totally enclosed, fan cooled, ball bearing, thrust type with ring base and drip cover, model 5K225A4264, frame 225VY, type K, 220/440 v., 3 ph., 60 cy., 1730 RPM, 8.54/4.27 amp., cont. 55°C. rise.
Order B18443 on 8/23/40, Req. 12560 on 8/23/40.
Chg. out $92.24 on 10/31/40. On P-0929 Taber.
Replaced by M-01501.

M-01718 Louis Allis Motor 7½ HP-1800 RPM, Serial 335985. Totally enclosed, fan cooled, weatherproof conduit connection box. Type JX, frame 284, 220/440V, 3 ph., 60 cy., 1750 RPM, Class D, form R, 19.6-9.8 amp., full load temp. rise 55°C. trine hours cent. Order B21071 on 9/30/40, Req. 13674.
Chg. out $113.00 on 10/31/40.
Drives (Falk Reducer MSC-01288) on Turbo Mixer for CT-01321.

M-01752 Motor 1 HP-1800. Serial 77640.
Totally enclosed, ball bearing, squirrel cage, weather-proof threaded type connection box, type CS, frame W-204, 220/440 v., 3 ph., 60 cy., 1750 RPM.
Order B26350 on 12/4/40 and Req. 15836.
Chg. out $36.98. On B-034.

M-01772 Lewis Motor 1/2 HP 3600 made by G. E. Serial J33, CABI 169, totally encl., model 5K49BC756A, type K. rise 55°C., 440 v., 3 ph., 3450 RPM, amp. 7.
Chg. out $25.00, Req. 16663 on 12/30/40.
Use with P-0378 on OT-0640.

XII. EQUIPMENT LIST, contd.

Motors, contd.

M-01811 Louis Allis Motor 2 HP 1800 RPM Serial 385335.
Totally enclosed, fan cooled, normal starting current, CI conduit connection box, less base and pulley. 220/440 volts, 3 ph., 60 cy., 1750 RPM, type JS, frame 225, class M, form R, code H, 5.6/2.8 amp.
Order B4136 on 3/7/41, Req. 18313 on 2/17/41
Chg. out $65.36 on 6/30/41.
On ground floor N. E. of P-0172 on P-01037.

M-01850 Louis Allis Motor 1 HP 1800 RPM Serial 395205
Totally enclosed, fan cooled, ball bearing, 220/440 v., 3 ph., 60 cy., 1740 RPM, type IS, frame 204, class L, form B, 3.1/1.55 amp.
Order B7411 on 3/26/41, Req. 19634 on 3/26/41.
Chg. out $36.98. On ground floor.

M-01856 Louis Allis motor 5 HP 1800 RPM Serial 391009.
Totally enclosed, fan cooled, vertical flgd. mounted (CI conduit connection box) normal starting current, 3 ph, 60 cy., 220/440 v., 1750 RPM, type JS, frame 254 VB, class N, form R, code H, 1.3/6.5 amp. full load temp. rise 55°C.
Order B6380 on 3/13/41, Req. 19213 on 3/13/41.
Chg. out $109.74 on 6/30/41. On P-0997 top of S-062.

M-01859 Unit heater from Am. Blower Corp. Serial 1939.
Order B8936 on 4/11/41 and Req. 20240.
Chg. out $48.73.
In MSC-01393.

M-01995 Motor 1/3 HP 1800 RPM made by G. E.
Explosion Proof, class 1, group d, underwriters No. FA352-094. Totally enclosed, fan cooled, ball bearing, type K, frame 45A, model 5K45AC1024A, temp. rise 55°C. trine rating cont., 440 v., 3 ph, 60 cy, 1725 RPM. 55 amp.
Order B4625 on 2/21/41, Req. 18520 on 7/21/41.
Chg. out $29.75 on 9/30/41. On P-01054.

XII. EQUIPMENT LIST, contd.

Motors, contd.

M-02170 Geared head motor 5 HP 1800 RPM. Made by Master Elec. Serial PD-9. Parallel, air jacketed, fan cooled, totally enclosed, frame # 254, 80 RPM on mixer shaft, barrel mounting for vertical operation, style 103543, 220/440 v., 3 ph., 60 cy., 1725 RPM, type PA, amp. 13/6.5, 3 ph, trine hours cont. FLTR 55°C. Order B3580 on 4/8/42, Req. 30060 on 2/10/42. Chg. out $259.25. On CT-01399, #2 blender.

M-02175 Office Fan.

M-02877 Drives P-01111 at loading dock - 5 HP.

M-03133 Drives P-01540.

M-04592 Drives Side entering agitator in #2 mix tank CT-02621.

M-04691 Drives P-02077 at TTCB storage.

M-04817 Exhaust fan - located in pyranol press room.

M-04025 Drives P-02077.

M-0514 Drives P-02251.

XII. EQUIPMENT LIST, contd.

Mills

ML-045 "Helix-Seal" impact mill purchased from Williams P. C. & Pul. Co. Serial #9394. Size #1.

Less drive pulley. Driven at 5500 RPM thru V belt drive furnished by Monsanto.

Order B2371 on 2/1/37. Req. 76578. Price $420.00. West lean-to.

Hand fed.

For solid Aroclors.

Dismantled 1952.

XII. EQUIPMENT LIST, contd. MSC-0639 - 0675

Miscellaneous Equipment

MSC-0639 Speed reducer made by W. A. Jones Foundry, Serial 85957, #105DW, assembly #1, style 4, 36 to 1 ratio, low speed shaft to be 7½" instead of 4" extension.
Order B8242 on 4/24/36, Req. 69409 on 4/24/36,
Price $156.00
Driven by M-0827, drives D-012. CR, lean-to.

MSC-0655 Shepard Electric Liftabout Hoist. Serial 36306.
440 volts, AC, 3 ph, 60 cy., single speed control with motor drive trolley. Hoist speed 18' per min., lift 19'. Hoist motor 3 HP. Travel motor 3/4 HP.
Order B7405 on 4/14/36, Req. 69120.
Chg. out $906.70.

MSC-0663 Multiple temperature recorder 40112-291 Micromax Model S strip chart, 2 prints, surface panel $300.00.
Made by Leeds and Northrup, Serial 276758.
Order B9975 on 5/19/36, Req. 69970.
In lean-to, Bldg. CR.

MSC-0668 L & N Temp. Recorder made by Leeds and Northrup.
Dwg. B-666, Serial 276807.
(1) #40354-291 Micromax model S strip chart, multiple temp. recorder, 4 point. (Multiple colored dots instead of numbers on print wheel). Surface panel mounting $465.00.
(2) Extra for high contact for operating alarm $20.00
Order B9976 on 5/19/36, Req. 69969, Chg. out $491.82.
South wall, west instrument, Bldg. CR.(See note on next pg.)
Replaced by I-0244.

MSC-0675 Temperature Recorder purchased from Leeds and Northrup.
Serial 276784. #40353-291 Micromax, model S, strip chart multiple point temperature recorder for 3 prints. (Multi-colored dots instead of numbers on print wheel.)
Surface panel mounting $400.00. Extra for high contact for operating alarm, $20.00. 3 thermocouples to fit wheels. Our Dwg. B-666.
Order B9977 on 5/19/36, Req. 69968, Chg. out $324.05.
South wall, east instrument, Bldg. CR.
(See note on top of next page.)

XII. EQUIPMENT LIST. contd.

Miscellaneous Equipment, contd.

MSC-0668 -0675 Note:

Record the following temperatures:

Batch temperatures in chlorinators: CT-0744
0745
0833
01283
0808

Goode temperature in diphenyl etore tank CT-0748

Coil inlet temperature on the etille S-043 and 062.

" outlet " " " " " " "

Vapour temperature entering the condenser.

Goode temperature in receiver.

Goode temperature in blending tank, CT-0779.

Goods temperature in finished product receiver,CT-0780.

Drawing B-666 shows thermo-couple wells.
Drawing B-6868 shows monel thermo-couple wells as used in distilled Aroclors.

MCS-0676 Gas Electric Water Cooler for drinking water. Made by G. E. Compressor 6541356, cabinet 6600807. Model RM-51, pressure type, 110 v., single phase, 60 cy.
Order B14045 on 7/14/36, Req. 71432.
Chg. out 7/31/31, $176.00. On 12' level, Bldg. CR.

XII. EQUIPMENT LIST, contd.

Miscellaneous Equipment, contd.

MSC-0681 Rail truck purchased from Nutting Truck Company. Dwg. C-827. Welded construction, wheels equipped with Hyatt Roller Bearings. Used as weigh truck for still pots on SC-095. Includes track.
Order B11134 on 6/3/36, Req. B70395.
In lean-to Bldg. CR.

MSC-0682 Brown mech. flowmeter. Serial 115969. Recording and integrating steam at 65# ga. press. Dry sat. orifice monel in 4" std. horiz. line. (used on 80 lb. main). Max. flow 4000#/hr. Model 2221-x40. 2 lgs. 25' of ½" copper tubing and connectors - Monometer valves. Elec. clock for 110 v - 60 cy.
Order B14604 on 7/22/36, Req. 71548 on 7/20, chg. out $280.00

MSC-0705 Palmer Industrial Thermometer CABI #89. #249 - 45° reclining industrial therm. 12" scale, steel separable socket - 30" long with 1" std. pipe thread. Range 0-200°C. No nickel plating, case painted reg. lacquer.
Order B18261, chg. out $28.05 on 10/31/36.
On Buffer tank CT-0750.

MSC-0718 Lab and Office of Dept. CABI #89 - 1936.
20' x 10' x 10' high includes partition and elec. lights on NW corner of CR.

MSC-0725 Laboratory testing equipment. See reports on C. E. testing.

MSC-0734 Electric drying oven. CABI 89-1936. Cat. 7764, 3 heat oven with one shelf and 9525 thermometer for 110 v., AC current. Belongs to the Pyranol Dept.
Order B23080 on 11/16/36, Req. 74628. Chg. out $26.60.

XII. EQUIPMENT LIST, contd.

Miscellaneous Equipment, contd.

MSC-0760 Vacuum jet made by Worthington.
#2½ JPD-S std. 3 stage steam jet ejector with 2nd stage condensing and fitted with jet type intercooler.
Jet to be CI bronze nozzles, heads, monel nozzles.
Order B7404 on 4/14/36, Req. 69211 on 4/14.
Chg. out $796.00 on 6/30/36.
N of MSC-01392 Bldg. CR.

Ejectors MSC-0760, 01392, and 01686 are in a row running north and south in the building, and they are interconnected so that the centre one can serve as a spare for either of the other two, to serve the vacuum stills S-043 and 062. Cast iron bodies with monel jets. Karbate ejectors were to be tried. (Anniston were using ejectors with two stages of Karbate jets, then a wet condenser, and then two more Karbate stages.)

Faulty behaviour, due to erosion or corrosion, or to wet or dirty steam, is very objectionable as allowing water to get back into the goods. Karbate units have to be very carefully supported to prevent strains from the pipe lines.

More recently procelain units have been installed at the Krummrich plant.

MSC-0770 Super Tank Gauge made by Varec.
Fig. 68, Gastight. Use on tank according to B/P E-4366, Monsanto Drawing.

All material to be standard, aluminum float, stainless steel tape and float guide wires.
Order B3569 on 2/16/37, Req. 77035. Chg. out $174.80. On CT-0848. TCB store tank.

MSC-0903 Steel cabinet made by Medart. CABI #139. 1 unit 48" wide and 24" deep x 6'3" high 9" ledge, bin fronts, dividers and 2 doors on lower part with lock.
Order B3013 on 2/18/38, Req. 86579 on 2/17/38.
Chg. out $50.51.

XII. EQUIPMENT LIST, contd.

Miscellaneous Equipment, contd.

MSC-0971 10 steel box lockers made by Medart. CABI 139. Olive green steel arranged 2 wide x 5 high. Complete with locks, 2 keys for each lock x 3 master keys common to all. Lockers 12 x 12 x 15" deep.
Order B15781 on 9/23/38, Req. 91603 on 9/21/38. Cost $25.75.

MSC-01061 Two loading ramps made by Monsanto. For one ton chlorine cylinders, using I-beam supports and concrete footings with I-beam rails. East side, outside Bldg. CR.

MSC-01094 Drying Oven purchased from G. E.
Used with P-0159 in the Pyranol plant.
4 compartment electric drying oven with 115-230 volt heating elements.
3 HP motor.
Order B18935 on 9/21/39, Req. 1991 on 9/20/39.

MSC-01191 Metal Desk and Stool. Desk 36-5/32" wide, 42" high front, 54" high back, 31" deep. Stool 30" high.
Order B5169 on 3/4/40, Req. 7148 on 2/29/40.

MSC-01205 Speed reducer made by Falk. Serial M0127-928.
Size 28DZX, RPM 1750 to 180, ratio 9.7.
Order B8337 on 5/20/40, Req. 8941 on 4/9/40. Chg. out $169.94. Driven by M-01629 on CT-0808.

MSC-01288 Falk Motor Reducer 7½ HP. Serial M0131-842.
#44DZX, output speed 1750 to 41.9 RPM, service factor 1½, ratio 41.9.
Order B21071 on 9/30/40, Req. 13674 on 9/30/40.
Chg. out $341.94 on 10/31/40. On CT-01321, Pyranol blender.

MSC-01392 #2½ Worthington vacuum jet 3 stage. Type 9-10-11.
North of MSC-0760.
Same as MSC-01686.

Body Burdens, Metabolism, and Kinetics

Some general observations derive from consideration of the data on the storage, distribution, metabolism, and excretion of commercial PCB mixtures (with associated impurities such as the PCDFs) in mammalian systems. The dynamics of the pathways by which these processes occur in test animal models have been explored intensively and have been fairly well worked out. The variability of PCB effects with species of test animal model has been investigated for a number of important effects, and some general structure versus activity rules have emerged from these studies. There thus exists a conceptual framework, but not experimental data, for describing such phenomena in humans. Further, important data on the biochemical interactions of PCBs, PCDFs, and metabolites with tissues have been obtained that bear directly on interpretation of toxic effects in these tissues.

General Toxicity

From acute, subchronic, and chronic studies of PCB effects in test animal models, a general summary of health effects encountered includes: (a) a low order of acute toxicity; (b) skin lesions; (c) effects on liver tissue that are generally reversible at lower doses but that trend toward irreversibility with increased dosing; (d) effects on the gastric mucosa; (e) effects on the menstrual cycle and on reproduction;

XII. EQUIPMENT LIST, contd.

Miscellaneous Equipment, contd.

MSC-01393 Control Room. Drawing C-9646.
Structural steel, floor plate, Bldg. tile 12 x 12 x 3.
Pyrobar roof, door and instrument panel for I-0441.

MSC-01495 ½ ton Peerless hoist and trolley. Model C, 11' lift.
Model J trolley.
Order B17508 on 8/6/41, Req. 23095 on 8/6/41.
Chg. out $72.74 on 11/27/41.
Used to remove plates of filter F-0172 for cleaning.

MSC-01686 #2½ Worthington 3 stage vacuum jet. Type 9-10-11.
North of MSC-01392. Same as MSC-01392.

MSC-01699 Lockers (4) made by Medart. CABI 152,1939.
2 only 15 x 18 x 60 dark green. #14 and #15.
2 only 15 x 15 x 36 double tier. #12 and #13.
Order B3439 on 3/8/39.

MSC-01877 Canvas tent for tank car. Approx. 7' dia. x 7' high with swing boom, to raise and lower tent into a wooden box along west wall of CS. To be located at load dock at track #11, SW corner CS. Also elec. light in tent.
order B20696 on 9/7/43, Req. 48441 on 9/4/43.

MSC-01879 South dock, wood, muriatic loading. Also swing plank and wood decking.
On track 11 west of CS. 5' x 5'6". 1943.

MSC-01916 North load dock made of steel with swing plank. 5' x 7' long, 9'6" high. 5 x 5 angle columns with 6" channels to support ¼" steel decking. 1½" pipe railings.
North of MSC-01879. SW of CS on track 11. 1936.

MSC-02071 Stoneware sink.

MSC-02108 Steel Hood and Duct. 2' x 4' counter balanced with 6" dia. steel duct to outside of Bldg. Hood located over F-0159 G. E. Filter Press.

XII. EQUIPMENT LIST, contd.

Miscellaneous Equipment, contd.

MSC-02426	Ducts, hoods, dampers.	
MSC-03417	Air cond. unit.	
MSC-03523	Vac. ejector. Worthington, Porcelain, Karbate. 10" Porcelain condenser. 10 lb. hr. air at 2 mm cbs. 150 psig steam. 65°F. well water.	
MSC-03611	Duct and hood.	
MSC-03689	Haveg sink. 4' 8" x 19" x 18".	
MSC-03706	Water cooler. Drinking water.	
MSC-03741	1/2 T chain hoist above F-0172.	Pyranol plant
MSC-03835	1/2 T chain hoist - #2 mix tank.	
MSC-04018	Work bench	
MSC-04109	Lightnin mixer (only - not motor) 7½ HP side entering metallized with 0.015" Al. See CT-02621.	
MSC-04132	Water cooler.	
MSC-04442	Hand hoist.	

Heaters for plant office and for instrument and control room.
Gas supply and metering.
Water hose with steam mixing jet for cleaning the floor.
Desks.
Clothes lockers.
Test bench.
Phone.
Clock.
Framed instructions for special pieces of equipment.
Drinking water supply.
First aid cabinet.
Fire alarm & extinguishers. Sprinklers installed in all rooms.
Hose connections for casual gas heating.
Waste cans.
Used water collection.
Lighting.

XII. EQUIPMENT LIST, contd.

Open Tanks

OT-0640 Drum, 110 gal. ICC5, CABI #217-1941. With float valve on city water line. Connect 3 GPM pump P-0378. To pump from drum through rotometer to acid absorption system.
Black Iron
$18.30 as trans from Dept. 360.

Seal cans for barometric legs of the ejectors.
MSC-0760, -01292, -01685. On the ground floor.

OT-0751 Steel vessel 4'0" I.D. x 6'0" high, for city water, to conform to state law.

XII. EQUIPMENT LIST, contd.

Pumps

Note: The pumps are changed around from one duty to another, in the course of ordinary maintenance work, but the details given below will serve to show what type of pump is used for any given duty. Oversized pumps may be used in some cases to diminish the number of types required in the department.

P-0346 Swaby Submerged Pump made up 11/18/29. Size #1½, Cast Iron. On CT-0848. In TCB store tank, CT-0848.

P-0378 Chas. Lewis pump Serial 4597, Type BA-481, cast iron vertically split shell cent. pump. CI bed plate connected with flex. coupling, direct to 1/4 HP 3600 RPM motor. GE M-0466, 3 gal. PM - 35' head, 3450 RPM. Order B693 on 1/15/31. Price $68.00 incl.motor, M-01772. Boosts city water to HCl absorber.

P-0427 Horizontal cast iron pump 1½ HP Monsanto Design. Direct connected, cold rolled steel shaft, includes base, coupling and c guard.

P-0565 Blackmer pump, Serial 197033, type PA-50L bronze rotary pump, bronze lining, bronza steam jacketed heads, monel shaft, CI base, 1.65 sp. gr., temp. 350 to 500°F. - 50 gal. Order B-8170 on 4/23/36. Chg. out $155.45 on 6/30/36. Distillate transfer pump.

P-0571 Oberdorfer gear pump for filter press. Motor M-01650.

P-0573 Vertical submerged centrifugal pump purchased from The Engineering Equipment Co. Serial 33007, Size L-OB with 1½" inlet and 1" outlet. Compare P-0604, which is a Taber pump on #4 scrubber CT-0759.

P-0574 Ditto.

P-0575 Taber submerged pump. Serial 33009. Order B7517 on 4/16/36. Req. 9161. Chg. out $177.80 on 6/30. Direct to vertical M-0848 in CT-0756 on #1 scrubber. Same as P-0573 and 0574.

XII. EQUIPMENT LIST, contd.

Pumps, contd.

P-0578 Taber horizontal centrifugal pump. Serial 33040. Type L-2, 2½" inlet 2" outlet connections. Semi-steel with monel shaft and water jacketed stuffing boxes. Bed plate ready to receive motor. 20' static head, rate 80 g.p.m. 1.5 sp. gr. at 500°F. Uses M-0849. On #2 chlorinator, CT-0744.
Order B8237 on 4/24/36, Req. 69401.
Chg. out $152.92 on 6/30.

There are four pumps P-0578, 0579, 0629 and 0907, one for each main chlorinator.

Liquor in from chlorinator bottom outlet and out back to the chlorinator. The charge can be pumped, if necessary, from one chlorinator to another, or to the air-blowing vessels CT-0750 and CT-2086.

No. 1 chlorinator can be emptied by gravity to the gas-fired chlorinator CT-0808, and there is also a pump line for the same service (disused). The charge from No. 1 chlorinator can be pumped directly to No. 1 vacuum still S-043.

There is a line by which partly chlorinated diphenyl can be pumped from a chlorinator to any scrubbing tank, CT-0759, -0760, -0761 or 01014.

There is a sampling cock on each pump delivery, with a small box to hold the used sample material, and to deliver it back to the pump intake.

P-0579 Taber horizontal centrifugal pump. Serial 33041. Same as 0578-80. For middle chlorinator CT-0744, uses M-0850. On #3 chlorinator CT-0833.

P-0580 Taber horizontal centrifugal pump. Serial 33042. Same as 0578-79. From blow tank CT-0750. Uses M-0851.

XII. EQUIPMENT LIST, contd.

Pumps, contd.

P-0582 Taber vert. submerged centrifugal pump. Serial 33048. , Fig. 1940, size C-3, 2½" inlet, 2" outlet connections, bronze except shaft which is monel metal. 11'6" length of column pipe. Spare pump for underground tanks. Order B7514 on 4/16/36, Req. 69158. Chg. out $409.20. Direct to M-0852. Same as P-0583 and 0584. Used in Aroclor 1260 store tank.

Submerged pump in CT-0768 TCB store.

P-0583 Taber vert. subm. cent. pump. Serial 33049. In CT-0769, direct to M-0853. Same as P-0582-0584. Aroclor storage.

P-0584 Taber vert. sub. cent. pump. Serial 33050. In CT-0768, 1254 store tank, direct to M-0854. Same as P-0582 and 0583.

P-0585 Taber vert. sub. cent. pump. Serial 33069, Dwg. A387, Type C-3, fig. 1940, 2" inlet and outlet. CI body, renewable bronze bearings, bronze impellor mounted on nickel steel shaft. Length 11'6", sump cover plate, cap. 50 gal. p.m., 60' static head, sp. gr. 1.18 at temp. 165°-170°F. Driven by M-0856 in CT-0748, Diphenl store tank. Order B7518 on 4/16/36, Req. 69162. Chg. out $257.62.

P-0592 Taber vert. sub. cent. pump. Serial 33113, type C-3, Fig. 1940, 2" inlet and outlet. All iron construction on nickel steel shaft length 11'6". Cap. 50 g.p.m., 60' static head, sp. gr. 1.368 at 70° to 90°F. In CT-0749* driven by M-0873. Order B7516 on 4/16/36. Req. 69160, chg. out $255.41.

* general service and diphenyl tank.

P-0593 Taber vert. sub. cent. pump. Serial 33111. Type L-2, fig. 1940, 2½" inlet and 2" outlet, casing, yoke, impellor made of steel shaft nickel steel, column supporting intermediate bearing, wrought iron. Length 7'9".

XII. EQUIPMENT LIST, contd.

Pumps, contd.

P-0593 contd.
Cap. 75 GPM, static head 15', sp. gr. 1.8 at temp. 700°F.
Driven by M-0871. On Number 1 still.
Order B7515 on 4/16/36, Req. 69159. Chg. out $382.91.
In still S-043. Same as P-0574. Sump plate.
Drawing A-493.

P-0594 Spare motor same as P-0593. Serial 33112.
Driven by M-0872.

P-0595 Oberdorfer gear pump. Serial 2835. #7AXZ unloader pump, all bronze gear type. 10-15 GPM at 20# pressure. Used to circulate Aroclor on No. 1 still cooling system.
Order B13188 on 7/2/36, Req. 71152. Cost $78.80.

P-0604 Vert. sub. cent. pump. Taber. Serial 33207, Size L-OB, 1½" inlet and 1" outlet. All iron const., open impeller on nickel steel shaft. Same as P-0573-4 and 5. In CT-0754.
Order B13195 on 7/2/36, Req. 71148 on 7/2/36. On #3 scrubber, CT-0761.

P-0615 Blackmer Pump Serial #201747.
Size 502, 50 gallon per min. right hand rotary gear pump. Bronze with bronze liner and monel shaft. Steam jacketed heads.
Order B20818 on 10/16/36. Req. 73912 on 10/16/36
Chg. out $148.27 on 11/30
Direct to 3 HP 1800 M-01449.
On filter press P-0159.

P-0617 Blackmer pump. Serial 201902. Size 100L, all iron, jacketed right hand pump, base plate for motor, and flex. coupling, direct connected (M-0914). Order B21241 on 10/22/36, Req. 74034. Chg. out $145.20.
Spare pump.

P-0629 Taber horiz. cent. pump. Serial 33708. Type L-2, 2½" inlet and 2" outlet, Size 103. Order B2833 on 2/9/37. Req. 76766 on 2/5/37. Chg. out $152.52. Direct to M-0975.
On No. 1 chlorinator.

XII. EQUIPMENT LIST, contd. P-0674 - 0984

Pumps, contd.

P-0674 On #1A scrubber, CT-01013, driven by motor M-0848 on No. 1 chlorinator.

P-0731 Taber sub. cent. pump. Serial 84722, Size L-OB, 1½" inlet and 1" outlet. Order B3854 on 3/4/38, Req. 86891 on 3/3/38. Chg. out $174.25.
In CT-01013.

P-0907 Taber horiz. cent. pump. Serial 36622. Size 103, type L-2, 2½" inlet and 2" outlet connections, semi-steel through out with monel shaft and water jacketed stuffing boxes, with bed plate ready to receive motor, 20' static head, rate 80 GPM, 1.5 sp. gr. at 500°F.
Order B12801 on 6/5/40, Req. 10230 on 6/5/40.
Chg. out $155.28, driven by M-01656 to circulate liquor for chlorinator CT-01283, #4 chlorinator.

P-0909 Taber sub. pump. Serial 36676. Size L-OB with 1½" inlet and 1" outlet, all iron const., open impeller on nickel steel shaft. Order B13110 on 6/10/40. Req. 10366 on 6/10/40. Chg. out $193.75. On CT-0968 scrubber liq. tank. Also on CT-0760.

P-0929 Taber sub. pump. Serial 36853. Size C-3, fig. 1940, vertical 2½" inlet and 2" outlet. Bronze except shaft to be monel metal, lg. of col. pipe 11'6". Order B18442 on 8/23/40. Req. 12559 on 8/23/40. Chg. out $404.59. On stg. tank CT-01310.
Driven by M-01706.

P-0932 Roper cast iron pump. RIBI #169. Size 1" rotary, geared, complete with base, gears, pinion, big stand and adapter plate for motor mounting.

P-0984 Roper pump. All iron series "O" rotary pump for 35 GPM. 1.6 sp. gr. 50' head pump, spiral gears pkgd. stuffing box with non-graphitic white asbestos pkg. built in by-pass and complete with base, drive gears.
Order B4118 on 2/17/41, Req. 18322 on 2/17/41. For filter in CR. On Sparkler filter P-0172. Replaced by P-0571.

XII. EQUIPMENT LIST, contd.

Pumps, contd.

P-0997 Taber vert. sub. pump. Serial 37682. Type CLA, 2½" inlet and 2" discharge for 75 GPM against 25' head. Pump of dynamo steel with wrought iron pipe column and nickel steel shaft, water cooled, stuffing box.
Order B6379 on 3/13/41. Req. 19214 on 3/13/41.
Chg. out $446.53. In S-062.
Driven by M-01856. Shaft has two intermediate C.I. bearings.

P-01037 Blackmer pump.. Serial 246058. 5WG3202 bronze, size 51L with base and relief valve. Still receiver to blender.
Order B16057 on 7/21/41. Req. 22429 on 7/21/41.
Chg. out $177.56. On gr. fl. NE of P-0172.

P-01054 Pump made by Weil. Serial 13132. Type DSI, size 1". Uses city water. Order B4625 on 2/21/41. Req. 18520 on 2/21/41. Cost $65.00. On TW-0221. Driven by M-01995.

P-01056 Taber horiz. cent. pump. Serial 38318. Type L-2, size 103, 2½" inlet 2" outlet complete with base. Order B19730 on 9/3/41, req. 24125 on 9/2/41.
Chg. out $157.44 on 4/31/44. On #4 chlorinator CT-01283.

P-01111 Blackmer Pump Serial 249113. #5 OL all iron steam jacketed pump with CI base plate and gear drive ready to receive our 3 HP 1800 RPM motor size 511. Order B16349 on 7/23/41, Req. 22597. Chg.out $105.05. Driven by M-02877. For discharging rail tanks.

P-01258 Blackmer pump, Serial 269500, Size 1202-50. Fig. 3203 complete with relief valve. No base. #2 still receiver to blending tanks.
Order B29303 on 1/28/43. Req. 40312 on 12/30/42.
Chg. out $134.63.
Bronze.

XII. EQUIPMENT LIST, contd.

Pumps, contd.

P-01277 Taber vert. sub. cent. pump. Serial 40890. Type CL-4, 2½" inlet, 2" outlet, size 384. Pump to be dynamo steel with wrought iron pipe, column sup. of pump 75 GPM at 25' head for liquid 1.8 sp. gr.
Order B8875 on 7/12/43, Req. 43713 on 4/16/43.
Chg. out $434.00 on 12/27/43.
At S-062 Spare. Same as P-0997.
#2 still pump (spare).

P-01509 2" Taber pump. 80 GPM. 130 ft. TDH. Steel with monel shaft. Flexible coupling. M-03014.
S. G. 1.5 500°F.

P-01540 G. E. Filter pump - N. W. corner of lean-to. Taber pump 304 stainless steel, 2" suction, 1½" discharge. Located indoors. Pumps from old Pyranol blender CT-01321 to filter presses.

P-01757 On Sweetland filter P-0239. Now used on P-0238. 304 stainless steel 2", 100 gpm. Motor M-03718.

P-02052 2" Taber. Semi-steel, monel shaft, water jacketed stuffing box. 1.5 S. G.,500°F.

P-02077 Blackmer pump, from TTCB store to blenders. Bronze lined, with monel shaft. N.W. of Bldg. CR.

P-02078 Taber 3" x 2½" 150 gpm. 80 ft. head. Horizontal impeller.

P-02179 Taber Pump from new blender CT-02621 to filters. Motor M-04025.

P-02251 Viking pump on Aroclor mixers. M-0514. Pyranol plant.

(f) porphyria; (g) effects on the kidney; and (h) miscellaneous changes including hematologic alterations, thymic atrophy, and lymphatic changes.

There is a considerable range of species susceptibility to biological activity of the PCBs, with one representative comparison of order of decreasing activity being mink, monkey, rat. It is concluded that there is no basis for determining which species most accurately serves as a model for prediction of general subchronic/chronic toxicity in man; rather, the judgment of the most suitable surrogate for man must be made independently for each major health effect. Finally, it is noted that although there is some similarity between acute health effect phenomena produced by PCB exposure in the monkey and human Yusho disease, it would be incorrect to equate Yusho disease with PCB intoxication because of the much more complex mixture of compounds encountered in Yusho oil than in a commercial PCB mixture.

Skin and Other Cutaneous Tissues

Commercial PCBs are capable of producing skin lesions in the monkey model and in exposed humans. Chronic administration of PCBs to the monkey produces chloracne. In humans occupationally exposed to PCBs skin disorders including chloracne have occasionally been observed. These skin disorders have been shown to be reversible in some of the animal and human studies.

XII. EQUIPMENT LIST, contd.

Pumps, contd.

Note:

London Engineering Dept. Final Report on the start-up of the Newport Aroclor plant states that Hamworthy pumps were not found satisfactory in use. Good jacketing is needed.

There was trouble from corrosion of core plugs in some pumps, leading to leakage of steam into the goods.

Steel end covers were used later.

The same reports discuss the difficulties encountered with the still pump, which was located in a small secondary vessel, below the vacuum still.

XII. EQUIPMENT LIST, contd.

Retorts

R-026 Aroclor 1269 Retortassembled and erected by Monsanto.
Pots from Wooter. $516.00 for 4.
Jacket from Graver. Req. B69906.
Burners from Surface Combustion. Req. 69374.
Burners - gas fired.
Jacket, steel, firebrick lined, holding 3'0" OD x 3'8" lg. over dished bottom still pot with cover. Equipped with 2 gas burners and stack. Still pot 1/2" fire box steel,removable so residue can be dumped.

R-027 Aroclor 1269 Retort - Same as R-026.

Drawings: B-646 Retort.
E-865 Setting.
B-374 General arrangement of solid Aroclor plant.
C-830 Gas heater for discharge line.
C-821 Platform for retorts.

Mr. Soffranko in 1947 commented that the retorts would be better with thicker bottoms than shown in drawing B-646, and that spare retorts should be held.

XII. EQUIPMENT LIST, contd.

Stills

S-043 No. 1 Vacuum still purchased from Graver. Plant A Drawing C-809. Size 6' dia. x 5'6" long on straight side, 1/2" shell, dished head 5/8" supporting brackets 60# Hydro press test.
Order B-7705 on 4/17/36, Req. 69225, Chg. out $336.00 on 2nd floor, 12' level.

S-043, No. 1 still, at the Krummrich plant, is of the shallower type, like the Anniston stills, and like them it has a vertical vapour pipe (with Hagan separator inside the still), leading to the top of a vertical condenser, CT-0770, whereas No. 2 still is of the deeper type, and has a cyclone, CT-0141J in place of the vertical vapour pipe and the separator. The cyclone returns a considerable amount of darkish liquid, through a sight glass, to a return line going nearly to the bottom of the still body. Mr. Purzey, December 11, 1951 reported that the cyclone gave better coloured distillate than did the Hagan separator. Anniston, January 1950, reported satisfactory performance of their Hagan separators. Newport have the internal Hagan separator.

In a report dated March 31, 1952, Mr. Dalton of the Krummrich plant mentions a modification to the Hagan separator at the Krummrich plant. The Aroclor colour was better after the change, but it was not certain that the alteration really caused the improvement.

There is no attempt at fractionation, and the condensing systems were planned to give the lowest pressure drop attainable, consistent with removal of coloured entrainment particles. The deeper pattern of still S-062 was chosen to give more disengagement space for vapour, but it does not appear to have given any better coloured distillate, and it has the disadvantage of requiring a longer shaft etc. for the submerged pump. The condenser on No. 1 still delivers to receiver CT-0771

XII. EQUIPMENT LIST, contd.

Stills, contd.

S-043 contd.
No. 2 still has heat exchanger CT-01491, head tank CT-01398 with gravity flow (of cooling water only) to condenser CT-01378. CT-01398 has an internal coil (not used) and there is no temperature control instrument .

The distillate goes to receiver CT-01377.

The temperature of the distillate is roughly controlled by hand adjustment of the flow of water from CT-01398 to the condenser CT-01378.

The Newport vacuum still was provided with a subsidiary vessel, located at a lower level than the main vessel, and containing the submerged pump. With this arrangement, it was hoped to diminish the liability of cavitation of the pump, and to permit the use of a much shorter shaft for the pump impeller.

The arrangement, however, was unsatisfactory, largely because the pump gland was exposed to hot liquid Aroclor (See the London Engineering Dept. Final Report on the start-up of the Newport plant).

Numerous different gland packings were tried, the gland was given a lantern ring, fed with liquid Aroclor etc. etc., but finally a long vertical steam jacketed pipe was fitted on top of the secondary vessel, to carry the stuffing box above the level of the charge in the main still. This location also put the driving motor into cooler surroundings, and the new arrangement has been made to work satisfactorily, though it brought back the troubles of the long shaft.

In the pump assembly, the pump is hung from a manlid on the still cover, on a wide pipe down the centre of which the pump shaft runs. The delivery pipe from the pump runs independently up through the same manlid on the cover of the still (welded through). Differential expansion may distort the alignment of the parts, and may

XII. EQUIPMENT LIST, contd.

Stills, contd.

S-043 contd.
displace the impeller axially within its casing. Another trouble which appeared was that air leaking in through the gland could travel down the central pipe around the shaft and cause cavitation in the pump. The remedy for this is to have holes in the pipe, communicating with the main vapour space in the vessel.

The stuffing box is water cooled; the bearings inside the still may give trouble, this clearance must be just right. Carbon bushings have shown some promise. It has to be remembered that the charge contains a fair amount of solid (lime) etc. which might lodge to some extent in the still instead of flowing to the secondary vessel.

The internal bearings are lubricated by Aroclor bled off the pump delivery line, but they may become choked by the solid matter in the charge.

See also the description of the Anniston still and pump on pages 20-, Section VI, above, and comments on the distillation process, pages 4-, Section VII.

From the bottom of the condenser at the Krummrich plant, the distillate passes through a jacketed line to a jacketed sight glass with sampling fitting, and so to one of the receivers CT-0771 or CT-01377. There is a ring of gas burners around each condenser exit, to deal with the heavier Aroclors, but the burners are not much used.

Condenser CT-0770 can be cooled by Aroclor circulated by pump P-0595 through the condenser shell space then through heat exchanger, CT-0831 (cooled with well water) and through a sight glass to head tank CT-0766, and so back to the pump. This system is alternative to the cooling by distilled water used on this condenser, but it has gone out of use since the Krummrich plant gave up the production of the higher Aroclors.

XII. EQUIPMENT LIST, contd.

Stills, contd.

S-043 contd.
There is a steam and water coil in the head tank to keep the Aroclor at around 110-120°C. There is a Taylor Fullscope temperature controller I-0510 controlling a valve on the steam inlet to the coil. This Aroclor cooling is more convenient for higher Aroclors, but the water system is preferred for the lower Aroclors.

The system normally works at about atmospheric pressure though the vent (on the top of heat exchanger CT-0831 is usually kept closed, and there is a pop valve at the same point).

The sketch on page XII - 82 will serve to show the arrangement and to indicate certain minor features not described above.
Each still has a bottom outlet which will completely empty the still, also an outlet at about the same level of the top of the bottom dish, which will leave about 80 U.S. gallons of bottoms in the still. Both deliver to open topped cans on small wheeled "dollies" under a hood ventilated by suction fan B-0148. Rising stem gate valves are used on these outlets and gas flames are freely used to heat them for some time before the still is to be tapped.

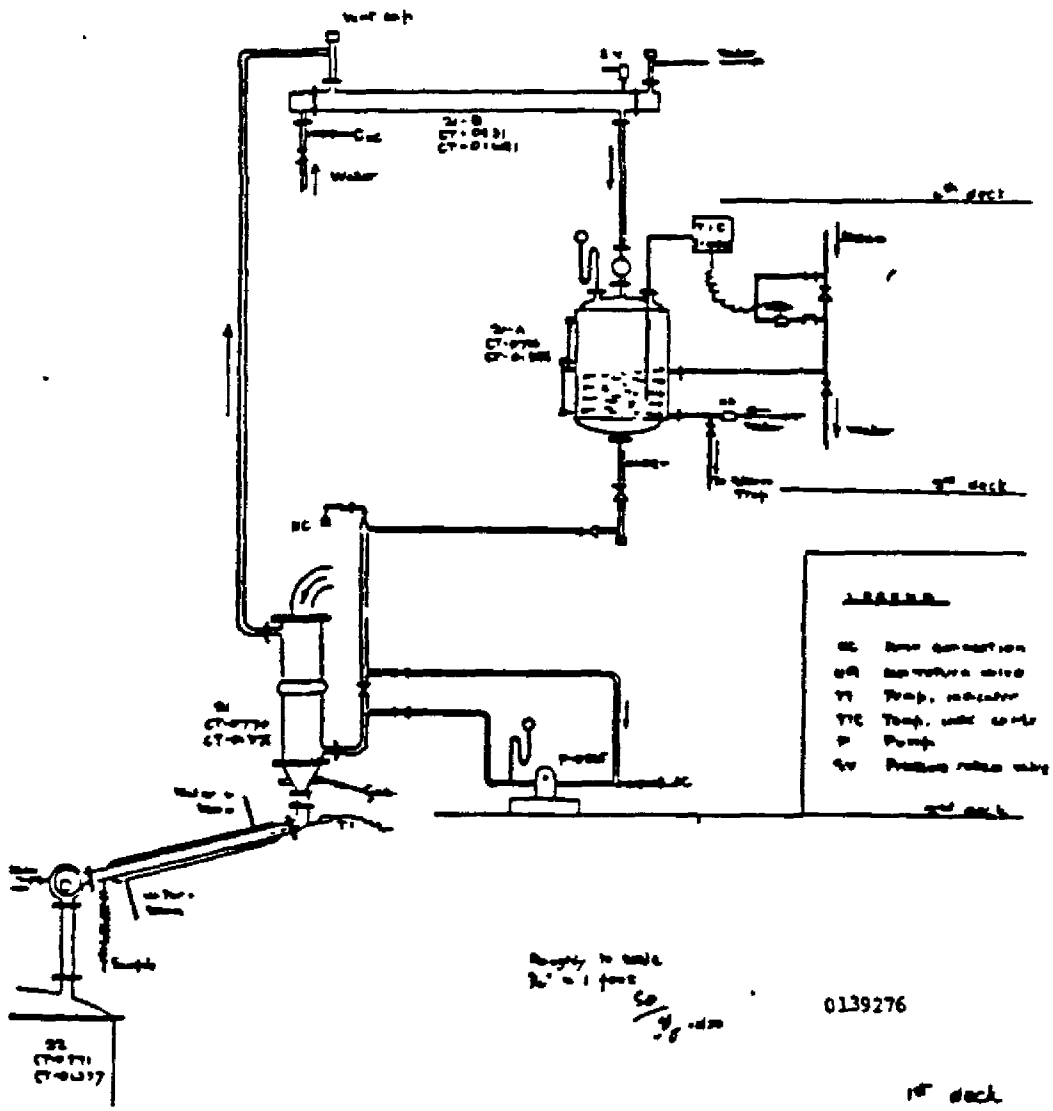
Bottom outlet also to emergency tank CT-0749, but this vessel is now used as extra storage for diphenyl.

The deeper still has a thermo well obliquely through the side wall, about 7'6" below the cover, but this well was not in use May 1955. Each still body has a BS & B relief disc of AlPb, 8" diameter, vacuum supported, calibrated to rupture at 25 psig. The receivers do not have relief discs.

XCI - 82
Equipment List

COOLING SYSTEM, AROCLOR CONDENSERS.

Plant "B" July 1936



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XII. EQUIPMENT LIST, contd.

S-043, contd.

Drawings.

B 483	Water-cooled condenser on No. 1 still	CT-0831, -01397, -01491
A 493	Sump plate for submerged pump	S-043
B 644	Head tank for cooling medium	CT-01398
B 651	Tubular condenser	CT-0770, -01378
B 662	Vapour exit pipe	S-042
C 795	Receiver	CT-0771
C-807	Coke tower	CT-0753
C 809	No. 1 Still	S-042
C 815	Piping of vacuum still - PC-045,CT-0770,-01377	
C 864	like B 483, on No. 2 still	S-062
C 6942	Piping diagram, No. 2 still	S-062
C 6943	Piping diagram, No. 2 still	S-062
D 6944	No. 2 still	S-062
E 6952	General layout No. 2 still	S-062
D 6956	General layout, No. 2 still with cyclone, receiver, and coke scrubbers.	
D 6957	Cyclone on No. 2 still	S-062
B 7082	Monel condenser on No. 2 still	CT-01378

XII - [redacted]
Equipment
List
S-062
-0459

XII. EQUIPMENT LIST, contd.

Stills, contd.

S-062 #2 Vacuum still purchased from Nooter. Serial #52. Dwg. D-6944, 6' ID x 11'10" str. shell, internal pipes, etc. Std. dished heads. Glass wool insulation 3" with 1/2" finish coat.
Order B10730 on 5/12/41, Req. 20421 on 4/28/41.
Chg. out $950.00. Suspended between 20'6" and 12' platform in CR.

S-0459 is another number for C-0808, gas fired chlorinator.

XII. EQUIPMENT LIST, contd.

Scales

SC-094 Howe Portable Scale #822, Serial 1363205, all iron platform 30½" x 30½". Cap. 1500 lb. Order B9986 on 5/20/36, Req. 69955, Pyranol Plant.

SC-098 Howe scale. Serial 1364566. #1420 Skeleton type, ball bearing, dormant scale, cap. 2500# with double beams. Platform 46 x 38. All metal incl. steel shaft. Order B14351 on 7/20/36. Req. 71536 on 7/17/36. Price $213.85.

SC-0100 Scale purchased from The Exact Weight Scale Company. Serial 39992. Style 1226, cap. 200# on ratio of 10 to 1. Dial with indicator travel 12½" under wgt, and 2½" over wgt. Fitted with bag holder for 100 to 200# bags. All on swinging rack.

Order B17906 on 9/9/36. Req. 72843. Chg. cut $289.41.

In lean-to near V-044 and V-045.

SC-0246 1000 lbs. capacity, Pyranol Plant.

Liver Effects

PCB mixtures are capable of generating important effects on liver tissue in animal models. These effects include: (a) increase in liver weights; (b) histopathologic changes in liver including enlarged hepatocytes, deposition of fat droplets in tissue, and tissue necrosis and cell death; (c) enlargement of the liver; (d) the occurrence of adenofibrosis, a benign lesion; and (e) an increase in proliferative lesions of the liver, including increases in hyperplastic foci and nodular hyperplasia. These increases in proliferative lesions appear to increase in severity with increasing degree of chlorination of the PCB mixture, as seen in the greater potency of Aroclor 1260 over Aroclor 1254. The effects on liver tissue are generally reversible at lower doses but trend toward irreversibility with increased dosing.

However, in contrast with the positive findings of PCB effects on liver tissue in animal models, no significant effects on liver function tests have been observed from clinical data on human populations exposed to PCBs in the occupational setting. Furtber, there has been no epidemiological finding of liver disease in U.S. occupationally-exposed personnel. Also, as noted in the Yusho discussion about persons exposed to contaminated cooking oil with a PCB content of 1000 ppm, there was no finding of liver disease in the categories of either jaundice or hepatocellular injury.

XII. EQUIPMENT LIST, contd.

Transformer

T-014 Transformer made by Westinghouse. Serial 530335. 200 KVA, type SK, now used 440 volt primary 110/220 volt secondary. On the heater of the Lectrodryer FC-046. Cost $10.00. Outside SW corner Bldg. CR.

Also used formerly for strip heaters in the still receivers, etc.

XII. EQUIPMENT LIST, contd.

Towers

TW-0166 Fused Silica Tower purchased from Amercel Co. Inc. 1 "U" bend trap. 12 absorbers sections B/P Gill 8" ID x 6'6" C to center. Order B8161, Req. 69399. Same as TW-0165. Regarded as obsolete design.

