

Letter to Dr. Selinkoff:

Thank you for the informative meeting and hospitality you extended to Dr. ^{Casey}~~Brown~~ and me last Wednesday. We were most interested in the several potential approaches you outlined for treatment of our PCB exposed employees. On Thursday, March 17, Dr. ^{Casey}~~Brown~~ and I had the opportunity to review your preliminary thoughts with our management and they enthusiastically supported the notion of working with you and your associates in this general area.

At this meeting, ²~~Dr. Brown~~ presented an overview of data ^{we have}~~which~~ accumulated relative to the toxicity of PCBs. Before finalizing a joint program with Mt. Sinai, Dr. John F. Welch, Vice President and Group Executive of the Components and Materials Group, who has responsibility for the Hudson Falls operation, asked ^{me to make a}~~that we expect Dr. Brown's~~ presentation to you and your associates. We want to be sure that any proposed therapeutic methodology be relatable to the overall patterns of PCB accumulation, persistence, and toxicology revealed by the available scientific literature, and to the substantial evidence for large differences in such patterns between PCB specimens that differ in brand, grade (i.e., homolog distribution), or specimen history (i.e., impurity levels). In order to explain why we are so concerned about these issues, ^{my associates and I have accumulated}~~let me summarize much of Dr. Brown's~~ background information about the nature of the PCB literature, the comparative toxicology of PCB products, the nature of PCB effects on humans, and their implications regarding the design of therapeutic treatments for persons exposed to capacitor-grade PCBs.

(Continue with last paragraph on page 1 "By early...." through first paragraph on page 10 ".....and augmenting its level.")

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EXHIBIT

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Casey-Salikoff Letter, Middle Section

DRAFT of 3/21/77

J.F. Brown, Jr.

In addition to being concerned about having something available for treatment of PCB-exposed individuals in the event that it should be needed, I believe it most important that we have something that can be rigorously defended as the right thing to use for the particular PCB and exposure pattern involved. We cannot ignore the prospect of intense public scrutiny of any proposed therapeutic methodology by the press, the Union, the FDA, and the NYS Health Department. To be defensible, a proposed approach must be relatable to the overall patterns of PCB accumulation, persistence, and toxicology revealed by the available scientific literature, and to the substantial evidence for large differences in such patterns between PCB specimens that differ in brand, grade (i.e., homolog distribution), or specimen history (i.e., impurity levels). In order to explain why we are so concerned about these issues, *summary, much of Dr. Brown's background information* let me say a bit more about the nature of the PCB literature, the comparative toxicology of PCB products, the nature of PCB effects on humans, and their implications regarding the design of therapeutic treatments for persons exposed to capacitor-grade PCB's.]

JF Nature of Available Literature on PCB Effects.

By early 1976, approximately 1500 publications on the chemical, physical, biological, and environmental properties of PCB's had appeared in the technical and semi-technical literature. A published bibliography (Quinby, 1972) covered the 870 reports appearing through 1971, and about 600 subsequent titles were listed by the Chemical

GENP 003261

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Abstracts and Toxline computerized search services. An excellent reference work on the chemistry of the PCB's was also available (Hutzinger, 1974).

Of these 1500 publications, nearly 400 presented some kind of description of biological effects, though not necessarily toxic effects. A bibliography listing and classifying such reports appearing through 1975 has been prepared (Bellamy, 1976; ~~copy attached~~). Several fairly extensive reviews of the biological effects of PCB's have also appeared. Notable are those of Kimbrough (1972, 1974); Fishbein (1974); Peakall (1975) and Nisbet (1976). (In addition, three significant publications of symposium proceedings have appeared: one on the December 1971 NIEHS symposium on PCB's (NIEHS, 1972); one on the April 1973 NIEHS Symposium on chlorinated dibenzodioxins and dibenzofurans (NIEHS, 1973); and one on the November 1975 National Conference) on the PCB's (EPA, 1976).