TW-0182 Scrubbing HCl tower made by Haveg. Drawing C-4705. "41" std. 2'6" dia. 10'2" deep, 5/8" thick walls x 3/4" thick bottom, machined dished head, and connecting material, 2" thick Haveg drilled plate with necessary supports 4-3", 1-8" and 1-10" std. Haveg nipple type outlets with flgs. Order B20284 on 10/5/37, Req. 83234 on 10/5/37. Chg. out $668.56 on 12/31/37. On 38' level steel struct. south side of CR.

TW-0206 Scrubbing Tower purchased from Nooter. Drawing B-5815 support, drawing C-5814 tower. 17-18" ID x 8' welded steel const..tower, welded steel scrubber support for tower. Order B7346 on 3/27/40. Req. 8063 on 3/27/40. Chg. out $277.00 on 4/30/40. Above CT-0756, scrubber by pump tank.

TW-0221 HCl absorption tower purchased from Fan Steel Metallurgical Corp. Serial 955-1941. Drawing D-4300 foreign. PA #147. Type AL-400. The tower, fittings and piping made of Karbate. Gas line of Haveg. Cap. to produce 20Be° Baume HCl at 4620# per hour. Order B4625 on 2/21/41. Req. 18520 on 2/21/41. Chg. out $5321.13 on 8/21/41. On steel struct. S of CR.

Schwarting and others "Process Description --- For Aroclors", November 12, 1953, state that the Fansteel off-gas absorbers are constructed of Haveg 60, and have Tantalum heat exchange surfaces.

TW-0312 Absorption tower. Fansteel AL-300. Haveg 60 parts. Tantalum tubes, (some tantalum parts salvaged from an older unit.)

XII. DRAWING LIST

Note:

Some of the earlier drawings were made at the JPQ plant, and the later ones at the Krummrich plant. As the two plants have independent numbering systems it is necessary to specify which plant is concerned. The drawings marked "A" in column 2 on the following pages are from the JPQ plant, whereas those marked "B" are from the Krummrich plant.

In column 3, on the following pages, the letter

"L" indicates that prints of drawings were sent to Mr. Cooper, London, by air mail, April 24, 1947.

"S" indicates that prints of drawings were sent to Mr. Cooper, London, by surface mail, April 24, 1947.

"N" indicates that the drawings in question do not appear to be of interest to MCL.

"M" indicates that the drawings were not available April 23, 1947.

"F" indicates that the drawings were found July 28, 1950, and that prints were sent to Mr. Buis, London.

XII. EQUIPMENT LIST, contd.

Conveyors

V-044 Screw conveyor made by Easmueller MF Co. Drawing C-816. Size 6", 6'8½" trough length with outlet at each end. Cover of galvanized iron. CI trough ends with zinc and tin sprayed. Req. 69909. On bottom CT-0764 - North Conveyor. From stg. bin to bagging scale and back to boot of elevator, driven by M-0835.

Layout - E-877.
Flow Sheet - E-640

V-045 Screw conveyor made by Easmueller MF Co. Drwg. C-816. Size 6", 6'8-½" trough length with outlet at each end - cover of galv. iron. CI trough ends with zinc and tin sprayed.

Req. 69909. On bottom of CT-0765 south conveyor. From storage bin to bagging scale and back to boot of elevator, driven by M-0836.

V-046 Screw conveyor made by Easmueller MF Co. Drawing C-816. Same as V-044 and 045. From flaker discharge to elevator boot. Driven by chain on M-0827.

All these were part of the equipment for Solid Aroclors: dismantled in 1952

XII. DRAWING LIST

Drawing Number	*	*	Title	Equipment Number
A-324	A	L S	Gas-heated chlorination pot(see E-888)	CT-0808
E-346		N	Muriatic treatment vessel	CT-0861
P-352		N	Fractionating column(not Aroclor plant)	
P-370	A	L S	General Layout	Layout
P-373	A	L S	Ducts for process fumes,solid Aroclors	D-012 etc.
P-374	A	L S	Layout, solid Aroclors	Layout
P-375		N	Structural steel	
P-376		N	Steel and foundation	
P-380		N	Electrical layout	
P-381		N	Electrical conduits	
P-382		N	Lighting	
P-383		N	Service lines	
P-384		N	Foundation details	
P-385		N	Structural steel, Muriatic tower	
P-386	A	L S	Piping layout	Piping
P-389		N	Electrical details	
P-394		N	Gen. arrt. HCl absorption	
A-459	A	L S	Bearing for blender shaft	CT-0779

* * See note on page 86 in this section.

XII - Drawing List

XII. DRAWING LIST, contd.

Drawing Number	*	*	Title	Equipment Number
B-483	A	L S	Water-cooled condenser for vac.still	CT-0831 CT-01307
A-493	A	L S	Sump plate for submerged pump in vac. still	CT-01491 S-043
A-501		N	Lead-lined tray for HCl absorber	
C-502B		N	Sand filter for muriatic acid	
D-512	A	L S	Storage hopper for solid Aroclor	CT-0764 CT-0765
D-518	A	L S	Chute for Aroclor flake	D-012
C-605	A	L S	Shear pin on drive of gas-heated chlorinator	CT-0808
D-609	B	N	Store tanks	CT-0748 CT-0749 CT-0768 CT-0769 CT-01310
B-613	A	L S	Relief door gas-fired chlorinator furnace	CT-0808
B-640	A	L S	Flow sheet	Flow sheet
B-643		N	Separator, not installed	
B-644	A	L S	Cooler on vac. still system	CT-0766 CT-01398
B-645	A	L S	Cyclone on solid Aroclor plant	CT-0751
B-646	A	L S	Still pots for solid Aroclor	R-026 R-027
B-651	A	L S	Heat exchanger on vacuum still	CT-0770 CT-01378

* * See note on page 86 in this section.

XII. DRAWING LIST, contd.

Drawing Number	*	*	Title	Equipment Number
B-653	A	L S	Stack for solid Aroclor plant	CT-0751
B-654	A	L S	Support for stack	CT-0751
B-658		N	Floor gratings	
B-659	A	L S	Chlorine inlet	CT-0745 CT-0833
B-660	A	L S	Cyclone - not identified	
B-661	A	L S	Elevator drive, solid Aroclors	L-031
B-662	A	L S	Vacuum still vapour pipe	S-042
B-663	A	N	Supports for vent line scrubber	CT-0762
B-664	A	N	Vac. still furnace vent pipe	S-042
B-666	A	L S	Thermocouple wells	
B-675	A	L S	Hood, etc. of flaker	D-102
B-684	A	obsol-ete	Strip heater clamp for chlorinator	CT-0808
B-685	A	obsol-ete	Heater for Sperry press	P-0172
B-686	A	N	Vent stack	FC-045
B-689		N	Vent stack	FC-045
C-795	A	L S	Vacuum still receiver	CT-0771 CT-01377
C-798	A	L S	$CaCl_2$ breather	CT-0762
C-799	A	L S	Diphenyl head tank	CT-0767
C-800	A	L S	Scrubber liquor tank	CT-0754 CT-0755 CT-0756

* * See note on page/in this section.

XII. DRAWING LIST, contd.

Drawing Number	*	*	Title	Equipment Number
C-804	A	N	Hot water collection tank	CT-0752
C-807	A	L S	Coke scrubber	CT-0753 CT-01396
C-809	A	L S	#1 vacuum still	S-043
C-810	A	L S	Melt tank for high boilers etc.	CT-0763
C-815	A	L S	Piping of vacuum still	PC-045 CT-0770 CT-01378
C-816	A	L S	Aroclor conveyor	V-044
C-818	A	L S	Chlorine vapourizer	CT-0743
C-821		N	Platform for still pots	R-026, R-027
C-822	A	L S	Chlorinator relief connection	CT-0744
C-823	A	L S	Muriatic acid store tanks	CT-0784 CT-0785 CT-0786 CT-0795
C-827	A	L S	Weighing truck, solid Aroclor plant	MSC-0681
C-829		N	List of motors	
C-830	A	L S	Gas-heater for discharge of gas-heated chlorinator	CT-0808
F-838		N	18" fractionating column, not in Aroclor plant	
C-847		N	Holder for strip heater	CT-0771

* * See note on page 86 in this section.

XII. DRAWING LIST, contd.

Drawing Number	*	*	Title	Equipment Number
C-848		N	Holder for strip heater	CT-0771
E-876		N	Floor grating	
E-862		L S	#1 Blending tank and #1 Filtrate receiver	CT-0779 CT-0760
E-863		L S	Buffer tank (air blowing tank)	CT-0750
C-864	A	N	Heat exchanger for #2 vacuum still (see drawing B-483)	S-062
E-865	A	L S	Setting for stills for solid Aroclor	R-026, R-027
E-867	A	L S	Setting for fireheated chlorinator	CT-0808
E-870		N	Conveyor for Aroclor flake	L-031
E-877		L S	Conveyor for Aroclor flake (layout)	V-044
E-880	A	L S	Chlorinator	CT-0744 CT-0745 CT-0833
E-881	A	L S	Shell for gas-fired chlorinator furnace	CT-0808
E-886		L S	Shell for above and brick setting	S-043 P-045
E-888		L S	Drive for gas-fired chlorinator	CT-0808
E-889		N	HCl absorption tower	
E-896		N	Floor grating, HCl tower	
D-978	B	L S	Diphenyl store tank	CT-0347

* See the note on page 86 in this section. 0139288

XII. DRAWING LIST, contd.

Drawing Number	*	*	Title	Equipment Number
C-1117	B	N	Foundation of D-978	
D-2076	B	L S	Turbo agitator for blending tank	CT-0779
D-2077	B	L S	Stator for above	CT-0779
C-3479	B	N	Heating furnace for coil of #2 vacuum still	FC-066
C-3775	B	L S	Filter for HCl gas	F-0106
D-4252	B	L S	Muristic tank	CT-01260
D-4300		N	Pansteel drawing HCl absorber	
E-4366	B	P N	Varec. Gauge on Pyranol mixer	CT-01321
E-4413	B	L S	T.C.B. Store tanks	
D-4459	B	L S	Rubber-lined treatment tank with agitator	CT-0861
C-4616	B	L S	Scrubber liquor pump tank	CT-0968 CT-01013
E-4679		N	Obsolete, Layout for HCl absorber	
E-4689		N	Obsolete, Piping of HCl absorber	
C-4705	B	L S	Haveg tower (obsolete) for HCl abs.	TW-0182
C-4845	B	L S	Scrubber liquor tank	CT-0104
E-C5711		N	Goodrich rubber-lined tanks	CT-01575
C-5743	B	L S	Scrubber in Pyranol plant	CT-01162
C-5814	B	L S	Obsolete, HCl tower	TW-0206

* * See the note on page 86 in this section.

Gastric Lesions

When tested in monkeys and rodents, PCBs show species specificity with respect to a toxic effect on the gastric epithelium, or stomach lining. In the monkey, with Aroclor 1242, there is a mucous conversion of the gastric epithelium that can best be described as a dysplastic growth pattern. This growth pattern does not constitute a neoplastic transformation. In rodents, PCBs do not evoke this effect on the gastric mucosa. In humans occupationally exposed to PCBs there are no clinical findings to date of gastric lesions, and no evidence of stomach cancer due to this exposure.

Carcinogenesis: Experimental and Clinical

A sizeable volume of animal experimental work has been directed toward chronic studies in several species: the mouse, the rat, and the dog. There are some areas of interpretation that are still under debate by the investigators concerned, but in the opinion of the Category I team the following represents conclusions that can be drawn from presently available data: (a) the evidence on carcinogenicity is negative for gastrointestinal carcinoma and bladder carcinoma in rats and hepatocellular carcinoma in the dog; (b) some studies have reported an increase in hepatocellular carcinoma in mice and rats exposed to commercial PCBs chronically, whereas other studies have afforded negative results.

XII. DRAWING LIST, contd.

Drawing Number	*	*	Title	Equipment Number
B-5815	B	N	Obsolete, HCl tower support	
B-5821		P	Cyclone	CT-01259 CT-01279 CT-01280 CT-01282
C-5825	B	L S	Monel gas chamber on firehested chlorination system	CT-01258
C-6144	B	M P	Monel condenser	CT-01263
E-6209	B	L S	Chlorinator	CT-0744 CT-01283
D-6455	B	L S	Pyranol mixer	CT-01321
E-6838	B	L S	Assembly of blending tank	CT-0779 CT-01399
A-6853		M	Agitator in blending tank	CT-01399
B-6868		M	Thermocouple wells	
C-6863	B	L S	Filtrate receiver	CT-01400
E-6941		M	Platform of still	
C-6942	B	L S	Piping diagram for #2 vac. still	S-062
C-6943	B	L S	Monel piping diagram for #2 vac.still	S-062
D-6944	B	L S	#2 Vac. Still	S-062
D-6945			Exhaust System,mentioned on p.XII-6.	
D-6946		M P	Control room	S-062
E-6952	B	L S	General layout #2 still	S-062

* * See the note on page 86 in this section.

XII. DRAWING LIST, contd.

Drawing List	•	•	Title	Equipment Number
D-6956	B	L S	General layout #2 still	S-062
C-6957	B	L S	Cyclone on #2 vac. still	S-062
B-7082	B	L S	Monel condenser #2 vac. still	S-062
B-7121		N	Support for Sperry press	P-0113
A-7136		N	Pipe coil under Sperry press	P-0113
A-8853		N	Bearing for blending tank (See drg. A-459)	
D-10252	B	L S	Piping of air blowing tank	
Hand sketch	B	L S	Dryer for Attapulgus Earth (See corresp. file Mar. 25/47)	
Anniston Drawings				
9C-8000			Layout of chlorinators } to MCL, June 7, 1946	
9C-8245			#2 Aroclor still }	
C-6836.1			Detail of chlorinator (Swan Chemical Co.) } to MCL March 12, 1947	

• • See the note on page 86 of this section.

XIV. HISTORY OF THE PROCESS IN MONSANTO.

In the years 1927 - 1928, the Swann Chemical Company developed a process for making diphenyl, but as the expected demand for it did not continue, other outlets were sought for the diphenyl. Aroclors were produced in the laboratory in 1929, and as they showed good electrical properties, fire resistance, and general inertness, the General Electric Company became interested, and developed the use of Aroclors in transformers and capacitators.

A plant was installed to produce 3000 lbs./day at Anniston.

In 1935 Monsanto acquired the Swann Company, so gaining access to their Aroclor patents. As the demand for Aroclors increased, additional production equipment was installed, located at the Monsanto Illinois factory (then plant "B" and now called the Krummrich plant). This equipment came on stream in September 1936.

The Krummrich plant site was chose partly because of the availability of chlorine there, but when chlorine consumption overtook the production, and chlorine had to be purchased, proximity to the diphenyl production at Anniston had more weight, and additional capacity, largely designed on the plant "B" model, was installed at Anniston in 1941.

By 1946 both plants had doubled their capacity, to give a total production capacity approaching 2 million pounds a month. About 1954 chlorine cells were installed at Anniston.

The Newport plant was designed, mainly on Krummrich plant information, but to a less extent on Anniston information, under Newport Project No. 12 of the London Central Engineering Department.

Chlorination started at Newport in June 1951, Mr. Clegorn from Anniston spending some time at Newport to assist in starting the diphenyl and Aroclor plants there.

The first production of Pyranol by MCC was in 1936, when Pyranol 1488 was made for the General Electric Company, the blending being done at first in rail tanks. Pyranol 1495 was made in July 1938.

The use of tin-tetraphenyl started in 1944, since when the main production has been of 1467 (TCB - 1260 mixture plus tin-tetraphenyl)

XV. OPERATING INSTRUCTIONS.

Operating instructions were given in the report of Lyles, Soffranko and Becker, November 1947, pages 84 - and a revised version was put out by the Krummrich Plant Standards Department, August 10, 1954, (copy sent to Newport, May 23, 1955).

Points calling for special mention are: --

1. Care in melting diphenyl received in cars. The first move is to melt a hole, from the surface, down to the bottom of the tank to prevent development of pressure from the heat of the tank coil or jacket.

2. Usual rail track routine in handling cars.

3. Exclusion of rain etc.

4. Proper use of tracing on pipe lines. Lines to be blown clear after use where necessary.

5. Tank vents and overflow lines to be maintained above the melting point of diphenyl

6. Charges in the diphenyl measuring tank to be kept hot.

7. Fire precautions in handling diphenyl, toluene, and butyl acetate and mixtures containing them.

8. Chlorinator charges kept as cool as possible, and not circulated in the early stage of chlorination.

9. Watch inlet pressure on chlorine line to chlorinator.

10. Care in emptying chlorinators not to suck back the scrubber charge.

11. Keep chlorinator charge out of the chlorine feed line.

12. Watch gravity and temperature of scrubber for indication of poor absorption of chlorine in the chlorinators.

XV. OPERATING INSTRUCTIONS, contd.

13. Control air-blowing temperature to suit the Aroclor being handled.

14. Check dryness of air from Lectrodryer at proper intervals.

15. Guard against burning or coking the still coils.

16. The usual care in lighting gas furnaces.

17. Care in dealing with hot material tapped from the stills.

18. Cleanliness in handling finished Aroclors.

19. With higher Aroclors take special care against blockage of lines.

20. Safety precautions as discussed under "Hazards", Section XI, above.

Pyranols

Operating Instructions relating specifically to the Krummrich plant are given on pages 33- of the report "Dept. A-246 Pyranol Process", Lyles, Soffranko and Miller, March 24, 1947, (copy #8 sent to MCL October 15, 1947).

Points mentioned are:

1. Checking the moisture content of incoming cars of trichlorobenzene. Air blowing at about 50°C. to remove excess moisture.

2. Sampling of materials at various stages for submission to General Electric Company.

3. Exclusion of moisture, HCl fume and dirt.

4. As a working rule, in adjusting blends of TCB with Aroclor 1260, 1 part of 1260 added to 80 parts of the blend will raise the Sp. Gr. about 0.001 and the refractive index about 0.0001.

XV. OPERATING INSTRUCTIONS, contd.

Pyranols, contd.

5. Blends containing tin-tetraphenyl are to be warm (about 80°C.) when filtered, otherwise some TTP may come out of solution.

6. Waterproof cloth over the domes of the filtered rail tanks to exclude moisture and dirt while travelling.

7. Avoidance of delay in dealing with samples because of the numerous testing stages required.

ACKNOWLEDGMENT

To Mr. J. Soffranko who was in charge of the Krummrich plant Aroclor Dept. in 1947, and to the foreman, Mr. Errol Smith.

The report "Dept. 246, Aroclor Process" by Lyles, Soffranko and Becker, November 6, 1946 was of very great help in assembling information for the Newport project, also the companion report "Dept. A-246, Pyranol Process" Lyles, Soffranko and Miller, March 24, 1947.

The reports by Schwarting and others, 1953 and 1954, have been used in the present revision of the process details.

Acknowledgment is due also to other Krummrich plant people who helped then and later.

Dr. E. E. Hardy was of great help at Anniston in 1947 in explaining the process and locating information.

To Messrs. Ellenburg and Wood for guidance around the Anniston plant, and to Messrs. Baker and Dunlop for analytical information.

Mr. Clegorn was very helpful during a visit in March 1955.

I N D E X

With respect to the possibility of cancer linked to exposure of humans to PCBs, epidemiological studies show to date essentially negative results for hepatocellular carcinoma, gastrointestinal carcinoma and all other forms of cancer. There is a single preliminary study that purports to show an increase in melanoma (skin cancer) in occupationally exposed people, but the full data display and analysis have not been made for this study. In contrast, in two larger and more detailed studies, this finding has not been confirmed; no excess incidence of melanoma in exposed personnel has been observed.

Retrospective mortality studies of PCB-exposed human populations have not demonstrated a consistent relationship between extent of exposure and the development of any particular type of cancer. The human studies in hepatocellular carcinoma are not comprehensive, but to the extent that they have been developed the results do not confirm the projection of a risk for liver cancer based on the animal studies. Some findings of increases in lymphatic and hematopoietic malignancies were below the level of statistical significance, and were refuted by observations of changes in the opposite direction in other epidemiological studies. Even findings of statistically significant differences between exposed and control populations with respect to the incidence of rectal cancer in women at one plant have not been confirmed by observations in other studies. The variance in these findings points up the important principle that the Standard Mortality Ratio (SMR) may vary widely in different

studies, and that undue emphasis should not be placed on the SMR found in one study unless it has been confirmed by similar findings in repeat or parallel studies.

Reproductive Effects

Experimental work with commercial PCB mixtures and animal models has been directed to the reproductive process itself, to teratogenesis in the offspring, and to possible fetotoxicity. In most test species PCBs produce deleterious effects on reproduction at high doseages. In the female monkey at relatively high dosages, difficulties are encountered in conception, in implantation of the fertilized ovum, and in carrying the fetus to term. Similarly dosed, the male monkey does not transmit these difficulties to the reproductive process. In the human, exposed occupationally or otherwise to PCBs, there is in general no evidence for adverse effects on the reproductive process, although there are little data from which to draw conclusions. In the very special case of Yusho exposure to high levels of PCBs and other polychlorinated hydrocarbons, the newborn in significant proportion were pigmented, small, and showed a retarded rate of growth. However, this pigmentation disappeared and the infants caught up with control population infants in total growth.

The potential for PCB-induced teratogenesis, or production of defects in the embryo or fetus, has been investigated in several species of test animals. Most animal tests have yielded negative results when PCBs were administered to pregnant females during the critical periods for organogenesis.

several possible exceptions to this statement might be noted. In mice, a single congener, 3,4,3',4'-tetrachlorobiphenyl, induced a behavioral defect ("waltzing syndrome") that may be related to an anatomical defect in the inner ear. PCBs in mice may produce some delay in implantation. In rats, no gross teratological changes were observed, but some alterations in thyroid structure or function produced by PCB administration might fall under the definition of terata. In dogs and in swine, no teratological effects were noted at lower PCB doses; however at the highest doses of PCB in the feed, at which the dam suffers marked reduction in food consumption and is therefore nutritionally deficient, there are dose-related teratological effects in the offspring. In monkeys dosed with PCBs, there are no dose-related abnormalities in the offspring, but they are smaller in size. Based on those observations, it is the Category I team's conclusion that commercial PCBs present no appreciable risk of teratogenicity in offspring of human females exposed under occupational conditions.

In test animals, i.e. rats, dogs, and rabbits, PCBs are fetotoxic when administered at relatively high doses to the pregnant female. In the human, the only reported epidemiological evidence for fetotoxicity in exposed populations stems from the unique Yusho event, in which causation may not be linked to PCBs.

Mutagenesis

Investigations of possible mutagenesis from acute or chronic exposures to commercial PCBs have shown negative results in a series of *in vitro* and *in vivo* test systems. Isolated bacterial test systems (Ames test) and human lymphocytes in culture showed no evidence for PCB-induced mutation or transformation. With *in vivo* systems in intact animals: (a) cytogenetic tests for alterations of cell structures or for induction of chromosome abnormalities yielded negative results; and (b) both the mouse micronucleus test and the dominant lethal test demonstrated negative results. Incubation of human lymphocytes in culture with PCBs caused an alteration in glucose transport through the cell membranes.

There is no significant evidence that PCBs are mutagenic in test systems, and no reports of such activity in human populations. It is quite unlikely that commercial PCB mixtures would exert mutagenic activity in humans. This conclusion is consistent with the lack of excess cancer incidence observed in PCB-exposed human populations.

Other Health Effects

This grouping includes enzyme induction, immunocompetence, and porphyria. PCBs induce mixed function oxidases (MFO) in the liver of test animals. The important issue is whether or not this process includes the specific induction of cytochrome P-448 as a general property of the PCBs, with the added implication that some oxidase system is being induced that

could be involved in chemical carcinogenesis. Several conclusions were reached with respect to this issue: (a) the predominant effect of commercial PCBs is cytochrome P-450 induction, not P-448; (b) commercial PCBs in the U.S. can contain up to about 2 ppm of PCDFs; and (c) the PCDFs can induce cytochrome P-448. From these observations in animal model systems and our judgment, it is concluded that under conditions of U.S. occupational exposure to PCBs, none of the MFO-inducing actions of the commercial mixtures will be of toxicological significance over the lifetime of a PCB-exposed person.

With respect to potential PCB effects on immunocompetence in test animal systems, some observations are pertinent to the assessment of probable hazard in the human. It has been observed in chicks that if the PCB dosages are high enough, atrophy of the splenic pulp and necrosis of the lymphoid system can be demonstrated. Similar indicators of change in immunocompetence can also be produced in ducklings, mice, and monkeys as a consequence of severe change in nutritional status. High doses of PCBs leading to marked reduction of food intake and utilization can lead to such changes in nutritional status. These considerations lead to two general conclusions relative to the PCB-exposed humans: (a) as projected from animal studies, if the PCB dosage is high enough to lead to general toxicity in the human (e.g., decreased food intake, fall in body weight, fall in weight gain),

immunosuppression may be demonstrable secondary to malnutrition; and (b) at lower dose levels, there is no likelihood of significant immunosuppression.

Porphyria, or deposition of porphyrin-derived pigments in liver and urine, has been observed in experimental animals such as the rat and rabbit dosed with PCBs. The effect has a delayed onset, and, especially in the rat, seems to take place by mechanisms different from those employed by known chemical porphyria-producers in the human. It is concluded that, aside from the unique case of Yusho disease, no evidence has accrued for the occurrence of porphyria in populations exposed to PCBs even under high level occupational exposure conditions.

Epidemiology

This section (XII) of the study presents a separate, independent assessment of the recorded epidemiological literature and data bases on human exposures to commercial PCBs, and on the significance of the health effects attributed to these exposures.

Summary points in this assessment include the following: (a) mortality data, based on very small numbers of deaths, do not confirm a carcinogenic effect of PCBs in man; (b) data on human skin lesions in relation to PCB exposures have shown variability in incidence of this effect with geographical locus and with increasing blood level indicators of exposure; (c) data from studies of liver enzymes and liver function suggest changes in one or more enzymes related to PCB exposure that are not associated

with liver disease and that occur at levels below those at which chloracne occurs; (d) there is frequently a positive correlation between PCB levels and triglyceride levels in blood; and (e) epidemiological data on reproductive effects, hematology and immunology in humans exposed to PCBs do not suggest abnormalities in these systems or processes.

Human Occupational Exposure Levels

Of the various effects noted in animal test systems, only dermatological effects, including some chloracne, have been clearly demonstrated in human populations at the dosage levels associated with occupational exposures. Table 1 summarizes the nature and intensity of some exposures that have occurred to personnel involved occupationally with PCBs and the biological indices that have accompanied these exposures, measured as PCB content in blood and adipose tissue.

Since the risk to human health from even high level occupational exposures has been shown by the studies available to be low, it may be concluded that much lower human exposure levels do not present significant risks.

TABLE 1

INDUSTRIAL OCCUPATIONAL EXPOSURE OF WORKERS TO PCBs
(Capacitor plant workers unless otherwise noted)
Data reported in human epidemiology references

Reference				PCB Concentration in Air		Chronic Disease Noted?	PCB Level in Blood Plasma Parts per billion**			PCB Level in Adipose Tissue Parts per billion**		
				Range	mg/m³		No. Subjects*	Mean	Range	No. Sub.*	Mean	Range
Fassbender	(1964)				3200-6000							
Honegger	(1972)	Plant	A (PCB Mfg.)	50- 200								
		"	B	100- 500								
		"	D	500- 700			99	370	60- 920			
		"	E	200-1700								
		"	F									
Karpuchova	(1972)			< 1000			12	440	110-1900	3	360	160-635
Kitamura	(1973)						13	820	320-2100			
Ouw	(1976)			320-2220		Yes	34	~ 600	Tr.-1200			
Fischbein	(1979)		Lo expos.	70- 410			158	L- 73 M- 41				
			Mod. "	410- 600			62	L-171 M- 25				
			Hi "	600-1100			43	L-266 M- 82				
Wolff	(1981)			An Above			26	L- 83 M- 19	2-1412 1-60	26	L-24 M- 6	2-271 .2-19
Bahn	(1981)			24- 391 170-1260								
Smith	(1981a)			M.D.- 264		Yes	14	L-502 M- 44	210-3130 20- 150			
							12	L-237 M- 51	34-2400 10- 250			
							55	L-140 M- 27	8-(500 7- 130			

TABLE 1 (continued)

Reference	PCB Concentration In Air $\mu g/m^3$ Range	Dermal Contact Hazard?	PCB Level in Blood Plasma Parts per billion** No. Subjects*	Mean	Range	PCB Level in Adipose Tissue Parts per million** No. Sub.*	Mean	Range
Smith (1981b)	37- 215		14	L- 23	5- 52			
				H- 24	7- 74			
(2 utility worker transformer repair groups)			8	L- 16	1- 52			
				H- 7	4- 10			
			4	L- 36	23- 59			
				H- 10	7- 17			
			13	L- 24	12- 35			
				H- 6	1- 18			
			7	L- 11	1- 30			
				H- 6	4- 10			
	>- 82	Yes	15	L- 22	5- 47			
				H- 31	11-140			
			18	L- 22	12- 48			
				H- 26	7-250			
			12	L- 23	13- 53			
				H- 8	5- 25			
			8	L- 19	12- 42			
				H- 6	3- 11			
Maroni (1981)	48-275	Yes	48	377	88-1319			
			12	200	61-470			
Chase (1981)		Yes	86	31.4	10-312	36	5.6	1.0-21.6
(locomotive repair)			15	14.2	10- 30	5	1.4	1.0- 1.8

* Excluding controls

** Note: PCB plasma analyses are expressed in parts per billion (including some ng/ml), while adipose tissue analyses are expressed in parts per million.
"L" PCBs (lower homologs) and "H" PCBs (higher homologs) are defined as species having, respectively, shorter and longer gas chromatographic retention times than the DDT metabolite p,p' (former) -DDE.
"L" PCBs include 3-PCBs through 4-PCBs, plus some 5-PCBs; "H" PCBs include 5-PCBs and higher, plus some 4-PCBs.

I. INTRODUCTION

A. Origins and Methodology of the Study

In August 1981, the firm of consultants in toxicology, Drill, Friess, Hays, Loomis and Shaffer, Inc., Arlington, Virginia, (DFHLS) entered into a contract with the Edison Electric Institute (EEI) and the National Electrical Manufacturers Association (NEMA) whereby DFHLS agreed to examine the toxicological and epidemiological literature on polychlorinated biphenyls (PCBs) and provide EEI and NEMA with DFHLS' independent, professional opinion on the human health effects of PCBs at varying dosages or exposure levels. To this end, the principal scientific studies and data compilations available on toxicological and epidemiological effects of PCBs, as commercial mixtures and as purified single congeners, have been reviewed by a team of scientists designated as the Category I team. Members of the Category I team are Drs. V.A. Drill, S.L. Friess, H.W. Hays, T.A. Loomis, and C.B. Shaffer from DFHLS. Additionally, Dr. G. Matanoski of the Johns Hopkins University has acted as an independent member of the Category I team charged with study of the pertinent epidemiological literature on PCBs and their human health effects, leading to an independent assessment and evaluation of the probability, causality, and reality of these effects.

Category I team review of the animal and human data resulted in draft material on the relationships between PCB exposure and specific health effects in test animals and in

exposed human populations. Further, where human data were lacking or incomplete, the Category I team members developed specific projections or opinions as to the probability of occurrence of certain health effects in exposed humans, based on the existing animal/human data bases. Health effect areas scrutinized included: general toxicity; effects on skin and other cutaneous tissues; effects on liver; effects on gastric tissues; carcinogenesis (experimental and clinical observations); reproductive effects including fetotoxicity and teratogenicity; mutagenesis; Yusho disease and occurrence of cancer; and other health effects including enzyme induction, changes in immunocompetence, and porphyria. Dr. Matanoski's treatment of epidemiological observations constituted an independent section of the draft report.

Draft sections from the Category I team were then reviewed for content, conclusions, and opinions by the members of a scientific team of pharmacologists and toxicologists designated as the Category II team: Dr. F.G. Standaert (Georgetown University), Dr. A. Alvares (Uniformed Services University of the Health Sciences), Dr. J.A. Thomas (West Virginia University), and Dr. P.E. Enterline (University of Pittsburgh). Dr. Enterline was the prime reviewer of the epidemiological contribution made by Dr. Matanoski.

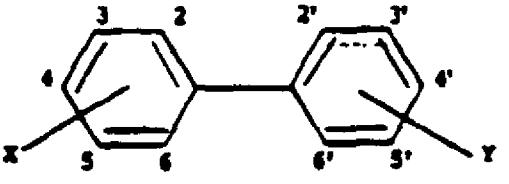
Comments and critique from Category II team members, singly and as a group, were then transmitted to the Category I team for consideration, leading to revisions and amplifications

that are in place in the final draft of this study. Comments and suggestions from scientists representing the sponsors of this study, EEI and NEMA, were also considered.

In the final version of the study, to the extent possible, a section on summary and opinion is appended to each discussion of a potential human health effect attributable to PCB exposure. The primary responsibility for each of these sections is assumed by the Category I team, even though the content may have benefitted from useful contributions by Category II personnel.

B. Commercial PCB Mixtures

Polychlorinated biphenyls (PCBs) are members of a class of non-polar chlorinated hydrocarbons based on the biphenyl nucleus, in which multiple chlorine atoms are substituted on



either or both the primed and unprimed aromatic rings. Certain individual members of the PCB family have been prepared in a relatively pure state, with substitution of ring positions by chlorine ranging from dichloro isomers (symbolized as 2-CB) up to the nonochloro (9-CB) and decachloro (10-CB) derivatives. Commercially, PCBs were marketed in the United States under the trade name of Aroclors. They were also manufactured abroad under the tradenames "Phenoclor" and "Pyralene" (France), "Clophen" (Germany), and Kanechlor (Japan). They are comprised of mixtures of chlorinated biphenyls. The last two digits of the U.S. commercial name denote the percentage of chlorine in each mixture, e.g., Aroclor 1242 contains 42% by weight of Cl corresponding to an average of approximately three chlorines per biphenyl molecule. Likewise, Aroclor 1254, Clophen A50, and Kanechlor 500 all contain 54% chlorine corresponding to five chlorine atoms per molecule on the average.

Commercially useful mixtures of PCBs have been widely distributed over the world in the past few decades, usually in applications that have precluded excessive exposures of user populations. However, because of the great chemical stability of these polychlorinated molecules, their persistence in the environment after accidental release can be lengthy leading to possible exposures of people and biota in the biosphere. The results of these exposures, as well as those of personnel occupationally exposed to PCBs in the course of chemical synthesis

and manufacturing operations, are of great importance from the standpoint of potentially harmful health effects that might occur on an acute or chronic basis.

C. PCB Impurities

Commercial PCB mixtures are truly complex, containing variable numbers and amounts of congeners within a given family of compounds, and traces of impurities, all of which are potentially toxic to humans and animals. Impurities that have been identified in PCBs as manufactured are polychlorinated derivatives of napthalene (PCNs), terphenyls (PCTs), methylbiphenyls, and dibenzofurans (PCDFs).

The occurrence of PCDFs is particularly noteworthy in view of the higher toxicity for certain congeners, relative to PCBs. It is important to note that there are theoretically 135 possible PCDF congeners, a few of which are believed to be highly toxic.

While reviewing PCB toxicological or epidemiological data, a number of factors related to the actual material involved must be considered. The PCDF content of commercial PCBs varies: for Aroclors the reported range is 0-2 ppm of total PCDF congeners. For European and Japanese PCBs, the reported range for PCDF content is 5-20 ppm. The impurity levels can also be affected by exposure to high temperatures and oxygen. For example, Aroclor 1254 is converted to 2-3% PCDFs at 550-600 degrees C. These same conditions result in the formation of polychlorinated quaterphenyls (PCQs).

II. Yusho Episode

In 1968 a mass outbreak of food poisoning occurred in Japan, following ingestion of a cooking oil contaminated with PCBs and other compounds, that aroused worldwide concern over the potential human health effects from exposure to PCBs. However, this poisoning, which became known as Yusho disease, differs significantly in several ways from occupational exposure to PCBs in the United States so that data from the Yusho incident cannot be extrapolated to indicate the effects of PCBs in industrial situations.

Recent studies of the rice oil involved in the Yusho poisoning show that the oil contained relatively large amounts of other chlorinated hydrocarbons such as PCDFs and PCQs (see Kuratsune et al., 1976; and Hayabuchi et al., 1979). The rice oil that caused the disease was found to contain about 1000 ppm of PCBs, 5 ppm of PCDFs, and 1000 ppm of PCQs; the amounts of the latter two classes of chlorinated hydrocarbons in the rice oil are higher than in the Aroclors used in the United States. Hayabuchi reanalysed the intake data for the Yusho patient, and calculated that the average intake for the mean latent period was PCB 466 mg, PCDF 2.5 mg, and PCQ 439 mg; the smallest intake by a patient was estimated to be 111, 0.6, and 105 mg respectively.

PCB concentrations in the tissues of Yusho patients were much lower than those of asymptomatic individuals with body

burdens of PCBs resulting from occupational exposure. Further, PCB fractions of blood, tissues, and breast milk of Yusho patients yielded gas chromatographic patterns showing a larger amount of late-eluting peaks than do PCB fractions of tissues of individuals subject to other types of PCB exposure (Koda and Masuda, 1975). These patterns have never been observed in individuals (human or animal) exposed to PCBs in other situations. They are unique to Yusho disease. Also, PCDFs have been found in tissues of Yusho patients.

Further evidence for the uniqueness of the syndrome in humans exposed to the Yusho oil is furnished in two recent studies. Hayabuchi et al. (1981) in follow-up studies on these patients five or more years after the poisoning found significant positive correlations for the years 1973-1976 between blood concentrations of PCBs and the total amount of rice oil consumed, but not with the dosage of rice oil consumed per unit of body weight per day. Kashimoto et al. (1981) found that Yusho is quite different from ordinary PCB toxicity in the sense that, even 12 years after the first outbreak, PCQs have been found in the patients' blood and both PCQs and PCDFs have been found in their tissues and organs.

It is obvious from this brief review that Yusho cannot be considered a model to reflect the possible effects of the PCB exposure in man. Although much can be learned from the Yusho

incident, it would be misleading to attempt to interpret the observations on Yusho patients as valid signs and symptoms of overexposure to PCBs or to attempt to quantify the possible effects of PCB exposure based on Yusho disease.

A. Yusho Disease

Yusho disease is characterized by the ingestion of a mixture of chlorinated hydrocarbons containing PCBs in large amounts over a relatively short period of time (latent period from start of ingestion to onset of the disease averaged 71 days). In contrast, the studies of PCB exposure in workers in the United States have been concerned with the possible effects of chronic exposure to small amounts of PCBs through inhalation or skin contact.

The principal signs of Yusho disease are skin conditions such as acneform eruptions, pigmentation of the skin and nails, and hypersecretion of the Meibomian glands. Chloracne and hypersecretion of the Meibomian glands are believed now to be caused predominantly by PCDFs. Hyperpigmentation of the skin is observed rarely, if ever, in human populations with heavy occupational exposure to primarily PCBs.

The actions of PCDFs appear to differ in several ways from those of the PCBs. Kuratsune et al. (1976) showed, for example, that the liver appears to concentrate PCDFs selectively relative to PCBs. It was also found that relative to PCBs, the concentration of PCDFs was about 250 times higher in the rice oil than in unused Kanechlor-400. Additionally, the PCDFs appear to

be highly toxic, at least in the rabbit; a single oral dose of 0.5-1 mg/kg of the tri- and tetrachlorodibenzofurans caused severe and often lethal necrosis in the rabbit (Hofmann, 1958; Bauer et al., 1961).

B. Yusho Disease and Liver Function

In view of the effect of PCBs on the liver of the rat and the highly toxic action of PCDFs on the liver of the rabbit, it was anticipated that the Yusho patient would have severe liver damage, but such has not been found.

In their review of Yusho disease, Kuratsune et al. (1972) list "the subjective symptoms of Yusho as stated by 189 patients"; 11% report jaundice. Data to confirm the patients' "subjective symptoms" are not provided, nor is the presence of this "symptom" confirmed by other statements of clinical findings. Prof. Urabe (Chief of the Study Group) did not list jaundice as a sign or symptom of Yusho disease and the diagnostic criteria adopted in 1972 do not make reference to jaundice or the need for a liver function test in these patients (see Kuratsune et al., 1976).

The following two papers on Yusho disease and liver function are in Japanese and the brief summary given below is taken from the report of Kuratsune et al. (1976).

Okumara and Ketsuki (1969): They examined 24 patients soon after the onset of the disease:

(i) There were no objective signs of liver disorders; (ii) No patients were jaundiced and only three had palpable livers (in one patient examinations of a liver biopsy showed marked hypertrophy of the smooth endoplasmic reticulum).

Okumara (1972): Liver function tests were performed in 38 Yusho patients with various subjective symptoms. An increase in lactic dehydrogenase (LDH-5) and in thymol turbidity titer was observed in some of the severe cases, "but no definite evidence for liver disorders was obtained."

In a follow-up study of 121 Yusho patients the mean serum bilirubin was 0.48 mg/100 ml compared with 0.87 mg/100 ml in control patients (Hirayama et al., 1974). The difference was statistically significant and the authors suggest that there may be accelerated bilirubin disposal from the blood.

It may be concluded that the Japanese findings do not provide evidence for the development of hepatocellular injury or jaundice in patients with Yusho disease.

C. Yusho Disease and Carcinogenicity

Urabe and co-workers (1979) report that 51 of 737 Yusho patients in the Fukuoka district had died and they list the cause of death for 31 of the patients. There were 11 deaths (35.4%) from neoplasms which they state is substantially higher than the 21.1% rate that is "the mortality rate from neoplasms in the

same prefecture this year." A further analysis is not provided. The following malignant neoplasms were listed as the cause of death for the 11 patients with cancer.

Anatomical Site	No. of Cases
Stomach Cancer	2
Stomach Cancer & Liver Cancer	1
Liver Cancer & Liver Cirrhosis	2*
Lung Cancer	2*
Lung Tumor	1
Breast Cancer	1
Malignant Lymphoma	2
TOTAL:	11

*Autopsied

Information on age and other relevant epidemiological data are not given, and even a tentative conclusion regarding Yusho disease and any malignancy must await further analysis.

III. Body Burdens, Metabolism, and Kinetics

A. Introduction

The degree of chlorination (two to 10 atoms of Cl per PCB molecule) and the positions of the chlorine substituents on the biphenyl rings both exert a profound influence on how mammalian systems handle any given PCB molecule. The degree and position of chlorination play a major role in determining the pathways for metabolism and elimination of the parent molecules and their metabolites by animal models and the human. These structural factors also bear on lipid solubility of the molecules, and therefore influence to some extent the kinetics of PCB tissue distribution and storage. The following sections deal with the present state of knowlege on these PCB handling mechaniems employed by animal models and the human, recognizing that there is a strong linkage in the dynamic processes beginning with expoeure and ending in excretion. These topics will be treated in three groupinge: (1) distribution and storage of PCB metabolites in tissues; (2) metabolism and excretion; and (3) kinetics or the dynamice of PCB turnover in animal models and the human. Presently, some generalizations emerge with regard to PCB structure versus reactivity relationships end mechaniems for handling PCBs in test animal aystems that make reasonable extrapolation to potential events in the human organism poesible, even when direct evidence for actions of a given compound or PCB mixture in human populations is not available.

Additional attention has been directed to available information on the actions of PCDFs in animal models and the human, and to a variety of biochemical effects recorded for PCBs and their metabolites in mammalian systems. PCDFs may be contaminants of some commercially used PCBs. Although 10-20 ppm of these contaminants have been found in PCBs manufactured in Europe and Japan, only trace amounts on the order of one or two micrograms of total PCDF congeners per gram of PCB have been reported in the American manufactured mixture Aroclor 1254 (Bowes et al., 1975).

B. PCB Distribution and Storage in Tissues

A considerable body of literature exists on studies of the time dependence of the distribution, movement, and storage of PCBs and their metabolites in the tissues of experimental animal models and of humans, following exposures to chlorinated biphenyls as pure compounds or mixtures. In test animal models using unlabeled or radiolabeled (^{14}C or ^{3}H) PCBs, controlled exposures were generally by the oral route (stomach tube, or in the feed) or by intravenous injection, followed by study of the changing distribution of the agent and its metabolites in the circulating blood, in tissues, in bile fluid, and in excreta as a function of elapsed time after dosing. In the human, exposures with resulting body burdens of PCBs were generally of the subchronic type stemming either from massive poisoning events, as in the Yusho events, from chronic occupational exposures in air and via skin contact, and via PCB contaminants in air, water, food, and surface contacts in the ambient. Humans

may also have been exposed to PCBs occupationally in the chemical manufacturing process, in the manufacture of capacitors, and in the manufacture and repair of transformers. Until recently, several microscope immersion oils contained 30-40% PCBs as Aroclor 1254, causing potential exposures of students, pathologists, microscopists, etc.; the degree of exposure is low and the penetration through skin from these products may not be as extensive as in large scale manufacturing processes.

In human studies, PCB distribution and storage in readily obtained tissues was generally followed epidemiologically in exposed populations by monitoring levels in blood, sometimes in mother's milk as a function of time and sometimes by measuring PCBs in adipose and other tissue samples obtained clinically and post mortem.

Animal Model Results

The picture of distribution and storage of PCBs and their metabolites in tissues over time has been developed most completely from controlled dose experiments in animal models. Generally, rats and mice were the animals of choice for this work (Burse et al., 1974; Geyer et al., 1980; Guiney et al., 1978; Mattews and Anderson, 1975; Morales and Matthews, 1979; Albro and Fishbein, 1972; Burse et al., 1976), but the dog, as well as the monkey, has also been used (Hsu et al., 1975a; Milling et al., 1979; Sipes et al., 1980). The dynamics of tissue distribution vary with different isomers and congeners, and depend in large measure on whether or not the specific PCB

molecular structure allows rapid metabolism and excretion of polar metabolites via bile, feces, and urine (Milling et al., 1979; Safe et al., 1975; Sipes et al., 1980; Matthews et al., 1978; Guiney et al., 1978; Guzelian, 1979) or slower metabolism with retention of parent compounds and metabolites in tissues. As will be discussed in the following section, metabolic transformation in the liver is particularly facile for those PCBs with lower chlorine content (2-CB through 4-CB, i.e. 2-4 chlorines per PCB molecule) and with adjacent ring carbon atoms unsubstituted by chlorine atoms (Matthews and Tuey, 1980; Sundstrom et al., 1976; Kato et al., 1980; Jensen and Sundstrom et al., 1974b; Ghiasuddin et al., 1976; Matthews et al., 1978). For many PCB molecules in which metabolic transformation and excretion is not excessively rapid, the dynamic distribution of parent compounds and metabolites in tissues following dosing has been studied carefully (Mizutani et al., 1980; Safe et al., 1975; Sipes et al., 1980). The following generalizations appear valid in animal models for structures ranging from 1-CB to 6-CB and higher.

First, the PCBs are readily absorbed from the gut following oral administration and appear rapidly in the bloodstream (Albro and Fishbein, 1972; Berlin et al., 1975; Chen and Matthews, 1974). Within minutes to hours, the materials largely clear from the blood and accumulate in the liver and in muscle tissue (Berlin et al., 1975; Burse et al., 1974; Chen and Matthews, 1974). However, traces of PCBs have been found in the

blood of humans, probably by redistribution from other tissues, years after exposure. The liver is the primary locus for metabolism of the PCBs, especially for reactive species, leading to mixtures of parent molecules and metabolites that then either translocate to other tissues or are excreted by both bile/gut, lumen/feces, and urinary pathways. As translocation from liver and muscle occurs in the rodent model and other species over time periods ranging from hours to many days, the ultimate depots for major amounts of the non-polar PCBs and their polar metabolites appear to be adipose tissue and skin (Berlin et al., 1975; Haneen, 1979; Guiney et al., 1978; Burse et al., 1974). The general distribution pathway in rodents may therefore be characterized as sequential migration from gut and bloodstream entry points to liver and muscle tissues, in a rapid process, and thence to depot storage in body fat and skin.

When the PCB structure is such as to permit ready metabolism to polar hydroxy, dihydroxy or diol derivatives, the metabolic process may be closely linked in time with excretion of the metabolites (Jensen and Sundstrom, 1974; Lay et al., 1979; Matthews and Tuey, 1980; Matthews et al., 1978; Matthews and Anderson, 1975). Animal studies on urinary and fecal excretion of PCBs (Guzelian, 1979; Matthews and Anderson, 1975; Berlin et al., 1975; Lay et al., 1979; Chen et al., 1976; Van Miller et al., 1975), and rates of elimination of PCBs from liver into bile and then into gut/feces, show that the larger

proportion of excretion in rodents is by fecal elimination (Kato et al., 1980; Lay et al., 1979; Chen et al., 1976; Van Miller et al., 1975; Chen and Matthews, 1974) of polar metabolites, mostly glucuronides, eliminated via the bile.

The dynamics of distribution and elimination of PCBs in two monkey species have been studied (Hsu, et al., 1975a; Sipes et al., 1980; Hsu et al., 1975b), and are found to follow a similarly complex pathway, but with wider tissue distribution ultimately than that seen in the rat. In our opinion, this difference may relate in part to the ability to analyze more tissues in larger animals. With fat tissues present in only small proportions in the infant Rhesus monkey, the ultimate depots included bone marrow and the adrenal glands, in addition to skin (Hsu et al., 1975a).

Long-term studies involving chronic administration of PCBs at low dosage levels to animal models for significant fractions of their lifetimes, with determinations of total burdens and tissue distributions achieved over time periods of one to two years of ingestion, are lacking.

Human Body Burden Results from Epidemiological Studies

Experimental data on body burdens and tissue distributions of PCBs in humans as a result of precisely-measured intakes are not available. However, there are several population sectors for which exposures to PCBs can be at least roughly estimated, and from which tissue samples (blood, subcutaneous and other fatty tissue, etc.) have been taken to obtain indices of

body burden. These sectors include: (1) humans occupationally exposed to PCBs during years in which they were employed in manufacturing processes (Karppanen et al., 1972; Hasegawa et al., 1972; Kitamura et al., 1973; Ouw et al., 1976; Fischbein et al., 1979; Wolff et al., 1981; Maroni et al., 1981a, b; Smith et al., 1981a, b; Chase et al., 1981); (2) humans accidentally poisoned by PCBs ingested in contaminated foods, as in the Yusho experience in 1968 and in corresponding ingestions of contaminated rice oil in Taiwan (Chen, 1980; EPA summary, 1980); and (3) humans living in areas in which PCBs have somehow entered the food chain or water supply in measurable amounts, leading to long-term, low-level body burdens in adults that may also be present in the human milk supply for transmission to infants (Humphrey, 1975, 1980; Kuwabara et al., 1979a; Kuwabara et al., 1979b; Mes and Davies, 1979; Watanabe et al., 1980). An additional source of exposure that is more difficult to characterize quantitatively stems from the exposure of families to contaminated clothing of PCB workers. Survey work has been done in all of these population sectors worldwide. The results are sketchy, but tentative qualitative generalizations can be drawn.

Blood or plasma levels of PCBs are most readily followed in potentially exposed population data using highly sensitive analytical techniques such as gas chromatography and mass spectrometry. For occupationally exposed people (NIOSH, 1977; Smith et al., 1980a) values ranging from 10 ppb up to a maximum of 3330 ppb have been observed, with the additional

qualitative finding from Japanese references that the half-life for disappearance of PCBs from blood following cessation of exposure ranges from three to 30 months. PCB blood levels were higher with increased duration of exposure. For Yusho victims in Japan, with blood samples taken five to seven years following exposure to PCBs, in the 1973-1975 time frame (NIOSH, 1977) values in the range 3-33 ppb were observed. Enhancement factors over control group levels (mean, 3 ppb) as great as 10 were calculated, but the observed blood levels were still much lower than levels found in Japanese capacitor workers. It is of interest to note the observation of Humphrey (1975) on the very slow clearance of PCBs from the tissues of humans exposed by eating fish. In general populations, blood plasma or serum levels of PCBs in the range 5-29 ppb have been found (NIOSH, summary p. 36).

A current and well-documented study of body burdens of PCBs in persons employed for many years in capacitor manufacturing (Wolff et al., 1981) is of special value from the standpoint of its correlations of tissue concentrations with extent of exposures. With highly chlorinated PCBs (H-PCBs), plasma concentrations of 1-546 ppb in exposed personnel correlated with total accumulated exposure time. For the less highly chlorinated PCBs (L-PCBs), plasma levels in the range 6-2530 ppb correlated better with specific tasks of individuals working with these 2-CB to 4-CB molecules. Also observed in this study was a correlation of levels in plasma with levels in adipose

tissue for each class of PCBs, with H-PCBs and L-PCBs taken as separate classes, and an overall adipose/plasma partition coefficient of 190.

The levels of PCBs and metabolites in subcutaneous fat in humans have also been surveyed in general populations (NIOSH, 1977), in groups such as Yusho patients with high exposures, and in some occupationally exposed individuals. For the general population, levels in fat range from less than 1 ppm to greater than 2 ppm. For Yusho individuals, elevated fat PCB levels in the range 13-75 ppm have been observed, corresponding to peak enhancement factors as high as 30 over the population at large. It should also be noted that the spectrum of compounds in human tissues is not necessarily identical with the spectrum in the mixture to which a given population was exposed (Kuwabara et al., 1971a). Ranges of adipose tissue PCB levels in occupationally exposed individuals have been reported as 160-635 ppm (Karppanen et al., 1972), 1-12.6 ppm (Chase et al., 1981), and 2-271 ppm (Wolff et al., 1981).

Special surveys have been made of PCB levels in the milk of lactating human mothers (Mes and Davies, 1979; Watanabe et al., 1980; NIOSH summary) and of levels in human embryonic and fetal tissues resulting from in utero transfer from Yusho females (NIOSH, 1977). Human milk samples with values of PCBs in the range 0.008-0.1 ppm have been observed. Clearly, concentrations in milk are higher than those in blood primarily because milk is rich in fat. Organs from the embryonic and

fetal tissue displayed PCB levels in the range 0.002-0.750 ppm for whole tissues, with fat derived from these organs yielding levels in the range 0.06-1.14 ppm.

C. PCB Metabolism and Excretion

Animal experiments involving exposure by feeding, intubation, or injection of purified PCB isomers in test animal models have yielded some important generalizations on the mechanisms employed by mammalian species to metabolize PCBs to more polar derivatives, and to excrete both parent compounds and metabolites. Beginning with ready absorption from the gut and transfer to circulating blood, or with direct injection into the bloodstream, a given PCB molecule ultimately reaches the liver where major metabolic actions are initiated. The processes of metabolism and excretion as a result of these actions are complex, and dependent on the molecular structure of the PCB. General features of these processes include the following points:

(1) Variable amounts of PCB metabolites are excreted via the feces after delivery to the gut lumen via the bile flow pathway. Unchanged PCBs can occur and be discharged in milk. Relatively lesser amounts are excreted as polar metabolites in urine than in feces in most animal models (Kato et al., 1980; Lay et al., 1979; Chen et al., 1976; Van Miller et al., 1975; Chen and Matthews, 1974).

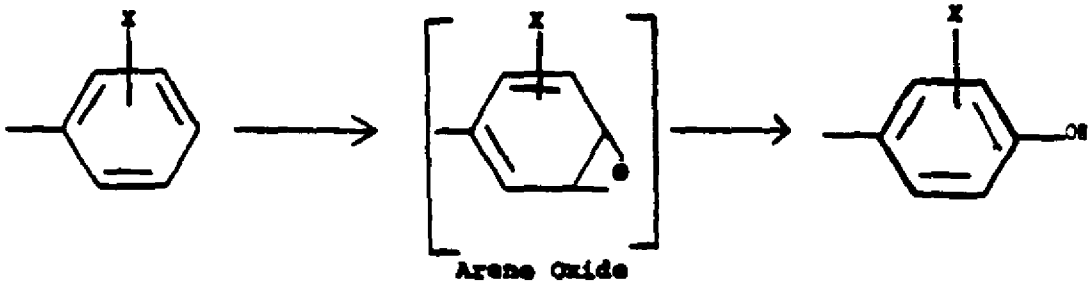
(2) Metabolites are formed in patterns that differ quantitatively or qualitatively among mammalian species. They are generally formed by oxidative processes that are thought

to involve an arene oxide formation that results in monohydroxylation, dihydroxylation, hydroxylation and methylation, or diol formation accompanied by partial reduction of an aromatic ring (Berlin et al., 1975; Lay et al., 1979; Lucier et al., 1978; Milling et al., 1979; Sundstrom et al., 1976; Gardner et al., 1973; Chen et al., 1976; Matthews et al., 1978; Van Miller et al., 1975; Hsu et al., 1975a; Hsu et al., 1975b; Burse et al., 1976). Evidence also exists for dechlorination of a PCB in the process of metabolism (Kato et al., 1980; Hutzinger et al., 1974b). For some PCB structures, the process of oxidative metabolism may be closely followed by excretion via the liver-bile-feces pathway (Chen and Matthews, 1974).

(3) Compounds with lower levels of chlorination (2-CB to 3 or 4-CB) generally undergo metabolism more readily, and faster than the more highly chlorinated PCBs. The more highly chlorinated PCBs may persist in tissues for years because they are not metabolized. Indeed, 10-CB is virtually inert.

(4) In the case of metabolism by oxidative pathways, the most facile process involving formation of hydroxylated products occurs when one or both aromatic rings contains adjacent pairs of ring carbon atoms (called vicinal ring atoms) that are unsubstituted by chlorine atoms. In the absence of unsubstituted vicinal positions, direct hydroxylation can occur in the ring, but with greater difficulty (Geyer et al., 1980; Matthews and Tuey, 1980).

The importance of vicinal unsubstituted positions on PCB rings in facilitating oxidative metabolism in the liver is explained by a mechanism that involves an arene oxide intermediate (Daly et al., 1972). When either or both of the vicinal positions contain chlorine, reaction rates will be lower, but the mechanism is not entirely ruled out. Additional molecular rearrangements, including the so-called NIH (National Institutes of Health) shift of a ring substituent (Daly et al., 1972), may be involved. Less is known about mechanisms of direct enzymatic hydroxylation that do not proceed through an arene oxide intermediate.



Arene Oxide

(5) Hydroxylated metabolites of the PCBs and their conjugates will generally display different orders of toxicity than those shown by the parent molecules.

(6) A general point of interest with respect to PCB metabolites lies in the observation that they are usually more polar than their parent compounds. Conjugation of the hydroxy and dihydroxy metabolites as glucuronides or sulfates can occur, leading to polar conjugates that can readily be excreted. The polar character of metabolites, in contrast with the non-polar

characteristics of the starting PCBs, can lead to differing distribution, storage, and excretion patterns for the two classes of chemical compounds. Polar metabolites are not readily partitioned into fat or reabsorbed from the urinary or gastrointestinal tracts. Therefore they are excreted relatively rapidly.

D. PCB Kinetics

Profiles of the dynamic growth and decay of PCB/metabolite concentrations in each key tissue can be drawn from controlled toxicological experiments. The distribution of a given PCB and its metabolites in the blood, tissues, and excreta of test animals is followed as a function of time after administration. Tissues are viewed as body compartments into which materials are delivered from the arterial blood supply, in which some metabolic processes may occur, and from which materials are delivered into the venous drainage systems. A collection of such compartments communicating with the blood supply and controlled by rates of flow through the compartments, with postulated equilibration of any given chemical in a compartment with its venous blood flow, constitutes an appropriate modeling system for correlating PCB distribution, storage, metabolism, and excretion kinetics in an animal over time. This multi-compartment model has been employed by Matthews and co-workers and others (Anderson et al., 1977; Bungay et al., 1979; Tuey and Matthews, 1977; Lutz et al., 1977), to sort out the kinetics of specific PCB isomers in rodent models. The PCB administration can be either direct

injection of a PCB into the blood circulation, or its absorption into blood from the gut after feeding or intubation of the compound. Excretory pathways are via the liver/bile/gut route or the blood/kidney/urinary elimination system.

The success of a model equation system in fitting analytical data for a given PCB and predicting the shape of its concentration versus time curve for each organ or compartment depends in large measure on several factors, including: (1) the assignment of suitable values for distribution coefficients of PCB compounds in each compartment; (2) the differential blood flow to various organs; and (3) the clearance from organs and the body. This fitting process has now been carried out for a number of PCBs for which kinetic data are available (Anderson et al., 1977; Chakraborty, 1978). The goodness of fit of the model to each set of PCB kinetic data available attests to the validity of the assumption that materials partition at equilibrium between blood and tissue according to purely physical properties involving solubility parameters of the chemicals.

E. Miscellaneous Biochemical Effects of PCBs

Studies of the actions of PCBs in animal models and humans exposed to these chemical agents accidentally or in the occupational setting have revealed a variety of biochemical effects on mammalian organisms. Some, such as alteration of drug metabolism by virtue of PCB induction of microsomal mixed function oxidases (MFO), are treated elsewhere in this documen

Other effects appear to be unrelated to MFO actions, and have been detected in the course of acute or chronic toxicological experiments with laboratory animal models or epidemiological surveys of exposed human populations.

In an animal study (Bastomsky et al., 1975) aimed at probing the previous evidence on reduced serum bilirubin levels in Yusho patients, it was found that Aroclor 1254-treated rats showed increased liver microsomal protein, as expected, but with no significant elevation in liver bilirubin UDP-glucuronyl transferase activity that could have accounted for reduced serum levels. Other studies (Grote et al., 1975; Lake et al., 1979) have shown enhanced levels of this transferase activity. At present therefore, the mechanism underlying the hypobilirubinemia in Yusho patients remains speculative.

From epidemiological studies of Yusho patients (Strik, 1979), a rather general biochemical finding has been the observation of porphyrins in urine and porphyrin accumulation in liver, as a result of exposure to chlorinated hydrocarbons including PCBs. Chronic hepatic porphyria is the designated condition, which increases with exposure and can therefore be taken as an indicator of the extent of PCB exposure. Porphyria is discussed elsewhere in this text (section XI).

A biochemical factor that may bear on the toxicity of PCBs in certain sensitive human populations, e.g., fetuses, neonates, enzyme deficient adults, etc., is related to the ability to excrete the toxic phenolic metabolites rapidly and efficiently.

Since a common route of excretion involves preliminary conjugation of the phenolic hydroxyl groups with glucuronic acid in the body, or sulfate conjugation, it has been pointed out (Calabrese, 1977b) that human groups that are biochemically deficient in the ability to conjugate could be predisposed to accumulate PCBs and metabolites because of this deficiency. A more serious consequence of altered liver capability would be a reduced capacity to deal with arene oxide intermediates effectively.

An interesting biochemical defect in human lymphocytes has been studied (Lee and Park, 1980) that can be attributed to direct action of PCBs on these white blood cells. For both human lymphocytes and monocytes, it has been found that incubation of the cells with Aroclor 1254 in culture medium causes a decrease in their ability to take up glucose from the medium. A non-metabolizable analog of glucose, 2-deoxyglucose, was used to detect the biochemical defect, which was attributed to PCB exposure but which may well be more general for any organic chemical that concentrates in the fat of the cell wall. It may entail direct action of PCBs on an active transport process in cell membranes. In this regard, liver glucose-6-phosphatase has been found to be inhibited in rats fed various Aroclor mixtures (Litterest et al., 1972).

The processes by which PCB pretreatment influences rates of protein and nucleic acid (RNA) synthesis and turnover in rat liver tissues have been investigated systematically

Imbonne, 1979a, b, c, e), using radiolabeled substrates. It is clear that liver tissue, in vivo and in vitro, responds to PCB treatment (Phenochlor DP6) by increasing the protein synthesis in liver microsomal fractions in a process that is both age and sex dependent. Concomitant increases in liver fat are also seen in vivo, as well as changes in levels of RNA synthesis in various liver fractions and increases in liver weights. From the turnover experiments in rats, it is also observed that microsomal membrane protein metabolism is enhanced by ingestion of Phenochlor DP6.

Some further biochemical effects of PCB exposures on the human are seen in workers occupationally exposed to these chemicals for extended periods of time (Smith et al., 1978). The findings, as yet unexplained in terms of requisite dosages or underlying mechanisms, are that: (1) the circulating triglyceride levels in blood plasma are elevated for exposed workers over controls, but are still within normal levels; and (2) the circulating levels of high density lipoprotein are lowered in exposed groups of workers.

Another biochemical effect seen in PCB-treated rats is worthy of note, since it relates to an impairment of excretion of an important drug and its metabolites (Schmoldt et al., 1979). In the Wistar rat pretreated with Aroclor 1248, the drug digitoxin and its metabolites were blocked to a significant degree from excretion via the bile. The results suggest that the

blockage is due at least in part to a PCB-induced impairment of the cleavage of one of the sugars from digitoxin.

Finally, the action of PCBs leading to induction of mixed function oxidases (MFOs) in the liver, with elevation of associated cytochromes P-450 or P-448, has potential consequences. These are discussed elsewhere (section XI).

F. Some Observations on Polychlorinated Dibenzofurans

The PCDFs are of special interest since they are known to be highly toxic in their own right, and the degree to which, as contaminants, they add to the potencies of PCB mixtures in production of adverse health effects in animal models and humans has not been fully evaluated. However, toxicological studies in animals with PCDFs containing one to four or more Cl atoms per molecule (Morita and Oishi, 1977; Goldstein et al., 1976; Veerkamp et al., 1981) have shown that the PCDFs are qualitatively quite similar to their structural PCB analogs with respect to properties of tissue distribution, metabolism, and excretion. In the mouse, the heavily chlorinated isomers localize in liver, spleen, and fat (Morita and Oishi, 1977), with a half-life for clearance from the body of about two weeks. In the rat, metabolism occurs by oxidative pathways leading to mono- and dihydroxylated derivatives (Veerkamp et al., 1981), with a wide variation in ring position by the hydroxy function among the lower chlorinated PCDFs. The octachloro derivative yields no metabolic products in tissues or excreta (Veerkamp et al., 1981). In

the chick (Goldstein et al., 1976), the 2,3,7,8-tetrachlorodibenzofuran (TCDF) has been shown to be relatively poor in enzyme induction. However, Goldstein et al. (1978, 1979a) have shown that 2,3,7,8-TCDF is a potent inducer of cytochrome P-450 and aryl hydrocarbon hydroxylase.

Some important data on PCDF metabolism and excretion in the human were obtained (Rappe et al., 1979) by analysis of liver tissue from two deceased patients in the Yusho disease group in Japan. From the differences in PCDF structural relationships in the contaminated rice oil and in the PCDF fractions isolated from the livers, inferences could be drawn with respect to PCDF structure (all containing four to six chlorine atoms per molecule) retained by the liver versus those that had disappeared from liver by processes of metabolism/elimination. In striking parallelism with PCB disposition in mammalian tissues, it was found that none of the PCDFs retained in liver had two vicinal unsubstituted (by Cl) positions in either aromatic ring. Apparently, all such molecules had been sufficiently susceptible to oxidative metabolism to be hydroxylated and excreted from liver in the bile.

The above observations are not to be taken as all-inclusive with respect to the body of information that must be developed in the toxicology of the PCDFs. This class of compounds, even at low contaminant levels, is an important contributor to the total spectrum of toxic effects from commercial PCB mixtures.

G. Summary and Opinion

Some general reflections and opinions can reasonably be drawn from the previous discussion regarding the use of animal-derived biochemical and kinetic information to predict certain events and hazards in human PCB intoxications.

(1) Pathways of absorption, distribution, metabolism, and excretion have been explored fairly extensively in animal models. From the species variability seen, coupled with limited observations in the human, educated guesses and predictions can be made on the occurrence of certain toxic effects and processes in the human.

(2) Mathematical analyses of kinetic data from animal modeling experiments lead to some generalizations (Luts et al., 1977) that could apply to PCB turnover kinetics in the human: (1) kinetic rate constants for metabolism of PCBs by the liver decrease as the degree of chlorination increases; (2) rate constants for biliary clearance of PCB metabolites from the liver are nearly the same for all PCBs; (3) urinary clearance rates for PCBs decrease as the degree of chlorination of the parent molecules increases; and, (4) for each PCB, the value of the distribution coefficient between fat and blood is greater than that in any other major tissue, indicating that the fat compartment of all tissues may constitute the major PCB depot.

(3) Kinetic models derived from animal data may be useful for prediction of time courses of action in the human once

additional data on metabolism and clearance rates for individual PCBs in human tissues are obtained.

(4) Some general PCB structure versus activity relationships have emerged from animal studies, particularly rodents, that can have useful predictive power for the human.

(5) There is some relevance of the features of the absorption/distribution/metabolism/clearance processes discussed in this section to the toxicology of PCBs in animals and humans. For example:

(a) The possibility that an arene oxide intermediate can occur in PCB metabolism has special significance in terms of potential reactions with protein, RNA, or DNA to cause tissue damage or damage to a cell's nuclear functions.

(b) The retention of PCBs in adipose or other tissue can have major significance by creating reservoirs from which material can be leached over time for reaction at other tissue sites.

(c) There is little evidence in humans for acute cytotoxicity of the kind usually associated with reactive metabolites. Rather, some of the adverse effects of PCBs, e.g., chloracne, could stem from the physical presence of unreacted material in the cells along with oils and/or sebaceous materials of the skin.

IV. General Toxicity

A. General Considerations

Any attempt to undertake a systematic evaluation of the toxicity of PCBs is confounded by a number and variety of factors that complicate the interpretation of the findings and limit their generalization. Therefore, these factors should be recognized at the outset of consideration of the available body of toxicological literature. The more important of these factors are listed as follows:

(a) The multiplicity of commercial products of both U.S. and foreign manufacture;

(b) The multiplicity of isomeric forms of PCBs in commercial products;

(c) Qualitative and quantitative differences in metabolism of different isomers within the same species;

(d) Qualitative and quantitative differences in metabolism of the same isomer between species;

(e) Differences in rates of metabolism of different isomers within the same species;

(f) Differences in rates of metabolism of the same isomer between species;

(g) Differences in the biological half-lives of different isomers within the same species;

(h) Differences in the biological half-life of the same isomer between species;

(i) The presence in commercial products of impurities of much greater toxicity than that of PCBs;

(j) The variability between commercial products of the same type (i.e., same degree of chlorination) in the concentration of impurities of much greater toxicity than that of PCBs;

(k) The variability between commercial products of the different types (i.e., different degrees of chlorination) in the concentrations of impurities of much greater toxicity than that of PCBs; and

(l) Differences between species in susceptibility to the toxic action of (i) individual isomers and their metabolites, and (ii) the impurities that may be present in commercial products.

The preceding factors may underlie the conclusion reached by the Panel of Hazardous Trace Substances (1972) that "[t]here is no consistent relationship between toxicity and degree of chlorination which is valid for different species and different routes of exposure." To this might be added the observation that there is often no consistent relationship between the results of investigations on products of the same degree of chlorination from different manufacturers. These observations constitute caveats that should be borne in mind as individual toxicological experiments and results are evaluated.

B. Impurities in Commercial Products

The work of Vos and his associates (Vos and Koeman, 1970; Vos et al., 1970; Vos and Beems, 1971) led to a recognition

the significant role played by traces of impurities in commercial PCBs in influencing the apparent toxicity of the latter. In studies involving three commercial PCBs of the same degree of chlorination, these investigators found marked differences in toxicity that were traced to the presence, in two of the products, of small amounts of chlorinated dibenzofurans (PCDFs) and chlorinated naphthalenes. The PCDFs are related closely, both structurally and toxicologically, to the chlorinated dibenzodioxins. The 2,3,7,8-tetrachlorodibenzo-p-dioxin isomer is an extremely potent toxicant in mammals, especially for the fetus. The chlorinated naphthalenes are less toxic than the chlorinated dioxins, but nevertheless cause chloracne and other symptoms in man similar to those produced by PCDFs.

The extent of the contribution made by contaminants to the toxicity of commercial PCBs is uncertain, but the consensus is that it is substantial. There seems little doubt that the skin lesions, including chloracne, are caused by PCDFs. The Panel on Hazardous Trace Substances (1972) states that the PCDFs "are probably the chief if not exclusive cause of chloracne in man." Fishbein (1974), in his review of the toxicity of chlorinated biphenyls, observes that "[l]iver damage and skin lesions are believed to be caused primarily by chlorinated dibenzofuran contaminants and to a minor extent by PCB itself." Furthermore, since the chlorinated dibenzodioxins exhibit pronounced embryotoxicity, it is not unreasonable to expect that the PCDFs share this property and, hence, are largely responsible for the fetal

deaths and resorptions that have been observed experimentally with commercial PCBs.

An appreciation of the role played by contaminants in the toxicity of commercial PCBs is important for two reasons. First, it may explain discrepancies between the results of studies of apparently similar commercial products. Second, it points up the difficulty of attempting to use PCB tissue levels to correlate the results of laboratory studies with observations of occupationally or environmentally exposed populations. For example, some animal populations in the environment appear to be uneffected by PCB tissue levels that are equal to or greater than those associated with adverse effects on comparable species in the laboratory.

C. General Toxicology

1. Acute Toxicity

The Aroclors of the PCB class have a low order of acute toxicity. The acute oral LD50s for rats range from 1-10 g/kg. The LD50s by single application to the skin of rabbits are approximately 1-3 g/kg. Oral and dermal LD50 data have been summarized by Fishbein (1974), Kimbrough et al. (1978), and the Panel on Hazardous Trace Substances (1972).

2. Subchronic and Chronic Toxicity

(a) General

Subchronic and chronic toxicity are grouped together for purposes of this discussion since the effects of chronic

exposure to PCBs are essentially extensions of those observed from repeated exposures of shorter duration.

There are numerous published studies in which commercial PCBs (Aroclors) have been administered by various routes for varying periods of time to most common mammalian species of laboratory animals. Out of this mass of observations, one may identify two principal classes of biological effects of these substances. These classes are (a) alterations in the liver, and (b) skin lesions.

(b) Alterations in the Liver

Enlargement of the liver, both in absolute terms and as a percentage of body weight, has been observed consistently in most species consequent to repeated exposure to PCBs, although it is more pronounced in rodents than in others. This phenomenon has been reported for mice (Kimbrough and Linder, 1974), rats (Bruckner et al., 1973, 1974a, b), guinea pigs (Voe and Van Driel-Grootenhuis, 1972), rabbits (Koller and Zinkl, 1973), dogs (Calandra, 1976), and monkeys (Allen et al., 1973). Early enlargement of the liver is primarily the result of an increase in the size of the hepatocyte associated with an increase in the amount of the smooth endoplasmic reticulum (SER). These developments are associated also with increased enzymatic activity of the liver (Bruckner et al., 1973).

A detailed discussion of the effects of PCBs on liver in test animal systems is given in section VI.

(c) Skin Lesions

Cutaneous effects from repeated exposure to commercial PCBs can be elicited by feeding to monkeys or skin application to rabbits, although the results are somewhat more dramatic in the former. The results of these animal studies are discussed in section V.

(d) Miscellaneous Effects

Hyperplasia and dysplasia of the gastric mucosa have been observed in monkeys fed a diet containing 300 ppm of Aroclor 1248 for three months (Allen and Norback, 1973). Gastrointestinal lesions do not appear to occur in rodents, except at very large single doses by mouth (Rimbrough, 1979). A dietary concentration of 2.5 ppm of Aroclor 1248 produced alterations in the menstrual cycles of adult, female rhesus monkeys (Allen et al., 1979). Menses were prolonged, and there was an increase in menstrual bleeding. Hepatic porphyria has been demonstrated in mice after feeding Aroclor 1254 (Rimbrough and Linder, 1974), in rats after feeding Aroclors 1254 or 1260 (Rimbrough, et al., 1972), and in rabbits after repeated skin application of Aroclor 1260 (Vos and Beems, 1971). Urinary excretion of coproporphyrin was increased in rats fed Aroclor 1242 (Bruckner et al., 1974), and both urinary and fecal excretion of porphyrins was increased in rabbits receiving repeated skin applications of Aroclor 1260 (Vos and Beems, 1971). Other effects reported for one species or another include structural changes in the kidney (Vos and Beems, 1971; Bruckner et al., 1974a, b), hematologic alterations

Bruckner et al., 1974a, b), and thymic atrophy together with a reduction in the number of germinal centers in the spleen and lymph nodes (Vos and Beems, 1971).

D. Summary and Opinion

Voluminous literature establishes that commercial PCBs are capable of producing a variety of biological effects when administered in large quantities to experimental animals. The majority of these effects can be grouped into two categories, namely, those involving the skin and those involving the liver. A number of miscellaneous effects that have been observed in one species or another can be considered secondary to the action of the substances on the liver. In general, these effects are only elicited by relatively high dosages of the PCBs, reflecting the low order of acute toxicity of the U.S. commercial mixtures.

There is a considerable range of species susceptibility to the biological activity of PCBs as measured by the size of the dosage, the duration of the exposure, and the severity of the effect. Mink appear to be the most susceptible, monkeys somewhat less so, and rodents the most resistant. There is no basis for a judgment as to which species most accurately serves as a model for man. A comparison of the observations on humans in the Yusho incident with those on monkeys fed relatively small amounts of PCBs has led some investigators to conclude that the latter species is an appropriate surrogate for man. Although there are some similarities between Yusho disease and the findings in monkeys, they are not sufficient to justify such a conclusion.

There is evidence throughout the literature that some of the biological effects observed experimentally with commercial PCB mixtures are caused not by PCBs themselves but by other chlorinated aromatic compounds present as impurities, such as the PCDFs. The significance of this finding is that PCB levels resulting from occupational or environmental exposures cannot be interpreted in the same way as those observed in experimental animals. A broader implication of this circumstance is that the results of laboratory studies are not necessarily predictive of what may be expected from incidental exposures since the nature of the exposure may have differed in the two instances.

As is always the case in experimental toxicology, the validity of test results as predictors of hazard to man must await confirmation or denial by observations of exposed human populations. Fortunately, the reports of actual injury to man from PCB exposure are few, although extensive epidemiological surveys have been conducted and others are in progress. An evaluation of the epidemiology of exposure to PCBs is the subject of section XII of this report. Still other sections of the report deal with specific potential health effects in greater detail.

V. Skin and Other Cutaneous Tissues

Epithelial and follicular hyperplasia and hyperkeratosis have been reported to occur following the application of PCBs on the skin of rabbits (Vos and Beems, 1971). Skin lesions have also been observed in rats and guinea pigs from the application of PCBs. Repeated application of Aroclor 1260 to the skin of rabbits caused thickening of the skin as a result of hyperplasia and hyperkeratosis of the epithelium (Vos and Beems, 1971).

Cutaneous effects have been elicited in male rhesus monkeys fed a diet containing 300 ppm Aroclor 1248. Within one month the animals lost considerable hair from the head, neck, and back (Allen et al., 1973, 1975). Similar effects have been observed in female rhesus monkeys fed a diet containing 25 ppm Aroclor 1248 for two months (Allen et al., 1974). Within six weeks the animals began to lose hair and developed obvious signs of edema of the lips and eyelids. Small pustules involving hair follicles appeared about the mouth, cheeks, and neck. Abraham and Allen (1973) showed that the infant monkey was able to tolerate doses of PCBs that produce extreme morbidity in adult monkeys. They suggested that there may be variations in absorption, distribution, metabolism, storage, and excretion in adult and infant monkeys that may account for these differences.

Follicular hyperkeratosis is an important feature of the occupational disease known as acne, which is characterized by the appearance of papules, comedones, and cysts. Industrial

dermatosis of the acneform type has been observed among workers exposed to chlorinated hydrocarbons (Jones and Alden, 1936; Mayers and Silverberg, 1938; Maroni et al., 1981). Seven cases of chloracne of the face and head have been reported among 14 chemical operators exposed from 5-19 months intermittently to low concentrations of chlorinated biphenyls (Meigs and Albom, 1954). Puccinelli (1954) and Hofman et al. (1962) report chloracne in several capacitor workers, whereas Smith et al. (1981) noted that none of the capacitor workers examined in this recent survey were found to have acneform lesions suggestive of chloracne.

The acneform eruptions that occur in the skin of both monkeys and rabbits may be caused by a squamous metaplastic change in the epithelium lining the sebaceous glands, which result in a change in the character of the secretion from normal oily to keratinaceous. This condition frequently results in plugging and rupture of the glands with consequent inflammatory reactions (acne). The question of whether a similar condition can occur in man from exposure to PCBs will be dealt with in another section of this report.

It has been suggested that the cutaneous eruptions that occur in both animals and man from exposure to commercial preparations of PCBs may be due to certain impurities. Chemical analysis of the PCBs that contaminated the rice oil that caused the Yusho disease in Japan showed high levels of polychlorinated dibenzofurans (Kuratsune, 1976).

VI. Effect of PCBs on Liver

A. Experimental Data

1. Liver Weight

The administration of PCBs may induce an increase in liver weight (Table 2). The effect is more prominent at the higher dose levels; the lower doses of PCBs do not increase liver weight. The detailed data of Kimbrough et al. (1972) are not included in the table. They found that Aroclor 1260, administered with the diet in doses of 500 and 1000 ppm for eight months, significantly increased liver weight in male and female rats; doses of 20 and 100 ppm were effective only in male rats. Aroclor 1254 increases liver weight in both male and female rats at doses of 20, 100, and 500 ppm.

Although the data in Table 2 illustrate the effect obtained in subchronic and chronic studies, it should be noted that liver weight may also be increased in acute toxicity studies. PCB congeners (penta-, hexa-, and heptachlorobiphenyls) given in a high single dose of 50 mg/kg, can increase liver weight in the rat; in most but not all tests, liver triglycerides, cholesterol, and phospholipids were increased (Yoshihara et al., 1979). In the monkey a single oral dose of 1.5 g or 3.0 g/kg of Aroclor 1254 produced slight enlargement of the liver in 4 days (Allen, Norback, and Hsu, 1974).

The increase in liver weight is correlated with hepatic cell hypertrophy and an increase in smooth endoplasmic reticulum

Table 2

Effect of PCBs on Liver Weight and Morphology

			Weight Changes +=increase 0=no change	Major Histological Findings
Studies in Mice				
Kimbrough & Linder, 1974, Aroclor 1254			+	Pleomorphism, necrosis
Studies in Rats				
Bennett, et al., PCB, 45% Cl	300 mg 250 mg	4 days up to 100 days	+ +	Cells swollen, hyaline granules
Koplinger et al. 0247	100 ppm	10 months	+	
Aroclor 1254, 1260	10 ppm	10 months	0	
	1 ppm	10 months	0	
Aroclor 1242	100, 10, 1 ppm	10 months	0	
Litterest et al., 1972	500 mg	4 weeks	+	
Aroclor 1242, 1248	50 mg	4 weeks	+	
1254, 1260	5 mg	4 weeks	+	
	0.5 mg	4 weeks	0	
Allen & Abrahamson, 1973, Aroclor 1248, 1254, 1262	0.1% in diet	6 weeks	+	Fat droplets, areas of necrosis
Brunner et al., (1973) Aroclor 1242	100 mg/L every 2nd day	3 weeks	+	Eosinophilic vacuolation
Brunner et al., 1974	25 ppm 5 ppm	2,4,6 months	0	No change with H&E stain, increase lipid with Sudan IV stain

CONTINUED

Table 2 (CONTINUED)

Effect of PCBs on Liver Weight and Morphology

			Weight Changes +=increase 0=no change	Major Histological findings
Studies in Rats (Continued)				
Purse et al.. Aroclor 1242, 1016	100 ppm	up to 18 months	0	Enlarged hepatocytes, vacuolated cytoplasm, characterized as mild changes
Studies in Rabbits				
Yee et al., Aroclor 1260 hexachlorobiphenyl	120 dermal 5 x week	4 weeks	+	Hydropic degeneration, necrosis
Keller & Siahi, 1973				
Aroclor 1254	100 mg each/wk	14 weeks	+	Enlarged hepatocytes, necrosis
Aroclor 1242	" "	" "	+	Enlarged hepatocytes, some necrosis
Aroclor 1221	" "	" "	0	No histological changes
Studies in the Monkey				
Allen et al., 1973				
Aroclor 1260	100 ppm	90 days	+	Enlarged hepatocytes, no necrosis
Aroclor 5460	5000 ppm	" "	+	" "

Table 2A

Liver Lesions in Albino Rats Treated with Aroclors for 2 Years*

(Data from Levinskas, 1981)

	Control	Aroclor 1242			Aroclor 1254			Aroclor 1260		
Diet level, ppm	0	1	10	100	1	10	100	1	10	100
No. animals examined	23	32	29	16	30	26	26	26	25	25
Vacuolar change	1	7	8	9	7	9	13	5	7	9
Focal necrosis	1	1	1	8	3	1	1	4	3	6
Focal lymphoid infiltration	1	0	0	0	2	0	1	0	1	0
Focal hypertrophy hepatocytes	0	2	3	0	3	4	14	3	13	9
Nodular hyperplasia	1	1	1	0	0	3	14	0	7	6
[illegible] hyperplasia	5	3	3	3	6	1	14	6	7	12
Hepatoma	0	0	0	3	0	0	4	0	1	7
Cholangiohepatoma	0	0	0	1	0	0	2	0	0	4
Hepatocellular carcinoma	0	0	0	0	0	0	0	0	0	0

*The results of this study were presented in a summarized form by Calandra (1975) and were later reanalyzed and tabulated by Levinskas (1981)

the rat, rabbit, and monkey (Vos et al., 1972; Allen and Hanamson, 1973; Bruckner et al., 1974a; Allen, Norback, and Hsu, 1974; Allen, Carstens, and Barsotti, 1974). Ecobichon and Comeau (1974a, b) found that the effect of PCBs administered intraperitoneally on liver weight and on hepatic enzymes associated with hepatic endoplasmic reticulum was related to the position of the chlorine substitution on the biphenyl nucleus. However, all of the congeners and isomers administered at a dose of 50 mg/kg intraperitoneally for three days produced an increase in smooth endoplasmic, lipid droplets and microbodies, although the quantitative response varied (Hansell and Ecobichon, 1974).

2. General Histology

The administration of PCBs to experimental animals will produce histopathological changes in the liver. The main effects obtained are the production of enlarged hepatocytes, fat droplets, and slight degree of necrosis; the occurrence of these changes depend particularly on the dose of the PCB and to some extent on the particular Aroclor (Tables 2 and 2A). Necrosis seems to be more severe in the rabbit than in the rat. In general, the morphological changes observed in the liver of PCB-treated animals are similar to those found after treatment with other chlorinated hydrocarbons.

In a detailed study, Kimbrough et al. (1972) found that Aroclor 1260 (20, 100, 500, and 1000 ppm) and Aroclor 1254 (20, 100, and 500 ppm), given in the diet of rats for eight months, produced

enlarged liver cells and cytoplasmic inclusions. At the higher doses, there was evidence of lipid accumulation, which was associated with a foamy cytoplasm, and pigment accumulation in the Kupffer cells. The pigment gave a positive Prussian-blue reaction, indicating the presence of hemosiderin. Studies of rats four to six months after exposure to different doses of Aroclors 1016 and 1242 indicated that the morphological changes are reversible and disappear gradually after dosing is stopped; the hepatocytes were still larger than controls, but the frequency of vacuolated cytoplasm or inclusions within the cytoplasm had decreased (Burse et al., 1974).

Aroclor 1254 was evaluated by the National Cancer Institute (1978). Fischer rats receiving 25 ppm in the diet for eight weeks had enlarged livers, but without evidence of histological abnormality. The administrations of doses of 25, 50, and 100 ppm for 104-105 weeks did not increase the frequency of liver lesions such as congestion, inflammation, necrosis, or angiectasis.

3. Adenofibrosis

Adenofibrosis (synonyms: bile duct proliferation, bile duct adenomatosis, cholangiofibrosis, fibroadenoma) has been observed in some rats receiving PCBs. Adenofibrosis is generally regarded as a benign lesion. In their review of experimental tumors, Stewart and Snell (1957) stated that there is no convincing evidence that adenofibrosis is a precancerous lesion.

It should be noted, however, that Reuber (1968), studying 2-acetamidofluorene and 2-diacetamidofluorene, suggested that adenofibrosis is a precancerous lesion for the development of cholangiocarcinoma.

(i) Studies in mice. Kimbrough and Linder (1974) observed foci of adenofibrosis in the liver of some mice with 300 ppm of Aroclor 1254 in the diet for 11 months. Ito et al. (1974) comment that they did not observe cholangiofibrosis in mice receiving Kanechlor.

(ii) Studies in rats. Kimbrough et al. (1972) observed adenofibrosis in rats treated with Aroclor 1260 and 1254; the effect was observed at the higher dose levels and particularly in animals receiving Aroclor 1254. When the feeding of 500 ppm of Aroclor 1254 was discontinued and the animals studied up to 10 additional months, the fat and liver content of PCB remained high and the adenofibrosis persisted (Kimbrough et al., 1973). In a later paper involving treatment with Aroclor 1260 at 100 ppm for 21 months, mention is only made that a few rats showed areas of adenofibrosis, indicating a low degree of response, but data are not tabulated (Kimbrough et al., 1975). In further studies by the same group adenofibrosis was not observed in rats fed Aroclor 1016 or 1242 (100 ppm) for up to 10 months (Burse et al., 1974).

In a study with three Aroclors, administration of 100 ppm in the diet for 24 months produced a low incidence of

cholangiohepatoma (Table 2A), but concentrations of 1 ppm or 10 ppm were without effect (Calandra, 1976; Levinskas, 1981). Treatment did not significantly affect ductal hyperplasia.

The study of the National Cancer Institute (1978) did not observe adenofibrosis in rats receiving Aroclor 1254 at doses of 25, 50, and 100 ppm for 104-105 weeks.

In studies with various Kanechlors, Ito et al. (1974) administered Kanechlor 500, 400, and 300 in the diet at concentrations of 1000, 500, and 100 ppm. At the concentration of 1000 ppm of the Kanechlors, the incidence of cholangiofibrosis ranged from 13 to 30% in the rats; cholangiofibrosis did not occur at levels of 500 or 100 ppm. Kimura et al. (1976) also reported cholangiofibrosis in rats treated with Kanechlor 400.

4. Hyperplastic Foci and Nodular Hyperplasia in the Liver

Hyperplastic foci or hyperplastic areas represent minimal changes in the hepatocytes. Such foci or areas of hyperplastic changes are uncommon in untreated young rats, but increase with age. The hyperplastic areas or foci may coexist with nodular hyperplasia and/or hepatocellular carcinoma. The significance of hyperplastic foci is that they may be part of a spectrum capable of progressing to a nodule (Squire and Levitt, 1975).

The hyperplastic nodule (nodular hyperplasia, neoplastic nodule, hepatoma) is generally as large or larger than the area of several lobules, and the lesion is sometimes elevated

[redacted]ove the surface of the liver. The lesion is frequently re-[redacted]rred to as a neoplastic nodule and some consider it to be a [redacted]anifestation of a carcinogenic process, the earlier stages [redacted] which may be represented by the hyperplastic foci discussed [redacted]bove. The use of these terms in the literature is confusing, [redacted]s some who use the word "hyperplastic nodule" regard the [redacted]esion to be part of the neoplastic process whereas others consider it to be unrelated to neoplasia. Some investigators [redacted]se the terms adenoma or hepatoma to designate the lesion, implying that it is a benign neoplasm.

Despite the differing terminology, it may be considered that the hyperplastic foci and nodular hyperplasia (neoplastic nodules) occurring in the liver are benign lesions rather than carcinomas. However, such nodules may be part of a sequence of neoplastic changes that eventually progress on to hepatocellular carcinomas. Although the data on hyperplastic foci and nodular hyperplasia are discussed in this section and hepatocarcinogener[illegible] are discussed in section VIII, the experimental data on the incidence of benign and malignant lesions are given in the same table so that the overall biological effect of the treatment can be observed as a unit.

(i) Studies in mice. Ito et al. (1973) observed nodular hyperplasia in mice only at the highest dose level of Kanechlor 500. (Nagasaki et al., 1972, reported the same data.) Whereas Kanechlor 500 produced nodular hyperplasia at 500 ppm, lesser doses were not active and Kanechlor 400 or Kanechlor 300

was inactive at all doses studied (Table 3). There was some evidence that the administration of Kanechlor 500 increased the nodular hyperplastic response induced by α or β isomers of benzene hexachloride.

Kimbrough and Linder (1974) observed adenofibrosis and hepatomas in nine of 24 mice fed Aroclor 1254 (300 ppm in the diet) for 11 months; in animals fed Aroclor for only six months followed by a five month recovery there was no adenofibrosis and the incidence of hepatoma was only 1/24 mice.

(ii) Studies in rats. Keplinger et al. (1971) did not observe hepatic lesions in rats receiving different Aroclors for 18 months; however, re-evaluation of the slides indicated a significant increase of nodular hyperplasia in the treated animals (see National Cancer Institute, 1978).

Ito et al. (1974) obeerved nodular hyperplasia in rats receiving 100, 500, or 1000 ppm of Kanechlor 500; a lesser effect was observed with Kanechlor 400 and there was no significant effect of Kanechlor 300.

Kimbrough et al. (1975) reported a significant increase in the incidence of hyperplastic foci or areas and neoplastic nodules in female rats given 100 ppm of Aroclor 1260, mixed with the diet for 21 months (Table 4). In another study, the dietary administration of 100 ppm of Aroclor 1242, 1254, and 1260 for 24 months increased the incidence of nodular hyperplasia (Table 2A); a lesser effect was obtained with 10 ppm.