negative

Revised by [unclear]

insistent { An unusual strength of the toxicological literature on PCB's is the presence of a large amount of human case material. In fact, it is probably safe to say that PCB-related toxicants are one of the few such groups where the effects on humans are better characterized than those on experimental animals. This has resulted largely from the massive and continuing efforts of the Fukuoka group in Japan to analyse the cause and effects of the "Yusho" incident, in which some 1200 people were poisoned by rice oil that had been contaminated with heat-aged Kanechlor-400 from a leaky heat exchanger. Two excellent English language summaries of the 50-odd Japanese reports on this effort have

GENP 003262

appeared; one covering the work through 1971 was reported ~~at the~~ ^{by} 1971 NIEHS Symposium (Kuratsune, 1972); the second, covering the work through 1975, at the 1975 EPA Symposium (Kuratsune, 1976). In addition, there are some very significant, albeit long-overlooked, observations in the older industrial hygiene literature on the effects of PCB exposure in manufacturing plants. *(what's the references)*

*incorporated
p. 2.*
is a summary
A peculiar weakness of the toxicological literature on PCB's is the almost universal absence of information on the chemical composition of the materials fed to experimental animals, particularly as regards the content of the highly toxic polychlorinated dibenzofurans (PCDF's). Despite the fact that PCB toxicity in humans was immediately recognized as impurity-dependent (Jones and Alden, 1936), despite the fact that the agent responsible for the characteristic edema disease and teratogenicity in chickens (Vos and Koeman, 1970) and for the characteristic dermal and hepatic effects in rabbits (Vos and Beems, 1971) was identified as PCDF, and despite the prominence given these latter findings in subsequent symposium reports and review articles (notably, NIEHS, 1972; NIEHS, 1973; and Fishbein 1974), only one of the many animal toxicity studies (other than Vos') reported in the 1970-75 period included a determination of the PCDF content of the PCB being used. This one (Ax and Hansen, 1975) showed that even specially-synthesized individual isomers could be contaminated with PCDF's, and, in fact, that the only correlations between PCB composition and biological effects in chickens that could be drawn were those based on

PCDF content. The failure of most of the other experimental toxicologists to analyse their PCB samples has led to a toxicological literature characterized by grotesque inconsistencies and much discussion of putative correlations between PCB molecular constitution and biological activity that probably have no basis in fact.

B. J. Brown
To dramatize this point, I am reminded that when we were visiting you on the 16th, you pointed out that polychlorinated dibenzodioxins, (PCDD's), which are known to be very similar to PCDF's in their manner and degree of toxicity (Kimmig and Schultz, 1957; Bauer, Schultz, and Spiegelburg, 1961) have just been shown to be carcinogenic at the parts-per-trillion level. This means that the reported carcinogenicities (at the 100 ppm feeding level) of Aroclors 1254 and 1260 (which contain about 1 ppm PCDF, see Table II below) can be fully accounted for on the basis of the PCDF content alone. In fact, at present there does not seem to be any evidence that all the toxic effects associated with chronic feeding of PCB's to warm-blooded animals cannot be associated to the PCDF impurities rather than to the PCB's themselves.

Comparative Toxicology of PCB Products. - Whether or not the implications of the above-mentioned defect in the PCB literature be quite as dramatic as just portrayed, ^{*factual*} the fact remains that different PCB products can differ enormously in both accumulation and toxicity. ^{*what is it*}
This is not unexpected in view of their marked differences in chemical composition. As you know, the major constituents of the commercial PCB products are complex mixtures of isomers of homologous PCB species representing varying levels of chlorine content. The distribution of

such homologous species (each representing a family of isomers) is shown in the appended Table I. From this, one may note, for example, that Aroclor 1016 has essentially no components in common with Aroclor 1260, and typically only 0.05-0.2% of the penta-, hexa-, and heptachlorobiphenyls (i.e., the "higher homologs") that make up the great bulk of Aroclor 1254. Thus, there is no particular reason to expect that biological effects exhibited by Aroclor 1254 or 1260 will also be manifest for Aroclor 1016.