TABLE 3

Incidence of Liver Lesions in Male Mice

Treated with PCBs for 24 Weeks

(Data of Ito et al, 1973)

	ppm in diet	Incidence	
		Nodular Hyperplasia	Hepatocellular Carcinoma
Kanechlor 500	500	7/12	5/12
	250	0	0
	100	0	0
Kanechlor 400	500	0/12	0/12
	250	0	0
	100	0	0
Kanechlor 300	500	0/12	0/12
	250	0	0
	100	0	0
Controls	-	0/6	0/6

TABLE 4

Incidence of Liver Lesions in Female Rats Treated with Aroclor 1260 (Data from Kimbrough et al., 1975)

Lesion	Incidence	
	Controls	Experimental
Hyperplastic foci or areas	28/173	182/184
Neoplastic Nodules	0/173	144/184
Hepatocellular Carcinoma	1/173	26/184

TABLE 5

Incidence of Liver Lesions in Male and Female Rats
Treated with Aroclor 1242, 1254 and 1260
100 ppm in Diet for 24 months
(Data from Calandra, 1975)

	Aroclor		
	1242*	1254**	1260
Nodular hyperplasia	8/20	13/27	7/27
Hepatomas	2/20	4/27	5/27
Hepatocellular carcinoma	0/20	0/27	0/27

*10 males and 10 females
**13 males and 14 females

TABLE 6

Incidence of Liver Lesions in Male and Female Rats Treated with Aroclor 1254

(Data from National Cancer Institute, 1978)

	Males			Females		
	Low Dose	Mid Dose	High Dose	Low Dose	Mid Dose	High Dose
Number of animals necropsied	24	24	24	24	22	24
Hyperplastic foci** or areas	5	8	12	6	9	17
Adenoma, NOS*	0	0	1	0	1	2
Hepatocellular carcinoma	0	1	2	0	0	0

* Hyperplastic foci, hepatocellular adenomas or carcinomas were not diagnosed in the controls.

+ Not otherwise specified

** As defined in report

[redacted] 1 ppm did not produce a positive response (Calandra, 1976; [redacted]inskas, 1981). All three Aroclors produced an increased [redacted]mber of hepatomas at the high dose (Table 5). There was no [redacted]vidence of metastaeis or invaeivenese, and the lesions were [redacted]garded by the pathologists as benign tumors.

The results of a bioassay of Aroclor 1254 for carcino-[redacted]nicity, using dosee of 25, 50, and 100 ppm in the diet, are [redacted]mmarized in Table 6 (National Cancer Institute, 1978). Their [redacted]se of terms is confusing, for although they use the words "nodular [redacted]yperplasia" in their table, they state in the text that "the [redacted]reas of nodular hyperplasia appeared to be microscopically [redacted]milar to what is currently termed 'focal areas of cellular [redacted]lteration.'" Thus, we have used the term "hyperplastic foci or [redacted]reas" in Table 6 to describe their results. It is evident from [redacted]he data in Table 6 that the hyperplastic foci were present in a [redacted]ose-related frequency. Although the incidence of the hyper-[redacted]plastic foci did not differ significantly from the controls, this [redacted]ncidence appeared to be related to treatment. The biological [redacted]ignificance of the increase in "focal areas of cellular altera-[redacted]tion" is not clear as relatively few adenomas were found.

Both the above studies (Kimbrough et al., 1975; National Cancer Institute, 1978) demonstrate an increase in proliferative [redacted]eeions of the liver; the effect is greater with Aroclor 1260 [redacted]than with Aroclor 1254.

(iii) Studies in dogs. Hepatic nodular hyperplasia [redacted]id not occur in the dogs receiving dietary levels of 1, 10, or 100

ppm of Aroclor 1242, 1254, or 1260, respectively, for two years (Calandra, 1976). Each treatment group consisted of eight dogs (four female and four male).

5. Summary and Comment

The administration of high doses of PCBs to animals can produce hepatic enlargement and an increase in liver weights, which is associated with an increase in smooth endoplasmic reticulum. Other effects include a slight degree of necrosis and the presence of fat droplets and a vacuolated cytoplasm. These changes, which are similar to those found after treatment with other chlorinated hydrocarbons, are readily induced by high doses of PCBs, but are absent when lower doses of PCBs are given. The response appears to be greater with increased chlorination of the biphenyl nucleus but, depending on dose, even the high chlorinated derivatives may not produce a positive response.

Treatment with PCBs usually increases the occurrence of hyperplastic foci. The nodular hyperplasia, neoplastic nodules or hepatomas have been reported to be increased in some studies, but other evaluations have not confirmed these effects. The effects of PCBs on the occurrence of nodular hyperplasia, neoplastic nodules, hepatomas, or adenofibrosis is highly variable; some studies have reported a positive effect whereas others failed to show an effect of treatment. Again the change in histological response or in frequency of benign hepatic tumors is related to both the dose of PCB administered and the degree of chlorination of the PCB.

Data on hepatocellular carcinoma in PCB-treated animals are discussed in section VIII.

B. Clinical Data

1. Liver Function in PCB-exposed Workers

Based on results in animals, it was expected that if PCBs produced a significant degree of injury in man, it would be to the liver. Such has not been the case, as the clinical studies summarized below have provided little evidence for the occurrence of hepatic dysfunctions in PCB-exposed workers even though the blood level of PCB may be relatively high.

(i) Ouw et al. (1976) studied liver functions in 34 workers exposed to Aroclor 1242 for one month up to 23 years; 31 were exposed for more than one year and 16 for five or more years. Scattered individual abnormal test results were obtained: serum bilirubin was normal and in all 34 subjects, alkaline phosphatase was elevated in one of 34 subjects and serum transaminase (SGPT) was increased in five tests.*/ There was no relationship of the results to the blood level of PCB and the mean of each hepatic function test for the whole group was within normal limits. BSP

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*/ The abbreviations used in this section are as follows:

SGOT = serum glutamic oxaloacetic transaminase
SGPT = serum glutamic pyruvic transaminase
SGGT = serum gamma glutamyltranspeptidase
LDG = serum lactic dehydrogenase
AST = aspertate aminotransferase
ALT = serum alanine aminotransferase
SOCT = serum ornithin-carbamoyltransferase
BSP = bromsulfonphthalein

tests were also performed on seven workers with relatively high blood PCB; four of the seven tests were slightly above the normal limit of 5% but, as the authors state, since other conditions such as fever may increase BSP retention, these results by themselves could not be taken as proof of hepatic damage. The BSP test results did not show a significant correlation with blood PCB levels or the length of exposure (five to 23 years) to PCB.

(ii) Fischbein et al. (1979) studied liver function tests in 321 workers exposed to PCBs in an electrical manufacturing plant for less than five years to more than 25 years. The percent of tests that gave an abnormal test result was SGOT 2.2%, SGPT 7.2%, LDH 2.5%, alkaline phosphatase 1.2%, and serum bilirubin 5.3%, and indicated a "very low prevalence of abnormal liver findings." There was no comment or analysis to state that a certain number of the subjects showed a pattern of abnormal liver function tests indicative of hepatic dysfunction. These data can be taken to represent a series of random test results that might be expected in a population of 321 individuals ranging in age from less than 30 years to over 70 years. Control subjects or non-exposed workers were not included for comparison. There was perhaps some indication of a relationship of SGOT levels to plasma levels of PCBs, but the two exposure categories of PCB levels are too broad and require a finer analysis.

(iii) Baker et al. (1980) studied liver function in 148 individuals with various degrees of exposure to PCBs; the

[redacted]n PCB serum levels for the four test groups varied from 17.4 [redacted] to 75.1 ppb. There was no change in liver function tests [redacted]GOT, SGPT, LDH, alkaline phosphatase, or serum bilirubin) in [redacted]sition to PCB blood levels in either drinkers or nondrinkers of [redacted]lcohol. Serum GGTP (gamma glutamyl transpeptidase) correlated [redacted]th serum PCB, but a correlation did not exist when alcohol [redacted]rinkers were removed from the analysis.

(iv) Maroni et al. (1981a, b) studied liver function [redacted]n 80 workers exposed to PCBs for an average of 12 years and [redacted]eported that 16 individuals had an abnormal liver finding as [redacted]udged by clinical examination or by laboratory tests.

Inspection of the data shows relatively few instances of abnormal liver function tests. The most frequently altered laboratory tests were as follows:

8 of 80 subjects with increase of SGGT activity

7 of 80 subjects with increased serum amino-transferase activity (AST or ALT)

6 of 80 subjects with increase of SOCT activity.

It is evident from their data that many of the changes are slight, and as test results from control subjects were not included, we do not know what the normal test variations may be for 80 control subjects of a similar age. Further, examination of the data for the 14 subjects with clinical hepatomegaly shows only one subject with an abnormal test in three types of tests (SGGT, AST/ ALT, and SOCT); only two of the subjects gave a positive response in two of

the test types; eight subjects had an abnormality in only one test; three subjects had normal test results. Serum bilirubin and alkaline phosphatase activity were within the normal range in all subjects.

Based on the above review, it is evident that only one of the 80 subjects showed a pattern of test results indicative of abnormal liver function; the other test results reflect only random variations from normal.

Maroni et al. also reported that the mean level of blood PCBs in the 16 workers with abnormal liver findings was significantly higher than that of 64 workers without abnormal liver findings, but the ranges for the two groups show considerable overlapping and the two subjects with the highest blood PCB levels had normal liver function tests. The only control we can use to evaluate the suggested relationship between PCB blood level and liver function are the 10 subjects with chloracne; these 10 individuals had normal liver test results despite the fact that their mean blood PCB concentration was high and not significantly different from the mean blood PCB level found in the 16 workers discussed above. Thus, it cannot be said that this study demonstrates a relationship between a high blood PCB level and abnormal liver function tests, attesting further to the randomness of the liver function test results in the study.

(v) Smith et al. (1981a, b, c) evaluated liver function tests in PCB-exposed employees from an electrical manufacturing plant, a municipal electric utility company, and

[redacted]rivately-owned electric utility company. The data on SGOT [redacted] GGPT are difficult to evaluate as the results of the measurements are not given, and therefore may be assumed to be [redacted]thin normal population levels; rather, the authors sought [redacted]rrelations between the log of SGOT and GGTP with the log of [redacted]e lower serum PCBs and the log of high serum PCBs. Calculations include simple correlations, separate regressions with [redacted]e confounders as predictors, and squared partial correlation, [redacted]lus other computations to see if associations existed. Their [redacted]ables 6, 7, and 8 summarize many of their calculations, and [redacted]ata for transaminases from table 7 are summarized below.

	Correlation With Serum log L-PCB	Serum log H-PCB
Electric equipment company		
log SGOT	NS	Sig
log GGTP	Sig	Sig
Municipal electric utility company		
log SGOT	NS	NS
log GGPT	NS	NS
Privately-owned utility company		
log SGOT	Sig	NS
log GGTP	NS	NS

Sig = statistically significant

[redacted] = not significant

L-PCB = lower chlorinated biphenyls

H-PCB = higher chlorinated biphenyls

Correlations (associations) were found at the equipment company but the data cannot be examined to determine if the calculated value has any medical significance. Correlations at the publicly-owned utility company were not significant. At the privately-owned utility company, the only positive finding was a positive association of SGOT with serum L-PCB. It is not clear what the change in this one test result means as the serum L-PCBs were not significantly different between the exposed and nonexposed groups.

The test results for total bilirubin, alkaline phosphastase, and lactic dehydrogenase are not discussed, and it is presumed that these measurements of liver function were not abnormal.

2. Liver Disease in PCB-Exposed Workers

Medical examination of PCB-exposed workers has not shown the presence of liver disease. In the study of Fischbein et al. (1979), physical examination of 326 individuals (age less than 30 to over 70 years) revealed four individuals with abnormal liver size, two of whom had a history of heavy alcohol intake; one of the four had a slight elevation of one liver function test (SGOT of 55).

In another study of 148 individuals with varying degrees of PCB exposure, there was no evidence of liver disease as determined by medical history and physical examinations (Baker et al., 1980). Smith et al. (1981) did not find evidence for liver

disease in their subjects, there being no significant findings on physical examination of workers at an electrical equipment manufacturing plant who were heavily exposed to PCBs, or workers at a municipal utility company or a private utility company who were less heavily exposed.

Deaths from cirrhosis of the liver were not increased by exposure to PCB (Brown and Jones, 1981); six deaths were observed (three of the six consumed alcohol regularly) versus 5.6 expected.

3. Summary and Opinion

The review of clinical data demonstrates that exposure to PCBs does not significantly affect liver function tests. Liver function remains normal in individuals with measurable, and frequently high levels of serum PCB. Also, exposure to PCBs does not result in the production of clinically detectable liver disease. The induction of enzyme systems in the liver and the biological significance of this process, as mediated by PCBs, are discussed in section XI.

MONS 222002

VII. Gastric Lesions

The oral administration of PCBs to nonhuman primates has been shown by Allen and co-workers to induce hypertrophy and hyperplasia of the gastric mucosa. Mucosal cysts may be present within the epithelium of the stomach, but in the mucosal lining and the submucosa, there may be edema of the submucosa of the stomach. In addition, there is frequently invasion of the underlying mucosa by isolated glandular elements of the mucosal epithelium. General effects of this nature have been produced in the monkey by:

(i) A single oral dose of 1.5 g or 3 g of Aroclor 1248 (Allen, Norback, and Hsu, 1974).

(ii) Aroclor 1248, 300 ppm and Aroclor 5460 (a polychlorinated triphenyl), 5000 ppm in the diet for 90 days (Allen, Abrahamson, and Norback, 1973; Allen and Norback, 1973).

(iii) Aroclor 1248, 25 ppm in the diet for 2 months (Allen, Carstens, and Barsotti, 1974).

(iv) Aroclor 1248, 100 ppm in the diet for 2-3 months (Allen, 1975).

(v) Aroclor 1248, 2.5 ppm and 5.0 ppm in the diet for up to one year (Barsotti and Allen, 1975). (Gastric changes were not listed for these doses in Allen's review.)

(vi) The hyperplastic gastritis may persist for over one year following discontinuance of PCB exposure (Allen, 1975).

A mixture of low chlorinated biphenyl (Clophen A-30) was not observed to produce gastric lesions in the monkey (Iatropoulos et al., 1977).

The findings of Allen et al. were recently confirmed and extended by Becker et al. (1979). Their study involved six monkeys, one untreated and one each receiving a diet containing 3, 30, or 300 mg/kg of PCB (Aroclor 1242); two monkeys received a diet containing 10 mg/kg. Monthly biopsies taken from the greater curvature of the stomach showed a dramatic decrease in the number of parietal cells with a concomitant increase in the number of mucous neck cells. The zymogenic (chief) cells were also reduced in number. This was followed in all treated animals by a mucous conversion of the gastric epithelium, with downgrowth of the gastric glands into the submucosa and the eventual formation of cysts. It is noteworthy that the lesions were confined to the stomach; no changes were found in other regions of the gastrointestinal tract.

The gastric changes can be described as a dysplastic growth pattern, but there is no neoplastic transformation (Allen and Norback, 1973). However, the authors speculate that they are "suggestive" of an eventual neoplastic transformation.

Analysis of the results obtained in the monkey indicates that the PCB-induced morphologic changes in the gastric mucosa

may be specific to this species and not predictive of possible effects in man.

(i) Even within the monkey a specificity of action is present, as the lesion induced by PCBs is found only along the greater curvature of the stomach; neither the cardiac nor pyloric portions were affected (Becker et al., 1979).

(ii) Hypertrophy and hyperplasia of the gastric mucosa have not been reported in the rodent (Allen and Abrahamson, 1973), rabbit (Voe, 1972), or in other species (Vos and Koerman, 1970).

Clinical findings to date have not suggested or indicated that exposure to PCBs increases the occurrence of cancer of the stomach in the human (see also section VIII, relating to carcinogenicity).

VIII. Carcinogenesis: Experimental and Clinical

A. Experimental Studies

All authors do not use the words tumorigenesis and neoplasia to indicate the same type of response. Tumorigenesis is a general term that refers to both benign growths and malignant growths; compounds may affect the occurrence of benign tumors without inducing cancer. Neoplasia means simply a new growth. The term "neoplasia" can refer to a benign or malignant growth. Oftentimes authors may combine data relative to benign and malignant growths so that when the terms tumorigenesis or neoplasia are used, they must be carefully defined.

1. Hepatocellular Carcinoma

(i) Studies in mice. Ito et al. (1973) observed hepatocellular carcinomas in mice only in the high dose group given Kanechlor 500; lower doses of Kanechlor 500 or the other Kanechlors did not produce a carcinogenic response (Table 3). The administration of 300 ppm of Aroclor 1254 in the diet for 11 months did not induce hepatocellular carcinomas in mice (Kimbrough & Linder, 1974).

(ii) Studies in rats. The administration of Kanechlor 400 for 400 days did not induce hepatocellular carcinoma (Kimura & Baba, 1973), but the period of treatment may have been too brief to detect a carcinogenic effect. In a further study Kimura et al. (1976) administered Kanechlor to rats for six months but due to body weight changes a variable dosage schedule was employed. Following the cessation of treatment, the rats were

fed on a normal diet for 270-410 days; autopsy, after a total experimental period of 450-590 days, did not reveal hepatocellular carcinoma in any of 12 rats.

Ito et al. (1974) treated rats with different doses of Kanechlor 500, 400, and 300 for periods up to 52 weeks; hepatocellular carcinomas were not observed, but the duration of treatment was probably too short to rule out the possibility of a positive response.

The three major studies pertaining to PCBs and hepatic carcinoma in the rat are those of Kimbrough et al. (1975), Calandra (1975), and the National Cancer Institute (1978). Kimbrough and co-workers, using the Sherman strain of rat, found that 100 ppm of Aroclor 1260 in the diet for 21 months produced a significant increase in the incidence of hepatocellular carcinoma in female rats (section VI, Table 4). Male rats were not studied.

The administration of three different Aroclors at a dose of 100 ppm to rats for 24 months (Table 5) did not induce hepatocellular carcinoma (Calandra, 1975). The author states that this negative finding was based on evaluation of the liver sections by three pathologists, who read the slides independently and separately. He states further that Professor P. Pour re-evaluated the Kimbrough slides and did not agree with the reported findings (see also section VI, Table 2A).

The results of the National Cancer Institute (1978) bioassay of Aroclor 1254 for possible carcinogenicity are shown in section VI, Table 6. Fischer 344 rats were used and the PCB

[illegible]xture was administered at three dose levels (25, 50, and 100 ppm) [illegible]n the diet for 104-105 weeks. The effect of the treatment on [illegible]ody weight and mortality at the higher dose levels demonstrated [illegible]hat maximum tolerated doses were used, thus providing a satis-[illegible]factory test of carcinogenic potential. A sufficient number of [illegible]ats of both sexes was available for meaningful statistical [illegible]nalyses of the incidence of late-developing tumors. Treatment [illegible]as associated with only three hepatocellular carcinomas in male [illegible]rats, which was not significantly different from the controls, [illegible]nd it was concluded that Aroclor 1254 was not carcinogenic in the [illegible]bioassay.

(iii) Studies in dogs. Hepatocellular carcinoma did not occur in dogs (four male and four female per group) receiving 1, 10, or 100 ppm of Aroclor 1242, 1254, and 1260, respectively, in their diets for two years (Calandra, 1975).

(iv) Discussion. Data from the mouse provide only limited and restricted evidence for a carcinogenic effect of the Japanese compound Kanechlor 500 (Table 3). Studies on the rat give conflicting results on hepatic carcinoma. (Section VI deals with the benign hepatic proliferative lesions found in the treated rats, which may or may not indicate carcinogenic potential.) Kimbrough et al. (1975) reported an increase of hepatocellular carcinomas in female rats receiving Aroclor 1260, whereas the studies of Calandra (1975) and the National Cancer Institute (1978) did not observe a significant increase in hepatocellular carcinomas in rats receiving different Aroclors. Whether the

divergent results are related to the different strains of rats that were used, represent differences in the effect of the two Aroclors, or are due to other factors is not known. It is obvious, however, that in view of the differing results obtained it is not possible to extrapolate or project possible effects in man. Hepatocellular carcinomas did not develop in dogs treated with Aroclor for two years.

2. Bladder Cancer

Kimbrough (1972) observed bladder cancers in two rats fed 100 ppm of Aroclor 1260 for eight months. In a later study with 200 rats receiving 100 ppm of Aroclor 1260 for 21 months the only bladder tumor observed (a transitional cell papilloma) was in a control animal, and it was concluded that "the occurrence of the bladder tumor in the previous experiment was apparently unrelated to the ingestion of Aroclor 1260" (Kimbrough et al., 1975). This type of variation demonstrates the unreliability of attaching significance to small changes in tumor incidence in a given experiment, particularly when the incidence does not show a statistically significant difference from a control group.

Benign or malignant bladder tumors did not occur in rats treated with Aroclors 1254 (25, 50, and 100 ppm) for 104-105 weeks (National Cancer Institute, 1978).

The above studies do not demonstrate that administration of Aroclor 1254 or Aroclor 1260 induces bladder cancer in the rat.

3. Stomach, Intestinal Tract Cancer

Treatment of female rats with Aroclor 1260 (100 ppm in diet) for 21 months did not induce tumors in the gastrointestinal tract (Kimbrough et al., 1975).

Treatment of rats with Aroclor 1254 (25, 50, and 100 ppm in the diet) for 104-105 weeks did not induce gastrointestinal carcinomas (National Cancer Institute, 1978). Tumors occurred in random manner as illustrated in Table 7.

4. Carcinogenesis - Other Organs

Studies with PCBs in relation to cancer of the liver, gastrointestinal tract, and urinary bladder have been discussed separately above. In the studies with PCBs other organs have been evaluated in detail without finding any effect of chronic administration of Aroclors on the incidence of benign or malignant neoplasms. The following appraisals refer to tumors of these other organs.

Kimbrough et al. (1975) found that the chronic administration of Aroclor 1260 to rats did not affect the incidence of benign tumors or carcinomas of the thyroid gland, adrenal gland, uterus, lung, and other organs. Frequently investigators look only for increases in tumor incidence, when in fact decreases are often obtained. It is worth noting that mammary adenocarcinoma occurred in 5/173 control animals versus an incidence of 1/184 in treated animals. If the incidence had been reversed, some authors may have commented or suggested that PCBs may increase the occurrence of mammary cancer, but such would not have been

Table 7

Incidence of Gastrointestinal Carcinomas
in Rats Treated with Aroclor 1254
(Data from National Cancer Institute, 1978)

	Number of Carcinomas			
	Control	Low Dose	Med. Dose	High Dose
Males				
Stomach, adenocarcinoma	0	0	1	0
Jejunum, carcinoma	0	0	0	1
Cecum, adenocarcinoma	0	0	1	0
Females				
Stomach, adenocarcinoma	0	1	1	0

the case as the number of mammary adenocarcinomas in control groups can vary significantly from study to study. If the incidence of spontaneous tumors can vary, then the number of malignancies in the treated group will vary with each experiment independent of the treatment given. An additional illustration of tumor variability is the incidence of ovarian granulosa theca cell tumors which was 5/149 in controls versus 0/163 in the treated animals.

In the National Cancer Institute (1978) study, the chronic administrations of Aroclor 1254 was without effect on the development of benign or malignant neoplasms in the various body organs of the rat (the liver, gastrointestinal tract, and urinary bladder were discussed separately above). In the study, interstitial cell tumors of the testes were present in nearly all control and treated animals, there being no effect of treatment. Leukemias, which were the second most common neoplasms, were found in 13% of control males and 17% of control females. A statistically significant dose-related trend for leukemia was present in the treated males but not in the female rats. However, direct dose comparisons between each treatment group (male or female) and the control group were not statistically significant, so that an effect in males could not be clearly related to the administration of Aroclor 1254. Adding the few lymphomas to the leukemias for the analysis did not change the

conclusion. Kimbrough et al. (1975) also did not find a significant effect of Aroclor 1260 on leukemia incidence (1/173 in controls versus 0/184 in treated animals).

It may be concluded from these studies that the chronic oral administration of high doses of Aroclors 1260 or 1254 does not induce benign or malignant tumors of the thyroid gland, adrenal gland, uterus, lung, hematopoietic system, pituitary gland, thymus, kidney, and other organs in rats.

5. Summary and Opinion

Animal studies do not provide convincing evidence that PCBs induce liver cancer. Of the major studies in the rat, one has been judged positive and two have been negative. Hepatic carcinoma was not produced in the dog. Chronic administration of Aroclors in the rat did not induce bladder cancer, gastrointestinal carcinomas, or cancer of the thyroid gland, pituitary gland, adrenal gland, uterus, lung, hematopoietic system, or other organs.

B. Clinical Studies

The studies of Brown and Jones (1981) and Bertazzi and co-workers (1981) have evaluated the relationship between exposure to PCBs and the subsequent development of cancer. Both analyses are retrospective mortality studies of workers to determine the cause of the death and, for malignancies, the specific type of cancer causing the death; the deaths are designated as "observed cases." The person-years of exposure

of the workers to PCB were determined and combined into calendar time periods and five-year age groups to calculate from mortality statistics the number of "expected" deaths. The number of observed versus expected deaths was then compared. Background data relative to these studies are summarized briefly, as follows:

(i) Brown and Jones (1981). The authors analyzed 163 known deaths occurring among 2,567 workers exposed to PCBs for 39,018 person-years. Exposure to PCBs ranged from three months to over 20 years. The type of PCBs used at the plants were Aroclor 1254, 1242, and 1016.

(ii) Bertazzi et al. (1981). The authors analyzed 27 deaths occurring in 1,310 workers exposed to PCBs for 20,565 person-years, determining "observed" versus "expected" rates for malignancies. Mortality was studied for a 25-year period (1954-1978). Exposure up to 1964 was mainly to Aroclor 1254 and Pyraline 1476; starting in 1965 mixtures with 42% chlorine were used (mainly Pyraline 3010 and 3011).

(iii) Behn et al. (1976, 1977). These authors report two cases of malignant melanoma in 31 men exposed to Aroclor 1254. It is not clear from their studies if they are discussing morbidity or mortality; Brown and Jones (1981) interpret the report as mortality.

Pertinent data on the mortality from malignancies are summarized in Table 8 and are discussed below.

All Malignancies. Brown and Jones reported 39 observed cases of cancer versus 41.8 expected cases, whereas Bertazzi et al. found a statistically significant increase in males, but not in female workers (Table 8). There was no increase in the risk of mortality from all malignancies with length of exposure or with the number of years of employment (Brown and Jones, 1981).

Rectum. The only statistically significant difference observed in the study of Brown and Jones was for rectal cancer in females from Plant 2 (Table 8). There was no significant finding for females in Plant 1, males in Plant 1 or 2, or for the combined data for males and females. The incidence of rectal cancer showed a slight, but statistically insignificant, increase with increase in latency; no direct relationship with increased length of exposure is apparent.

Bertassi et al. (1981) did not report a case of rectal cancer in PCB-exposed individuals.

Stomach, Pancreas. The studies did not demonstrate an increased risk for stomach or pancreatic cancer (Table 8).

Hepatocellular Carcinoma. Three cases of liver cancer were observed in the study of Brown and Jones (1981), but the difference from the control rate was not reported to be statistically significant (Table 8). Bertassi and coworkers did not mention observing any case of hepatic cancer. Examination of the data for latency effect or for length of exposure to PCBs did not show any relationship to development of liver cancer (Brown and Jones, 1981).

Table 8

Deaths From Specific Types of Cancer

Comparison of Observed Deaths in PCB Workers With Expected Deaths

Reference	Malignancy	Sex	Number of Cases: Observed	Expect	SMR	Statistical Significance
1	All	M,F	39	43.79	89	NS
2	"	M	8	3.32	241	P=0.04
2	"	F	8	3.33	250	NS
1	Rectum	M	1	0.51		NS
1	"	F(plant 1)	0	0.18		NS
	"	F(plant 2)	3	0.58		P<0.05
1	"	M,F	4	1.19	338	NS
1	Stomach	M,F	1	1.68	60	NS
1	Pancreas	M,F	1	1.90	53	NS
2	Digestive Organs	M	3	0.88	340	NS
	(stomach, pancreas, biliary tract)	F	0	-	-	NS
1	Hepatic Carcinoma	M,F	3	1.07	280	NS
1	Lymphatic & Hematopoietic	M,F	2	4.34	46	NS
2	"	M	2	0.46	433	NS
2	"	F	2	0.45	444	NS
3	Melanoma	M	2	0.04		P=0.001
1	"	M,F	0	-	-	NS
2	"	M,F	0	-	-	NS

Ref 1. Brown and Jones, 1981
Ref 2. Bertazzi et al., 1981
Ref 3. Kahn et al., 1978, 1977
SMR. Standardized mortality ratio (observed deaths/expected deaths x 100)
NS. Not significant

Lymphatic and Hematopoietic Cancer. The two studies show diametrically opposite risk values, although neither is statistically significant (Table 8).

Melanoma. Bahn et al. (1976, 1977) reported two cases of malignant melanoma occurring among 31 men who had been exposed to Aroclor 1254. Based on the Third National Cancer Survey incidence rates, Bahn et al. calculate for a person-year analysis that only 0.04 malignant melanomas would be expected, the difference being statistically significant (P=0.001). The extensive studies of Brown and Jones and of Bertazzi et al. fail to confirm the increased risk of mortality for malignant melanoma reported by Bahn and co-workers (Table 8), raising doubts about the significance of the Bahn studies. Even an association with the low P value of 0.001 has not been confirmed.

Summary. The clinical evaluation of PCBs relative to cancer is currently based on a limited amount of data, and any conclusion regarding their effects must be regarded as tentative. Nevertheless, some detailed analyses are available and conclusions based on them, as listed below, are of some significance.

1. Retrospective mortality studies have not demonstrated a consistent relationship between exposure to PCBs and the development of a particular type of cancer.

2. The clinical findings on hepatocellular carcinoma are of great interest as some experimental studies report an

increase in liver cancer in rodents receiving PCBs. Although Brown and Jones (1981) observed three cases versus 1.07 expected cases, the difference is not statistically significant. Their analysis of PCB exposure and risk of mortality from liver cancer is also noteworthy since it did not demonstrate an effect of latency (number of years from date first employed) or a relationship to increased duration of employment in jobs involving PCB exposure. These latter observations are, however, based on small numbers. Bertazzi et al. (1981) did not report any significant relationship between PCB expoeure and liver cancer. Taken together these atudies do not confirm the projection of a risk for liver cancer in humans based on the animal studies.

3. The SMR (Standard Mortality Ratio) may vary widely in different studies, and emphasis should not be placed on an increase in the SMR found in one study unless a significant change in SMR can be confirmed in several repeat studies. For example, Brown and Jones found the SMR for lymphatic and hematopoietic malignancy to be decreased while Bertazzi et al. reported an increase, although neither result was statistically significant (Table 8).

4. Brown and Jones observed a statistically significant increase in SMR for rectal cancer in women at one plant, but not in a different plant, and no significant effect in male workers at either plant was observed. Bertazzi et al.

did not report any rectal cancer (Table 8). Overall, therefore, a convincing demonstration of rectal cancer as a result of extended exposure to PCBs has not been made.

Reproductive Effects

n

s have appeared in the literature on
nated biphenyls on reproduction in
son (1979) showed that female Sprague-
g Aroclor 1221, 1242, and 1260 by gavage
20 of pregnancy had no effect on the
of the offspring as judged by (a) normal
al appearance of ovaries and uteri, and
feeding 550 ppm of Aroclor 1254 for 67
lted in fewer litters, smaller litter
by day three of the $F1_a$ pups. At 100 ppm
$F1_b$ offspring was reduced. The pups
s but appeared normal at weaning.
tary level of 500 ppm (35.4 mg/kg) for
arkedly reduced litter size and
e $F1_a$ and $F1_b$ generation. Dietary
254 and 100 ppm Aroclor 1260 had no
rats exposed through two generations
dietary concentration of 2.5 ppm of
eration in the menstrual cycle of
ys. Menses were prolonged and menstrual
llen et al., 1979).
. (1971) fed rats and dogs Aroclor 1242,
f 1.0, 10.0, and 100 ppm. No adverse

effect on reproduction was observed in rats given 1.0 and 10 ppm Aroclor 1242, but there was a decrease in survival of pups at 100 ppm of Aroclor 1242, 1254, and 1260 as well as a decrease in mating indices. The effect of PCBs on reproduction in beagle dogs and swine has been studied by Earl et al. (1974). Aroclor 1254 interfered significantly with reproduction in dogs at doses above 2.5 mg/kg/day while in swine 10.0 mg/kg/day lowered fertility and survivability of neonates. The reproductive effects in dogs are questionable because of unexplained changes in the reproduction pattern among controls.

B. Teratogenicity

1. Introduction

Teratogenicity is that property of an agent whereby it is capable of inducing congenital defects in the developing embryo. Such agents that are chemical substances are known as "teratogens" and the defects they induce are known as "terata." Although teratogenicity is considered generally to involve only anatomical defects, some authorities regard functional or biochemical changes as manifestations of teratogenicity.

A distinction must be made between teratogenicity and fetotoxicity, i.e., toxicity to the fetus. The finding of dead or resorbing fetuses in the uterus of an experimental animal is not evidence of a teratogenic action of the test substance. Similarly, a smaller size of the newborn is indicative of fetotoxicity rather than teratogenicity.

A substance may appear to be teratogenic if it produces severe toxic effects on the pregnant female. Maternal disease and malnutrition affect the number and quality of the offspring. Defects in the offspring that are secondary to toxic effects of the substance on the mother are not considered terata.

Teratogens produce their harmful effects during the period of formation of cells, tissues, and organs. Hence, once development of the fetus has been completed, a teratogenic event can no longer occur. Chemical substances administered to the mother can be transmitted, together with their metabolites, via the milk to the suckling young, and may produce toxic effects in the latter. However, such effects are not indications of teratogenicity.

Conventional tests for the detection of teratogenicity involve administration of the test substance to pregnant females at repeated intervals throughout the period of organogenesis, e.g., days six through 15 of the gestation in the rat. The treated females are sacrificed on the day prior to parturition, and the fetuses removed from the uterus surgically for examination. Alternatively, the test substance may be administered over relatively long periods of time, and the animals allowed to breed normally as in the usual one- to three-generation reproduction studies. The appearance of malformed offspring among the succeeding generations would be evidence of teratogenicity.

In order for a chemical substance to which the mother is exposed to exert a direct action on the conceptus, it or one

or more of its metabolites must be able to cross the placental barrier. Transplacental passage of PCBs has been demonstrated in several animal species (Allen et al., 1980; Curley et al., 1973; Couvillion et al., 1974; Grant et al., 1971), and is known to occur in the human (Funatsu et al., 1972).

2. Mice

PCBs were not teratogenic in mice at dosages up to 500 mg/kg given on days one through six or days seven through 11 of gestation (Toeruek, 1973). However, a recent study (Marks et al. 1981) with the hexachlorocongener 3,3',4,4',5,5'-hexachlorobiphenyl in mice at dosages in the range of 0.1-16 mg/kg/day during days six through 15 of gestation produced a significant increase in fetal malformation, a significant decrease in average fetal weight, and an increase in the percentage resorptions.

Torok (1976) reported that oral administration of 375 mg/kg or 750 mg/kg of 2,2'-dichlorobiphenyl to mice on days one through three of gestation resulted in prolongation of the interval between breeding and parturition. He attributed this observation to delayed implantation. Although the treated animals had fewer litters and lesser mean litter sizes, there was no indication of teratogenicity.

Some mice exposed to 3,4,3'4'-tetrachlorobiphenyl were reported to exhibit a "waltzing syndrome" (Davis et al., 1979; Tilson et al., 1979). The dosage was 32 mg/kg administered by gavage to the mothers on days 10 through 16 of gestation. The

syndrome consisted of increased motor activity, hyperreflexia, and episodes of head bobbing and rotational movements that were present up to at least eight months of age. Not all exposed mice were affected similarly, but even those that did not exhibit the syndrome showed diminished performance in various neurobehavioral tests. Tilson et al. (1979) refer to these observations as the "behavioral teratology" of 4-CB.

3. Rats

There are a plethora of studies in which the reproductive effects of feeding various Aroclors to rats have been investigated (Calandra, 1976; Gellert and Wilson, 1979; Keplinger et al., 1971; Keplinger et al., 1972; Linder et al., 1974; Villeneuve et al., 1971a). Collectively, these studies reported fetotoxicity as the dosage was increased, but no teratogenicity was demonstrated. It may be useful to note the order of magnitude of the dosages involved. Villeneuve et al. (1971a) found no effect from the administration of dosages of up to 100 mg/kg per day orally to pregnant females from the sixth through the fifteenth day of gestation.

Ultrastructural lesions in thyroid follicular cells and a reduction in serum thyroid hormones have been reported in neonatal and weanling rats whose mothers had been fed a diet containing 50 ppm or 500 ppm of Aroclor 1254 throughout the period of gestation (Collins and Capen, 1980). The authors suggest that alterations in thyroid structure and function in the fetus or neonate may be related to subsequent disturbances in growth or development.

4. Dogs

In the study conducted by Earl et al. (1974), pregnant bitches were given dosages of 0.25, 1.0, or 5.0 mg/kg of Aroclor 1254 from the day of breeding to the day on which they were necropsied. At 5.0 mg/kg, there was an increase in the percentage of resorptions, a decrease in the number of live pups per litter at birth, and a reduction in the percentage of those surviving to two weeks. The terata observed consisted of enlarged fontanelles, cleft palates, and superfluous phalanges. This dosage was said to limit diet consumption severely. The authors state that one litter of the controls "may have had a genetic defect that caused an unusually high incidence of terata."

5. Swine

Earl et al. (1974) included miniature swine (Hormel strain) in the investigation described immediately above. Pregnant sows were given daily oral dosages of 1 mg/kg, 10 mg/kg, or 30 mg/kg of Aroclor 1254. Dosing began 21 days before breeding and was continued until the day of necropsy. The authors concluded that dose-related effects were seen at all treatment levels as evidenced by decreases in the number of pregnancies, number of live pigs farrowed per litter, and percentage of live offspring after two weeks of age. Syndactyly and cleft palates were observed in the young of sows receiving 10 mg/kg, and patent fontanelles and cleft palates in the offspring of those receiving 30 mg/kg. As in the case of the dogs, the higher dosages caused a marked reduction in food consumption.

6. Monkeys

In a study reported by Allen et al. (1974), six adult, female rhesus monkeys were fed a diet containing 25 ppm of Aroclor 1248 for two months. During this period, all animals developed characteristic signs of toxicity, although they maintained a regular menstrual cycle. One animal died. At the beginning of the fifth month, or three months after discontinuance of exposure to the test substance, an attempt was made to breed the survivors. Three animals appeared to conceive, but only one succeeded in carrying her fetus to term. Although this infant was well developed, its body weight was considerably lower than that of the average rhesus infant. Examination of the tissues showed no gross or microscopic lesions.

In a second study by the Wisconsin group (Barsotti et al., 1976) involving 18 adult, female rhesus monkeys, nine were fed a diet containing 2.5 ppm, and nine were fed a diet containing 5 ppm of Aroclor 1248. After seven months on these diets, the eight surviving animals from the 2.5 ppm group and eight from the 5 ppm group were mated with control males. All animals in the 2.5 ppm group became pregnant, but three of these resorbed their embryos; the remaining five gave birth to live infants. In the 5 ppm group six animals became pregnant. These impregnations resulted in three abortions, one resorption, one stillbirth (suffocation during difficult delivery), and one uncomplicated birth. At birth, the six infants were small; however, other than their small stature and focal areas of dermal

hyperpigmentation, their general appearance, hemograms, and osseous development as evaluated radiographically were normal.

The adult, female rhesus monkeys that were the original subjects in the study discussed above were fed the diets containing 2.5 ppm or 5 ppm of Aroclor 1248 for six months prior to breeding, throughout gestation, and for three months after delivery for a total of about 18 months (Allen et al., 1980). Only 16 females were bred, inasmuch as one had died and another was dropped from the study for some reason not explained. About one year after discontinuance of the Aroclor-containing diets, the animals were bred again to control males. All of the seven survivors in the 5 ppm group conceived, but only four gave birth to live infants. In the 2.5 ppm group, one animal had an abortion and the remaining seven had uncomplicated deliveries. Apart from their somewhat smaller size compared to the young of the control animals, the infants appeared normal. Analyses of adipose tissue from two stillborn infants of mothers in the 5 ppm group showed the presence of PCBs, but histological evaluation of adipose and other tissues showed no abnormalities.

7. Clinical Data

Funatsu et al. (1972) studied in detail four babies born to mothers who had ingested rice oil contaminated with a heat-exchange fluid containing PCBs, PCDFs, and PCQs. The mothers were among the population exposed in the "Yusho" episode. Three of the four babies exhibited some evidence of intrauterine malnutrition or retardation of growth, and all four had dark brown

pigmentation of the skin that was most pronounced at the genitalia, axillae, and near the fingernails. The same pigmentation was noted on the lips, gums, and palate. While one or more of the infants displayed other clinical signs, no neurological or cardiovascular abnormalities, nor any malformations were observed. The pigmentation of the skin and mucous membranes disappeared within two to five months of age in all cases.

8. Summary and Opinion

(a) In a variety of tests, commercial PCB mixtures (Aroclors) showed no teratogenic activity in mice, rats, rabbits, and monkeys.

(b) Earl et al. (1974) have not demonstrated convincingly a teratogenic action of Aroclor 1254 in dogs or swine. An evaluation of their work suffers from a paucity of information and the possible presence of a genetic defect in the dog colony. The published abstract tends to be misleading. Examination of the unpublished manuscript shows that the authors did not regard the two lower dosages as teratogenic for either species. The highest dose is said to limit food consumption severely in both species. Therefore, it is likely that the defects observed in the offspring were the result of severe maternal malnutrition. Hansen et al. (1975) failed to find teratogenic effects in swine when the mothers were fed a diet containing some 20 ppm of Aroclor 1262 throughout gestation and nursing.

(c) The observations of Collins and Capen (1980) on ultrastructural alterations in the thyroid glands of perinatal

rats whose mothers were exposed to Aroclor 1254 are indicative of functional changes rather than of teratogenicity.

(d) The occurrence of a "waltzing syndrome" in mice exposed prenatally to 3,4,3',4'-tetrachlorobiphenyl might represent a true teratogenic effect (Davis et al., 1979). This phenomenon usually results from a structural or functional defect of the middle ear. The dosage used to produce the syndrome is relatively high. While the exposed animals were not uniformly affected insofar as the overt signs are concerned, Tilson et al. (1979) presented evidence to show a wider prevalence of more subtle neuro-behavioral effects. It is not known whether this condition could be induced by a commercial PCB mixture.

(e) The scientific literature presently supports the conclusion that PCBs present no appreciable risk of teratogenicity for humans, in our opinion, in view of the essentially negative test results in four test species and the questionable positive findings in the dog and in swine.

C. Fetotoxicity

Rabbits given 1.0 mg/kg of Aroclor 1254 daily for 28 days of gestation had no effect on the developing fetus but doses of 12.5 to 50 mg/kg were fetotoxic. Rats appear to be more resistant than rabbits, as doses up to 100 mg/kg do not cause fetal deaths or malformations (Villeneuve et al., 1971a). Embryotoxic effects of Kanechlor 300 and 500 were produced in

Sprague-Dawley JCL rats when fed at levels of 500 ppm in the diet throughout gestation (Shiota, 1976b). Diets containing 0 ppm of Aroclor 1248 were fetotoxic to rhesus monkeys.

Fetuses and neonates of mothers with Yusho disease have developed some of the characteristic signs of disease as a result of transfer of PCBs to the fetus and infant through the placenta and breast feeding (Yamashita, 1977; Matsuda, et al., 1978; Yakushijji et al., 1978). Studies in mice on the tranefer of PCBs to fetuses and offspring indicate that the amount transferred depends upon the chemical structure of the individual compounds and the position of the chlorine atoms within the chemical structure (Matsuda et al., 1978, 1979).

Aroclors 1242 and 1254 are potent inducers of hepatic microsomal enzymes. A single intraperitoneal injection of 100 mg/kg of Aroclor 1242 to rats increased liver weight, total microsomal activity, as measured by hydroxylation of acetanilide and N-demethylation of aminopyrene, and hepatic cytochrome P-450 (Bruckner et al., 1973). The breakdown of endogenous substances such as progesterone, estrediol, and testosterone has been shown to be increased in animals pretreated with chlorinated biphenyls (Orberg, 1978). It is possible that alterations in the metabolism of the endogenous substances by PCBs may upset the normal balance that is essential for implantation of the fertilised ova in the uterus (Smith, 1968). Feeding a PCB mixture containing 60% chlorine significantly increased the uterine weight of guinea pigs (Vos, 1972).

Yamashita (1977) studied the clinical features of PCB, PCDF, and PCQ induced fetopathy in four babies born from mothers poisoned by contaminated rice oil. There was intrauterine retardation of growth, dark brown pigmentation on the skin and mucous membranes, edematous face, and exopthalmus. In some cases the retardation persisted for many months but the infants eventually gained their weight for the age group.

Although over 100 nursing mothers residing in Michigan during 1977-1978 had residues of PCBs in breast milk ranging from 1.0 ppm to over 3 ppm, there have been no reports of serious adverse effects on reproduction or infant mortality (Wickizer, 1981).

Summary and Opinion

1. It is apparent from studies on humans and animals that certain classes of polychlorinated biphenyls are more toxic than others and that the degree of chlorination is one of the determinant factors in their toxicity. But, as stated previously under cutaneous toxicity, the presence of contaminants may be responsible for the adverse effects on reproduction. Oishi et al. (1978, 1980) compared the activities of PCBs and dibenzofurans in rats and found that dibenzofurans markedly depressed body weight, decreased weights of the thymus, ventral prostrate, and seminal vesicles and reduced hemoglobin and hematocrit values, while PCBs had little or no effect.

2. On the question of fetotoxicity in PCB-exposed females, positive results are seen in certain test animals (rats, dogs, rabbits) when the PCBs are administered at relatively high doses (greater than 10 mg/kg) to pregnant animals. In the human, the only reported evidence for fetotoxicity in exposed populations stems from the unique Yusho event, in which causation may not be linked to PCBs. No such reports have been made on other exposed human populations, suggesting the absence of this effect in the human under occupational exposure conditions.

X. Mutagenesis

A. General

The term "mutagenesis" refers to any process that produces a permanent change (mutation) in the genetic composition of a cell, thereby causing that cell to differ in a consistent way from its parent. If a mutation occurs in a germ cell, the offspring resulting from the union of that cell with another will have an altered genetic composition that will persist in the germ line unless the alteration is lethal. Mutations occur spontaneously through unknown mechanisms, but they also may be caused by radiation or chemical substances (mutagens). While in a strict sense the term "mutation" applies only to changes in the DNA at the molecular level, it is considered broadly to include alterations in the number and structure of chromosomes.

Mutagenicity is the property of an agent, chemical or physical, to induce mutations. Chemical substances may be tested for mutagenicity by a variety of methods, among which are those that employ (a) bacterial test systems, (b) cytogenetic analysis *in vivo*, (c) cytogenetic analysis *in vitro*, and (d) dominant lethality in a rodent.

B. Bacterial Test Systems

The "Ames test" is the most popular test of mutagenesis employing a bacterial test system. It is a so-called "backward" mutation system that uses a series of mutant strains of *salmonella typhimurium* that have lost the ability to synthesize the amino

acid histidine. Hence, they can grow only if exogenous histidine is supplied. A mutation has occurred if, after exposure to the chemical substance, the organisms regain the ability to grow in the absence of histidine.

Aroclors 1221, 1254, and 1260 showed little mutagenic activity in the Ames test (Wyndham et al., 1976) with indications that Aroclors with lower chlorine contents are weakly positive in the Salmonella test systems. However, these results must be discounted since they could not be replicated (McMahon et al., 1979; Safe, 1980). As a general finding, Heddle and Bruce (1977), McMahon et al. (1979), Schoeny et al. (1979), and Safe (1980) were unable to find evidence of mutagenicity of PCBs in bacterial test systems.

C. Cytogenetic Analysis in Vivo

In this procedure, the experimental animal is treated with the test substance and, after a suitable period of time, sacrificed for examination of rapidly dividing tissues. Bone marrow and the seminiferous tubules are generally the most frequently used tissues for this purpose. It is customary to inject the animals with colchicine several hours before sacrifice in order to promote the accumulation of cells in the metaphase stage of division. In this stage, the chromosome can be examined more readily for abnormalities.

In two investigations, PCBs were judged not to have produced chromosomal abnormalities. Dikshith et al. (1975)

examined seminiferous tubules of rats at different intervals after daily doseages of 50 mg/kg of Aroclor 1254. Green et al. (1975a) examined both bone marrow and spermatogonial cells of rats after either a single dose of 5000 mg/kg of Aroclor 1242, or four daily doses of 500 mg/kg. In all cases, it was concluded that no significant chromosomal damage had occurred.

The micronucleus test is a test for agents that tend to break chromosomes (clastogens). A micronucleus is a fragment of chromatin that has broken away from a chromosome during cell division and has failed to be included in either of the daughter nuclei. The phenomenon can be observed best in newly formed erythrocytes since these stain differently from the mature erythrocytes in that they exhibit polychromasia for a period of 24 hours or so. Furthermore, the nucleus has been extruded at the last maturation division so that the micronuclei, which remain behind, are readily visible in an otherwise chromatin-free cell. Micronuclei occur in a small fraction of normal red cells, but their incidence is increased by the action of clastogens. The test is carried out by administering the agent to the test animal, and examining the polychromatic erythrocytes in bone marrow smears after some interval of time has been allowed for micronuclei to form.

Heddle and Bruce (1977) reported Aroclor 1254 as negative in a micronucleus test.

D. Cytogenetic Analysis in Vitro

Hoopingarner et al. (1972) activated cultured human lymphocytes with phytohemagglutinin and treated them with 100 ppm of Aroclor 1254 at various stages of a division cycle. The cells then were examined for chromosomal aberrations for the different stage treatments. Aroclor 1254 had no apparent effect on chromosomal integrity as measured by cytological evidence.

E. Dominant Lethality in Rodents

A dominant lethal mutation is one that occurs in a germ cell. While it does not impair the function of that cell, it kills the fertilized ovum or the developing embryo. Mice and rats are the preferred experimental species. In its simplest form, the test consists of treating males with the suspected mutagen, mating them with normal females, and counting the number of viable offspring. The test could be used to detect dominant lethal mutations in females, but it would be difficult to rule out adverse effects on the embryo that might be secondary to non-genetic effects on the mother.

Green et al. (1975b) concluded that Aroclors 1242 and 1254 were not mutagenic since they failed to induce dominant lethal mutations in rats. In similar studies reported both by Keplinger et al. (1972) and Calandra (1976), Aroclors 1242, 1254, and 1260 were administered to male, albino mice in a single intraperitoneal dosage of either 500 mg/kg or 1000 mg/kg. Subsequent matings of these animals to control females

showed no effect of treatment on the number of implantation or resorption sites, number of viable embryos, or preimplantation loss.

F. Summary and Opinion

There is no evidence from *in vivo* test systems that any commercial PCB mixture is mutagenic. The same observation holds true for the bulk of the investigations employing *in vitro* techniques. In our opinion, therefore, it is quite unlikely that the PCBs as a class evoke mutagenic activity in the human, either acutely or chronically. Since chemical mutagenesis and carcinogenesis often correlate for a given active chemical, this opinion is reinforced by the essentially negative findings on carcinogenesis in populations occupationally exposed to PCBs (sections VIII and XII).

XI. Other Health Effects

A. Enzyme Induction

1. Introduction

Most chemicals that are allowed to enter the body are converted by the body to a variety of different chemical entities. In this manner, food becomes transformed into energy. Chemicals, other than food or those that are naturally present in the body, that are introduced into the body are generally called "xenobiotics," and they also are frequently converted by the body to derivatives of the original compounds. The conversion processes are regulated by the enzymatic systems generally termed biotransformation systems. Although there are a multitude of xenobiotic substances to which humans are exposed, there are only a few different enzyme systems involved. The body basically biotransforms chemicals by oxidizing, reducing, hydrolysing, or combining (conjugating) the agent with other chemicals. Although each of these systems is important, of particular interest here are those systems that result in conversion of the original compound to the oxidized derivatives.

It is not uncommon for the body to react to some xenobiotic compounds that it normally biotransforms by increasing its ability to perform the biotransformation function by producing an increase in the amount of enzymes available. This process, which is called "induction" of the enzyme system, effectively makes the body more capable of biotransforming not only the compound that initiated the induction but also all other compounds

that are oxidized by the same enzymatic system. In this manner it is feasible for a given xenobiotic agent to induce a biotransformation system that affects the ability of the body to biotransform not only the original compound but also a large number of other xenobiotics as well as some naturally existing chemicals within the body. Shortly, it will be shown that the PCBs in general have been described as being effective, that is, potent inducers of major oxidative biotransformation systems in experimental animals and in the human. Via induction of enzymes, the concentration of various normally occurring chemicals may be altered. The scientific evidence associated with these subjects will be evaluated in terms of the available current literature.

The major oxidative biotransformation system in the body, as far as xenobiotics are concerned, is present in greatest activity in the liver and is present in lesser activity in most other tissues. In experimental studies, the liver generally serves as a monitor of drug or chemical effect on the oxidizing enzymes. The enzymes are located in the "microsomal" fraction of the liver cells. This is a fraction of the cell that can be obtained by proper ultracentrifugation techniques. The biotransformation system of interest is known as the "microsomal mixed function oxidase system" (MFO). Functionally this system operates to incorporate oxygen into the xenobiotic agent via a series of enzymatic actions. The system does this by making an "active" oxygen atom available via a hemeprotein enzyme. This hemeprotein is in fact a family of proteins

[redacted]llectively identified as "cytochrome P-450." The ability [redacted] the enzyme to operate as an oxidative system is dependent [redacted] the existence of several naturally occurring substances [redacted]d, in particular, on the existence and quantity of available [redacted]tochrome P-450 in the microsomal fraction of the liver.

Microsomal P-450 can be measured directly or indirectly [redacted]ing various substratee. Direct measurement of P-450 is based [redacted] measurement of the protein system from which these enzymes [redacted]btained their name, that is, when the enzymes are reduced and [redacted]combined with carbon monoxide they exhibit, in a spectrophotometer, maximal absorption of light energy at the wavelengths of 450 nanometers, hence the name cytochrome P-450 system. The P-450 system can also be measured in terms of its activity on specific substrates such as ethylmorphine and antipyrine. Induction of this system is measured in terms of an increase in P-450 and/or its activity (based on units of protein per sample of microsomes). Investigations of enzyme induction have separated the P-450 enzymes into two groups, identified as P-450 and P-448 groups, on the basis that various components of the P-450 group of enzymes are "induced" to different degrees by different xenobiotic agents. The P-450 enzymes are those that are mainly induced by the barbiturates, whereas the P-448 enzymes are mainly induced by 3-methylcholenthrene and show maximal absorption at 448 nanometers. The literature includes studies that suggest that the P-448 enzymes as well as the P-450 enzymes are induced

by certain PCBs although there appears to be some species and tissue specificity in their inductive properties.

Investigations of the effects of PCBs on cytochrome P-450s have centered on two areas of interest. One involved the induction mechanism via the use of either a commercially available sample of a single PCB congener (such as 2,4,5,2',4',5'-hexachlorobiphenyl) that was synthetically prepared and could be tagged with a radioactive atom to facilitate analytical work. Generally, a group of experimental animals (rats) was administered the PCB. Samples were then obtained at various levels. Livers were then examined directly for the quantity of cytochrome P-450 or indirectly for P-450 and P-448 activity via its enzymatic action on various substrates. The liver may also be examined histologically and for evidence of the state of protein synthesis. Induction of the P-450 enzymes in the human is estimated by measuring the plasma elimination rate (plasma half-life) of antipyrine in controls as compared to exposed subjects. Antipyrine is a drug that is completely absorbed when given orally and completely metabolized by the liver P-450 microsomal system.

The second area of interest concerned the ability of the liver microsomal system to biotransform PCB. Of particular interest was the nature of the intermediate and final products of the biotransformation process. This subject is important in understanding the toxicology of the PCBs because of the following hypotheses:

(a) Certain PCBs induce the microsomal mixed function oxidation systems thereby influencing not only their own metabolism but also the metabolism and time course of action of available endogenous hormones as well as other xenobiotics (including drugs) administered to humans.

(b) Certain PCBs or contaminants of commercial preparations of PCBs may lead to the formation of intermediate epoxide type derivatives, and these derivatives can covalently bind to macromolecules in the liver thereby leading to hepatic toxicity.

2. Induction of Liver Enzymes

Various studies have reported on the effect of short term exposure of rats to mixtures of chlorinated biphenyls. One such study by Ecobichon et al. (1974) used the Aroclors identified as Aroclor 1016, 1221, 1242, and 1254, and another study by a French investigator, Narbonne (1980), used a French preparation known as Phenoclor DP6. In both studies the sample material consisted of a mixture of congeners of the chlorinated biphenyls. These studies showed that when rats were administered 10 ppm of the PCBs in their diet for only one day, the livers from the animals showed induction of P-450, aniline hydroxylase, and aminopyrine-N-demethylase. The induction of these enzymes was maximum in about five days. If the rats were given 10 ppm of the PCBs in the diet for eight consecutive days, induction occurred in three to five days and to a lesser extent over the remain-

ing eight-day interval. In the Ecobichon study, intraperitoneal injection of the Aroclors in doses of 50 mg/kg was made for three consecutive days. Animals were sacrificed 96 hours later. Mixed function oxidative enzymes were found to be induced in the liver. The greatest induction was seen with the more highly chlorinated Aroclors. The conjugation enzyme induction occurred rapidly on exposure to the Aroclors, and perticularly to those Aroclors that are more highly chlorinated. The PCBs used in these studies were commercial grade.

In order to better understand which of the P-450 cytochromes are induced by the PCBs, Ryan et al. (1979) treated groups of rats with Aroclor 1254, phenobarbital, or 3-methylcholanthrene. The livers were used to prepare three different P-450 fractions on the basis of differing molecular weights and they identified the three fractions as P-450$_a$, P-450$_b$, and P-450$_c$. All three of the P-450s were obtained from the PCB-treated animals. P-450$_a$ and P-450$_b$ were obtained from the phenobarbital-treated rats and P-450$_a$ and P-450$_c$ were isolated from the 3-methylcholanthrene-treated rats. (P-450$_c$ is probably equivalent to P-448). Therefore, this study showed that the Aroclor induced at least three identified cytochromes including the type induced by phenobarbital and the type induced by 3-methylcholanthrene.

In 1980 Parkinson et al. investigated the validity of the concepts that were current at that time regarding the structure-activity relationship between specific PCB congeners

hepatic enzyme induction. The study was designed to yield structure versus activity data. Basically, they conducted experiments in rats using eight synthetic PCB congeners plus phenobarbital and methylcholanthrene as enzyme inducers. They concluded that in order for a PCB to induce a methylcholanthrene-type or a mixed-type liver enzyme system, the PCB would have to contain chlorine substituted at specific positions on the phenyl rings, whereas the PCB inducers of the phenobarbital type had multiple diverse structures that could not readily be defined.

Whether PCBs are administered for as short a time as one to three days or whether they are administered daily for up to a year, various liver enzymes appear to be induced, but the phenomenon of induction does not seem to be specifically very harmful to the animals. Allen and Abrahamson (1979) fed rats diets containing 100 ppb of Aroclor 1248, 1254, and 1260 for 13, 26, and 52 weeks. The growth rate of these rats was comparable to the controls but the test animals did show liver hypertrophy, some focal cellular degeneration, and an increase in serum lipids. In general, the effects were no greater in those animals that received the diet for a year than in those that received the diet for 13 weeks.

Alvares et al. (1973) published results from experiments that involved treatment of rats with Aroclor 1254. Intraperitoneal administration of 25 mg/kg/day for six days

produced a tripling of cytochrome P-448 content of the livers and a 10-fold increase in the enzyme activity involving benzo(a)-pyrene hydroxylation (which is a typical 3-methylcholanthrene type of induction), as well as an increase in ethylmorphine-N-demethylation (a typical phenobarbital type of induction). They therefore concluded that Aroclor 1254 induced a mixture of both P-448 and P-450. In 1977, Alvares and Kappas described some additional work that showed the ability of Aroclor 1254 to cross the placental barrier of the rat, to be transmitted to the neonatal rat through the mother's milk, and to cause increases in biotransformation enzymes in the fetus and newborn.

Goldstein et al. (1978, 1979) attempted to resolve the question of whether pure PCB congeners had enzyme-inducing properties that were different from those produced by commercial preparations of the single congeners or the PCB commercial mixtures (such as Aroclor 1254). These authors synthesized a "pure" sample of 2,4,5,2',4',5'-hexachlorobiphenyl and showed that it had different enzyme induction properties than did the same commercially obtainable, specially prepared, congener that was reported to be "99% pure." The difference in the induction capability of the two preparations was primarily in regard to the induction of P-448 cytochromes in which the synthetically pure isomer, at doses of 250 mg/kg administered to female rats, induced aryl hydrocarbon hydroxylase (AHH: a P-448 enzyme system) only five-fold; whereas the commercial isomer at a dose of 50mg/kg produced a 30-fold increase of AHH. Also, a GC-MS analysis

of the two preparations of hexachlorobiphenyl showed that the commercial preparation contained four contaminants that were not present in the pure congener. Two of these contaminants were identified as a tri- and a tetrachlorodibenzofuran (TCDF). TCDF was then shown to be a potent inducer of AHH and cytochrome P-448. The ED (effective dose, 50% of test animals) for TCDF re: enzyme induction was found to be 0.5 ug/kg for three days. Therefore, the conclusion was that even a 99% pure congener that was commercially obtainable can contain sufficient dibenzofuran to alter the enzyme induction action.

In one report, Alvares et al. (1977) had studied alterations in drug metabolism in both rats and humans. In the rat study Aroclor 1016 elicited a barbiturate type of induction of hepatic enzymes. That Aroclor did not induce cytochrome P-448; however Aroclor 1254 did induce cytochrome P-448. The human study involved five workers in a capacitor manufacturing plant who handled primarily Aroclor 1016. These exposed workers showed a low half-life (10.8 hours) of antipyrine as compared to control non-exposed subjects (who showed a half-life of 15.6 hours). The volume of distribution of the drug in the two groups was not different, so the comparison of the half-lives of the drug in the two groups is valid. Thus, enzyme induction occurs in the human in response to occupational exposure to Aroclor 1016 and the induction

as measured by antipyrine metabolism is a P-450 type of induction.

In 1975 Bickers et al. reported on the effects on liver enzymes associated with topical administration of immersion oils (as used in microscopy). These immersion oils were known to contain approximately 30% PCBs. One to 10 microliters of the oils were applied daily for six days to the shaved backs of rats and the animals were sacrificed on the seventh day. The authors found that both skin and liver enzymes were induced. In a second experiment 10 microliters of the oil were topically administered on one occasion only, and the animals were sacrificed at various intervals following application of the oil. P-450 and liver monooxygenases were induced (including benzo-a-pyrene hydroxylase, a P-448 enzyme system) showing maximal effect in two days with a slow return to normal by 28 days. In this study there must have been very large differences between individuals in the control group because their data show very large differences between groups with only a 95% significance. The immersion oils currently marketed in the U.S. do not contain PCBs.

3. Metabolites of PCBs

Shimeda and Sato (1980) studied the reactive metabolites of PCB metabolism. Their work involved the use of isotope-labeled PCB congeners. This work suggests that PCB epoxides may be the activated forms that covalently bind the macromolecules in the liver cells. A hexachlorobiphenyl congener

(2,4,5,2',4',5'-hexachlorobiphenyl) that has no adjacent unchlorinated atoms in the biphenyl ring and that cannot be converted to the epoxide was found not to be covalently bound although accumulation of this PCB in the liver was found to occur. Other PCBs show covalent binding that is principally with microsomal proteins rather than the ribosomal RNA; a conclusion based on the finding that various proteases would solubilize the radioactivity of the labeled atom. Treatment of the animals with phenobarbital produced livers that showed good covalent binding to the PCB, but treatment of the animals with methylcholanthrene produced livers with poor PCB binding capability. The authors concluded that PCB epoxides were formed by the monooxygenase system and these epoxides were responsible for the binding of the compound to microsomal proteins. Their conclusions are based on indirect findings.

4. Interactions Based on the Induction of Enzymes by PCBs

One report (Murphy et al., 1979) described studies that the authors claimed indicated the existence of a drug interaction in the form of potentiated lethality of fluroxene in Aroclor pretreated animals. The authors did show that the Aroclors induced hepatic enzymes. Their method of measuring enzyme induction was to measure the metabolism of warfarin by livers of the Aroclor-treated animals according to a procedure that they had developed and that they claimed could differentiate between induction of P-450 as compared to P-448. They found that Aroclor 1254 in rats mainly induced cytochrome P-448 whereas Aroclor 1260 induced mainly

cytochrome P-450. The authors then indicated that both Aroclors caused animals to show increased lethality on subsequent administration of fluroxene. We have difficulty interpreting this article. We do not believe that the conclusions are supported by the data that are given. In one case involving Aroclor 1260 the data are not given in the table and in the other case the data obtained following administration of fluroxene do not appear to be different from the control data.

5. Enzymes Other Than Cytochromes Affected by PCBs

Two additional reports deal with an action of the Aroclors on ATPase activity. One of these reports (Lee and Park, 1979) used cultured human lymphocytes and showed a dose-response relation for Aroclor 1254 and inhibition of mitochondrial respiration. From this effect they indicated that there may be a decrease in adenosine triphosphate (ATP) concentration. We can see no way to evaluate what this report means since the concentrations of the Aroclor used are not correlated with concentrations that might be involved in intact biological systems. The other report (LaRocca and Carlson, 1979) indicated that the Aroclors produced *in vitro* inhibition of rat magnesium ATPase activity at a concentration of 30 ppm. A weak correlation was found between increasing inhibition and increasing chlorination. A strong correlation was found between PCB-induced inhibition of the ATPases and decreasing aqueous solubility. We do not know what these results signify

other than that they seem seem to be incidental findings many other chlorinated hydrocarbons do the same thing.

6. Summary and Opinion

The available data from experimental studies on animals and man indicate that the commercially available preparations of the PCBs (Aroclors) as well as some highly purified PCB congeners act to induce some of the hepatic enzymes. Considerable effort has been devoted to determine which of the microsomal enzymes are induced by the Aroclors. There are some data that indicate that the predominant induction occurs for the P-450 type of cytochromes (identified as a phenobarbital-type of induction). When experiments are conducted with the "more pure" congeners there is very little evidence for induction of any enzyme systems other than the P-450 cytochromes. In general, induction is greatest with the most highly chlorinated derivatives, but the least chlorinated derivatives also induce the P-450 cytochromes.

The subject of whether the "pure" congeners of the PCBs have less action on the cytochrome systems than the commercial materials may be only of academic interest, since the preparations that are available to industry and the public are the commercial preparations such as the Aroclors. It should be recognised that authors tend to describe effects due to PCBs whereas they are usually referring to effects of Aroclors (such as Aroclor 1254), which are mixtures of PCBs plus various trace contaminants.

The commercially-available preparations of the PCBs are capable of inducing certain hepatic enzymes in the rat and there is one report suggesting that occupational exposure to

commercial PCBs may induce a hepatic enzyme. There are no data suggesting that the overall health of the animals or man is influenced as a consequence of PCB-induced microsomal enzymes. Although it is suggested by some people that changing the metabolic transformation capability is inherently detrimental to the animal, there is no real evidence to support such a hypothesis. When enzymes are induced and they are then involved in the bioactivation of xenobiotic agents, such enzyme induction could be harmful depending on the dosage sequence and the inherent toxicologic properties of any specific agent. On the other hand, if the enzymes that are induced are involved in bioinactivation of xenobiotic compounds, then induction may be beneficial to the animal again depending on the dosage sequence and inherent toxicologic properties of any specific agent. There is no good experimental or clinical evidence that PCBs may act through their enzyme induction capability to affect "hormone" levels and result in harmful effects on the body.

B. PCB Effects on Immunocompetence

A few reports appeared prior to 1970 that suggested indirectly that PCBs may influence immunocompetence. In 1970, Vos and Koeman showed that when chicks were fed 400 ppm PCB for 60 days they showed atrophy of the splenic pulp and lymphoid necrosis. (Chicks at higher doses all died during the test.) The chicks also showed porphyria and liver necrosis. In 1971, Vos and Beems reported that commercial PCB samples applied to

the skin of rabbits daily five times weekly for 38 days (27 applications each containing 118 mg PCB) produced histologic atrophy of the cortex of the thymus and a reduction in the number of germinal centers in the spleen. At this time the animals showed marked chloracne of the skin, increased fecal coproporphyrin and protoporphyrin, as well as liver and kidney damage. The authors stated that these effects were strong indicators of an immunosuppressive action of the PCBs.

In 1977, Loose and co-workers fed Aroclor 1242 to mice for six weeks. The animals were then immunogenically stimulated with sheep red blood cells as an antigen and the antibody response was measured. The method of measuring antibody activity involved plaque-cell estimation in the spleen and the measurement of the plasma immunoproteins. Positive findings were obtained as compared to controls and the authors particularly remarked about the reduced IgA levels found in the PCB-treated animals. It was also noted that clinically subtoxic levels of Aroclor 1242 were profoundly immunosuppressive. These authors also cite the work of Koller and Thigpen (immunosuppression by a PCB to pseudorabies virus in rabbits), Vos and van Driel-Grootenhuis (immunosupression by PCB in guinea pigs), and Friend and Trainer (increased mortality in ducklings that had been previously exposed to Aroclor 1254 and then inoculated with duck hepatitis virus).

In 1978, Loose and co-workers studied the effects of PCBs on host resistance systems. Mice that were fed diets containing 167 ppm Aroclor 1242 for three weeks and for six weeks exhibited increased sensitivity to salmonella endotoxin and a decreased survival time to inoculation with malaria. Thus they concluded that host resistance was impaired by prior treatment with PCBs.

Also in 1978, Thomas and Hindsdill reported on studies in which they fed monkeys 2.5 to 5.0 ppm PCB (Aroclor 1248). After six months the monkeys developed chloracne, alopecia, and facial edema. After 11 months control and treated monkeys were tested with antigens (sheep red blood cells and tetanus toxoid). The only positive finding was in the 5.0 ppm monkeys who showed significantly lower antisheep red cell antibodies as compared to controls. No effect was obtained regarding the antibody response to tetanus toxoid. These authors also fed mice up to 1000 ppm of the PCB for three to five weeks without evidence of overt toxicity, but these animals did show a higher mortality when challenged with the pathogen salmonella typhimurium as compared with the controls.

In 1980, Oishi and Hirage reported on their studies in which they had given mice PCBs (commercial product) by oral intubation once weekly for four weeks. Other groups of mice were fed CDF (chlorinated dibenzofuran) or CDD (chlorinated dibenzo-p-dioxin). Only the groups of animals that had received 10 or 100

pg/kg CDF showed decreased thymus weights. All groups were challenged with endotoxin and again only the CDF-pretreated animals showed increased lethality compared with the controls. It is noteworthy that the authors found no deaths in their control animals given endotoxin, a finding that raises doubt about their experimental design. In this study the PCB pretreated animals did not show increased susceptibility to endotoxin. In the same year (1980) Imanishi et al. showed that mice fed PCBs for 21 days at 100, 200, or 400 ug/gm were significantly more susceptible to herpes simplex virus and electromelia virus than were animals fed a PCB-free diet.

In 1981, Cheng et al. reported on the immunologic evaluation of patients from Taiwan who developed an acne-like skin disease, termed Yu-Cheng disease, that was related to the consumption of rice-bran oil contaminated with PCBs, PCDFs, and PCQs (in an accident very similar to Yusho). The authors had 30 such patients who showed average whole blood PCB levels of 45 ppb, with a range of 15 to 98 ppb, plus an additional control group of 23 healthy persons matched according to age and sex who showed no detectable levels of PCB in their blood. The patients had decreased concentrations of IgA and IgM immune globulin but not IgG. Their study of subpopulations of lymphocytes showed that the percentage of B cells was not affected by the disease but the percentage of some species of T cells was decreased as compared to the controls.

Environmental chemical effects on immunocompetence have been extensively reviewed by Faith, Luster, and Voe (1980). A number of studies cited by them found PCBs to be immunosuppressive in various species (from ducklings and chicks to mice and monkeys), in some cases at dose levels that produce little effect other than hepatocyte hypertrophy. Only one study (Street and Sharma, 1975), which involved feeding low levels (0.18 to 6.5 mg/kg/day) of Aroclor 1254 to rabbits, showed no significant effect on humoral or cell mediated response. Our review of the Street and Sharma report indicated that there was a dose-related trend toward immunosuppression in their animals and at the higher doses (2.1 and 6.5 mg/kg/day) for four to eight weeks the animals showed significant increase in liver weight. The Faith, Lueter, and Voe review lists several general factors (nutritional status, hormonal levels, and amounts of immunoregulatory proteins such as alpha-fetoprotein) that influence immune function. Therefore those studies in which immune function was studied following exposure to levels of the PCBs that resulted in overt toxicity are meaningless from an immunotoxicologic viewpoint. In contrast, immunosuppression at dosage levels that do not produce general toxicity would be significant.

Summary and Opinion

The overall conclusion that can be reached in regard to the studies on the effects of PCBs on immunocompetence is:

(1) with exposure conditions that lead to general toxicity, immunosuppression may be demonstrable, but it may be indirectly induced; (2) with experimental conditions wherein only subclinical toxicity is observed, such as hepatocyte hypertrophy, there is the possibility that immunosuppression is also produced; and (3) under still lower PCB exposure conditions it is impossible that immunosuppression is involved. Perhaps the best study to estimate a no-effect dose for exposure to PCBs would be the Thomas and Hindsdill (1978) study which suggests that six months' exposure to between 2.5 and 5 ppm of PCBs in the daily diet of monkeys is a threshold for effects on the immune system. Unfortunately, there are few data directly concerned with the dose-response relationship for effects of the PCBs on the immune system in animal models or the human.

C. Porphyria

The administration of PCBs to rats will produce a delayed type of porphyria, i.e., deposition of porphyrins and their degradation products in tissues and excreta. Although the mechanism of action of the PCBs is unknown, it apparently differs from that of other porphyrogenic compounds such as hexachlorobenzene or isopropylacetamide. It has been thought that the effect of PCBs in animals may indicate that these compounds can induce conditions such as porphyria cutanea tarda in man, but clinical data have not shown this to occur in PCB-exposed workers.

(1) Experimental Data. The fecal content of coproporphyrin and protoporphyrin of rabbits was increased by Aroclor 1260

and by hexachlorobiphenyl, but the difference was statistically significant only for coproporphyrin (Vos et al., 1972b). Bruckner et al. (1974) observed an increased excretion of urinary coproporphyrin in rats given Aroclor 1242, 5 or 25 ppm for two, four, and six months.

Goldstein et al. (1974) emphasized the delayed onset of the PCB-induced porphyria; rats fed 100 ppm of Aroclor 1254 became porphyric after two or seven months of treatment. Although the excretion of coproporphyrin and other porphyrins was increased, the largest elevation was in the uroporphyrin fraction. There was also a marked accumulation of uroporphyrin in the liver. The studies of Goldstein et al. suggest that PCBs may effect uroporphyrin formation or utilization. The induction of delta-aminolevulinic synthetase (ALA synthetase, a rate-limiting enzyme in heme synthesis) does not appear to be the mechanism by which porphyria is induced by PCB, as it is for many porphyrogenic chemicals. In their studies the increase in ALA synthetase activity was probably secondary to the porphyria. Also, Aroclor acts to increase liver cytochrome P-450 rather than to decrease it.

Hexachlorobenzene is known to induce a delayed type of hepatic porphyria similar to that produced by Aroclor 1254. However, the two responses apparently differ significantly as Goldstein et al. reported that the rats fed PCBs did not exhibit the nervous or cutaneous signs associated with hexachlorobenzene poisoning.

(ii) Clinical Studies. Some of the Yusho patients ingesting rice oil contaminated with PCBs reported pigmentation of the skin and nails, but there were no studies to evaluate a possible relationship of the reported symptoms to any change in porphyrin metabolism (Kuratsune, 1972).

Smith et al. (1981 a,b,c) determined urinary coproporphyrin, uroporphyrin and porphobilinogen in PCB-exposed workers; they did not find a correlation between the urinary porphyrins and the serum level of the lower chlorinated PCBs or the higher chlorinated PCBs. The subjects did not have any recognizable dysfunction and there was no clinically apparent illness with high levels of PCB exposure or with high serum PCB.

Other investigations evaluating the health effects of PCB exposure have not reported cases of porphyrin-related disease or cases of porphyria cutanea tarda (Fischbein et al., 1979; Maroni et al., 1981).

The observation that PCBs increase ALA synthetase in animals raises the possibility that PCBs can cause an attack of porphyria in patients suffering from acute, intermittent porphyria. However, a case of this type has not been reported in the medical literature. As noted above in studies on the rat, the action of PCBs appears to differ from that of other porphyric agents.

XII. Epidemiology

Although case reports of toxic effects, especially skin lesions related to exposure to chlorinated organic chemicals, have been recorded almost from the beginning of their use (Jones and Alden, 1936), few epidemiological studies appeared until the accidental exposure of a large Japanese population to PCBs, PCDFs, and PCQs from the contamination of rice oil. Since that time, numerous studies have been undertaken to determine the health effects related to exposure to PCBs in the workplace and general environment. It must be remembered that there were problems in these studies in assessing the effects because some of the environmental exposures may have involved PCBs that had been altered by processing at high temperatures (Brown, J.F., Jr. et al., 1981). The numbers of individuals exposed occupationally are relatively small, although some may represent the heaviest and most protracted exposures of any reported, and their added burden of PCBs from the workplace must be compared to the background levels that are currently present in all populations. Many of the commonest changes noted in biochemical and other medical measurements obtained in screening surveys have not yet been associated with any subsequent development of disease.

In order to evaluate the epidemiological studies that assessed the effects of PCBs, we will discuss the results of mortality data, morbidity data, and screening surveys separately even though many studies include data on several outcomes.

A. Mortality Studies

In 1968, an unknown number of persons in the western part of Japan ingested rice oil containing Kanechlor 400 that was contaminated with polychlorinated dibenzofurans (PCDFs) in amounts 250 times more than the usual levels in Japanese PCBs (IARC, 1978) and more than 1000 times the usual levels in U.S. Aroclors. By 1977, 1665 cases of "Yusho" had been recognized based on symptoms of ocular disturbances, skin lesions, primarily subjective neurological symptoms and blood PCB levels (Urabe, 1979). Fifty-one deaths have occurred in these patients and the causes have been reported to include liver cancers and lymphomas. However, there have been no reports on the numbers of expected deaths by specific causes based on the usual death rates in similar Japanese populations. The distribution of causes may simply represent the usual distribution of deaths found in the age groups characteristic of Yusho patients, and so it is impossible to assess the mortality patterns of these cases at the present time.

Bertazzi et al. (1981) have reported a study of 1,310 workers, predominantly women, who, beginning in 1946, initially were exposed to Aroclor 1254 and Pyralene 1476 and subsequently were exposed to mixtures with 42% chlorine content. Mortality data were collected on all individuals with six months or more of employment over a 25-year period ending in 1978. The total number of deaths (27) was small but there was an excess of mortality

in female workers compared to the general population, which is unusual for any working group. This study demonstrates a significant excess for all neoplasms for the combined sexes and an excess specifically of lymphomas. It is difficult to interpret these data since the type of cancer incriminated seems to differ from that of other studies. Further, the data of Brown and Jones (1981) (see below, and also the compilation in Table 8, section VIII) on workers in two manufacturing plants do not confirm a finding of excess malignancies in PCB-exposed personnel. The unusual two-fold excess in mortality of female workers in the Bertazzi et al. study deserves further attention.

A retrospective cohort mortality study of 2,567 workers in two electrical capacitor manufacturing plants that had used PCBs for over 30 years, identified 163 deaths (Brown and Jones, 1981). The type of PCBs used over the years had varied and include Aroclors 1254, 1242, and 1016. The overall mortality and total cancer mortality were low, but there were three-fold excesses of cancers of both the rectum and the liver (with a total of seven deaths) although the results were not statistically significant. The only significant excess was that of the subset of rectal cancers in females in Plant 2. The standardized mortality ratios (SMRs) for rectal cancer, liver cancer, or cirrhosis did not increase with increasing latency or duration of employment. Unless one can demonstrate that the risk of cancer increases in association with increasing duration of employment, which serves

as a proxy measure of dose, it is difficult to suggest that the agent is possibly causative for the disease.

Although this study has devoted strict attention to details such as the completeness of identification of workers and ascertainment of outcome it has not verified the diagnosis of cases nor investigated the presence of confounding variables. Rectal cancers are often misclassified by location in the intestinal tract. The classification "liver cancers" may include cancers of the gall bladder and biliary system as well as metastatic lesions to the liver from cancers at other sites. Therefore when one has an excess of liver cancers, verification of specific site within the liver system as well as identification of primary liver lesions is extremely important, especially since the number of deaths from this cause is small. The investigators have not verified the diagnosis of either liver or rectal cancers. Since alcohol is considered a frequent etiological agent for cirrhosis of the liver and possibly for liver cancer, some information on consumption would be relevant as a confounding variable. No data on possible confounding variables have been reported in the paper.

The mortality data from the occupational groups and the Yusho patients are based on very small numbers of deaths and at present do not confirm a carcinogenic effect in man. The observation of excess liver cancer deaths in workers occupationally exposed to PCBs is of major interest since the liver

was a target site for changes in animals and since man has demonstrated evidence of subclinical alterations in liver function. If liver cancers are to be evaluated, the diagnosis of primary cancers of the hepatic cells must be confirmed on the mortality studies since the number of cancers in the group will be very small. The available data demonstrate no consistency in the cancer mortality patterns in the studies and no data on a possible relationship of cancers to dose of PCBs.

8. Morbidity or Incidence Data

Skin

Skin lesions have been reported in association with exposure to chlorinated aromatic compounds since the early 1900's (Jones and Alden, 1936). Taylor has emphasized that acneform eruptions are more frequent with the chloronaphthalenes and the dibenzofurans and that the variation in the quantity of these substances that may be present as contaminants in PCBs may account for differences in reporting of skin eruptions with exposures. Taylor has also reported that the acnegenic capacity of various compounds changed according to their form (fumes, liquid, or solid) and the degree of chlorination (Taylor, 1979). These factors may also influence the presence of reported skin disorders in studies.

Not only the frequency but the characteristics of skin lesions have differed in the various studies. Jones and Alden's early description of the lesions they associated with chlorinated biphenyls included "blackheads" or "carbon-colored" comedones

sometimes distributed in unusual areas of the body and often associated with cystic areas and yellow pus (Jones and Alden, 1936). Taylor noted that the cystic swelling and hypersecretion of the meibomian glands are important characteristics of the chloracnegenic effect of PCBs compared to other similar chemicals. These were the typical lesions reported by Meigs et al. in seven of 14 workers exposed to a PCB vapor leak from a heat exchanger in a plant in Connecticut (Meigs et al., 1954). The exposure to vapors was intermittent but of extended duration. Liver function tests were normal in most of these workers and no PCB levels in individuals were obtained, although an air sample prior to the onset of skin disease was 100 ug per m^3, which was within the accepted standards.

The patients who were initially described with Yusho disease had lesions similar to that described above in about 33% and a brownish pigmentation of the skin and nails in 10% of patients. These frequencies were increased subsequently to include about 70 to 85% of patients because of new definitions of characteristics of disease or delayed development of the signs. The eyes were also involved, exhibiting swelling of the upper lids, hyperemia of the conjunctiva and eye discharge (Kuratsune, 1972). Pigmentation of the skin and eye discharges also occurred in newborns of affected mothers. No comparison groups have been included in these studies of Yusho patients. Where the lesions are pathognomic of PCB-related disease this may not be necessary

but when the lesions are more general, comparison groups are essential. There were histopathological changes in five patients autopsied that seem to be associated with contaminated rice oil ingestion. These changes included hyperkeratosis of hair follicles and increased melanin pigment in the basal layer of the epidermis (IARC, 1978). Three out of the five cases also had proliferation of ductal epithelium of esophageal glands. It would have been helpful if these pathological assessments had been made blindly so that qualitative judgments such as "increased melanin" could have been compared in exposed and non-exposed groups. Correlating these pathological findings with changing levels of PCBs, PCDFs, and PCQs would also have been helpful but there are no reported data relating to these issues in the papers available. It is known that the amount of used Kanechlor in the rice oil consumed by the patients was between 0.5 and 2.0 g, which would indicate a PCB exposure similar to levels in occupational settings.

Hara et al. in two separate papers (1974, 1975) have described the skin lesions in workers in a capacitor factory where Kanechlor had been used. The serum PCBs of all workers ranged from 7 to 300 ppb but it is not known how these values correlated with the presence of skin lesions (Hara et al., 1974; Hara et al., 1975). Discontinuance of the exposure not only decreased the overall PCB level to 75% of the original value but the skin lesions disappeared to "vestigial markings on a few individuals." The summary of the report does not indicate

the correlation of the blood PCB and skin lesions although there are data in this paper on the half-life of PCBs in relation to duration of exposure.

Hasegawa has reviewed the health of workers in five plants whose industrial process included exposure to Kanechlor (Hasegawa et al., 1972). The industries included capacitor manufacture, PCB manufacture, and biphenyl recovery. The vapor concentrations ranged from 13 to 965 ug/m^3. Skin lesions were reported to be unrelated to blood PCBs but generally related to direct skin contact. The average blood PCB level was 370 ppb. The principal dermal findings included brown chromodermatosis of the dorsal joints of hands, fingers and nail beds and acne. There were no further descriptions of the latter lesions so that the presence of chloracne could not be confirmed, but the brown skin discoloration certainly is typical of the Japenese worker reports.

Kitamura et al. described 13 workers from an electrical capacitor manufacturing plant (Kitamura et al., 1973). The lesions in 10 of the workers described in this group are even more vague. They did not include the typical coloration of nails; chloracne was not directly diagnosed; and the follicular lesions did not occur at points of contact with PCBs. From the description of the study it is not clear that the author's conclusions that the skin lesions were due to PCBs was justified without further information on the usual frequency of similar types of skin lesions in normal populations or a description of typical chloracne. The blood PCB level in this group was 820 ppb average.

Inoue et al. studied the health of workers who were exposed to Kanechlor 500 in a thread-glossing factory (Inoue et al., 1975). The frequency of skin lesions was low. The blood PCBs were over 50 ppb in seven out of 54 individuals studied. One person had representative chloracne with blood PCBs of 190-210 ppb.

Ouw et al. described one case of chloracne among 34 workers exposed to Aroclor 1242 in capacitor manufacture (Ouw et al., 1976). The average blood PCB was 400 ppb. In addition five workers complained of eczematous rash but there was no description of lesions. Seven out of 15 process workers and six out of 19 impregnation room workers complained of burning and irritation of the eyes, face, and skin. It is difficult to reconcile these complaints with level of exposure since it should have been higher in the latter group of workers than the former. However, Aroclor concentrations in air as high as 2220 ug/m^3 were measured. The investigators indicated that the "dermatological complaints" occur more often among workers with higher "blood Aroclor levels" but they also indicate there is no clear correlation. It is difficult to be sure of the true meaning of dermatitis as elicited by history when the answers can be biased and the authors do not indicate which cases are related to physical findings only.

As part of a health hazard evaluation at a facility that manufactured electrical distribution equipment, NIOSH studied the

health of eight workers and found no symptoms or physical signs of chloracne (NIOSH, 1977). There were several subjects who reported skin rashes but not those typical of PCB exposure. The mean PCB level in blood was 98 ppb with the highest value being 286 ppb.

Another health hazard evaluation was done after an accidental spill of PCBs (NIOSH, 1980). In this situation there were no signs of chloracne. However, the mean blood PCB level of exposed workers was only 6.4 ppb; this was below the mean for unexposed workers. Humphrey studied the PCB level of individuals on the basis of fish consumption (Humphrey, 1975). He found that the PCB level was correlated with fish consumption with mean blood levels ranging from 46 ppb to 82 ppb and a maximum individual level of 366 ppb. There were no skin lesions or other health problems associated with PCBs.

A medical and biochemical survey was made of 120 male workers exposed to PCBs in the maintenance of railroad cars and locomotives (Chase et al., 1981). Among the exposed group of 86 workers the "medical histories and physical findings" revealed "several cases of chloracne" -- "with none being found in the other groups." No further details are given as to whether the conditions were currently active, nor was there a description of the lesions. It would be of interest to confirm these cases as true chloracne since the current mean plasma PCB level in the exposed group is only 33.4 ppb (range 10-312 ppb), a very low level of PCBs to be associated with chloracne.

Fischbein et al. (1979) completed a medical survey of capacitor manufacturing workers who were self-selected for physical and bio-chemical examinations. A high proportion (45-55%) of both male and female workers complained of skin disorders with 7% giving a history of acne beginning after the onset of exposure. "Dermatologic findings" were present on physical examination in 38 to 41% of female and male workers, respectively. However, these lesions included "erythema, swelling, dryness, and thickening," which would not be lesions characteristic of PCB exposure. Five percent of the study population had acneform eruptions. There is no mention of whether these were typical of chloracne or were the usual acne lesions found in any medical survey. Since skin lesions are common in the general population and since the population was self-selected initially it is difficult to evaluate these findings. The average lower PCB homologues in plasma were 124 ppb and of higher PCBs, 48 ppb. The authors report that the skin findings were correlated with plasma H-PCBs. Unfortunately, if the examinations were done with the observer knowing the job held by the participant, all results can be biased, since reporting might be related to the job held and the PCB levels were related to job. There was no note of skin hyperpigmentation but 15% of workers had eye abnormalities including "injected conjunctiva and palpebral hyperpigmentation and edema." Again, it is not clear how frequently these lesions would have been reported in normal subjects had examinations been done without knowledge of exposure categories.

Maroni et al. (1981) recently reported on two groups of workers who were exposed to PCBs in the manufacture of capacitors One group (A) had been exposed to both 54% and 42% chlorinated biphenyls. Although the levels of the trichlorinated chemical were similar in current employees in the two plants (128 ppb (A) and 137 ppb (B)), the levels of pentachlorinated agent differed (249 ppb (A) and 68 ppb (B)). It is of interest that 10 cases of acne and folliculitis appeared in the two plants and at least four were entirely typical of the condition. All four typical cases occurred in nine employees who had worked in a high power capacitor impregnation area of Plant A where levels of pentachlorinated biphenyls were high. Their mean blood PCB was 450 ppb, a value not different from that of the five unaffected workers but certainly higher than the overall levels in the two plants. Maroni et al. also noted two cases of bleeding hemangiomas, but one had existed from birth and the only difference in his condition was that bleeding had taken place after the job started and the lesion was excised. The other patient had bleeding from the tongue and a cavernous hemangioma was discovered as well as chronic myelocytic leukemia. Case reports such as this and particularly the unusual circumstances surrounding multiple conditions in one patient in the second case make such findings difficult to interpret. The reports of chloracne appear valid and suggest a problem.

Baker et al. examined sludge users, workers in a capacitor plant, workers' families, and community non-sludge users

Baker et al., 1980). Since the sludge contained PCBs, it was felt that its use as fertilizer might seriously affect the PCB level in the blood. The level of Aroclor 1242 ranged from 7.2 to 48.6 ppb and for Aroclor 1254 from 10.1 to 26.5 ppb, with the lowest levels being found in sludge users and the highest levels in workers. No cases of chloracne or other symptoms of toxicity were noted but only two PCB values were above 200 ppb.

Smith et al. examined workers involved in the maintenance, repair, and overhaul of electrical transformers and measured levels of PCBs by job (Smith et al., 1981). The mean serum levels of L-PCBs in the municipal utility workers were 11 to 36 ppb with a maximum of 59 ppb, and of H-PCBs of 6 to 24 ppb with a maximum of 74 ppb. In the privately-owned facility workers had similar values with L-PCB levels between 19 to 22 ppb with a maximum of 52 ppb, and H-PCB levels between 6 and 31 ppb with a maximum of 250 ppb. There was no significant difference in either place in the frequency of skin lesions between those with less than 10 ppb and those with greater than 10 ppb H-PCBs. There was a significant excess of symptoms of eye irritation in one and a history of bronchitis and loss of smell in the other among those with serum levels of H-PCBs greater than or equal to 10 ppb compared to less than 10 ppb. However, since these are subjective measures of disease and since workers may have been influenced to report subjective symptoms differently depending on job it is impossible to evaluate the importance of these observations.

Smith et al. reported on the physical findings and symptoms in 197 workers who manufactured electrical equipment. The serum levels of L-PCBs in the workers varied by job, with the geometric means ranging from 89 to 502 ppb, the highest levels (2400 to 3330 ppb) being found in the department where capacitors were processed, finished, and tested, and in a department that had assigned work throughout the plant. The geometric mean level of H-PCBs ranged from 22 to 51 ppb, with the highest values (150 to 250 ppb) in these departments. This plant had always used 42% chlorinated biphenyls, both Aroclor 1242 and 1016. Although there were some symptoms of skin and eye lesions (darkening of skin and nails, skin rash, and irritated eyes) that appeared to be different between the groups with L-PCB 200 ppb greater than or equal to 200 ppb compared to those with lower values, these differences disappeared when the comparisons were corrected for age and job. Thus one can conclude that symptoms were primarily related to age and job with the latter association being either real or biased. The symptoms were not related to the body burden of PCBs independent of job. No evidence of skin lesions suggestive of chloracne was found on physical examination, in spite of some extraordinarily high PCB blood levels.