The minor constituents of the commercial PCB products include traces of polychlorinated methylbiphenyls, terphenyls, naphthalenes, and dibenzofurans. The available data on the latter are shown in Table II. Evidently, the PCB specimens examined to date have exhibited a >12,000,000-fold range in PCDF content. This PCDF apparently has two sources: first, particularly in the European and Japanese PCB's, there may be several ppm PCDF already in the PCB at the time it leaves the factory; second, PCDF can be generated in PCB by thermal aging in the presence of air, and conceivably by other forms of aging as well.

The available data on PCB accumulation and persistence (inverse of elimination rate) in many types of organisms, and of toxicity to fish (~~which probably results from a general anesthetic effect, following massive bioaccumulation~~) can be correlated closely with the average degree of chlorination of the PCB. The data on toxicity to warm-blooded animals can be no more than roughly correlated with degree of chlorination alone. Thus, Kimbrough and her colleagues have reported that Aroclor 1254 or 1260 in rats could provoke a progression of hepatic

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changes, beginning with hypertrophy and hyperplasia, and going on to adenofibrosis, neoplastic nodules, and carcinomas, whereas with Aroclor 1016 or 1242 no such changes occurred; however, between the two toxic Aroclors, the activity level appeared slightly greater for 1254 than for 1260.

In hopes of better defining the comparative toxicology of different PCB/PCDF compositions, we have drawn together the best estimates of maximum no-effect chronic dosages^(in mammals) that we could extract from the literature. These are presented in Table III. This shows that the toxicity probably correlates more closely with the estimated PCDF content than with the degree of chlorination, and at any event, there appears to be a 2000-fold range in the toxicity levels reported to date.

Toxic Effects of PCB/PCDF Compositions in Humans. - In humans, PCB/PCDF-containing products induce a characteristic pattern of highly persistent dermal effects (chloracne), sometimes hyperpigmentation (common in the Japanese Yusho cases, where the exposure was by ingestion; rare in the older US and Italian cases, where it was by vapor contact), general lassitude and discomfort, and a variety of other symptoms (Jones and Alden, 1936; Kuratsune, 1972; Kuratsune, 1976).

The characteristic chloracne has now been observed in connection with the 1200 Japanese affected by PCB/PCDF in the 1968 Yusho incident, and perhaps 30-40 American and Italian factory workers affected in the four previously reported episodes of PCB/PCDF poisoning (Jones and Alden, 1936; Puccinelli, 1954; Hoffman and Meneghini, 1962; Meigs et al., 1954; Birmingham, 1964). It is a serious and persistent

acneform eruption accompanied by significant histopathological changes in the skin. The pattern presented bears no relationship to that seen in allergic dermatitis. This latter is a mild, transient condition, produced in small minorities of the population, by PCB's as well as by many other common materials, including (according to recent news reports) almost all cosmetics on the average drug store shelf.

The incidence and persistence of chloracne were observed by the Japanese investigators to correlate with the PCDF contents of the PCB's involved. Thus, chloracne was rarely observed among production workers exposed to Kanechlors containing, presumably, ca. 2-33 ppm PCDF, despite the appearance of high levels of PCB in their blood. (This correlates with the general U.S. and Italian industrial experience showing no problems arising from the handling of ordinary Aroclors, presumably running 0-2 ppm PCDF's; all of the reported chloracne cases involved contact with heat-aged or recognizably contaminated PCB's). Likewise, the chloracne and hyperpigmentation produced in the Yusho episode was observed to persist long after the PCB levels in the bodies of the victims had returned to normal ranges. The persistently toxic agents that remained, however, were the PCDF's, particularly the higher homologs (e.g., the penta- and hexachloro-PCDF's), which were specifically retained in the liver. It is noteworthy that these chronically-accumulated toxic agents could not be formed from a material like Aroclor 1016, which is lacking in penta- and hexachlorobiphenyls.