In a preliminary report, Bahn (1976) indicated the incidence of cancer in 64 employees exposed to Aroclor 1254 in a research and development laboratory and 65 refinery workers

with a similar exposure from the same area. The investigator reported a significant excess in the incidence of melanoma of the skin as well as pancreatic cancer based on expected cancer rates from the Third National Cancer Survey. In a subsequent letter to the New England Journal of Medicine, Bahn et al. have reported only on the excess of melanoma (Bahn et al., 1976). When Lawrence criticized the study on the basis of the fact that individuals could have been exposed to multiple chemicals in the laboratory environment (Lawrence, 1977), Bahn and colleagues suggested that the reason for emphasizing the melanoma risk was the biological plausibility of such an association whereas an excess risk of pancreatic cancers could have indicated an association with multiple chemicals (Bahn et al., 1977).

The investigators themselves have discussed several of the flaws of this study. Information on true exposure is limited and perhaps more importantly one-fourth of the exposed workers had to be omitted. The author has also suggested that she underestimated the death ratio by including individuals during their early years of employment when there had not been a sufficiently long latency from the time of first exposure of PCB to the expected time of cancer development.

There are other problems with this study related to the identification of cases in the exposed population and the comparability of case ascertainment in the Third National Cancer Survey data. Apparently the investigators identified cases

without attempting to validate the accuracy of diagnosis. Pancreatic cancer is very difficult to recognize and diagnose. The diagnoses of the two cases need to be validated from hospital records in order to make them comparable to data from the survey. Skin cancers such as melanomas may be diagnosed in doctors' offices. Thus, the lesions could be missed in the cancer survey data where records were obtained primarily from hospitals but identified in populations with routine medical care. It would be necessary to validate the cases in this study through the use of hospital and pathology records and then to compare these cases to a comparable group of employed individuals who have had active medical surveillance by physicians.

In summary, the data on skin lesions in relation to PCB exposures have indicated a remarkable consistency. Individuals who have a body burden indicated by a blood level of 200 or more ppb PCBs have an increased risk of chloracne. There is little evidence of risk below this level and those studies that do suggest a risk at lower levels usually do not have a comparison group or they have not collected the data in a manner such that bias might be avoided. The data also suggest that typical skin lesions may occur more frequently in workers exposed to PCBs that have been heated and to PCBs that have 54% or more chlorination. Since the skin lesions occur more frequently after heating, it is possible that chloracne is actually due

to some alteration or contamination of the PCBs with more genegenic materials such as dibenzofurans, as found in the Yusho incident. Symptoms of chloracne are reported frequently among those who use Kanechlor; this could be related to level of exposure or its high level of PCDFs relative to PCBs. Such a possibility could not be evaluated with the information in these papers. The relationship to direct skin exposure could also not be evaluated.

C. Biochemical Changes and Liver Function

Extensive studies of liver function have been included among the recent papers on PCBs. Some of these are summarized in Table 9. The early study of Meigs et al. involving a PCB leak from a heat exchanger indicated that there were no abnormalities in seven workers with chloracne except for some transient changes in liver function tests in one worker (Meigs et al., 1954). These changes could not be definitely attributed to PCBs.

The study of Hasegava et al. of 99 workers in six industrial plants in Japan indicated that increases could occur in enzymes such as SGOT, SGPT and decreases in blood cholinesterase (Hasegava et al., 1972). The authors regarded the changes in liver function as mild and not clinically significant. Kitamura et al. (1973) indicated that in the 13 capacitor workers the hepatic function tests were normal.

Table 9

Biochemical Studies of Enzymes and Liver Function

Study	No. Subjects		Average Dose ppb	Correlation or elevation with dose: SGOT	SGPT	GGTP	AK	LDH	Bilirubin	Notes
Hasegawa et al., 1972	99	Tot.	370	+	+	N.T.	N.T.	N.T.	N.T.	cholinesterase
Kitamura et al., 1973	13	Tot.	820	Hepatic function tests normal						
Chu et al., 1976	7	Tot.	>500	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	BSP abnormal in 57 percent
NIOSH 1977	7	Tot.	98.4	Norm.	Norm.	N.T.	Norm.	N.T.	Norm.	
Fischbein et al. 1979	321	Lo	124	Reported % above normal						No comparison group. No correction confounding variables
		Hi	48	2.2%	7.2%	1.9%	1.2%	2.5%	0%	
Baker et al., 1980	89 Sludge users	Tot.	Hi 17.4 (18.)	Correlations with PCB						Analyzed with non-drinkers
	18 workers		75.1 (26.5)	None	None	None after correction alcohol	None	None	None	No other variable controlled Hi-PCB used in analysis
	19 worker fam.		33.6 (14.8)							
	22 Community		24.4 (12.8)							
Moroni et al., 1981	80	Lo	215	?	?	50% elev. Norm.		?	Norm.	Hepatomegaly 80% Significantly higher PCBs in liver cases
	Liver abnorm. 16	Hi	388							
		Tot.	524	Positive association abnormal liver findings and PCBs						
	Liver norm. 64	Lo	92			T				
		Hi	176							
		Tot.	298							

TABLE 9 (continued)
Biochemical Studies of Enzyme and Liver Function (continued)

Study	No. Subjects		Average Dose ppb	SGOT	SGPT	GGTP	AK	LDH	Bilirubin	Notes
Chase et al., 1981	120	Tot.	33.44 (10-312)	Pos.	None	None				Corrected for age Not other risk factor as alcohol
		Exposed								
		Non-exposed	T 12.0 (10-27)							
Smith et al., 1981a	244	Lo	80-588 ng/ml (approx ppb)	None	None	None	None	None		Correlation include corrections
		Hi	22-61	Pos.	None	Pos.	None	None	None	
Smith et al., 1981b	47	Pub.Lo	11-36 ng/ml	None	None	None	None	None	None	
		Hi	6-24	None	None	None	None	None	None	
	46	Priv. Lo	19-23 ng/ml	Pos.	None	None	None	None	None	
		Hi	6-31	None	None	None	None	None	None	
Reanalysis Smith et al., 1 & 2 above	224	Lo		None	None	Pos.	None	None	None	Analysis each PCB independent of other
		Hi		Pos.	None	Pos.	None	None	None	
Smith et al., 1981c	47	Pub.Lo		None	None	None	None	None	None	
		Hi		None	None	None	None	None	None	
	46	Priv. Lo		Pos.	None	None	None	None	None	
		Hi		None	None	None	None	None	None	
Kreiss et al.,	468		17.2 microg./L (3.2-157.9)	N.T.	None	Pos.	N.T.	N.T.	None	

Ouw et al. tested the liver function of capacitor workers through the use of biochemical markers and found the overall test data for the group to be normal (Ouw et al., 1976). The BSP liver function test was conducted only on individuals with blood PCBs above 500 ppb; four out of seven workers were above normal levels, but it is not clear whether these values were above the range of error of the test or whether there were other factors that might have influenced the results. It is indicated that the blood PCB level and the BSP test do not correlate.

NIOSH (1977) evaluated the liver function of seven of eight workers exposed to PCBs in the manufacture of electrical equipment. The levels of SGOT, SGPT, alkaline phosphatase, and total bilirubin were normal in a group of seven workers with a mean PCB level of 98 ppb.

Fischbein et al. (1979) examined a group of 321 workers from two capacitor manufacturing plants. The workers had mean levels of L-PCBs of 124 ppb and H-PCBs of 48 ppb. A small proportion of the workers had abnormalities in the biochemical tests. Two percent had abnormally high levels of SGOT, 7% high levels of SGPT, 2% high levels of GGTP, 1% high levels of alkaline phosphatase, and 3% high levels of LDH. However, there were no abnormally high levels of bilirubin. The results of this study have not been corrected for important confounding variables such

as age, alcohol intake, and other diseases currently or in the past (e.g. hepatitis) that may influence these findings. There is no unexposed group for comparison. The investigators have not presented data correlating increasing enzyme levels to increasing PCB levels, which would be an appropriate method of presenting the relationship between two variables that are continuous. The study does include a comperison of the data dichotomized by two levels of SGOT, less than 50 and greater than 50 i.u. and two levels of both lower and higher homologues of PCBs. These data indicated significant differences between the proportion of individuals with high and normal SGOT levels for H-PCBs greater than 75 ppb compared to lower levels and for L-PCBs greater than 200 ppb compared to lower levels. It is not clear whether these PCB levels were selected after examining the data, in which case the conclusions would be questionable.

The 16 individuals involved in a PCB spill (NIOSH, 1980) had normal liver function tests that included total bilirubin, transaminase, alkaline phosphatase, and lactic dehydrogenase. The triglyceride changes could not be evaluated by the investigators because of inappropriate test procedures. Cholesterol levels were normal. This group had very low blood PCB levels of 6.4 ppb as a mean value, a level lower than that of non-exposed groups.

Baker et al. (1980) studied PCB levels in users of PCB-contaminated sludge as a fertilizer compared to workers in

a PCB-using facility, their families, and non-sludge users in the community. The PCB level varied from 17.4 to 75.1 ppb in the four groups with the lowest level being found in the sludge users. There were no signs of changing levels of SGOT, SGPT, alkaline phosphatase, LDH, or bilirubin in relation to blood PCBs in drinkers and non-drinkers of alcohol. The GGTP level correlated with PCB level in the total population but, when alcohol consumers were removed, the correlation disappeared.

Maroni et al. (1981) studied liver abnormalities in 80 workers from a capacitor manufacturing and testing plant. Sixteen workers (20%) had asymptomatic liver abnormalities. Over 80% of these had enlarged livers. Among this group the most frequent enzyme elevations were the gamma glutamyl transpeptidase (GGTP) in half the cases, the transaminases in 44% and the ornithin-carbamoyl-transferase (SOCT) in 38% of cases with enlarged livers. The mean L-PCB level was significantly higher in workers with abnormal liver findings compared to controls (215 to 92 ppb), mean H-PCB level was significantly higher (308 to 176 ppb), and total mean PCB level was significantly higher (524 to 296 ppb). The levels of PCBs in these workers are high compared to values from many of the exposures recently reported. It is interesting that the authors report that although there is an association between liver disease and PCBs there was no such association for chloracne, but the number of cases was smaller for the latter parameter.

Chase et al. (1981) examined the serum PCB levels and the biochemical markers of liver and lipid activity in 120 maintenance workers who had had varying exposures to PCBs in their work. Plasma PCBs were correlated with SGOT and, after adjusting for age, the correlation between these two variables is still significant. There is no significant correlation between plasma PCBs and GGTP or SGPT. If this correlation is correct it has occurred with levels of PCBs in the blood of exposed workers (33.4 ppb) that are lower than those found in other studies relating subclinical changes in liver function with PCBs (NIOSH, 1977). However, without corrections for other potentially confounding variables such as alcohol intake and the history of other diseases such as hepatitis, it is difficult to assess the finding.

Recently, NIOSH has completed three studies representing cross-sectional medical surveys in two groups, individuals working in capacitor manufacturing (Smith et al., 1981a) and individuals working in maintenance and repair of electrical transformers (Smith et al., 1981b). The third study combined the data from each study in an overall analysis.

In the capacitor manufacturing group there were 224 participants for whom L-PCBs and H-PCBs were determined, as well as biochemical studies. Several simple correlations were calculated and, for all those that were significant, multiple regression equations were developed using all other predictor

variables for which information was available. This included drug intake, smoking history, other biochemical markers, age, sex, and others. Serum H-PCB was significantly correlated with SGOT and GGTP. There were, however, no clinical findings suggestive of liver disease and no indication that the levels of these enzymes were abnormally high. Exposures in this plant were high with plasma PCB levels being eight to 50 times the level found in the community.

Smith et al. (1981b) have reported in the survey information on 93 individuals who were about equally distributed between a municipal electric system and a privately-owned electric utility company. The levels of H-PCBs and L-PCBs are similar in the two facilities. There were very few enzyme tests related to liver function that were significantly correlated with PCB levels. The only significant correlation was a positive relationship between L-PCBs and SGOT for the private company.

Smith et al. (1981) subsequently reanalyzed the data for the three sites presenting partial correlations for L-PCBs and H-PCBs independently without correcting the level for alternate homologues since they were closely interrelated. Under these circumstances, there is not only a positive correlation between H-PCBs and SGOT and GGTP at the manufacturing plant but also a correlation with L-PCB and GGTP. The positive correlation between L-PCB and SGOT still remained after corrections for the private utility company. Combining the data for all sites it is

noted that log SGOT and log GGTP demonstrate both significant and homogeneous trends in relation to log L-PCB level. Only log SGOT is related to log H-PCB and in this case the trend for all sites is homogeneous but not significant. In these analyses, the only confounding variables considered were age and sex for one study site whereas the analyses in the previous papers controlled multiple variables such as smoking and other diseases. Reducing the number of variables and increasing the number of subjects available for study may have accounted for the changes in the relationship with biochemical markers and symptoms to the levels of PCBs. Because of the many changes in relationship, it is difficult to indicate precisely the association between specific liver enzymes and specific homologues of PCBs. It does appear that in these studies one or more enzyme levels within normal ranges may be related to one or more types of PCBs in the blood.

In order to identify the enzyme system that is induced by the various chlorinated forms of biphenyls, Alvares et al. (1977) tested the induction of liver cytochrome P-450 and P-448 by Aroclor 1016 in rats and in workers occupationally exposed to the agent. In rats, the lower chlorinated PCB elicited a barbiturate type of effect on the oxidative enzyme system inducing cytochrome P-450, ethylmorphine-N-demethylase, and microsomal protein. Unlike Aroclor 1254, which induces both P-450 and P-448, the rats with Aroclor 1016 showed little effect on benzo(a)pyrene

hydroxylase activity, which suggests little induction of P-448 by the chemical. The tests in exposed workers were conducted by determining the half-life of the antipyrine whose metabolism is stimulated by the barbiturate class of inducing substances. The workers had a significantly shorter metabolic half-life of the drug than the controls suggesting that the Aroclor 1016 had induced cytochrome P-450.

In a study of 458 community residents in a town that had high levels of PCBs in fish, Kreiss et al. (1981) found a correlation between PCBs as measured against Aroclor 1260 and GGTP. There were no correlations with other liver enzymes. Corrections were made for several other variables such as age, sex, fish and alcohol consumption, and obesity.

In summary, the data from the studies of liver enzymes and function suggest that the populations exposed to PCBs usually do not have clinical liver disease, although in one study there was asymptomatic hepatomegaly (see Table 9). Few of the early studies allow us to separate the various homologues of PCBs in order to correlate enzyme response to level of chlorination of PCBs. Recent studies suggest that SGOT and/or GGTP are the most sensitive markers of change in the liver enzyme systems related to PCB exposure. In the studies that included extensive testing of all enzyme systems as well as characterisation of the PCBs, the data have inconsistencies that do not allow us to judge clearly the level or the specific type of

PCB that is related to increased levels of specific liver enzymes. Many of the studies have not corrected for other confounding variables such as alcohol consumption. The data are suggestive that there are changes in one or more liver enzymes related to PCB exposure that are not associated with disease and may occur at levels below those at which chloracne occur.

D. Lipid Metabolism

The long-term studies of patients with Yusho disease have revealed several other abnormalities, among which were elevated blood triglycerides (Urabe et al., 1979). In recent reports of individuals exposed to PCBs, assessment of lipid metabolism has indicated some abnormalities, but in general no clinical manifestations of these abnormalities such as increased risks of cardiovascular disease have been noted. Some of these studies are summarized in Table 10.

Table 10

Lipid Studies

Study	Number Subjects	Average Dose	ppb	Correlation or elevation of lipids: Triglycerides	Cholesterol	H-Chol. HDL-	L-Chol. LDL-	Notes
Masegawa et al., 1972	99	Tot.	3703	Decr.	Decr.	N.T.	Decr.	
Mara et al., 1973	118	Tot.	7-300	Incr.	N.T.	N.T.	N.T.	
Bumgarner et al., 1975	37	Tot.	4	N.T.	Normal	N.T.	N.T.	
Fischbein et al. 1979	321	Lo Hi	124 48	Reported as % above normal 18.5%	17.8%			No comparison with control. No correction for confounding variabl
Baker et al., 1980	89 sludge users 18 workers 19 worker fam. 22 community	Tot. 17.4 75.1 33.6 24.4	Hi (10.1) (26.5) (14.8) (12.8)	Pos.	None	sl. neg. (NS)	N.T.	Compared for H-PCB onl Analyzed only on non-alcohol drinkers No other variables controlled.
Smith et al., 1981a	224	Lo Hi	50-502 ng/ml 22-51	Neg. Pos.	None Pos.	None None	None None	Corrected for other variables

TABLE 10 (continued)

Lipid Studies

Study	Number Subjects		Average Dose ppb	Correlation or elevation of lipids: Triglycerides	Cholesterol	N-Chol. HDL-	L-Chol. LDL-	Notes
Smith et al., 1981b	47 Pub.	Lo	11-36 ng/ml	None	None	None	None	Positive correlations corrected for other variables.
		Hi	6-24	Pos.	None	Neg.	None	
	46 Priv.	Lo	19-23	Pos.	Pos.	None	None	
		Hi	6-31	Neg.	None	None	None	
Smith et al., 1981c (Reanalyses of papers above)	Capacitor	Lo		None	None	None	None	Included fewer confounding variables
		Hi		Pos.	Pos.	None	None	
	Pub. ut.	Lo		None	None	None	None	
		Hi		Pos.	Pos.	Neg.	None	
	Priv. ut.	Lo		None	Pos.	None	None	
		Hi		None	None	None	None	
Kreiss et al.,	468		17.2 microg/L. (3.2-157.9)	None	Pos.	None	None	

Hasegawa et al. (1972) had noted changes in lipid metabolism of Yusho patients as manifested by decreases in the blood levels of cholesterol, triglycerides, phospholipids and beta-lipoproteins. Other studies such as that of Hara et al. (1973) on Yusho patients had noted elevated triglycerides in 55% of subjects who had blood PCBs above 50 ppb. The latter data were not corrected for any risk factors such as age or weight. Bumgarner et al. (1973) indicated normal cholesterol levels in 37 refuse workers who had a mean PCB level of 4 ppb.

Fischbein et al. (1979) has examined lipid metabolism in 321 capacitor workers. Cholesterol levels of 300 or more mg/100 ml were found in 17.8% of workers and triglyceride levels of 200 or more mg/100 ml were reported in 10.5% of the population. The total lipids were elevated (above 1 g/100 ml) in 3.4% of the population. These metabolic parameters, however, are influenced by age, personal habits, and the presence of other diseases; it is therefore essential that the data be compared to a population with similar age and sex distribution and that confounding variables be controlled before one can assess the role of PCBs in these observed changes. Since these comparisons were not made, no conclusions can be drawn from these observations.

In the study of Baker et al. (1980) in which PCB-contaminated sludge users were compared to exposed workers, their families, and community controls, there was a highly significant

positive correlation of plasma triglycerides and serum H-PCB. This correlation was strengthened when alcohol consumers were removed. There was a negative correlation of HDL cholesterol with H-PCBs that was not statistically significant. The investigators suggested that the mean level of serum PCB in fasting subjects with hypertriglyceridemia was only 25.0 ppb which is lower than the levels at which this abnormality was noted in previous studies (50-200 ppb, NIOSH document). It is not clear, however, whether the other studies with higher levels have used total PCBs, whereas this study used only H-PCBs in the correlation analyses. The H-PCBs constitute 35 to 59% of the total mean PCBs in the groups. Personal characteristics may influence triglyceride levels, and many factors were apparently considered by these investigators including age, sex, and drinking habits. These lipid abnormalities may be occurring at the lower PCB limits, or even below those limits reported previously.

Chase et al. (1981) in their study of maintenance workers exposed to PCBs found that levels of plasma PCBs were significantly correlated with triglycerides but not with cholesterol. Adjusting for age or length of employment does not change the significance of this correlation. The triglycerides are not significantly correlated with fat PCB levels. As mentioned previously the levels of plasma PCBs in this group of workers is low (33.4 ppb).

Smith et al. (1981a), in the study of 224 workers from a capacitor manufacturing plant, found that serum PCBs were correlated with measures of lipid metabolism. Corrections were made for relevant variables such as smoking, history of diabetes and heart disease, drug use, and others. The partial correlations indicated a significant correlation between serum H-PCB level and total cholesterol and triglycerides and a significant negative correlation of plasma triglycerides with serum L-PCB levels. When the levels of H-PCB and L-PCB were combined the correlation was positive as seen in other studies where total PCBs have been examined. There were no signs of clinical disease in relation to the elevated lipids. It was noted that several of the lipid measurements were correlated with GGTP level. As the authors suggested, this may indicate that PCBs induce hepatic microsomal enzymes, as has been found in laboratory animals and man, and these in turn may increase synthesis of specific lipids.

Smith et al. (1981b) in a health study of 93 workers divided between a public and private utility plant found correlations of lipid metabolites with PCB levels that conflicted with data from the previous study. Triglycerides were positively correlated with H-PCBs in one facility and negatively correlated with H-PCBs in the other. Both correlations were significant even after correction for multiple variables. Both triglycerides and cholesterol were positively associated with L-PCBs in only

[redacted]e facility even though the levels of the biphenyls in the [redacted]lood were similar in the two populations. High density lipoproteins were negatively correlated with H-PCBs in only one [redacted]tablishment. In this case, the other facility also demon[redacted]trated a similar negative relationship but the level of the [redacted]orrelation was much lower.

Smith et al. (1981c) have combined the data from these two studies and corrected the results for only age, sex, and study site. Under these circumstances there were less conflicting data in the correlations. Only one significant correlation with L-PCB was noted and that was a positive correlation with cholesterol at the private utility. Both cholesterol and log triglyceride were associated with H-PCBs at the equipment manufacturing site. Triglycerides and H-PCB were positively correlated and HDL-cholesterol and H-PCB negatively correlated at the municipal utility site. Combining the data from all study sites indicated that log triglyceride was significantly associated with both L-PCB and H-PCB but the trend for all sites was homogeneous only with L-PCB. Log HDL-cholesterol was significantly and negatively associated with H-PCBs and this trend was consistent across all sites. There was no significant relationship of PCBs with total cholesterol.

Kreiss et al. (1981) have studied a community where high levels of PCBs and DDT were founds in fish. Among the 458 participants, there was a positive correlation between cholesterol

and PCBs measured as Aroclor 1260. There was no additional contribution by serum triglyceride or HDL-cholesterol to the prediction of serum PCB in multiple regression analysis.

In summary, the studies in man suggest that there is frequently a positive correlation between PCBs in blood and triglyceride levels, although there are many studies that demonstrate no relationship. The correlation is often to the higher homologues of PCBs and occure in some cases with blood levels of H-PCB at 25 ppb or below. The data associating HDL-cholesterol and H-PCBs are not as often significantly correlated, but when they are, the relationship is negative. Lower levels of HDL-cholesterol may be an important risk factor for coronary heart disease but there is no evidence of a relationship of these lipid findings to clinical disease in these studies. The variation in the presence of lipid abnormalities in relation to PCBs in the studies and the variation in the specific lipid changes observed would suggest that there may be a confounding variable that has been ignored and that is influencing these relationships. A positive correlation of blood lipids with plasma PCB levels could in part be a consequence of the tendency of PCBs to distribute equally among all lipid pools in the body.

E. Reproductive Effects

Very few papers have addressed the problems of human reproductive effects related to PCB ingestion. The early paper

by Kuratsune (1972) on the Yusho patients had indicated that out of 11 women patients and two of the wives of patients who were exposed at any time during pregnancy, there were 10 live born and two stillborn infants and three of the live born were small for their age. The authors do not provide comparison figures on reproductive outcomes for that area of Japan so that it is impossible to assess the meaning of these figures. It is clear, however, that for all babies whose records were reviewed, skin staining and eye discharge were usually present. Kreiss et al. (1981) simply indicated that there was no association of miscarriage, still birth or infant death rate independent of age effects in a study of a community with high PCB levels. In general, the data on reproductive effects from exposure to PCBs are limited.

F. Hematology and Immunology

Most of the studies of hematological effects have found no abnormalities and these observations have been made in simple statements. The studies of Kitamura et al. (1973), Bumgarner et al. (1973), Karppanen and Kolho (1973), Fischbein et al. (1979), Baker et al. (1980), and Maroni et al. (1981) have not revealed any abnormalities of hemoglobin or leukocytes. Ouw et al. (1976) reported several protein and globulin tests on exposed workers that were higher or lower than the reported normal. However, the overall levels of globulins were not different in two groups of workers with high and low exposures. In the initial abstract

relating to the Baker et al. (1980) study, the authors reported increased hematocrit and hemoglobin in relation to PCB levels controlled for age. The second complete report corrects for several other variables that may account for the difference in results. In the three reported studies of Smith et al. (1981), the investigators looked at red cell count, white cell count, hemoglobin, and hematocrit and found no significant correlation with either L-PCB or H-PCB when corrected for confounding variables. In the latter studies they have also examined the correlation of total protein, albumin, and the various globulin fractions and found no significant correlations after correcting for other factors.

In general, there are no recent studies that suggest abnormalities of the heme system in man related to levels of PCBs. In addition, the Smith et al. (1981b) study of workers in electrical utilities showed no significant variation in PCBs related to urinary porphyrins, porphobilinogen, or 17-ketosteroids or 17-hydroxysteroids.

G. Other Factors

Kreiss et al. (1981) in the study of a PCB-exposed community found increased diastolic blood pressure to be correlated with PCB levels even after the correction for other variables. No comparison data for a control group were given. The study of workers in the equipment manufacturing plant also demonstrated

correlation between diastolic blood pressure and H-PCB but this disappeared when corrected for age. Other investigators have not found this relationship, so the difference may be associated with an unrecognized interrelated variable or a chance association related to the multiplicity of factors that have been examined.

Warshaw et al. suggested that workers in a capacitor manufacturing plant (population of Fischbein et al.) had decreased vital capacity and restrictive impairment of lung function in the absence of signs of radiographic change (Warshaw et al., 1979). They have compared the FVC to that of other worker populations in previous hazardous exposure studies as well as to a non-smoking normal population. The reported percent abnormality of PCB workers is 14% compared to 5.6% cited for non-smoking populations. The comparisons do not indicate that they have been controlled for smoking habits and sex.

Most studies have reported no clinical disease in PCB-exposed populations with the exception of Yusho disease and chloracne (Karppanen et al.; Humphrey, Smith et al.; Chase et al.; Kreiss et al.). Some have reported symptoms that are difficult to evaluate since most are subjective and could be related to worker bias. Fischbein et al. suggested that neurological symptoms were increased but there is no similar group with which to compare workers and thus make this assessment. Smith et al.

(1981) in the study of the combined work sites found that coughing at work and irritated eyes were related to both L-PCB and H-PCB. Loss of appetite and peripheral "tingling" were associated only with L-PCB. History of skin rash was associated only with H-PCB. Many of these differences were not observed when individual work site data were analyzed separately. The lack of a difference in each site may result because jobs were included as a confounder variable. Most studies have not even reported any symptoms or history of disease (Baker et al. and Kreiss et al.)

In all studies reviewed there was little evidence of clinical disease with the exception of chloracne and this condition seemed to be most frequent under specific conditions of exposure. The other common but not consistent findings were abnormalities of lipid metabolism, especially blood triglyceride levels, and abnormalities of liver enzymes, especially SGOT and GGTP, which were related to levels of PCBs. The lipid and liver changes appeared to occur at lower levels than the skin manifestations and were not associated with clinical disease or symptoms.

spectfully submitted,

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SHIMADA, T. and SATO, R. (1980). Covalent binding of polychlorinated biphenyls to rat liver microsomes. Toxicol. Appl. Pharmacol. 55, 490-500.

SHIOTA, K. (1976b). Embryotoxic effects of polychlorinated biphenyls (Kanechlors 300 and 500) in rats. Okajimas Fol. Anat. Jpn. 53, 93-104.

SIPES, I.G. et al. (1980). 4,4'-dichlorobiphenyl: Distribution, metabolism, and excretion in the dog and the monkey. Toxicol. Appl. Pharmacol. 55, 554-563.

SMITH, A.B., SCHLOEMER, J., LOWRY, L.K., SMALLWOOD, A.W., LIGO, R.M., TANAKA, S., STRINGER, W., JONES, M., and GLUECK, C.J. (1981a). Cross-sectional medical survey of a group of workers occupationally exposed to polychlorinated biphenyls (PCBs) at an electrical equipment manufacturing plant. Draft report prepared by National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations and Field Studies, Cincinnati, OH, and Lipid Research Center, University of Cincinnati Medical Center, Cincinnati, OH. (51 pages, 12 tables, 4 figures.)

SMITH, A.B., SCHLOEMER, J., LOWRY, L.K., SMALLWOOD, A.W., LIGO, R.N., TANAKA, S., STRINGER, W., JONES, M., HERVIN, R., and GLUECK, C.J. (1981b). Cross-sectional medical survey of two groups of workers occupationally exposed to polychlorinated biphenyls (PCBs) in the maintenance, repair, and overhaul of electrical transformers. Draft report prepared by National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations and Field Studies, Cincinnati, OH, and Lipid Research Center, University of Cincinnati Medical Center, Cincinnati, OH. (36 pages, 14 tables.)

SMITH, A.B., SCHLOEMER, J., LOWRY, L.K., SMALLWOOD, A.W., LIGO, R.N., TANAKA, S., STRINGER, W., JONES, M., HERVIN, R., and GLUECK, C.J. (1981c). Metabolic and health consequences of occupational exposure to polychlorinated biphenyls (PCBs). Draft report prepared by National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations and Field Studies, Cincinnati, OH, and Lipid Research Center, University of Cincinnati Medical Center, Cincinnati, OH. (58 pages, including 8 tables.)

SMITH, A.B. et al. (1978). Lipid lipoprotein alteration: Occupational exposure to polychlorinated biphenyl. Clin. Res. 26, 549A.

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STRIK, J.J.T.W.A. (1979). Porphyrins in urine as an indication of exposure to chlorinated hydrocarbons. N.Y. Acad. Sciences.

SUNDSTROM, G. et al. (1976). The metabolism of chlorobiphenyls - A review. Chemosphere 5, 267-298.

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VOS, J.G. and BEEMS, R.B. (1971). Dermal toxicity studies of technical polychlorinated biphenyls and fractions thereof in rabbits. Toxicol. Appl. Pharmacol. 19, 617-633.

VOS, J.G. and VAN DRIEL-GROOTENHUIS, L. (1972). PCB-induced suppression of the humoral and cell-mediated immunity in guinea pigs. Bull. Total Environ. 1, 289-302.

VOS, J.G. and NOTENBOOM-RAM, E. (1972). Comparative toxicity study of 2,4,5,2',4',5'-hexachlorobiphenyl and a polychlorinated biphenyl mixture in rabbits. Toxicol. Appl. Pharmacol. 23, 563.

VOS, J.G., KOEMAN, J.H., VAN DER MAAS, H.L., TEN NOEVER DE BRAUW, M.C., and DE VOS, R.H. (1970). Identification and toxicological evaluation of chlorinated dibenzofuran and chlorinated naphthalene in two commercial polychlorinated biphenyls. Fd. Cosmet. Toxicol. 8, 625-633.

WATANABE, I. et al. (1980). Distribution differences between polychlorinated terphenyls and polychlorinated biphenyls in human tissues. Bull. Environ. Contam. Toxicol. 25, 810-815.

WICKIZER, T.M. et al. (1981). Polychlorinated biphenyl contamination of nursing mothers' milk in Michigan. Am. J. Public Health 71, 132-137.

WOLFF, M.S., FISCHBEIN, A., THORNTON, J., RICE, L., LILIS, R., and SELIKOFF, I.G. (1981). Body burden of polychlorinated biphenyls among persons employed in capacitor manufacturing. Submitted for publication to Int. Arch. Occup. Environ. Hlth. Presented in part at the XIX International Congress on Occupational Health, Dubrovnik, Sept., 1978.

WYNDHAM, C., DEVENISH, J. and SAFE, S. (1976). The in vitro metabolism, macromolecular binding, and bacterial mutagenicity of 4-chlorobiphenyl, a model PCB substrate. Res. Commun. Chem. Pathol. Pharmacol. 15, 563-570.

YAKUSHIJJI, T. et al. (1978). Long-term studies of the excretion of polychlorinated biphenyls through the mother's milk of an occupationally exposed worker. Arch. Environ. Contam. Toxicol. 7, 493-504.

YAMASHITA, F. (1977). Clinical features of polychlorobiphenyls (PCB)-induced fetopathy. Pediatrician 6, 20-27.

YOSHIHARA, S. et al. (1979). Toxicological assessment of highly chlorinated biphenyl congeners retained in the Yusho patients. Chemosphere 8, 531-538.

XIV. Glossary of Terms or Abbreviations

alkaline phosphatase

bromsulfonphthalein liver function test

gamma glutamyl transpeptidase

PCBs with high degrees of chlorination

PCBs with lower degrees of chlorination

lactic dehydrogenase

polychlorinated biphenyls

polychlorinated dibenzofurans

polychlorinated naphthalenes

polychlorinated quaterphenyls

polychlorinated terphenyls

serum glutamic oxalic transaminase

serum glutamic pyruvic transaminase

serum ornithine carbamoyl transferase

the disease noted in Japan following human ingestion of cooking oil contaminated with PCBs, PCDFs, and PCQs.

parental test animals

litters derived from first generation animals at their first (a) and second (b) matings

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CURRICULUM VITAE
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DR. VICTOR A. DRILL

EDUCATION

Bachelor of Science (B.S.) degree, Long Island University, 1938.

Doctor of Philosophy (Ph.D.) degree, Princeton University, 1941.

Doctor of Medicine (M.D.) degree, Yale University School of Medicine, 1948.

EMPLOYMENT

Instructor in Pharmacology, College of Physicians and Surgeons, Columbia University, 1943.

Instructor in Pharmacology, Yale University School of Medicine, 1944-47.

Assistant Professor of Pharmacology, Yale University School of Medicine, 1947-48.

Professor of Pharmacology, Wayne University College of Medicine, 1948-53.

Associate Physician, Detroit Receiving Hospital, 1949-53.

Director of Education, Chairman of Intern Committee, Detroit Receiving Hospital, 1949-53.

Director of Biological Research, G. D. Searle & Co., 1953-70.

Lecturer, Department of Pharmacology, Northwestern University Medical School, 1954-67.

Director of Scientific and Professional Affairs, G. D. Searle & Co., 1970-74.

Lecturer in Pharmacology, University of Illinois College of Medicine, 1954-75.

Professor of Pharmacology, University of Illinois College of Medicine, 1976-.

Director; Drill, Prince, Kaye, Loomis & Shaffer, Inc., 1980-.

PROFESSIONAL SOCIETY MEMBERSHIPS

Alpha Omega Alpha.

American Association for the Study of Liver Diseases.

American Chemical Society, Division of Medicinal Chemistry.

American Fertility Society.

American Physiological Society.

American Society for Clinical Pharmacology and Therapeutics.

American Society for Pharmacology and Experimental Therapeutics.

International Society of Reproductive Medicine.

New York Academy of Sciences.

Pacific Coast Fertility Society.

Royal Society of Medicine.

Sigma Xi.

Society for Experimental Biology and Medicine.

Society of Toxicology.

HONORS

Distinguished Fellow, Society of Toxicology.

Fellow of the National Research Council, Northwestern University Medical School, 1942-43.

Fellow, New York Academy of Sciences.

Fellow, Royal Society of Medicine.

Honorary Member, International Family Planning Research Association.

Honorary Member, Pharmacology Society of Venezuela.

Jessup Fellow, Princeton University, 1941-42.

President, Society of Toxicology, 1972-73.

PROFESSIONAL ACTIVITIES

Member, Endocrine Panel, Cancer Chemotherapy National Service Center, National Cancer Institute, 1958-62.

Consultant, National Cancer Institute, 1965-67.

Member, Board of Directors, Barren Foundation, 1971-72.

Member, Drug Research Board, National Research Council-National Academy of Sciences, 1971-76.

Member, Organization Committee for the Symposium on the Future of Animal Cells, Models and Systems in Research, Development, Education and Testing, Institute of Laboratory Animal Resources, National Research Council-National Academy of Sciences, 1974-76.

Member, Science Advisory Board, National Center for Toxicological Research, 1975-76.

Member, Board of Directors, International Family Planning Research Association, 1969-79. (Vice-President, 1972-74.)

Co-Chairman, The Third Conference on Cutaneous Toxicity, (sponsored by the American Medical Association and Society of Toxicology), May 16-18, 1976, Washington, DC.

Co-Chairman, The Fourth Conference on Cutaneous Toxicity, (sponsored by the American Medical Association and Society of Toxicology), May 9-11, 1979, Washington, DC.

PUBLICATIONS: BOOKS

Drill, V.A., Editor, Pharmacology in Medicine, McGraw-Hill, New York.

First Edition, 1954

Second Edition, 1958

Drill's Pharmacology in Medicine, McGraw-Hill, New York, edited by J.R. DiPalma.

Third Edition, 1965

Fourth Edition, 1971

Drill, V.A., Oral Contraceptives, McGraw-Hill, New York, 1966.

Drill, V.A., Farmacologia Medica, La Prensa Medica Mexicana, Mexico, edited by J.R. DiPalma, 1968.

Trattato di Farmacologia di Drill, Piccin Editore, Padova, Italy, edited by J.R. DiPalma, Vols. 1 and 2, 1971.

PUBLICATIONS: BOOKS (continued)

A. Campos da Paz, V.A. Drill, M. Hayashi, W. Rodrigues and A.V. Schally, editors, Recent Advances in Human Reproduction, Proceedings of the First International Congress on Human Reproduction, Rio de Janeiro, Brazil, Nov. 11-14, 1974. Excerpta Medica ICS No. 370, Excerpta Medica, Amsterdam, 1976.

Drill, V.A., and P. Lazar, Cutaneous Toxicity, Academic Press, New York, 1977.

Drill, V.A., and P. Lazar, Current Concepts in Cutaneous Toxicity, Academic Press, New York, 1980.

PUBLICATIONS: PAPERS

Author or co-author of approximately 180 papers in the scientific literature. (Bibliography available upon request.)

PERSONAL DATA

Birth date: June 10, 1916

Married: September 14, 1940 (Ruth Craig)

Children: Craig A. (November 20, 1942)
Richard W. (March 15, 1945)
Gary A. (July 16, 1947)

August 1, 1980

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CURRICULUM VITAE
OF
DR. SEYMOUR L. FRIESS

EDUCATION

Bachelor of Arts (A.B.) degree, University of California at Los Angeles, 1943.

Master of Arts (M.A.) degree, University of California at Los Angeles, 1944.

Doctor of Philosophy (Ph.D.) degree, University of California at Los Angeles, 1947.

EMPLOYMENT

Research Chemist, Manhattan Engineering District, 1944-46.

Instructor, Department of Chemistry, University of Rochester, 1948-51.

Biosciences Research and Administration, Naval Medical Research Institute, 1951-79.
- Research Scientist; 1951-58.
- Head, Physical Biochemistry Division, 1958-65.
- Chairman, Physiological Sciences Department, 1965-70.
- Chairman, Environmental Biosciences Department, 1970-79.

Managing Director; Drill, Friess, Kaye, Loomis and Shaffer, Inc., 1980-.

PROFESSIONAL SOCIETY MEMBERSHIPS

American Chemical Society.

American Institute of Chemists.

International Society of Toxinology

Society of Toxicology

The Society of the Sigma Xi

Undersea Medical Society

Washington Academy of Sciences

HONORS

Adjunct Professor, Department of Pharmacology, Uniformed Services University of the Health Sciences, The Medical School, 1977-.

Honorary Chair, Institute of Biophysics, University of Brazil at Rio de Janeiro, as Chief of the Laboratory of Molecular Pharmacology, 1961-.

Phi Beta Kappa

Du Pont Fellow in Chemistry, 1946-47.

President, Society of Toxicology, 1975-76.

Member, Editorial Board, Toxicology and Applied Pharmacology, 1964-69; Associate Editor, 1970-79.

Member, Editorial Board, Toxicon, 1965-.

Member, Editorial Board, Toxic Substances Journal, 1978-.

Member, Editorial Board, Perspectives in Toxicology, 1979-.

Member, Scientific Advisory Board, Chemical Industry Institute of Toxicology, 1979-.

President, American Board of Toxicology, Inc., 1979-.

President, International Union of Toxicology, 1980-.

Distinguished Fellow Award, Society of Toxicology, 1981.

PROFESSIONAL ACTIVITIES

Member, Committee on Toxicology, Assembly of Life Sciences, National Academy of Sciences-National Research Council, 1967-76. (Vice-Chairman, 1968-71.)

Member and Chairman, Advisory Panels on Research Programs in Space Biology, National Aeronautics and Space Agency, 1970-75.

Member, Toxicology Information Program Committee, Assembly of Life Sciences, National Research Council-National Academy of Sciences, 1972-77. (Chairman, 1976-77.)

Member, Ad Hoc Advisory Committee on Carbon Monoxide, Department of Health, Education and Welfare, U.S. Public Health Service, Bureau of Community Environmental Management, 1972.

Chairman, Scientific Panel for the NASA Apollo-Soyuz Test Program, 1974-75.

PROFESSIONAL ACTIVITIES (continued)

Member, Environmental Protection Agency-National Academy of Sciences Advisory Committee on Tolerance for the Pesticide Leptophos, 1976.

Advisor, Sub-Committee on Program Development and Administration, Review Committee on the National Center for Toxicological Research, National Academy of Sciences-National Research Council, 1976-.

Member, Bureau of Biomedical Sciences (Consumer Product Safety Commission) Review Committee, National Academy of Sciences-National Research Council, 1977-78.

Liaison Representative, Department of Defense, to the Interagency Testing Committee, Advisory to the Administrator of the Environmental Protection Agency for the Toxic Substances Control Act, 1976-79.

PUBLICATIONS

Author or co-author of approximately 130 papers in the scientific literature. (Bibliography available upon request.)

AREAS OF SPECIAL INTEREST AND COMPETENCE

Toxicology of industrial and military chemicals; neuromuscular pharmacology and toxicology; enzyme kinetics and mechanisms of action; physiology and pathology of chemoreceptors; chemical kinetics; hazard assessment and safety evaluation; regulation of toxic substances; hyperbaric toxicology and physiology.

PERSONAL

Birth data:	July 1, 1922
Married:	July 11, 1953 (Mary Eugenia Tarver)
Children:	Philip L. (December 29, 1954) Martin C. (November 23, 1956)
Home address:	6522 Lone Oak Court Bethesda, MD 20034
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CURRICULUM VITAE

OF

DR. HARRY W. HAYS

EDUCATION

Bachelor of Science (B.S.) degree, Franklin & Marshall College, 1933.

Master of Science (M.S.) degree, Princeton University, 1937.

Doctor of Philosophy (Ph.D.) degree, Princeton University, 1938.

EMPLOYMENT

Research Pharmacologist, CIBA Pharmaceutical Company, 1939-48.

Associate Professor of Pharmacology, Wayne State University College of Medicine, 1948-57.

Director, Advisory Center on Toxicology, National Academy of Sciences-National Research Council, 1957-66.

Director, Pesticides Regulation Division, U.S. Department of Agriculture, 1966-70.

Staff Officer, National Program Staff, U.S. Department of Agriculture, 1970-80.

Director; Drill, Friess, Hays, Loomis & Shaffer, Inc., 1980-.

PROFESSIONAL SOCIETY MEMBERSHIPS

American Conference of Governmental Industrial Hygienists.

American Society of Pharmacology and Experimental Therapeutics.

Society for Experimental Biology and Medicine.

Society of Toxicology.

HONORS

Editor, Toxicology and Applied Pharmacology, 1959-60.

President, Society of Toxicology, 1964-65.

HONORS (continued)

Historian, Society of Toxicology, 1973-.

Merit Award, Society of Toxicology, 1977.

Distinguished Fellow Award, Society of Toxicology, 1980.

President, Toxicology Laboratory Accreditation Board, 1980-.

PROFESSIONAL ACTIVITIES

Member, Committee on Cutaneous Health and Cosmetics, American Medical Association, 1963-69. (Chairman, Legislative and Liaison Subcommittee, 1968-69.)

Member, Program Committee for Symposia on Cutaneous Toxicity, Society of Toxicology, 1968-79.

Member, Committee on Certification of Toxicologists and Accreditation of Laboratories, Society of Toxicology, 1973-79.

Member, Interagency Collaborative Group on Environmental Carcinogenesis, National Cancer Institute, 1973-79.

Member, Chemical Selection Working Group, National Cancer Institute, 1974-79.

Member, Human Studies Committee, U.S. Department of Agriculture, 1974-79.

Member, Technical Advisory Committee to U.S. Department of the Army on the demilitarization program, 1977-78.

Member, U.S. delegation to the Joint FAO/WHO/UNEP Conference on Mycotoxins, Nairobi, Kenya, 1977.

Chairman, Review Committee, Bureau of Biomedical Sciences, Consumer Products Safety Commission, 1977-78.

Member, Council on Accreditation, American Association for Laboratory Accreditation, 1980-.

PUBLICATIONS

Author or co-author of more than 75 scientific publications. (Bibliography available upon request.)

AREAS OF SPECIAL INTEREST AND COMPETENCE

Natural toxicants in food: food additives; toxicology of pesticides and industrial chemicals; regulation of pesticides; hazard assessment and safety evaluation.

PERSONAL

Birth date:	October 25, 1909
Married:	December 14, 1935 (Elsa C. Lutz)
Children:	Thomas Gregory
Home address:	3900 Watson Place Washington, DC 20016
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DR. TED A. LOOMIS

EDUCATION

Bachelor of Science (B.S.) degree, University of Washington, 1939.

Master of Science (M.S.) degree, University of Buffalo, 1941.

Doctor of Philosophy (Ph.D.) degree, University of Buffalo, 1943.

Doctor of Medicine (M.D.) degree, Yale University School of Medicine, 1946.

EMPLOYMENT

Intern, Marine Hospital, U.S. Public Health Service, Seattle, WA, 1946-47.

Assistant Professor, Department of Pharmacology, University of Washington School of Medicine, 1947-49.

Associate Professor, Department of Pharmacology, University of Washington School of Medicine, 1949-53.

Captain, U.S. Army Medical Corps (Active Duty), 1953-55.

Associate Professor of Pharmacology and State Toxicologist, University of Washington School of Medicine, 1955-57.

Professor of Pharmacology and State Toxicologist, University of Washington School of Medicine, 1957-76.

Professor of Pharmacology and Toxicology, University of Washington School of Medicine, 1976-.

Director; Drill, Prince, Hays, Loomis & Shaffer, Inc., 1980-.

PROFESSIONAL SOCIETY MEMBERSHIPS

American Society for Pharmacology and Experimental Therapeutics.

Society for Experimental Biology and Medicine.

Society of Toxicology.

Western Pharmacology Society.

HONORS

Diplomate, National Board of Medical Examiners.

Distinguished Fellow, Society of Toxicology.

President, Society of Toxicology, 1969-70.

President, Western Pharmacology Society, 1969-70.

Recipient, Toxicology Education Award, Society of Toxicology and Forum for Advancement of Toxicology, 1976.

PROFESSIONAL ACTIVITIES

Member, Committee on Tests for Intoxication, National Safety Council, 1951-.

Member, Editorial Board, Clinical Pharmacology and Therapeutics, 1960-.

Member, Agricultural Advisory Board on Pesticides and Insecticides, State of Washington, 1963-77.

Member, Advisory Committee on Protocols for Safety Evaluation, U.S. Food and Drug Administration, 1966-69.

Member, Advisory Committee, Pesticides Regulation Division, U.S. Department of Agriculture, 1966-70.

Member, Pharmacology-Toxicology Review Committee, National Institute of General Medical Sciences, National Institutes of Health, 1966-70.

Research Affiliate, Regional Primate Center, University of Washington, 1968-.

Member, Pharmacology-Toxicology Training Committee, National Institute of General Medical Sciences, National Institutes of Health, 1970-74.

Member, Committee for Identification of Research Needs in Water Supply, Engineering and Urban Health Sciences Study Section, Environmental Control Administration, Consumer Protection and Environmental Health Service, Public Health Service, U.S. Department of Health, Education, and Welfare, 1970.

Member, Advisory Committee to Review the Use of 2,4,5-T, Agricultural Research Service, U.S. Department of Agriculture, 1970-73.

Consultant, Criteria for a Recommended Standard: Occupational Exposure to Phenol, National Institute for Occupational Safety and Health, 1975.

PROFESSIONAL ACTIVITIES (continued)

Consultant, Criteria for a Recommended Standard: Occupational Exposure to Formaldehyde, National Institute for Occupational Safety and Health, 1974.

Member, Committee on Health Hazards of Pyrolysis Products of Polymers, National Materials Advisory Board, National Research Council-National Academy of Sciences, 1973-78.

Member, Committee on Chronic Toxicity Testing, Advisory Center on Toxicology, National Research Council-National Academy of Sciences, 1976.

Panelist, Committee on Marine Ecosystems Analysis (New York Bight Project), 1976-77.

Member, Advisory Board, Springer-Verlag Handbuch Series, 1973-.

Member, Editorial Board, Combustion Toxicology, 1975-.

Chairman, Committee for Peer Review of NASA Life Sciences Proposals, Pharmacology-Toxicology Section, American Institute of Biological Sciences, 1978.

Member, Committee on Sub-Chronic Toxicity Test Protocols, U.S. Environmental Protection Agency, 1979.

Member, Scientific Review Panel for Health Research, U.S. Environmental Protection Agency, 1980.

PUBLICATIONS: BOOKS

Essentials of Toxicology, Lea & Febiger, Philadelphia.

First Edition, 1968
Second Edition, 1974
Third Edition, 1978

PUBLICATIONS: PAPERS

Author or co-author of approximately 100 papers in the scientific literature. (Bibliography available upon request).

AREAS OF SPECIAL INTEREST AND COMPETENCE

Development of biological and chemical methodology for toxicity testing; clinical and forensic toxicology including evaluation of cause-effect relationships and interpretation of clinical analytical findings; development and presentation of special programs and instructional materials in toxicology for industry, educational institutions, and attorneys; effects of alcohol and drugs on automobile driving, including blood and breath tests for intoxication; animal and clinical drug and pesticide toxicology.

PERSONAL DATA

Birth date:	April 24, 1917
Married:	March 19, 1944 (Marion Adams)
Children:	Bonnie J. (November 15, 1946) Becky A. (December 7, 1953)
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DR. C. BOYD SHAFFER

EDUCATION

Bachelor of Science (B.S.) degree, Lebanon Valley College, 1938.

Doctor of Philosophy (Ph.D.) degree, Princeton University, 1941.

EMPLOYMENT

Senior Fellow, Chemical Hygiene Fellowship, Mellon Institute of Industrial Research, 1941-52.

Chief Industrial Toxicologist, Central Medical Department, American Cyanamid Company, 1952-58.

Director of Environmental Health, Central Medical Department, American Cyanamid Company, 1958-64.

Director of Toxicology, Central Medical Department, American Cyanamid Company, 1964-79.

Director of Corporate Toxicology, Environmental Services Division, American Cyanamid Company, 1979-80.

(Member of corporate Label Committee of American Cyanamid Company, 1957-80; Chairman, 1963-80.)

Director: Drill, Friess, Kaye, Loomis & Shaffer, Inc., 1980-.

PROFESSIONAL SOCIETY MEMBERSHIPS

American Industrial Hygiene Association.

American Society of Pharmacology and Experimental Therapeutics.

Society for Experimental Biology and Medicine.

Society of Toxicology.

The Society of the Sigma Xi.

HONORS

Adjunct Associate Professor of Environmental Medicine, Department of Environmental Medicine, New York University Medical Center, 1959-80.

HONORS (continued)

Chairman, Gordon Research Conference on Toxicology and Safety Evaluation, 1962.

Certified by the American Board of Industrial Hygiene, Inc., in the TOXICOLOGICAL ASPECTS of Industrial Hygiene.

President, Society of Toxicology, 1962-63.

Editor, Toxicology and Applied Pharmacology, 1965-67.

Distinguished Fellow Award, Society of Toxicology, 1980.

PROFESSIONAL ACTIVITIES IN TRADE ASSOCIATIONS

Chemical Manufacturers Association
(Formerly Manufacturing Chemists Association)

Labels and Precautionary Information Committee (Member since 1958; Chairman, 1965-67).

Intercommittee Task Group on Transportation Hazards, 1965. (Wrote, with input from the Group, the MCA Chem-Card Manual and the MCA Cargo Information Card Manual.)

Transportation Hazards Information Committee, 1967-69. (Wrote a proposal on Transportation Hazards Information System for submission to the U.S. Department of Transportation.)

Toxic Substances Control Group, 1971-76. (Chairman, 1972-76. Presented the MCA testimony on Toxic Substances Control legislation before Committees of both Houses of Congress during the three sessions of Congress over which this legislation was considered.)

Chemical Regulations Advisory Committee, 1976-77 (Chairman).

National Agricultural Chemicals Association

Environmental Advisory Committee (Chairman, 1973-74).

PROFESSIONAL ACTIVITIES IN GOVERNMENT

Member, Committee on Toxicology, National Academy of Sciences-National Research Council, 1969-75.

PROFESSIONAL ACTIVITIES IN GOVERNMENT (continued)

Member, Standards Advisory Committee for Hazardous Materials Labeling, 1974-75. (Convened by the Occupational Safety and Health Administration of the U.S. Department of Labor.)

Advisor on numerous occasions, 1972-78, to the Delegation from the U.S. Department of Transportation to meetings of the Group of Rapporteurs on the Packaging of Dangerous Goods of the Committee of Experts on the Transport of Dangerous Goods. (Meetings held semi-annually in Geneva, Switzerland, under the auspices of the Economic and Social Council of the United Nations.)

PUBLICATIONS

Author or co-author of approximately 40 papers in the scientific literature. (Bibliography available upon request.)

AREAS OF SPECIAL INTEREST AND COMPETENCE

Research design; toxicology of synthetic organic industrial chemicals; toxicology of synthetic organic pesticides; safety evaluation; precautionary labeling of hazardous industrial chemicals; precautionary labeling of household products under the Federal Hazardous Substances Act; precautionary labeling of pesticides under the Federal Insecticide Fungicide, and Rodenticide Act; regulation of chemicals under the Toxic Substances Control Act; transportation of hazardous materials; preparation, submission, and follow-up of food additive petitions.

PERSONAL

Birth date:	August 18, 1917
Married:	June 14, 1941 (Mary Louise Stoner)
Children:	Edward S. (November 20, 1942) William A. (December 17, 1945)
Home address:	2370 NE Ocean Blvd. A-302 Stuart, FL 33494 2660 Pennsquid Court Annapolis, MD 21401
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August 1, 1980

MONS 222135

CURRICULUM VITAE

[redacted]nevieve Elizabeth Matanoski (Nee Murray)

[redacted]cial Security No.: 034-22-2128

[redacted]ace of Birth: Salem, Massachusetts Date of Birth: August 26, 1930

[redacted]ucation: Punchard High School, Andover, Mass., 1947
Radcliffe College, Cambridge, Mass., 1947-1951
Johns Hopkins School of Medicine, Baltimore, Md., 1951-1955
Johns Hopkins School of Hygiene & Public Health, Baltimore, Md., 1960-1964

Degrees: Radcliffe College, A.B. in Chemistry, 1951
Johns Hopkins School of Medicine, M.D., 1955
Johns Hopkins School of Hygiene & Public Health, M.P.H. 1962; Dr.P.H. 1964
Research Presentation for degree of Doctor of Medicine, "Primary Biliary Cirrhosis in Children and Adults"
Certified a Specialist in General Preventive Medicine by the American Board of Preventive Medicine, December 1973
Fellow of the American College of Preventive Medicine, April 28, 1975

Honors: Member of the Alpha Chapter of the Delta Omega Honorary Society, May 1960

Genevieve M. Matanoski, M.D., Dr.P.H.
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School of Hygiene & Public Health
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POSITIONS:

Professor:
Johns Hopkins School of Hygiene & Public Health
July 1, 1976 to present

Associate Professor:
Johns Hopkins School of Health Services
September 1973-June 1978

Associate Professor:
University of Maryland Dental School
October 1970 to present

Coordinator & Evaluator of Special Projects:
Evaluation & Biostatistics Center of the
Regional Medical Program
March 1970 to 1973

Associate Professor:
Department of Preventive Medicine
University of Maryland
1970 to present

Associate Professor of Epidemiology
Johns Hopkins School of Hygiene & Public Health
July 1, 1969 to present

Instructor in Department of Preventive Medicine:
University of Maryland
1967-1969

Training Fellowship in Public Health:
Johns Hopkins School of Hygiene & Public Health
1962-1964

Assistant Professor of Epidemiology:
Johns Hopkins School of Hygiene & Public Health
1964-1969

Instructor in Epidemiology
Johns Hopkins School of Hygiene & Public Health
1959-1964

Pediatrician Out-Patient Department:
Johns Hopkins Hospital
1957 to present

Research Assistant in Epidemiology:
Johns Hopkins School of Hygiene & Public Health
1957-1959

Assistant Resident in Pediatrics:
Johns Hopkins Hospital
1956-1957

Intern in Pediatrics
Johns Hopkins Hospital
1955-1956

Research Assistant
Johns Hopkins School of Medicine
1955

CURRICULA VITAE

CATEGORY II TEAM

MONS 222138

CURRICULUM VITAE

Alvito Peter Alvares, Ph.D.

Personal:

Born: December 25, 1935: Bombay, India
Citizenship: U.S.A.
Married: two children

Education:

University of Bombay, India, 1951-1958
B.Sc. Degree: Major in Chemistry: Minor in Physics, 1955
B.Sc.(Tech) Degree: in Chemical Technology, 1957
University of Detroit, 1958-1960:
M.S. Degree: Major in Biochemistry: Minor in Chemistry, 1961
University of Chicago, 1960-1965
Ph.D. Degree: Pharmacology, 1966

Present Address

Department of Pharmacology
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, Maryland 20814
Telephone: (202) 295-3226

Appointments:

1. Post-doctoral Fellow: Department of Pharmacology, University of Minnesota Medical School, Minneapolis, Minn. 1965-1967.

2. Senior Research Biochemist: Wellcome Research Laboratories, Burroughs Wellcome and Co., Tuckahoe, N.Y. 1967-1970.

3. Research Associate: The Rockefeller University, New York, N.Y. 1970-1971.

4. Assistant Professor: The Rockefeller University, New York, N.Y. 1971-1975.

5. Assistant Professor: Department of Pharmacology, Cornell University Medical College, New York, N.Y. 1972-1975.

6. Adjunct Associate-Professor: Department of Pharmacology, Cornell University Medical College, New York, N.Y. 1975-1977.

7. Associate Professor: The Rockefeller University, New York, N.Y. 1975-1977.

8. Adjunct Professor: The Rockefeller University, New York, N.Y. 1977-1978.

9. Associate Professor: Department of Pharmacology, Uniformed Services University of the Health Sciences, Bethesda, Maryland. 1977-1978.

10. Professor: Department of Pharmacology, Uniformed Services University of the Health Sciences, Bethesda, Maryland. 1978-present.

B. Awards:

Irma T. Hirschl Scholar, 1974-1978
National Institutes of Health Career Development Award

C. Professional Societies:

Sigma Xi
American Association for the Advancement of Science
New York Academy of Sciences
American Society of Pharmacology and Experimental Therapeutics
American Society of Biological Chemists
American Society for Clinical Pharmacology and Therapeutics
Toxicology Section, International Union of Pharmacology (IUPHAR)
Society of Toxicology

D. Medical School and University Activities:

1. Lectures in Medical Pharmacology Course
2. Minicourse in Toxicology for 2nd year medical students
3. Graduate Student Advisory Committee
4. Member: Faculty Senate, 1978-80
5. Chairman: Grievance Committee, Faculty Senate, 1979-80
6. Member: Research Proposal Merit Review Committee, 1979-82.
7. Member: Biohazards, Controlled Substances, and Dangerous Materials Committee, 1981-84.

E. Graduate Students and Theses:

Julia L. Zieman. "Alterations in heme catabolism induced by gold." 1979.

F. Memberships:

1. Member, Steering Committee, Biochemical Pharmacology Discussion Group, New York Academy of Sciences, 1975-1977.

2. Ad hoc reviewer for Biochemical Pharmacology, Molecular Pharmacology, Life Sciences, Science, Clinical Pharmacology and Therapeutics, and Journal of Pharmacology and Experimental Therapeutics.

3. Member, Workgroup of the National Commission on Digestive Diseases, 1977-1978.

4. Member, Editorial Boards:

Clinical Pharmacology and Therapeutics
Pharmacology
Journal of Environmental Pathology and Toxicology

G. Participant (Invited Speaker)

1. First International Symposium in Microsomes and Drug Oxidations, Bethesda, Maryland, 1968.

2. International Symposium on Drug Tolerance, Addiction, Abuse and Methadone Treatment, New Orleans, Louisiana, 1971.

3. Second International Symposium on Microsomes and Drug Oxidations, Stanford, California, 1972.

4. IUB Symposium: Reaction Mechanisms of Cytochrome P-450 and Related Enzymes, Stockholm, Sweden, 1973.

5. Upjohn Conference on Hypnotics and Sedatives, Kalamazoo, Michigan, 1974.

6. European Society of Pediatric Endocrinology, Annual Meeting, Berlin, West Germany, 1975.

7. Third International Symposium on Microsomes and Drug Oxidations, Berlin, West Germany, 1976.

8. Gordon Research Conference - Drug Metabolism, Plymouth, New Hampshire, 1976.

9. Fourth Deer Lodge Conference on Clinical Pharmacology, Flathead Lake Lodge, Montana, 1976.

10. Gordon Research Conference - Toxicology, Kimball Union Academy, New Hampshire, 1977.

11. Symposium on Drug Disposition in Man, Sarasota, Florida, 1977.

12. Symposium on Influence of Nutritional Factors on Toxicology, International Congress of Pharmacology, Paris, France, 1978.

13. Symposium on Assessment of Drug Metabolism in Man, Rousseau, France, 1978.

14. International Conference on Critical Current Issues in Environmental Health Hazards, Tel-Aviv, Israel, 1979.

15. Seventh European Workshop in Drug Metabolism, Zurich, Switzerland, 1980.

16. Workshop on the Combined Effects of Xenobiotics, National Research Council, Ottawa, Canada, 1981.

17. Gordon Conference on Food and Nutrition, 1982.

PUBLICATIONS:

McKusick VA, Murray GE, Peeler RC, Webb CM: Musical murmurs, Bull of Johns Hopkins Hospital 97:136, 1955

Price WH, Matanoski GM, Morrison O, Prewer A, Wagner G: The fractionation of seromucoids from human serum. Bull of Johns Hopkins Hosp. 108:227, 1961

Price WH, Matanoski GM, Prewer A, Rector L: Seromucoid fraction patterns of individuals with pneumonia or leukemia. J General Physiology 45-205, 1962

Matanoski GM, Price WH, Ferencz C: Epidemiology of streptococcal infections in rheumatic and non-rheumatic families. I. Objectives, plan of study, and comparative frequency of streptococcal isolations. Amer. J. Epid. 87:179-189, 1968

Matanoski GM, Price WH, Ferencz C: Epidemiology of streptococcal infections in rheumatic and non-rheumatic families. II. The inter-relationship of streptococcal infections to age, family transmission and type of Group A. Amer. J. Epid. 87:190-206, 1968

Matanoski GM, Price WH, Ferencz C: Epidemiology of streptococcal infections in rheumatic and non-rheumatic families. III. Comparison of the immune response to streptococcal infections in the two populations. Amer. J. Epid. 87:207-225, 1968

Matanoski GM, Price WH, Ferencz C: Epidemiology of streptococcal infections in rheumatic and non-rheumatic families. IV. The effect of tonsillectomy on streptococcal infections. Amer. J. Epid. 87:226-236. 1968

Matanoski GM: The role of the tonsils in streptococcal infections: A comparison of tonsillectomized children and sibling controls. Amer. J. Epid. 95:278-291, 1972

Matanoski GM, Seltser R, Sartwell PE, Diamond EL, Elliott EA: Changing trends in mortality of specialists and U.S. white males. Proceedings and abstracts of papers presented at the seventh annual meeting of the Society for Epidemiologic Research, Berkeley, California, June 19-22, 1974

Ringelberg ML, Matanoski GM, Kimball AW: Dental caries-experience in three generations of families. Journal of Public Health Dent 34:3, pages 174-180, summer 1974

Matanoski GM, Seltser R, Sartwell PE, Diamond EL, Elliott EA: The current mortality rates of radiologists and other physician specialists: Deaths from all causes and cancer. Amer. J. Epid. 101:3, 188-198, March 1975

Matanoski GM, Seltser R, Sartwell PE, Diamond EL, Elliott EA: The current mortality rates of radiologists and other physician specialists: Specific causes of death. Amer. J. Epid. 101:3, 199-210, March 1975

Matanoski GM, Sartwell PE, Elliott EA: Letter: Hodgkin's disease mortality among physicians. Lancet 1:926, 1975

Matanoski GM, Landau E, Elliott E: Epidemiology Studies - Pilot Study of Cancer Mortality Near a Chemical Plant and Other Industries in Baltimore, U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, D.C. 20460, May 1976, Final Report

Matanoski GM, Henderson MM, Stine OC, Courpas C, Hepner R, Walker S: The effectiveness of phonocardioscan screening for the detection of heart disease in school-age children. AJP 67:7, 609-611, July 1977

Matanoski GM, Landau E, Elliott E: "Progress in a Community Arsenic Study" in Toxic Substances in the Air Environment. Air Pollution Control Association, Pittsburgh, 1977

Kaszuba AL, Matanoski GM, Gibson G: Evaluation of the Emergency Department as a Site for Hypertension Screening. JACEP 7:2, pages 51-58, February 1978

Mak H, Flynn JPG, Matanoski GM: Do Administrative Guidelines Modify the Application and Clinical Benefit of Home Oxygen? Abstract. American Review of Respiratory Disease, Supplement 119-4, April 1979

H. Areas of Scientific Interest:

(a) Factors influencing the metabolism and action of drugs, environmental chemicals and carcinogens.

(b) Interactions between nutritional factors and drug metabolism.

(c) Biochemical and toxicological effects of environmental chemicals and carcinogens.

(d) Heavy metal toxicity.

(e) Effects of foreign chemicals on heme biosynthesis and heme metabolism.

(f) Microsomal hemeproteins: differences in composition and turnover rates; regulation by drugs, chlorinated hydrocarbons and carcinogens.

ALVITO PETER ALVARES

List of Publications:

1. Alvares, A. P.: Utilization of wastes and by-products of the fatty oil industry. Bombay Technologist, 8: 1-4, 1957.

2. Harber, L. H., A. P. Alvares, A. I. Jacobson and W. J. Visek: Effect of barbituric acid and chlortetracycline upon growth, ammonia concentration and urease activity on the gastrointestinal tract of chicks. Journal of Nutrition, 80: 1-8, 1963.

3. Alvares, A. P., L. H. Harber and W. J. Visek: Effect of barbituric acid, chlortetracycline and carbohydrates upon growth and gastrointestinal urease activity of chicks. Journal of Nutrition, 82: 93-98, 1964.

4. Alvares, A. P., R. P. Hendrickson and W. J. Visek: Effects of isoniazid, chlortetracycline and copper upon growth and gastrointestinal urease activity of chicks. Journal of Nutrition, 83: 79-83, 1964.

5. Hendrickson, R. P., A. P. Alvares and W. J. Visek: Effects of chlortetracycline and isoniazid on body weight gain and intestinal urea hydrolysis of rats. Journal of Nutrition, 84: 65-70 1964.

6. Kabara, Jon J., A. P. Alvares, C. Riegel and J. T. McLaughlin: Brain cholesterol X: Effect of scheduling on the sterol lowering capability of methylphenidate (Ritalin). Proceedings of the Society of Experimental Biology and Medicine, 120: 37-41, 1965.

7. Anders, M. W., A. P. Alvares, and G. J. Mannering: Inhibition of drug metabolism. II: Metabolites of 2-diethylaminoethyl 2,2-diphenylvalerate HCl (SKF 525-A). Molecular Pharmacology, 2: 328-334, 1966.

8. Alvares, A. P., G. R. Schilling, W. Levin and R. Kuntzman: Studies on the induction of CO-binding pigments in liver microsomes by phenobarbital and 3-methylcholanthrene. Biochemical and Biophysical Research Communications, 29: 521-526, 1967.

9. Alvares, A. P., G. R. Schilling and R. Kuntzman: Differences in the kinetics of benzpyrene hydroxylation by hepatic drug-metabolizing enzymes from phenobarbital and 3-methylcholanthrene-treated rats. Biochemical and Biophysical Research Communications, 30: 588-593, 1968.

Matanoski GM, Seltser R, Sartwell PE, Diamond E, Elliott E: Risks of Radiologists Over Seven Decades. Abstract presented at SER Meeting, New Haven, Connecticut, 1979

Matanoski GM, Payton AJ: A Cohort Study of Cancer Mortality in Virologists. Abstract presented at the First Annual NIOSH Scientific Symposium 1978. Toxicological & Carcinogenic Health Hazards in the Workplace. Pathotox publishers, 1979

Sandler DP, Matanoski GM, Comstock GW: Health Consequences of Nasopharyngeal Radium Irradiation. Abstract presented at SER meeting, New Haven, Connecticut, June 1979. Amer. J. Epid. 110:3, page 358, September 1979

Matanoski GM, Landau E, Tonascia J, Lazar C, Elliott EA, McEnroe W, Keating R, Seifter J: Lung Cancer/Mortality in Proximity to a Pesticide Plant. EPA 560/11-80-013 (Epidemiology Studies), U.S. Environmental Protection Agency, Washington, D.C., March 1980 (an interim report)

Mak H, Flynn JPG, Matanoski GM: Do Clinical Guidelines Modify the Application and Benefit of Home Oxygen? Maryland State Medical Journal by the Medical and Chirurgical Faculty of the State of Maryland, Baltimore, Maryland, March 1980

Ferencz C, Matanoski GM, Wilson PD, Rubin JD, Neill CA, Gutberlet R: Maternal Hormone Therapy and Congenital Heart Disease. Teratology 21:2. 225-239, April 1980

Massey RM, Crochetiere CA, Matanoski GM: Hematologic Values in Benzene Exposed Workers. Journal of Environmental Pathology and Toxicology 5:2. 515-521, Pathotox, January 1981

Matanoski GM, Billings CE, Levine MS, Lees PJ, Elliott EA: Investigation of Health Hazards in the Painting Trades Industry Report. Unpublished report to NIOSH, The Johns Hopkins University, School of Hygiene and Public Health, Baltimore, Maryland, January 1980

Matanoski GM, West S: Occupation and Environmental Exposures and the Risk of Congenital Heart Defects. Abstract presented at SER Meeting, Minneapolis, Minnesota, June 1980

Alter MJ, Gerety RJ, Sampliner RE, Smallwood L, Tabor E, Matanoski GM, Nathanson N: Community Acquired Non-A- Non-B Hepatitis. Abstract presented at SER Meeting, Minneapolis, Minnesota, June 1980

Sandler D, Matanoski GM, Comstock G, Mitchell T: Health Consequences of the Nasopharyngeal Radium Exposure. Symposium on Biologic Effects, Imaging Techniques and Dosimetry of Ionizing Radiation. HHS Publication (FDA) 80-8126

Sandler DP, Comstock GW, Matanoski GM: Neoplasms Following Low-Dose Radium Irradiation of the Nasopharynx. Submitted to JNCI, September 1980

Some Metals and Metalic Compounds. International Agency for Research on Cancer Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 23, Julliet, 1980

Matanoski GM: Risk of Cancer Associated with Occupational Exposure in Radiologists and Other Radiation Workers. Proceedings of the 1980 International Symposium on Cancer, September 14-18, 1980. Cancer - Achievements, Challenges and Prospects for the 1980s, Volume 1:241-254, Grune and Stratton, 1981

Matanoski GM, Landau E, Tonascia J, Lazar C, Elliott EA, McEnroe W, King K: Cancer Mortality in an Industrial Area of Baltimore. Environmental Research 25:8-28, 1981

Matanoski GM, Elliott EA: Bladder Cancer Epidemiology. Epidemiologic Reviews Vol. 3: 1981 (In Press)

CONSULTANT ACTIVITIES:

Periodontal Diseases Advisory Committee, National Institute of Dental Research, January 1975-June 30, 1978

Subcommittee on Adult Health, Medical and Chirurgical Faculty of the State of Maryland, September 1975-June 1978

Program Development Board, American Public Health Association, 1977-1978

Food and Drug Administration Biometric and Epidemiological Methodology Advisory Committee, Bureau of Drugs, HEW Rockville, Maryland, November 1978-January 1978

Air Quality Control Advisory Council, Maryland State Department of Mental Hygiene, March 1978-present

Technical Panel on Environmental Hazards, American Public Health Association, 1978-1981

Center for Disease Control, Beryllium Meeting, Atlanta, Georgia, October 1978

Central Maryland Health Systems, Chairman, Technical Advisory Group on Maternal & Child Health, November 1978-1979

Craniofacial Anomalies Program, NIDR, HEW, December 1978

Symposium on Potentiation of Immune Response to Vaccines, NIAID, NIH, February 1979

U.S. Army Environmental Hygiene Agency, Residency Advisory Committee, Edgewood Arsenal, Maryland, 1978-present

Food and Drug Administration, Anesthetic & Life Support Drugs Advisory Committee, March 1979-1982

Human Health Studies Program, Division of Biomatric and Environmental Research, Dept. of Energy

Special Committee: Consultant to prepare a special report for HEW Secretary Califano - Review experimental and epidemiological data on the carcinogenicity of beryllium. Center for Disease Control, Atlanta, Georgia, October 9, 1978

CONSULTANT AND MEMBER:

Science Projection Paper Committee, CSR, Inc.
Public Meeting - A Proposed Federal Radiation Research Agenda -
held in the Jack Masur Auditorium, Clinical Center, NIH,
Bethesda, Maryland, March 10-11, 1980

Member ofthe Preventive Medicine and Public Health Test Committee
of the National Board of Medical Examiners, 1980-1984

Member of the International Agency for Research on Cancer (IARC)
Working Group on the Evaluation of the Carcinogenic Risk of Chemicals
to Humans: Some Metals. World Health Organization, Lyon, France,
October 23-30, 1979

Member of the AUA Review Committee for the Radiological and Environmental
Research Division, Argonne National Laboratory, July 1, 1980-June 30, 1983

Participant in the 1980 International Symposium on Cancer presented by
Sloan-Kettering Cancer Center with the American Cancer Society and the
National Cancer Institute, New York, New York
Conference entitled: "Cancer 1980: Achievements, Challenges, Prospects"
Dr. Matanoski Lecture: "Risk of Cancer Associated with Occupational
Exposure in Radiologists and Other Radiation Workers"
September 14-18, 1980

Participant and discussant in the joint U.S.A.-Commision of the European
Countries Seminar on Ambient and Biological Monitoring, Luxembourg,
December 8-12, 1980

Member of the Medical Radiation Advisory Committee, Bureau of Radiological
Health, 1981-

PROFESSIONAL SOCIETIES:

American Association for the Advancement of Science
American Public Health Association
New York Academy of Sciences
Society for Epidemiological Research
International Epidemiological Association
Association of Teachers of Preventive Medicine
American College of Preventive Medicine

RESEARCH INTERESTS:

Cancer risks from occupational and environmental exposures to radiation and other agents; evaluation of health programs; family-based population studies; dental disease; especially oral cancer and the role of immunology in periodontal disease; rheumatic fever and streptococcal infections; infant mortality and congenital malformations.

CURRENT RESEARCH:

Epidemiolgy of infant mortality and congenital malformations; survival rates following diagnosis of oral cancer-relation to type; factors associated with risk of oral cancer; physician mortality in relation to radiation exposure; cancer mortality in virologists and veterinarians; occupational risk from exposure to dyes and synthetic rubber; health hazards from paint application; etiological factors in multiple myeloma; environmental risks from exposure to arsenic ; the effects of exposure to low-levels of radiation in a population of shipyard workers.

10. Alvares, A. P., G. Schilling, W. Levin and R. Kuntzman: Alteration of the microsomal hemoprotein by 3-methylcholanthrene: Effects of ethionine and actinomycin D. Journal of Pharmacology and Experimental Therapeutics, 163: 417-424, 1968.

11. Levin, W., A. P. Alvares, M. Jacobson, and R. Kuntzman: Effect of storage of frozen liver microsomal preparations on the hydroxylation of testosterone and pentobarbital and the N-demethylation of ethylmorphine. Biochemical Pharmacology, 18: 883-889. 1969.

12. Kuntzman, R., W. Levin, G. Schilling and A. P. Alvares: The effects of 3-methylcholanthrene and phenobarbital on liver microsomal hemoproteins and on the hydroxylation of benzpyrene. In Microsomes and Drug Oxidations, Academic Press, New York, 349-363, 1969.

13. Alvares, A. P., G. Schilling, W. Levin, R. Kuntzman, L. Brand and L. C. Mark: Cytochrome P-450 and b_5 in human liver microsomes. Clinical Pharmacology and Therapeutics, 10: 655-659, 1969.

14. Alvares, A. P., G. Schilling, A. Garbut and R. Kuntzman: Studies on the hydroxylation of 3,4-benzpyrene by hepatic microsomes: Effect of albumin on the rate of hydroxylation of 3,4-benzpyrene. Biochemical Pharmacology, 19: 1449-1455, 1970.

15. Alvares, A. P. and G. J. Mannering: Two-substrate kinetics of drug-metabolizing enzyme systems of hepatic microsomes. Molecular Pharmacology, 6: 206-212, 1970.

16. Levin, W., A. P. Alvares and R. Kuntzman: Distribution of radioactive hemoprotein and CO-binding pigment in rough and smooth endoplasmic reticulum of rat liver. Archives of Biochemistry and Biophysics, 139: 230-235, 1970.

17. Alvares, A. P., G. Schilling and W. Levin: Species differences in the induction of microsomal hemoprotein and 3,4-benzpyrene hydroxylase by phenobarbital and 3-methylcholanthrene. Journal of Pharmacology and Experimental Therapeutics, 175: 4-11, 1970.

18. Rubin, E., C. S. Lieber, A. P. Alvares, W. Levin and R. Kuntzman: Ethanol binding to hepatic microsomes: Its increase by ethanol consumption. Biochemical Pharmacology, 20: 229-232, 1971.

19. Alvares, A. P., G. Schilling, and R. Kuntzman: Alteration in the microsomal hemoprotein and the kinetics of 3,4-benzpyrene hydroxylase induced by 3-methylcholanthrene: Time course study and effects of puromycin. Life Sciences, 10: 129-136, 1971.

20. Kuntzman, R., A. P. Alvares and M. Levin: Effects of inducers of liver microsomal enzymes on the composition of microsomal hemoprotein. Advances in Cytopharmacology, Vol. I, Eds. F. Clementi and B. Ceccarelli, Raven Press, N. Y., pps. 241-248, 1971.

21. Alvares, A. P., G. Schilling, M. Levin and R. Kuntzman: Inability of substrates to alter the carbon monoxide and ethyl isocyanide difference spectra of microsomal hemoprotein. Journal of Pharmacology and Experimental Therapeutics, 176: 1-10, 1971.

22. Mitani, F., A. P. Alvares, S. Sasse and A. Kappas: Preparation and properties of a solubilized form of cytochrome P-450 from chick embryo liver microsomes. Molecular Pharmacology, 7: 280-292, 1971.

23. Levin, W., R. Kuntzman, A. P. Alvares and A. H. Conney: Chromatography of radioactive microsomal hemoproteins on diethylaminoethyl cellulose. Molecular Pharmacology, 7: 500-510, 1971.

24. Mitani, F., R. Winchester, A. P. Alvares, A. Poland and A. Kappas: Interaction of cytochrome P-450 with antibodies raised against a solubilized P-450 preparation from hepatic microsomes. Molecular Pharmacology, 7: 689-696, 1971.

25. Alvares, A. P. and A. Kappas: Influence of phenobarbital on the metabolism and analgesic effect of methadone in rats. Journal of Laboratory and Clinical Medicine, 79: 439-454, 1972.

26. Levin, W., A. H. Conney, A. P. Alvares, I. Merkatz and A. Kappas: Induction of benzo(a)pyrene hydroxylase in human skin. Science, 176: 419-420, 1972.

27. Alvares, A. P. and A. Kappas: The influence of phenobarbital on the in vitro and in vivo metabolism of methadone in rats. In Drug Addiction: Experimental Pharmacology, Vol. 1, Futura Publishing Co., Mt. Kisco, N. Y., pps. 191-198, 1972.

28. Alvares, A. P., S. Leigh, J. Cohn and A. Kappas: Lead and methyl mercury: Effects of acute exposure on cytochrome P-450 and the hepatic mixed function oxidase system. Journal of Experimental Medicine, 135: 1408-1409, 1972.

29. Walsh, R. H., B. Gemmi, A. P. Alvares and A. H. Conney: Effect of enzyme induction on the metabolism of benzo(a)pyrene and 3'-methyl-4-monomethylaminoazobenzene in the pregnant and fetal rat. Cancer Research, 32: 973-978, 1972.

30. Bickers, D. R., L. C. Harber, A. Kappas and A. P. Alvares: Polychlorinated biphenyls: Comparative effects of high and low chlorine-containing Aroclors on hepatic mixed function oxidase. Research Communications in Chemical Pathology and Pharmacology, 1: 505-512, 1972.

31. Alvares, A. P., C. J. Parli and G. J. Mannering: Induction of drug-metabolism. VI. Effects of phenobarbital and 3-methylcholanthrene administration on N-demethylating enzyme systems of rough and smooth hepatic microsomes. Biochemical Pharmacology, 22: 1037-1045, 1973.

32. Alvares, A. P., A. Kappas, W. Levin and A. H. Conney: Inducibility of benzo(a)pyrene hydroxylase in human skin by polycyclic hydrocarbons. Clinical Pharmacology and Therapeutics, 14: 30-40, 1973.

33. Alvares, A. P., A. Kappas, W. Levin and A. H. Conney: Induction of aryl hydrocarbon hydroxylase in human skin. In Microsomes and Drug Oxidations. Eds. R. W. Estabrook, J. R. Gillette and E. C. Leibman, Williams and Wilkins Co., Baltimore, Md., pps. 386-390, 1973.

34. Bradlow, H. L., B. Zumoff, D. K. Fukushima, L. Hellman, D. R. Bickers, A. P. Alvares and A. Kappas: Drug-induced alterations of steroid hormone metabolism in man. Annals of the New York Academy of Sciences, 212: 148-154, 1973.

35. Alvares, A. P., D. R. Bickers and A. Kappas: Polychlorinated biphenyls: A new type of inducer of cytochrome P-448 in the liver. Proceedings of the National Academy of Sciences, 70: 1321-1325, 1973.

36. Alvares, A. P. and P. Siekevitz: Gel electrophoresis of partially purified cytochromes P-450 from liver microsomes of variously-treated rats. Biochemical and Biophysical Research Communications, 54: 923-929, 1973.

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55. Conney, A. H., E. J. Pantuck, K.-C. Hsiao, W. A. Garland, K. E. Anderson, A. P. Alvares and A. Kappas: Enhanced phenacetin metabolism in human subjects fed charcoal-broiled beef. Clinical Pharmacology and Therapeutics, 20: 633-642, 1976.

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60. Alvares, A. P. and A. Kappas: The inducing properties of polychlorinated biphenyls (PCBs) on hepatic monooxygenases. In Proceedings of the 4th Deer Lodge Conference on Clinical Pharmacology, Clincal Pharmacology and Therapeutics, 22: 807-816, 1977.

61. Kappas, A., A. P. Alvares, K. E. Anderson, W. A. Garland, E. J. Pantuck and A. H. Conney: The regulation of human drug metabolism by nutritional factors. In Proceedings of the Third International Symposium on Microsomes and Drug Oxidations, Pergamon Press, N. Y. 703-708, 1977.

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73. Alvares, A. P., A. Kappas, K. E. Anderson, E. J. Pantuck and A. H. Conney: Nutritional factors regulating drug biotransformation in man. In Advances in Pharmacology and Therapeutics, Vol. 8, Ed., C. Olive, Pergamon Press, N. Y. pp. 43-51, 1979.

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75. Sasea, S., A. Kappas, S. E. Bernstein and A. P. Alvares: Heme biosynthesis and drug metabolism in mice with hereditary hemolytic anemia: Heme oxygenase induction as an adaptive response for maintaining cytochrome P-450 in chronic hemolysis. Journal of Biological Chemistry, 254: 729-735, 1979.

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80. Kiesman, J. L., and A. P. Alvares: Heme metabolism in the feto-placental unit and neonatal livers during lactation. Effect of gold sodium thiomalate. Journal of Pharmacology and Experimental Therapeutics, 214: 250-256, 1980.

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83. Conney, A. H., E. J. Pantuck, C. B. Pantuck, J. G. Fortner, A. P. Alvares, K. E. Anderson and A. Kappas: Variability in human drug metabolism. In Proceedings of the World Conference on Clinical Pharmacology and Therapeutics, pp. 51-62, Macmillan Publishers, London, 1980.

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87. Eisenmann, J. L., J. von B. and A. P. Alvares: The effect of honeybee (*Apis Millifera*) venom on the course of adjuvant-induced arthritis and depression of drug metabolism in the rat. Biochemical Pharmacology, in press.

88. Alvares, A. P., T. -H. Ueng and J. L. Eisenmann: Polychlorinated biphenyls inducible monooxygenases in rabbits and mice: Species and organ specificities. Life Sciences, in press.

89. Alvares, A.P.: Oxidative biotransformation of drugs. In The Liver: Biology and Pathobiology, Eds: I. Arias, H. Popper, P. Schachter, and D. Shafritz. Raven Press, New York. In press.

June 9, . .

CURRICULUM VITAE

NAME:	Philip E. Enterline		
BIRTHDATE:	4/25/21		
BIRTHPLACE	Kittanning, PA		
CITIZENSHIP:	U.S.A.		
SOCIAL SECURITY NUMBER:	181-14-5618		
BUSINESS ADDRESS:	A315 Crabtree Hall, GSPH 130 DeSoto Street Pittsburgh, PA 15261	TELEPHONE:	412/624-3018
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EDUCATION AND TRAINING

Undergraduate

1938-42	Westminster College	BBA (1942)	Economics

Graduate

1948-54	American University	MA (1954)	Statistics
1955-60	American University	Ph.D. (1960)	Demography (Dr. Frank Lorimer

APPOINTMENTS AND POSITIONS

Academic

1960-65	American University	Professorial Lecturer
1965-67	McGill University	Professor of Medical Statistics
1967 - date	University of Pittsburgh	Professor of Biostatistics
1975	University of Michigan	Faculty, Summer Session on Health Care Organization

Non-Academic Positions

1942-45	U.S. Army
1945-50	U.S. Public Health Service Statistician

1950-54	U.S. Public Health Service	Asst. Chief Program Analysis Section Tuberculosis and Chronic Diseases
1954-59	"	Chief Statistician Heart Disease Control Program
1959-61	"	Chief, Morbidity and Health Statistics Branch, Public Health Methods
1961-65	"	Chief, Biometrics and Social Studies Branch, Occupational Health

MEMBERSHIP in PROFESSIONAL ORGANIZATIONS

1946 - present	American Public Health Association
1946 - present	American Statistical Association (Treasurer Pgh. Chapter 1972-74 Council Member 1971-73)
1968 - present	International Epidemiological Association
1973 - present	Society for Occupational and Environmental Health

HONORS

1955	Fellow, American Public Health Association
1972	Elected Fellow, American Statistical Association
1977	Pittsburgh Statistician of the Year
1957	HEW Departmental Superior Service Award
1957	HEW Departmental Nominee - Arthur S. Flemming Award for Ten Most Outstanding Young Men in Government
1958	Pi Gamma Mu (National Social Science Honor Society)
1979-81	Member, Editorial Board, American Review of Respiratory Disease

PROFESSIONAL ACTIVITIES

Teaching (current)

Biostatistics 211	Principles of Statistical Reasoning
Biostatistics 216	Introduction to Sampling
Biostatistics 219	Vital and Medical Care Statistics

Research and Training (1967 - date)

Grants and Contracts

Years Federal Grants	Title	Source	Amount
1968-74	Training in Public Health Statistics	NIH	$158,183
1972-75	Training in Industrial Biostatistics	NIOSH	$161,406
1971-75	Training in Medical Care Statistics	NCHSR	$274,376
1969-76	Study of the Effects of National Health Insurance in Quebec	NCHSR	$746,532
1976-77	Planning Grant on Childhood Lead Poisoning	NIH	$ 71,790
1977-81	Cancer in Arsenic Exposed Populations	NCI	$315,870

Non Federal Contracts

1975-80	Health of Workers in Mineral Wool and Fibrous Glass Manufacturing	TIMA	$305,559
1976-80	Mortality of Nickel Workers Huntington, W. Va.	HUNT. ALLOYS	$108,551
1975-	Surveillance of Health of Chemical Workers Deer Park Texas	SHELL OIL	$ 58,604
1981-	Mortality Among Smelter Workers	EPA	$450,377
1981-82	Cross-Sectional Study of Pulmonary Function in Alcoa Arkansas Workers	ALCOA	$ 34,586

Other Non-Federal -- $40,602

2. **Other Research and Training Related Activities**

1960-65	Panel Member, U.S. Board of Civil Service Examiners (Statistician)
1966-70	Health Services Research Study Section, DHEW
1967-date	Health Advisory Committee, National Bureau for Economic Research
1967-72	Advisory Fellow, Mellon Institute and Industrial Hygiene Foundation

1970-72	Health Services Demonstrations Study Section, HSMA
1972-75	National Advisory Food and Drug Committee, FDA
1972-74	Panel on Chromium, Committee on Biological Effects of Atmospheric Pollutants, National Academy of Sciences
1974-76	Chairman, Advisory Committee on Longitudinal Study of Submariners, U. S. Navy
1975-79	Pulmonary Diseases Advisory Committee, NHLBI
1979-80	Task Force on the Epidemiology of Respiratory Disease, NHLBI Chairman, Committee on Occupational Agents
1979-	Literature Reviewer-Epidemiology-J. of Occupational Medicine
1979-	Associate Director, Center for Environmental Epidemiology

Service (current)

1. Departmental: Chairman (1976-date)

2. School: Member, Dean's Cabinet

3. Local and State: Grants Review Committee, Pennsylvania Coal Workers Respiratory Disease Program

PUBLICATIONS

1. Refereed Articles

Enterline, Philip E., and Sauer, Herbert I: Community-wide X-ray surveys, VI, Records and Reports. Pub. Health Rep. 66:1613-1624. (December 7, 1951).

Enterline, Philip E: Group Chest X-ray Examinations and the Tuberculosis Death Rate. Pub. Health Rep. 67:762-766 (Aug. 1952).

Payne, Howard M., Enterline, Philip E., and Houck, Julia: A Study of the Positive Roentgenographic Findings for 1948 Washington Mass Survey. Am. Rev. Tbc. 66:548-566 (Nov. 1951).

Bowman, Walter M., and Enterline, Philip E: Delayed Blood Sugar Determinations--Evaluation of a Blood Preservative. Pub. Health Rep. 69:240-246 (March 1954).

Andersen, Robert J., Enterline, Philip E., and Turner, Otis D.: Undetected Tuberculosis in Various Economic Groups. Am. Rev. Tbc. 70:593-600 (Oct. 1954).

Andersen, Robert J., Enterline, Philip E., Hill, Rank J., and Roberts, Jean: An Evaluation of Tuberculosis Detection by Chest X-ray Surveys. Pub. Health Rep. 69:1053-1060 (Nov. 1954).

Kurlander, Arnold B., Hill, Elizabeth , and Enterline, Philip E: An Evaluation of Some Commonly Used Screening Tests for Heart Disease and Hypertension. J. Chr. Dis. 2:427-439 (Oct. 1955).

:erline, Philip E., and Stewart, William H: Geographic Patterns in Deaths rom Coronary Heart Disease. Pub. Health Rep. 71:849-855 (Sept. 1956).

;tewart, William H., and Enterline, Philip E: Ecology and Coronary Heart)isease. J. Chr. Dis. 6:86-89 (July 1957).

Brodeur, Armand E., Baker, James P., and Enterline, Philip E: Abnormalities Seen on Chest Photofluorograms and Diagnosable Heart Disease. Am. J. Roent. Rad. Ther., and Nuc. Med. 78:226-233 (Aug. 1957).

Enterline, Philip E., and Kordan, Bernard: A Controlled Evaluation of Mass Surveys of Tuberculosis and Heart Disease. Pub. Health Rep. 73:867-875 (Oct. 1958).

Enterline, Philip E., and Capt, Katherine G: A Validation of Information Provided by Household Respondents in Health Surveys. Am. J. Pub. Health 49:205-212 (Feb. 1959).

Zukel, William J., Lewis, Robert H., Enterline, Philip E., Painter, Robert C., Nelson, Lloyd S., Fawcett, Robert M., Meredith, Alle P., and Peterson, Beatrice: A Short-Term Community Study of the Epidemiology of Coronary Heart Disease. Am. J. Pub. Health 49:1930-2059 (Dec. 1959).

Sauer, Herbert I., and Enterline, Philip E: Are Geographic Variations in Death Rates for the Cardiovascular Diseases Real? J. Chr. Dis. 10:513-524 (Dec. 1959).

Enterline, Philip E., Kikli, Arthur E., Sauer, Herbert I., and Hyman, Morton: Death Rates for Coronary Heart Diseases in Metropolitan and Other Areas. Pub. Health Rep. 75:759-766 (Aug. 1960).

Meredith, Alle P., Enterline, Philip E., Peterson, Beatrice, and Pehover, Jean G: An Epidemiologic Diet Study in North Dakota. J. Am. Dietet. Assoc. 37:339-343 (Oct. 1960).