Despite repeated searches, no evidence of liver damage arising from PCB/PCDF poisoning of men or monkeys has ever been reported. 

This stands in sharp contrast to the human effects of chlorinated naphthalenes (Halowaxes), which produced several episodes of fatal liver disease during the 1930's and 1940's, or the effects of PCB/PCDF's on other experimental animals.

Implications Regarding Design of Therapeutic Treatments. - It seems to me that the above considerations pose three main questions as regards the development of PCB-antidotes or other therapeutic treatment methodologies.

First, there is little evidence thus far of any need for treatment. The epidemiological studies have not indicated any PCB-related chronic disease in the Hudson Falls plant population. The main PCB used since 1971 (Aroclor 1016) has been reported as of only minimal toxicity in animal studies, and that used over the period 1954-71 (Aroclor 1242) as only slightly less ^{innocuous} innocuous. In addition, all PCB's used for GE capacitor production since the 1930's have been subjected to a fuller's earth purification treatment that would also remove PCDF's; this is very likely the reason why no chloracne has ever been seen among GE capacitor workers. At any event, the absence of chloracne, classically the first and most conspicuous symptom of PCB/PCDF poisoning, argues strongly that other manifestations of such poisoning will also fail to appear.

Second, it is not yet obvious which specific species one should attempt to develop the antidote for, or even how to go about tracking their levels so as to establish the need for such antidotes. Presumably, anyone recently exposed to Aroclor 1016 still has traces of a

few of its less readily metabolized isomers in his blood and fatty tissues, along with the ubiquitous 1-2 ppm of the Aroclor 1254 type of PCB isomers that everyone else has as well, and all these could be readily analysed and followed over the course of time. However, Kuratsune's findings have shown that such gross PCB levels bear little relationship to the clinical status of the patient; hence there may be little point in either following their progression or in developing antidotes for them. Of greater significance might be data on the PCDF's, or on other toxic PCB impurities, conversion products, or metabolites. These, however, present great problems in measurement because of their extraordinarily low levels. Kuratsune's liver-PCDF data came from massive samples obtained from former Yusho patients at autopsy, and any data on the presumably far lower tissue-PCDF levels in capacitor workers would undoubtedly also have to be restricted to specimens of that type.

Third, it is not yet obvious what sort of therapeutic strategy should be employed to get the PCB/PCDF-associated toxicants out of the body. The PCB's themselves are very similar to fats in their solubility/adsorption behavior, and appear in the body non-selectively distributed throughout its fatty tissues. Removal by an adsorption or stimulated excretion route ^{might} ~~would~~ require massive non-metabolic removal of fat as well. The normal mechanism for PCB removal from the body appears to be via microsomal oxidation to soluble metabolites. This could undoubtedly be accelerated by dosage with agents that would stimulate the activities of drug-metabolizing enzymes; however, there are always the risks that (a) this would also accelerate the formation of

toxic metabolites, (b) the liver might be damaged by the treatment, and (c) that the metabolically-inert PCB isomers being attacked are harmless anyway. Conversely, if it really is the PCDF's, not the PCB's that one may want to get out of the body tissues, then a very different - though possibly simpler - therapeutic strategy may be appropriate. The PCDF's are probably capable of specific binding to certain tissue macromolecules, and their elimination and/or functional suppression may require no more than an identification of the normal biochemical species that would otherwise be attached to the PCDF (or PCDD??) binding site and augmenting its level.