Enterline, Philip E., and Stewart, William H: Estimated Morbidity in the United States based on Monthly Labor Force Report. Pub. Health Rep. 75: 1151-1160 (Dec. 1960).

Enterline, Philip E: Causes of Death Responsible for Recent Increases in Sex Mortality Differentials in the United States. Milbank Mem. Fund Quart. 39:312-328 (April 1961).

Enterline, Philip E: Work Loss Due to Illness in Selected Occupations and Industries. J. Occup. Med. 3:405-411 (Sept. 1961).

Stewart, William H., and Enterline, Philip E: Effects of the National Service on Physicians Utilization and Health in England and Wales. New England J. of Med. 265:1187-1194 (Dec. 1961).

Enterline, Philip E., and Stewart, William H: Health Program Requirements to Offset Effects on Levels of Living. Am. J. Pub. Health. 52:401-409 (March 1962).

Cooper, W. Clark, Enterline, Philip E., and Worden, Eloise T: Estimating Occupational Disease Hazards Through Medical Care Plans. Pub. Health Rep. 77:1065-1070 (Dec. 1962).

Enterline, Philip E., and McKiever, Margaret P: Differential Mortality From Lung Cancer by Occupation. J. Occup. Med. 5:283-290 (June 1963).

Syme, S. Leonard, Hyman, Merron J., and Enterline, Philip E: Some Social and Cultural Factors Associated with the Occurrence of Coronary Heart Disease. J. Chr. Dis. 17:277-289 (1964).

Enterline, Philip E: Sick Absence for Men and Women by Marital Status. AMA Arch. Environ. Health. 8:466-470 (March 1964).

Enterline, Philip E: Mortality Rates Among Coal Miners. Am. J. Public Health. 54:758-768 (May 1964).

Enterline, Philip E: Work Loss Due to Illness in Certain Western Nations. Mens en Onderneming. (May 1964).

Enterline, Philip E: Work Loss Due to Illness. Monthly Labor Review. 87:1181-1183 (Oct. 1964).

Enterline, Philip E: Sick Absence in Certain Western Countries. Ind. Med. and Surgery 33:738-741 (Oct. 1964).

Enterline, Philip E: The Estimation of Expected Rates in Occupational Disease Epidemiology. Pub. Health Rep. 79:973-978 (Nov. 1964).

Syme, S. Leonard, Hyman, Merton M., and Enterline, P.E.: Sociocultural Factors and Coronary Heart Disease. Sociological Inq. Vol. 34, No. 1, (Winter, 1964).

Syme, S. Leonard, Hyman, Merton M., Enterline, Philip E: Cultural Mobility and the Occurrence of Coronary Heart Disease. J. of Health and Human Behavior Vol. 6 (Winter, 1965).

Ashford, J.R., Enterline, Philip E: Radiologic Classification of the Pneumoconioses. Arch. of Environ. Hlth. Vol. 12, (March 1966).

Enterline, Philip E: Social Causes of Sick Absence. Arch. of Environ. Hlth. Vol. 12, (April, 1966).

Enterline, Philip E: The Effects of Occupation on Chronic Respiratory Disease. Arch. Environ. Hlth. Vol. 14, 189-200 (Jan. 1967).

Enterline, Philip E. and Lainhart, W.S.: The Relationship Between Coal Mining and Chronic Nonspecific Respiratory Disease. Am. J. of Pub. Health Vol. 57, No. 3, 484-495 (March 1967).

Enterline, Philip E. and Kendrick, Mildred A: Asbestos-Dust Exposures at Various Levels and Mortality. Arch. Environ. Hlth. Vol. 15, 181-186 (Aug. 1967).

Norowitz, I. and Enterline, Philip E: Lung Cancer Among the Jews. Am. J. of Pub. Hlth. Vol. 60, No. 2 (Feb. 1970).

Enterline, Philip E: Validating Thresholds Using Industrial Records. J. of Occup. Med. Vol. 12, No. 1 (Feb. 1970).

Enterline, Philip E: Epidemiology of Coal Worker's Pneumoconiosis. Ind. Med. and Surg. Vol. 39, 115-117 (March 1970).

Herman, B. and Enterline, Philip E: Lung Cancer Among the Jews and Non-Jews of Pittsburgh. Amer. J. of Epid. Vol. 91, No. 4, 355-367 (April 1970).

Enterline, Philip E., DeCoufle, Pierre, and Henderson, Vivian: Mortality in Relation to Occupational Exposure in the Asbestos Industry. J. Occup. Med. Vol. 14, No. 12 (Dec. 1972).

Enterline, Philip E., DeCoufle, P. and Henderson, V: Respiratory Cancer in Relation to Occupational Exposures Among Retired Asbestos Workers. Brit. J. Industr. Med., Vol. 30, 162-166 (1973).

Enterline, Philip E., McDonald, J.C., McDonald, A.D., and Salter, V: The Effects of "Free" Medical Care on the Practice of Medicine - The Quebec Experience. New England J. of Med. 228:1152-1155 (May 31, 1973).

McDonald, A.D., McDonald, J.C., Steinmetz, N., Enterline, P.E., and Salter V: Physician Service in Montreal before National Health Insurance. Medical Care II (July-August 1973).

Henderson, V., and Enterline, P.E.: An Unusual Mortality Experience in Cotton Textile Workers. J. Occup. Med., Vol. 15, No. 9 (September 1973).

Enterline, P.E., Salter, V., McDonald, A.D., and McDonald, J.C.: The Distribution of Medical Services Before and After "Free" Medical Care--The Quebec Experience. New England J. Of Med. 189:1174-1178 (Nov. 1973).

Enterline, P. E. and Henderson V: Type of Asbestos and Respiratory Cancer in the Asbestos Industry. Arch. Environ. Hlth., Vol. 24 (Nov. 1973).

Enterline, P.E., McDonald, J.C., McDonald, A.D. and Henderson, V.: Physician's Working Hours and Patients Seen Before and After National Health Insurance. Medical Care, Vol. 13, No. 2. (February 1975).

Enterline, Philip E: Respiratory Cancer Among Chromate Workers. J. Occup. Med., Vol. 16:523 (Aug. 1974).

Enterline, Philip E. and Henderson, V: Mortality and Morbidity Experience of Retired Fibrous Glass Workers. Arch. of Environ. Hlth., Vol. 30 (March 1975).

McDonald, A.D., McDonald, J.C. Salter, V. and Enterline, P.E.: Effects of Quebec Medicare on Physician Consultation for Selected Symptoms. New Eng. J. of Med. 291:649-652 (Sept. 26) 1974.

Enterline, Philip E: Pitfalls in Epidemiological Research. J. of Occup. Med. Vol. 18:150-156 (March 1976).

Enterline, Philip E: Estimating Health Risks in Studies of the Health Effects of Asbestos. Am. Rev. of Respiratory Disease, Vol. 113 (1976).

Pinto, S., Enterline, Philip E., Henderson, V., and Verner, Michael, O: Mortality Experience in Relation to a Measured Arsenic Trioxide Exposure. Environmental Health Perspectives, Vol. 19:127-130 (Aug. 1977).

McDonald, J.C., McDonald, A.D., and Enterline, P.E.: Some Effects of Medicare in Quebec (Etudes sur l'assurance-maladie due Quebec) Sociologie et Societes. IX, 1, pp. 56-75 (Spring 1977).

Ricci, E., Enterline, P.E., Henderson, V: "Contacts with Pharmacists before and After "Free" Medical Care -- the Quebec Experience," Medical Care, Vol. 16. No. 3, March 1978.

Pinto, S., Henderson, V. and Enterline, P.: Mortality Experience of Arsenic Exposed Workers. Arch. of Environ. Hlth. pp. 325-331, Nov/Dec. 1978.

Marsh, G. and P.E. Enterline: A Method for Verifying the Completeness of Cohorts Used in Occupational Mortality Studies. J. of Occup. Med., Vol. 21: 10, pp. 665-670, October 1979.

Enterline, P.E.: Attributability in the Face of Uncertainty, CHEST. Vol. 78, p. 377S-379S, Suppiment August 1980.

2. Proceedings

Enterline, Philip E: A Controlled Evaluation of Casefinding by Chest X-ray. Proceedings of the National Tuberculosis Association (May 1957).

Enterline, Philip E: Trends and Variations in Sick Absence in the United States, Proceedings of the Second Int'l Conf. on Sick Abs. Statistics. Amsterdam, The Netherlands (April 22, 1963).

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3. Abstracts

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4. Other

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Birthdate: November 12, 1929

Birthplace: Paterson, New Jersey

Citizenship: U.S.A.

Marital Status: Married, 3 sons

Education:

Harvard College, 1947-1951, A.B. (cum laude), Chemistry
Cornell University Medical College, 1951-1955, M.D.

Appointments and Positions:

Academic:

The Johns Hopkins Hospital
Interne (medicine) 1955-1956

Cornell University Medical College
Research Fellow, 1956-1957
Instructor in Pharmacology, 1959-1960
Assistant Professor of Pharmacology, 1960-1964
Associate Professor of Pharmacology, 1964-1967

Georgetown University Schools of Medicine and Dentistry
Schering Foundation Professor and Chairman of Pharmacology, 1967-

The Murray and Leonie Guggenheim Dental Clinic
Lecturer to the staff, 1960-1967

Naval Medical Research Institute, Bethesda, Maryland
Guest Scientist, 1967-1970

Walter Reed Army Institute of Dental Research
Consultant-lecturer, 1968-1972

Naval Dental School
Consultant-lecturer, 1970-1971

Appointments and Positions (Continued):

U. S. Government:

National Institutes of Health
Pharmacology and Endocrinology Fellowship Review Committee, 1968-1971
Neurological Disorders Program Project Review Committee, 1971-1975; Chairman 1973-1975
Pharmacology Toxicology Program Project Review Committee, 1976-1980; Chairman, 1977-1980
Fogarty International Fellowship Review Committee, 1975, 1976, 1979 (Chairman), 1981 (Chairman)
Biotechnology Resources Review Committee, 1981-
NINCDS Committee to review Antiepileptic Drug Development Program, 1981-1982

Veteran's Administration
Merit Review Board, Neurobiology, 1974-1977
Chairman, 1976-1977
Consultant, 1977

Congress of the United States
Commission on the Federal Drug Approval Process 1981-

Federal Trade Commission
Consultant 1971-1974; 1978

Occupational Safety and Health Administration
Consultant 1974

Private:

National Research Council
Committee on Toxicology, 1971-1977
Panel on Anticholinesterase Chemicals, 1981-
Division of Biology and Agriculture, Representative from American Society for Pharmacology and Experimental Therapy, 1967-1977
Safe Drinking Water Committee (consultant) 1976
Pesticide Information Review & Evaluation Committee 1977-1981
Committee on Military Environmental Problems, (Chairman) 1980-1981
Committee on Recommendations for U. S. Army Basic Scientific Research 1981-

American Heart Association
National Capitol Affiliate
High School Research Committee, 1970-1972
Chairman, 1971-1972
Research Committee, 1972-1977
Board of Directors, 1972-1978
Middle Atlantic Regional Heart Committee
Research Review and Certification Subcommittee, 1979-1981

U.S. Pharmacopeial Convention, 1970-

Exxon Health Research, Board of Scientific Advisors, 1981-

Professional Societies:

American Society for Pharmacology and Experimental Therapeutics
Committee on Intersociety Relations 1966-1968
Representative to Div. of Biol. and Agriculture, NAS-NRC, 1968-1977
Representative to Publications Committee of Federation of American Societies for Experimental Biology, 1970-1975
Educational and Professional Affairs Committee, 1971-1974; 1979-
Subcommittee on Graduate Convocation Program, Chairman 1972-1974
Program Committee (ad hoc member), 1968-
Ad Hoc Committee on Teaching of Pharmacology, 1970-1971
Task Force in Support of Training and Research, 1973-1975
Secretary-Treasurer, 1976-1977
Committee for Liaison with Society of Toxicology (Chairman) 1976-1978
Long Range Planning Committee, 1979- ; (Chairman) 1979-1981

Federation of American Societies for Experimental Biology
Publications Committee, 1970-1974, Chairman, 1971-1974
Life Sciences Research Office-Panel for evaluation of health hazards of irradiated beef 1977-1978.
Long Range Planning Group, 1980
Treasurer Elect 1981

Association for Medical School Pharmacology, 1969-
Councillor, 1974-1975
Secretary, 1975-1976

Society of Toxicology
Committee on Ethics of Animal and Human Experimentation (Co-Chairman, 1974-1978)
Toxicology-80's Commission, 1979

Sigma Xi 1960-
Vice President, Cornell Medical subchapter, 1966-1967
Executive Committee, Georgetown chapter, 1970-1973

The New York State Society for Medical Research
Vice President, 1965
Vice President and Treasurer, 1966-1967

Editorial Positions:

The Journal of Pharmacology and Experimental Therapeutics
Editorial Board, 1969-1971
Field Editor, Neuropharmacology, 1971-1978
Guest Field Editor, 1978-

Pharmacology for Physicians (now called Rational Drug Therapy)
Editorial Board, 1968-1971

Science; Anesthesiology (ad hoc)

Fellowships and Awards:

U.S.P.H.S. Career Development Awardee, 1961-1965, 1966-1967
Golden Apple Award, 1968

Military Service:

U. S. Navy, 1957-1959, Lt. (M.C.) U.S.N.R., Stationed at Naval Medical Research Institute, Bethesda, Maryland

Professional Societies:

American Association of Dental Schools
American Association for Laboratory Animal Science
American Association of University Professors
American Medical Association (Faculty Affiliate)
American Society for Clinical Pharmacology and Therapeutics
American Society for Pharmacology and Experimental Therapeutics
Association of Dental Pharmacology and Therapeutics Teachers
Association for Medical School Pharmacology
Drug Information Association
The Harvey Society
New York Academic of Sciences
Sigma Xi
Society for Experimental Biology and Medicine
Society for Neuroscience
Society of Toxicology
The Peripatetic Society

Professional Licenses:

District of Columbia
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Publications:

See appended list

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FRANK G. STANDAERT

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60. Standaert, F.G. and K.D. Bocher: Neuromuscular Blocking drugs. In: CRC Handbook on Pharmacology and Aging. Ed. R.J. Roberts; P. Goldberg, CRC Press, W. Palm Beach, 1982, (Submitted).

ABSTRACTS

1. Standaert, F.G.: The action of d-tubocurarine on the motor nerve terminal. Fed. Proc. 20: 304, 1961.

2. Standaert, F.G.: Mechanism of post-tetanic potentiation (PTP) in cat slow and fast muscles. Fed. Proc. 22: 309, 1963.

3. Levitt, B., A. Raines, J. Roberts and F.G. Standaert: Antagonism of digitalis arrhythmia: a neural phenomenon. Fed. Proc. 26: 402, 1967.

4. Raines, A., B. Levitt and F.G. Standaert: Factors influencing diphenylhydantoin antagonism of ouabain-induced ventricular arrhythmia in the cat. The Pharmacologist 9: 237, 1967.

5. Levitt, B., A. Raines, D. Moros and F.G. Standaert: Antagonism of ouabain-induced ventricular tachycardia (VT) and death by large doses of N-isopropyl p-nitrophenylethanolamine (INPEA) in the cat. Fed. Proc. 27: 348, 1968.

6. Sohn, Y.J., A. Raines, F.G. Standaert and B. Levitt: Antiarrhythmic properties of sodium 5,5-diphenyl-2-thiohydantoin (DPTH). The Pharmacologist 10: 221, 1968.

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9. Gillis, R.A., B. Levitt, A. Raines, Y.J. Sohn and F.G. Standaert: Effect of ouabain on sympathetic, vagus and phrenic nerve activity. The Pharmacologist 11: 244, 1969.

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22. Standaert, F.G.: Neuromuscular Transmission - What is a cholinergic receptor? Lectures Amer. Soc. Anesthesia, 133-1 to 133-4, 1980.

23. Day, N.S., Dretchen, K.L. and Standaert, F.G.: Comparison of Norcuron and Pancuronium on Neuromuscular Transmission. Fed. Proc. 141: 260, 1981.

24. Dretchen, K.L. and Standaert, F.G.: Cyclic nucleotides and antimyasthenic drugs. N.Y. Acad. Sci. (In Press)

CURRICULUM VITAE

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[redacted]RN: La Crosse, Wisconsin
April 6, 1933

[redacted]UCATION: La Crosse Public School, La Crosse, Wisconsin 1938-1950
University of Wisconsin-La Crosse, La Crosse, Wisconsin 1951-1953; 1955-1956
State University of Iowa, Iowa City, Iowa 1956-1961

[redacted]ADEMIC DEGREES: B.S., University of Wisconsin, 1956
M.A., State University of Iowa, 1958
Ph.D., State University of Iowa, 1961

MARITAL STATUS: Married (1957): one son - DOB June 12, 1962;
one daughter - DOB May 31, 1964

MILITARY SERVICE: Non-commissioned Officer (Sergeant)
U.S. Army - 1953-1955

[redacted]ICENSES AND [redacted]RTIFICATES: American Registry of Physical Therapists-State University of Iowa-1957 (inactive)
American Academy of Toxicologic Sciences - Diplomate, 1982-1985

MONS 222180

HONORS AND PROFESSIONAL RECOGNITION:

Dean's Lists, University of Wisconsin - La Crosse
Gamma Alpha, Science Honorary, University of Iowa
Pre-doctoral Fellowships, University of Iowa
Foreign Travel Award, American Society for Pharmacology and Experimental Therapeutics Mexico City, Mexico; San Paulo, Brazil, 1966
Chairman, Endocrine Pharmacology, American Society for Pharmacology and Experimental Therapeutics (University of Minnesota, 1968)
Chairman, Endocrine Pharmacology, Federation of American Society for Experimental Biology (Atlantic City, N.J.) 1971
Co-Chairman, Liver Microsomal Enzymes, Society for Toxicology (New York, New York) 1973
Visiting Professor and Senior Research Advisor, Faculty of Medicine, University of Ottawe, Ontario, Canada 1971
McLaughlin Award - Outstanding Teaching Award, West Virginia University School of Medicine (Shared Award) 1971
Adjunct Professor, Department of Allied Health Sciences, Kent State University 1975-present
Outstanding Teaching Award 1973-1974 West Virginia University
Co-Chairman, Endocrine Pharmacology, American Society for Pharmacology and Experimental Therapeutics (University of Montreal, 1974)
Co-Chairman, Endocrine Pharmacology, American Society for Pharmacology and Experimental Therapeutics (University of California, 1975)
U.S. Environmental Protection Agency - Certificate of Scientific Service, 1977
McLaughlin Awards - Outstanding Teaching Award, West Virginia University School of Medicine, (Shared Award), 1977
National Academy of Science Trevel Award, XII International Cancer Congress, Buenos Aires, Argentina, 1978
Co-Organizer, Epidemiology of Toxicology, ASPET/SOT Joint Meeting, (University of Texas, 1978)
Maurice O. Graff Distinguished Alumni Award (University of Wisconsin-La Crosse), 1978
Co-Organizer, N.I.E.H.S. - sponsored Target Organ Toxicity: The Endocrines Symposium, West Virginia University, 1980
Organizer, ASPET/SOT - Sponsored Symposium. "Innovating Models in Teratogenicity" (University of Louisville), 1982

RESEARCH APPOINTMENTS:

Research Associate, State University of Iowa, 1958-1959
Visiting Senior Scientist - Travenol Laboratories, Chicago, Illinois - 1982

TEACHING ASSISTANTSHIPS AND ACADEMIC APPOINTMENTS:

Teaching Assistant, Department of Physiology, School of Medicine, State University of Iowa, 1960
Instructor, Department of Physiology, School of Medicine, State University of Iowa,1961
Assistant Professor, Department of Pharmacology, University of Virginia School of Medicine, 1961-1964
Associate Professor, Department of Physiology-Pharmacology, Creighton University, School of Medicine, 1964-1967
Associate Professor, Department of Pharmacology, West Virginia University School of Medicine, 1967-1969
Visiting Professor and Acting Chairman, Department of Pharmacology, Pahlavi University School of Medicine, Shiraz, Iran, 1970
Professor, Department of Pharmacology and Toxicology, West Virginia University School of Medicine, 1970-present

ADMINISTRATIVE EXPERIENCE AND CURRENT RESPONSIBILITIES:

Associate Dean of Administration, West Virginia University School of Medicine, 1979-present
Assistant Dean of Administration, West Virginia University School of Medicine, 1973-1979
American Association of Medical Colleges Executive Development Seminar Program, 1976,(M.I.T. Sloan School of Management)
Fiscal Officer, West Virginia University School of Medicine, 1973-present
Promotion and Tenure, West Virginia University School of Medicine,1973-present
Chief Grants and Contracts Officer, West University School of Medicine,1973-present
Affirmative Action Liaison, West Virginia University School of Medicine,1973-present
Academic Review, West Virginia University School of Medicine, 1979-present
Biomedical Research Grant Support Officer, West Virginia University School of Medicine, 1973-present
Facilities and Scheduling, West Virginia University School of Medicine 1973-present

RESEARCH ACTIVITIES AND INTERESTS:

Co-Investigator, National Cancer Institute, (Prostate Cancer) 1970-present
Endocrine Pharmacology/Physiology
Reproductive System Toxicity
Drug-Hormone Interactions
Heavy Metal Toxicity (Zinc Metabolism)
Pesticide Toxicity
Gonadal Toxicants
Anti-androgenic Agents
Phthalate Acid Esters

ORGANIZATIONS:

American Society for Pharmacology and Experimental Therapeutics
Endocrine Society
Society of Toxicology
Western Pharmacology Society
Sigma xi
American School Health Association, elected Fellow, 1971
National Society for Medical Research
West Virginia Association of Academic Deans
Association of American Medical Colleges-representative

PRESENT COMMITTEES:

Executive Faculty Committee, 1973
Medical School Promotions Committee - 1973 - ex-officio
Medical School Admissions Committee - 1973 - ex-officio
Building Committee for Basic Sciences - Chairman, 1973 -
Medical Center Planning Committee - Chairman, 1974 -
Educational Program Committee, 1973 -
Learning Resources Committee, 1974 -
Senior Banquet Committee, 1974 -
Association of American Medical Colleges - Planning Coordinator, 1973 -
Faculty Council - School of Dentistry - 1976 -
Medical Student Financial Aids Committee - 1977 -
American Society for Pharmacology and Experimental Therapeutics - Committee on Environmental Pharmacology, 1973 -
Computer users Committee 1978 -
Medical School-Hospital Liaison to Student Body Committee, 1978 -
Dissertation Committees, 1968 -
Post-doctoral Training Grant (Endocrinology) 1977 -
NSF Committee to Stimulate Competitive Research in West Virginia, Chairman, 1978 -
W.V.U. Medical Center Bionazeros Committee, Chairman 1980 -

SELECTED LIST OF PAST AND PRESENT CONSULTANTSHIPS AND ADVISORY ROLES:

H.E.W. - Health Manpower Branch, Region III
Environmental Protection Agency
National Cancer Institute Committee on Carcinogenesis
University Park Press, Baltimore, Maryland
Mason Research Institute, Worchester, Mass.
ASHA-PMA Lecturer on Drug Abuse
Encyclopedia Britannica
Ad Hoc Reviewer - Journal of Animal Science
Editorial Board - Journal of Toxicology and Applied Pharmacology 1973-1981
Clinical Pharmacology - Texas Allergy Research Foundation
Baxter-Travenol Laboratories - Chicago, Illinois
World Health Organization - Narcotic Division
Ad Hoc Reviewer - Science
Ad Hoc Reviewer - American J. School Health
Ad Hoc Reviewer - American J. Physiology
Ad Hoc Reviewer - Journal of National Cancer Institute
Clement Associates, Inc. Scientific Regulatory Consultants, Washington, D.C.
Editorial Board, Technomic Publishing Company (Health Science Division) Westport,CT
National Institute Arthritis, Metabolic, and Digestive Diseases
Union Carbide Corporation, South Charleston, W.Va.
American Public Health Association
Urban & Schwarzenberg Medical Publishers, Baltimore, Maryland
National Science Foundation-Regulatory Biology Program
Editorial Board, J. Toxicology and Environmental Health
Editorial Board, Perspectives in Toxicology Raven Press, New York, New York
Professional Consultants in Occupational Health, Inc.,Washington, D.C.
Ad Hoc Reviewer - Proceedings Society Experimental Biology and Medicine
Ad Hoc Reviewer - Andrology
National Toxicology Program (NTP) Board of Scientific Counselors
Exxon Corporation, Newark, N.J.
Syntex Research (Division of Syntex[USA], Inc.), Palo Alto, California
Ad Hoc Reviewer - National Prostatic Cancer Project

SELECTED LIST OF PAST COMMITTEES AND OFFICES (CHRONOLOGICAL):

President - Virginia Academy of Sciences, Medical Sciences, 1964
Secretary - Virginia Academy of Sciences, Medical Sciences, 1962-1963
Research Fellowship Committee, University of Virginia, 1962-1964
Secretary-Treasurer, Society of Sigma XI - Creighton University, 1965-1967
Secretary, Society of Sigma XI - West Virginia University 1969
Curriculum Committee, West Virginia University School of Medicine, 1967-1969
Faculty Senate (WVU), 1969-1971; 1973-1976
Faculty Senate Committee (WVU) on Membership and Constituencies, 1970-1971
Medical School Promotions Committee (WVU), 1969-1973; Chairman 1970-1973
Medical School Admissions Committee (WVU), 1969-1973; Vice Chairman 1970-1973
Pre-Medical Advisory Group (WVU), 1970-1979
Basic Science Administrator for West Virginia University Comprehensive Cancer Center
Director of Graduate Studies in Pharmacology (WVU) 1967-1973
President's (West Virginia University) Task Force Committee on North Central Accreditation, 1972-1974
President's Ad Hoc Council for West Virginia University Research and Graduate Education, 1972-1974
Co-Director, USPHS Training Grant in Pharmacology, 1967-1973
Medical Center Long Range Planning Committee (WVU), 1968-1974
American School Health Association Committee on Drug Abuse, 1970-1975
Faculty Promotions and Tenure Committee (WVU School of Pharmacy) 1972-1974
Graduate Faculty, Kent State University, 1975
Board of Examiners, University of Madras, India
Board of Examiners, University of Ottawa, Canada
Search Committee for University Comptroller (WVU) Chairman, 1978
Research Strategy Committee (WVU), Chairman, 1977-1978
By-Laws Committee, West Virginia University School of Medicine, 1978

Selected List of Past Committees and Offices (Chronological):

Faculty of Reproductive Physiology, Institute of Biological Sciences, West Virginia University 1967
Radiation and Isotope Committee, 1968
Cancer Fellowship and Research Committee, 1968
Faculty Promotions and Tenure Committee - Department of Pharmacology, 1970-1978
Inter-Disciplinary Advisory Committee - Master's Program in Nursing, 1972-1974
University Energy Committee, 1977-1979
Executive Committee of the Gerontology Center 1978-1980
Thesis Committees, 1968

PUBLICATIONS (including 123 research papers/books/chapters/reviews; [illegible] tapes/films/media; 104 abstracts):

Glucose Tolerance in Rheumatoid Arthritis, J.A. Thomas, and W.O.Paul, Clinical Chemistry 4: 556, 1956 (Abstract).

Effect of 2450 Megacycle Microwaves in Dogs, Rats and Larvae of Common Fruit Fly, G.D. Seerle et.al., Biol. Effects of Microwave Radiation 1: 187, 1961.

Carbohydrate Metabolism in Patients with Rheumatoid Arthritis as Determined by Oral and IV Glucose Tolerance. J.A. Thomas, M.A. Thesis, State University of Iowa, 1958.

Effect of Microwave Irradiation on Spermatogenesis and Accessory Sex Organs in the Male Albino Rat. J.A. Thomas, Doctoral Dissertation. State University of Iowa, 1961. Dissertation Abstracts 22: 107, 1961 (Abstract).

The Effects of Microwave Irradiation on Spermatogenesis and Accesory Sex Organs in the Male Albino Rat. J.A. Thomas, and J.O. Thompson, Federation Proceedings 20: 401, 1961 (Abstract).

Alterations in Glucagon Response in Alloxan Diabetic Orchidectomized Rats by 17-ethyl-19-nortestosterone and Estradiol Benzoate. J.A. Thomas, Federation Proceedings 21: 199, 1962 (Abstract).

Effect of 17-ethyl-19-nortestosterone on Blood Glucose in the Alloxan Diabetic Rat. J.A. Thomas, Virginia Journal of Science 13: 293, 1962 (Abstract).

Modification of Glucagon-Induced Hyperglycemia by Various Steroidal Agents. J.A. Thomas, Metabolism 12: 207, 1963.

The Influence of 19-nortestosterone Derivatives on Glycogen and Phosphorylase Activity in Homogenates of Mouse Hepatic Tissue. J.A.Thomas and J.Lomax, Federation Proceedings 22: 331, 1963 (Abstract).

The Effect of Several Steroidal Agents on Liver Phosphorylase Activity. J.A. Thomas, Virginia Journal of Science, 14: 331, 1963 (Abstract).

Norethendrolone-induced Changes in Hepatic Phosphorylase Activity. J.A. Thomas, Metabolism 13: 63, 1964.

Effect of Testosterone Analogues on Sex Accessory Gland Fructose Levels in the Orchidectomized Mouse. J.A.Thomas, Federation Proceedings 23: [illegible] 1964 (Abstract).

Action of Norethendrolone or Testosterone on Mouse Sex Accessory Organ Fructose Levels. A.J. Strauss and J.A. Thomas, Virginia Journal of Science 15: 345, 1964 (Abstract).

The Action of Androgenic Steroids on Some Aspects of Accessory Sex Gland Metabolism. J.A. Thomas, Virginia Journal of Science 15: 346, 1964 (Abstract).

Structural Modifications of the Testosterone Molecule and Its Influence on Fructose Secretion in Sex Accessory Organs of Reproduction in the Castrate Mouse. J.A. Thomas, The Pharmacologist 6: 169, 1964 (Abstract

ublications (cont.):

ie Effect of Steroids on Mouse Sex Accessory Fructose Levels. J.A. homas and A.J. Strauss. Acta Endocrinologica (Copenhagen) 48: 619, 1955.

Endogenous Histamine in Mele Organs of Reproduction. T.A. Assaykeen and J.A. Thomas, Endocrinology 76: 839, 1965.

Effect of Simultaneously Injected Testosterone and Testosterone Analogues in Sex Accessory Organ Fructose. J.A. Thomas, Federation Proceedings 24: 638, 1965 (Abstract).

The Antagonistic Action of Estrogens on the Testosterone Dependent Process of Sex Accessory Organ Fructose Formation. J.A. Thomas, The Pharmacologist 7: 149, 1965 (Abstract).

Fructose Levels in Sex Accessory Organs of Mature Golden Hamsters. J.A. Thomas and R.V. Andrews, Endocrinology 77: 1147, 1965.

Antagonistic Action of Norethynodrel on the Testosterone Dependent Process of Fructose Formation in Mouse Sex Accessory Organs. J.A. Thomas and E.T. Knych,Jr., Acta Endocrinologica (Copennagen) 51: 244, 1966

The *in vivo* and *in vitro* Incorporation of ^{32}P in Mouse Prostate Glands. E.T. Knych, Jr., and J.A. Thomas, Federation Proceedings 25: 314, 1966 (Abstract).

Inhibitory Effects of Estrogens on the Testosterone-Dependent Process of Sex Accessory Fructose Secretion. J.A. Thomas and E.T. Knych, Jr., Endocrinology 78: 1084, 1966.

Some Actions of Reserpine on Sex Accessory Organ Fructose Secretion. J.A. Thomas, The Pharmacologist 8: 201, 1966 (Abstract).

Further Studies on the Influence of Estrogens on Androgen Dependent Fructose Formation in Sex Accessory Organs. J.A. Thomas and E.T. Kynch Jr., Acta Endocrinologica (Copennagen) 53: 455, 1966.

Effects of Cycloheximide on Salivery Gland Protein Metabolism. J.A. Thomas and M.F. Hill, Anatomical Record 157: 391, 1967 (Abstract).

Action of Cycloheximide on Prostate Gland Fructose. J.A. Thomas, Federation Proceedings 26: 646, 1967 (Abstract).

Effect of Reserpine on Prostate Gland Fructose. J.A. Thomas, R.V. Andrews and M.F. Hill, Acta Endocrinologica (Copennagen) 53: 599, 1967.

Effect of Salivariadenectomy Upon Gonadal Activity in Mele Rats. J.A. Thomas and M.F. Hill, Archives on Oral Biology 12: 921, 1967.

Action of Cycloheximide on the Submaxillary Glands in Normal and Castrate Mice. M.F. Hill and J.A. Thomas, European Journal of Pharmacology 1: 434, 1967.

Publications (cont.):

Some Aspects of Prostate Gland Metabolism Following the Administration of Cycloheximide. J.A. Thomas, The Pharmacologist 9: 252. 1967 (Abstract).

Effect of Cycloheximide on Mouse Sex Accessory Organs. J.A. Thomas, European Journal Pharmacology 2: 127, 1967.

Effect of Exogenous Dopamine on Rat Adrenal Ascorbic Acid. A.B. King and J.A. Thomas, Journal of Pharmacology and Experimental Therapeutics 159: 18, 1968.

Sex Accessory Fructose: An Evaluation of Biochemical Techniques. J.A. Thomas, M. Mawhinney and W. Mason, Proceedings Society of Experimental Biology and Medicine 127: 930,1968.

Relationship of Male Sex Hormone to Phosphorylated and Nonphosphorylated Fructose. J.A. Thomas and M.G. Mawhinney, Federation Proceedings 27: 624, 1968 (Abstract).

Action of Testosterone Analogues on Prostate Gland Phosphorylated and Non-phosphorylated Fructose. M.G. Mawhinney and J.A. Thomas, The Pharmacologist 10: 224, 1968 (Abstract).

Effect of Testosterone and Estrogen on the Activity of Alkaline and Acid Phosphatase in Mouse Sex Accessory Organs. E.T. Knych, Jr., and J.A. Thomas, The Pharmacologist 10: 224, 1968 (Abstract).

Changes in Submaxillary Gland Protein and Nucleic Acids Following Ethionine Administration. J.A. Thomas, W. Mason and M.G. Mawhinney, Journal of Dental Research 48: 192, 1969.

Hormonal Regulation of Free Fructose and Fructose Phosphate Esters in Prostate Glands of Mice. J.A. Thomas, M. Mawhinney, G. Wenger and E.T. Knych, Jr., Federation Proceedings 28: 774, 1969 (Abstract).

Effect of a Single Injection of Testosterone and/or Ethinyl Estradiol Upon Mouse Prostate Gland Fructose Levels. J.A. Thomas, M. Mawhinney and E.T. Knych, Jr., Acta Endocrinologica (Copenhagen) 62: 319, 1969.

Action of Synthetic Steroids on the Uptake of Testosterone-1,2-H^3 by Mouse Prostate Glands. J.A.Thomas, E.T. Knych, Jr., and M.G. Mawhinney. IV International Pharmacology Congress Proceeding (Basel, Switzerland) p. 396, 1969 (Abstract).

Factors Affecting the Uptake and Subcellular Distribution of Radioactive Testosterone in Sex Accessory Organs of Mice. E.T. Knych, Jr., J.A. Thomas and C. Smith, The Pharmacologist 11: 252, 1969 (Abstract).

Effect of 19-norsteroids on the Uptake of Tritiated Testosterone by Prostate Glands of Mice. J.A. Thomas, The Pharmacologist 11: 252, 1969 (Abstract).

Effect of Reserpine and Cycloheximide on Hexose Levels of Mouse Brain. G.R. Wenger, J.A. Thomas and T.J. Lee, The Pharmacologist 11: 290, 1969 (Abstract).

Effect of Reserpine on the Uptake of Testosterone-1,2-H^3 by Mouse Prostate Gland. J.A. Thomas, E.T. Knych, Jr., M.G. Mawhinney, European Journal of Pharmacology 8: 361, 1969.

PUBLICATIONS (cont.):

Subcellular Distribution of Radioactivity in the Prostate Gland Following a Single Injection of Testosterone-1,2-H^3. J.A. Thomas, C.G. Smith, M.G. Mawhinney and E.T. Knych, Jr., Acta Endocrinologica 63: 505, 1970.

Action of Various 19-norsteroids on the Uptake of Radioactive Testosterone by Sex Accessory Organs of the Mouse. J.A. Thomas, E.T. Knych, Jr., M.G. Mawhinney and S.R. Smith, European Journal of Pharmacology 9: 235, 1970.

Relationship of Fructose and Fructose Phosphate Esters in Accessory Sex Organs of the Mouse. M.G. Mawhinney, E.T. Knych, Jr., and J.A. Thomas, Journal of Endocrinology (Britain) 46: 345, 1970.

Uptake of 2-deoxyglucose-C^{14} (2dG) or 3-O-methyl-glucose-C^{14} (3mG) by Guinea Pig Seminal Vesicles in vitro. M.G. Mawhinney, J.A. Thomas and E.T. Knych, Jr., Federation Proceedings 29: 782, 1970 (Abstract).

Uptake of C^{14}-2-deoxyglucose and C^{14}-3-O-methyl-glucose by the Rat Ventral Prostate in vitro. M.G. Mawhinney, J.F. Lee, C.G. Smith, and J.A. Thomas, The Pharmacologist 12: 241, 1970 (Abstract).

Enzymatic Measurement of Prostate Gland Fructose. J.A Thomas, M.G. Mawhinney and G.R. Wenger, Journal Reproduction and Fertility 21: 22, 1970.

Assimilation of Non-utilizable Glucoses by Sex Accessory Organs in vitro. M.G. Mawhinney, O.F. Miles and J.A. Thomas, Federation Proceedings 30: 366, 1971 (Abstract).

Uptake of Non-utilizable Sugars by Guinea Pig Seminal Vesicles in vitro. M.G. Mawhinney and J.A. Thomas, Journal Pharmacology and Experimental Therapeutics 177: 447, 1971.

The Abuse of Medicinal Products. J.A. Thomas and G.R. Knotts, American Journal of School Health 41: 235, 1971.

How do Oral Contraceptives Work? M.G. Mawhinney, J.A. Thomas and G.R. Knotts, American Journal School Health 41: 301, 1971.

Uptake of Tritium-Labeled Testosterone by Rat Femur: Effect of Disuse and Age. M.A. Grant, J.A. Lindsey and J.A. Thomas, Canadian Journal of Physiology and Pharmacology 49: 717, 1971.

Formation of Radioactive Cyclic 3', 5' Adenosine Monophosphate (c-AMP) From H^3-Adenosine by Mouse Prostate Glands in vitro. Carol G. Smith, J.A. Thomas and M.G. Mawhinney, The Pharmacologist 13: 287, 1971 (Abstract).

Distribution of Non-utilizable Hexoses and Amino Acids in Everted Seminal Vesicel Sac of the Guinea Pig. M.G. Mawhinney, J.A. Thomas and C.G. Smith, The Pharmacologist 13: 308, 1971 (Abstract).

Effect of Estrogen Pre-treatment on the Uptake and Biotransformation of Testosterone-1,2-H^3 by Mouse Prostate Glands. J.A. Thomas, M.T. Smith, C.G. Smith and M.G. Mawhinney, The Pharmacologist 13: 286, 1971 (Abstract).

Publications(Cont.):

The Action of Testosterone on the Assimilation of Non-utilizable Sugars by the Prostate. J.A. Thomas, M.G. Mawhinney, T.J. Lee and C.G. Smith, Journal of Pharmacology and Experimental Therapeutics 179: 499, 1971.

Pesticides and the Environment. O. Taylor, J. Stevens and J.A. Thomas. American Journal of School Health 42: 82, 1972.

Localization of DDT-H^3 in Male Reproductive Organs and Its Actions upon Anorogenic Function. M.T. Smith, J.A. Thomas, C.G. Smith, M.G. Mawhinney and J.J. McPhillips. Society of Toxicology, 11th Annual Meeting, March 1972, p. 101 (Abstract).

Action of Dieldrin on the Uptake of Testosterone-1,2-H^3 by Prostate Glands of the Male Mouse. J.A. Thomas, M.T. Smith, M.G. Mawhinney and J.J. McPhillips, Society of Toxicology, 11th Annual Meeting, March 1972, p. 103 (Abstract).

Effect of Testosterone or Dihydrotestosterone on the in vitro Synthesis of Labelled Cyclic Adenosine Nucleotide (c-AMP-H^3) by Sex Accessory Organs of Reproduction. C.G. Smith, J.A. Thomas, M.G. Mawhinney and J.W. Lloyd. Federation Proceedings 31: 395, 1972 (Abstract).

Effect of Testosterone on Cyclic Adenosine Monophosphate-H^3 (c-AMP-H^3) and Adenyl Cyclase Activity in Rat Seminal Vesicles. R.L. Singhal, J.A. Thomas M.R. Parulskar and G.M. Ling. V International Congress of Pharmacology, p. 215, July 1972 (Abstract).

Assimilation of Adenosine-H^3 and Its Conversion to Cyclic Adenosine Nucleotide (c-AMP-H^3) by Normal or Hyperplastic Prostates of Dogs in vitro. M.G. Mawhinney, C.G. Smith, J.A. Thomas and O.F. Milam, IV International Congress of Endocrinology, p. 378, June 1972 (Abstract).

Characteristics of Hexose Uptake by the Prostate Gland. M.G. Mawhinney, J.A. Thomas, C.G. Smith and O.F. Milam, Investigative Urology 9: 459, 1972.

Failure of Beta-adrenergic Blocking Agents to Alter Estrogenic Induction of Uterine Enzymes. R.L. Singhal, J.A. Thomas, and M.R. Parulekar, Life Sciences 11: 255, 1972.

Relationship of Pituitary Hormones and Androgens on Prostate Gland Metabolism. J.A. Thomas, M.G. Mawhinney and J.W. Lloyd, Proceedings 1st Annual Carcinogenesis Symposium, p. 61, October 1-4, 1972 (Abstract).

Effects of DDT on Radioactive Uptake from Testosterone-1,2-H^3 by Mouse Prostate Glands. M.T. Smith, J.A. Thomas, C.G. Smith, M.G. Mawhinney and J.W. Lloyd, Toxicology and Applied Pharmacology 23: 159, 1972.

Current Assessment of Marijuana. J.A. Thomas, M.T. Smith and C.R. Knotts. American Journal of School Health 42: 382, 1972.

Uterine c-AMP-H^3 after Estradiol and/or Propranolol. J.A. Thomas, E. Czap and R.L. Singhal, Hormones and Metabolic Research 4: 313, 1972.

Adenosine Uptake and Metabolism of Cyclic 3', 5'-Adenosine Monophosphate by Normal and Hyperplastic Dog Prostate Glands. M.G. Mawhinney, C.G. Smith, J.A. Thomas and O.F. Milam, Investigative Urology 10: 243, 1972.

blications (cont.):

stosterone: Stimulation of Adenyl Cyclase and c-AMP-H^3 Formation in t Seminal Vesicles. J.A. Thomas and R.L. Singhal. Biochemical armacology 22: 307, 1973.

e Formation and Distribution of Cyclic 3' , 5'-adenosine Monophosphate the Everted Guinea Pig Seminal Vesicle Sac. C.C. Smith, M.G. wminney, R.L. Singhal, and J.A. Thomas. Investigative Urology 10: 278, 73.

stribution of C^{14}-Alpha-aminobutyric Acid, C^{14}-3-o-methylglucose d C^{14} Insulin in Everted Seminal Vesicle Sacs. M.G. Mawhinney, J.A. omas, C.C. Smith and O.F. Milam. Investigative Urology 10: 282, 1973.

tabolic Characteristics of Hyperplastic Dog Prostate Glands. M.G. wminney, F.L. Schwartz, J.A. Thomas, L.S. Oliver, E. Zapp and J.W. oyd. Proceedings Annual American Urology Association, 1973 (Abstract).

bstances with Abuse Potential at the Elementary and High School Level. A. Thomas, M.G. Mawhinney and G.R. Knotts. Clinical Pediatrics 12: 17, 73.

ffects of Chronically Administered Delta^1-tetrahydrocannabinol on renal and Gonadal Activity of Male Rats. C.M. Ling, J.A. Thomas, O.R. ther and R.L. Singhal. International Journal of Clinical Pharmacology 7: 1973.

tions of the Herbicide 2,4,5-T on the Uptake and Biotransformation of stosterone-1,2-H^3 by the Mouse Prostate Gland. J.W. Lloyd, J.A. omas and M.G. Mawhinney. Archives of Environmental Health 26: 217, 1973.

ffect of Prolactin on the in vitro Accumulation of Tritiated stosterone (T-H^3) by the Prostate Gland. J.W. Lloyd, J.A. Thomas. L. Keenan and B. Arsateh, Federation Proceedings 32: 298,1973 Abstract).

me Inhibitory Actions of Morphine on Sex Accessory Gland Metabolism. .A. Thomas, M.G. Mawhinney and J.A. Lloyd. Proc. Society of Toxicology, 2th Annual Meeting, p. 29, 1973 (Abstract).

me Actions of Organochloride Pesticides on Sex Accessory Organs of production. J.A. Thomas and J.W. Lloyd, in PESTICIDES AND THE VIRONMENT: A CONTINUING CONTROVERSY, p. 43, Symposium Specialist, publ. rth Miami, Florida, 1973.

ffects of 2,4,5-T and Other Organochlorides on the Metabolism of stosterone-1,2-H^3 by Male Organs of Reproduction. J.W. Lloyd, J.A. omas, M.G. Mawhinney, and C.S. Dieringer, Society of Toxicology, 12th nual Meeting, p. 5, 1973 (Abstract).

drogen Metabolism by the Epithelium or Muscle Layers of the Guinea Pig minal Vesicles. F.L. Schwartz, J.A. Thomas, J.W. Lloyd and M.G. wminney. The Pharmacologist 15: 257, 1973 (Abstract).

e Effect of Testosterone on the Concentration ATP in Accessory Sex rgans of the Guinea Pig and Rat. M.G. Mawhinney, L.G. Oliver, J.A. omas, C.J. Malanga and J.W. Lloyd. The Pharmacologist 15: 256, 1973 bstract).

PUBLICATIONS (continued):

Differential Response of Either Bovine or Ovine Prolactin on Testosterone-H^3 Metabolism in Various Lobes of the Rat Prostate Gland. E.A. Zepp, J.A. Thomas, M.G. Mawhinney and J.W. Lloyd. The Pharmacologist 15: 256, 1973 (Abstract).

Effect of Bovine Prolactin on Androgen Accumulation by the Mouse Prostate Gland. E.J. Keenan, J.A. Thomas, M.G. Mawhinney and J.W. Lloyd. The Pharmacologist 15: 256, 1973 (Abstract).

Influence of Carbaryl on Androgen Metabolism in the Prostate Gland and Liver. C.S. Dieringer, J.A. Thomas and R.E. Stitzel. The Pharmacologist 15: 226, 1973 (Abstract).

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