~~I hope that this lengthy recital about the complexities of the PCB literature, comparative toxicology of the PCB's, and the nature of PCB effects in humans has not discouraged you, or led you to suspect that we may be trying to discourage further research on PCB effects or treatment for PCB exposure. Quite the contrary. The same interdisciplinary team (under John Brown of our Corporate Research and Development Center) that conducted the literature search and analysis that led to all the concerns I've just stated is also available to help you work out a defensible program for attacking the PCB/PCDF treatment problem, and to collaborate as necessary in its implementation. If you're serious about wanting to find out what really should be done for people who have had past exposures to capacitor grade PCB, so are we. I'd suggest that you invite Dr. Brown down for a seminar on~~

Letter to Dr. Selinkoff (continued)

I hope ~~Dr. Brown~~^{my}'s background information which I have described in more detail than I originally intended, is helpful in developing your therapeutic plan. I suggest that it might be helpful if this same interdisciplinary team, lead by Dr. Brown who conducted the search and analysis which I have just summarized, could visit with you and your associates to work out a mutually satisfactory research program in this area.

After the joint meeting with our research team, Dr. Welch would be most interested in visiting Mt. Sinai to review a more formal proposal for General Electric sponsored research in this area. I can assure you that he is sincere in his desire to support efforts aimed at a better understanding of this PCB issue and will be an enthusiastic supporter of a well thought out proposal on the subject.

Again, my thanks for your continuing support. I will look forward to your reaction to the thoughts I have outlined in this letter.

Very truly yours,

Dr. T. R. Casey

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TABLE I. DISTRIBUTION OF PCB HOMOLOGS IN AROCLORS

Empirical Formula % Cl	Aroclor Grade				
	1221 21	1016 41	1242 42	1254 54	1260 60 (d,a)
C ₁₂ H ₁₀	11	<0.1	<0.1	<0.1	-
C ₁₂ H ₉ Cl	51	1	1	<0.1	-
C ₁₂ H ₈ Cl ₂	32	20	16	0.5	-
C ₁₂ H ₇ Cl ₃	4	57	49	1	-
C ₁₂ H ₆ Cl ₄	2	21	25	21	-
C ₁₂ H ₅ Cl ₅	<0.5	<1 ^c	8	48	12
C ₁₂ H ₄ Cl ₆	ND ^b	<0.1 ^c	1	23	38
C ₁₂ H ₃ Cl ₇	ND	ND	<0.1	6	41
C ₁₂ H ₂ Cl ₈	ND	ND	ND	ND	8
C ₁₂ HCl ₉	-	-	-	-	-

- a. Hutzinger et al., 1974, p. 23
 b. None detected, <0.01% = ND
 c. Product specification, <0.4% for total of all homologs above C₁₂H₆Cl₄ in degree of chlorination. Observed values in 1972-1975 Aroclor 1016 shipments in range 0.05-0.2%.
 d. Older data, may be less accurate

TABLE II. POLYCHLORODIBENZOFURANS (PCDF's) IN COMMERCIAL PCB's

Brand/grade	% Cl	History	PCDF Content (ppm)	Reference
Phenoclor DP-6	60	-	~20	Vos et al., 1976
Phenoclor DP-6	60	-	13.4	Bowes et al., 1975
Clophen A-60	60	-	~ 5	Vos et al., 1976
Clophen A-60	60	-	8.4	Bowes et al., 1975
Kaneclor 300	42	Unused	1.5	Kuratsune, 1976
Kaneclor 400	42	Unused	18-33.	Kuratsune, 1976
Kaneclor 400	42	Used in heat ex- changer	300.	Kuratsune, 1975 ^a
Kaneclor 400	42	Ditto, for "Yusho" oil production	5,000- 12,000.	Kuratsune, 1976
Kaneclor 500	54	Unused	2.5	Kuratsune, 1976
Kaneclor 600	60	Unused	2.7	Kuratsune, 1976
Aroclor 1248	42	1969 Product.	2.0	Bowes et al., 1975
Aroclor 1254	54	1969 "	1.7	Bowes et al., 1975
Aroclor 1254	54	1970 "	1.5	Bowes et al., 1975
Aroclor 1260	60	1969 "	1.0	Bowes et al., 1975
Aroclor 1260	60	Lot AK3	0.8	Bowes et al., 1975
Aroclor 1016	41	1972 Product.	<0.001	Bowes et al., 1975

- a. Verbal report at National Conference on PCB's, November 19-21, 1975, Chicago, Ill., not included in formal paper subsequently published as Kuratsune, 1976.

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TABLE III. CALCULATION OF MAXIMUM NO-EFFECT DOSE RATE FOR PCB/PCDF COMPOSITIONS

(1) Test Subject	(2) PCB/PCDF Tested	(3) Ppm PCDF in PCB (Estimated)	(4) Major Toxic Effect	(5) Max. no-effect, ppm PCB in food	(6) Intake rate, kg. food/kg. body wt.-day	(7) Maximum No-effect dose rate, mg. PCB/kg. body wt.-day
Human	Kaneclor-400 (heat aged)	10,000 ^a	Dermal	(0.5g.) ^c	(~1000 day) ^{k**}	~0.007
Monkey (adult)	Aroclor-1248 (shelf aged)	>>1 ⁿ	Dermal	<2.5 ^d	0.04	<0.1
Monkey (infant)	Aroclor-1248	~1 ^b	Dermal	>300. ^e	0.04	>12.
Mink	Aroclor-1254 (metabolized)	>>10	Hepatic	<0.6 ^f	0.05	<0.03
"	Aroclor-1254	~1 ^b	"	<5. ^g	"	<0.25
Dog	Aroclor-1260	~1 ^b	Hepatic	~10. ^h	0.03	~0.3
	Aroclor-1254	~1 ^b	"	<100.	"	<3.
	Aroclor-1242	~1 ^m	"	>100.	"	>3.
Rat	Aroclor-1260	~1 ^b	Hepatic	~10 ⁱ	0.05	~0.5
	Aroclor-1254	~1 ^b	"			
	Aroclor-1242	~1 ^m	"			
"	Aroclor-1016	0 ^b	"	~100 ^j	"	~5.

Sources

a. Kuratsune, 1976. b. Bowes et al., 1975. c. Kuratsune, 1972. d. Barsotti et al., 1975. e. Abrahamson and Allen, 1973. f. Platanow and Karsted 1973. g. Ringer et al., 1972. h. Keplinger et al., 1971; Calandra, 1975; as interpreted by FDA, 1973. i. Keplinger et al., 1971; Calandra, 1975; Kimbrough et al., 1972; as interpreted by FDA 1973. j. Burse et al., 1974. k. Assumption of FDA, 1973. m. Ax and Hansen, 1975. n. Estimated from progressive increases in toxicity observed in going from early to late (Ref.d) tests. o. Estimated from use of liver, known to concentrate PCDF relative to PCB (Ref.a) as mink food.

* This figure is the maximum no-effect dose in grams of PCB.

** This is FDA's assumption of number of days over which dose is accumulated by humans.

GENERAL ELECTRIC

CORPORATE RESEARCH AND DEVELOPMENT

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DIAL COMM 8*235-

Building K-1, Room 3B35
March 21, 1977

J.F. Welch, Jr.
Vice President and Group Executive
Components and Materials Group
1 Plastics Avenue
Pittsfield, Mass.

Subject: Proposed Middle Section of Letter from ,
Casey to Selikoff Regarding
Proposed R&D on PCB Antidotes

Dear Jack,

The attached represents the technical draft that you requested on March 17. Even after someone shrinks it down to single spacing it will still be a bit longer than you originally asked for; however, I think it may represent the level of detail needed to get our point across to Selikoff. I've also rushed the schedule a bit in hopes of hand delivery this afternoon. Let me know if a revision is needed.

Sincerely,



John F. Brown, Jr.
Mgr. - Life Sciences Branch
PHYSICAL CHEMISTRY LABORATORY

cc: WR Casey, M.D., Fairfield ✓
(+ draft and attach.)
M Aven
LS Moody
AM Bueche



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