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**COMMENTS OF AEROVOX INCORPORATED  
ON THE DRAFT  
"Toxicological Profile for Selected PCBs  
(AROC LOR -1260, -1254, -1248, -1242,  
-1232, -1221, and -1016)"**

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## I. INTRODUCTION AND SUMMARY

### Introduction

This document summarizes the comments of Aerovox Incorporated on the November 1987 Draft "Toxicological Profile for Selected PCBs (AROCOR -1260, -1254, -1248, -1242, -1232, -1221, and -1016)" published by the Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Public Health Service.<sup>1</sup> Aerovox Incorporated is pleased to have the opportunity to submit these comments to ATSDR. Although critical, these comments are designed to be constructive.

### Limited Scope of Critique

Because of time constraints, Aerovox Incorporated requested an extension of the comment period. This request was denied. In consequence, Aerovox Incorporated has had to limit the scope of this critique and focus attention on a few key toxicological and risk-related matters. Therefore, any failure to challenge other points in the ATSDR PCB draft should not be taken to indicate implicit agreement. We would be happy to furnish additional comments if ATSDR were to reconsider its decision and to extend the comment deadline.

### Summary

At the outset, it should be noted that the preparation of a toxicological profile for PCBs is a substantial undertaking. Unlike many chemicals, PCBs are not a single

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<sup>1</sup>This is referred hereinafter as ATSDR PCB draft, or as the Toxicological Profile.

compound, but rather as many as 209 separate compounds (congeners in this case), each with unique chemical/physical/toxicological properties. Various Aroclors, the subject of the ATSDR PCB draft, are mixtures of these congeners, and the concentration of the various congeners in PCBs in the environment may differ substantially from the "parent" Aroclor. Moreover, later evidence suggests that some of the early health effects ascribed to PCBs were actually caused by impurities in the PCBs and not by the PCBs themselves.

Much has been published on PCBs, but the quality of some of the research is uneven--the right variables may not have been measured, or the protocol was otherwise flawed.

For these and other reasons, it is difficult to draft an authoritative summary. The urge to simplify -- ever present in drafting a summary document -- creates a risk of over simplification. ATSDR faces a formidable challenge in drafting a rigorous, yet understandable document.

This difficulty acknowledged, it is Aerovox Incorporated's overall assessment that the ATSDR PCB document is overly simplified to the point of being misleading. The detailed comments that follow underscore this conclusion. Perhaps the most egregious errors in the document are:

- a failure to recognize adequately the congener-specific toxicity and other differences among PCBs,
- the uncritical acceptance of toxicity results based upon highly chlorinated (60% chlorine by weight) Aroclors -- which accounted for only a minority (10.6% over the period 1957-1977) of total Aroclors produced domestically -- as being representative of all Aroclors despite several studies that indicate that highly chlorinated PCBs are, in general, more toxic, and

- reporting only the latest EPA potency estimate, which is based upon highly conservative assumptions applied to a problematic study of what is generally regarded as one of the most toxic Aroclors, as being representative of health effects of all PCBs rather than presenting a more balanced compendium of potency estimates.

ATSDR has perhaps a unique opportunity to write a balanced toxicological profile. Aerovox Incorporated respectfully submits these detailed comments for ATSDR's consideration.

## II. DETAILED COMMENTS

### Detailed Comments

This section presents Aerovox Incorporated's detailed comments on the ATSDR PCB draft.

### Public Health Statement

Section I of the ATSDR PCB draft (pp. I et seq.) consists of an overall public health statement, designed to describe in nontechnical language the relevant toxicological profile of PCBs.

Five general comments on this section are appropriate.

- First, there are numerical errors in the cancer risk calculations presented. The carcinogenic potency,  $P$ , cited (p. 95) is  $7.7 \text{ (mg/kg/day)}^{-1}$  for all PCBs. (For reasons discussed below this potency is inappropriate, but that is another matter.) The carcinogenic risk is the product of the potency and the lifetime average daily dose (LADD). Ingestion of  $1 \text{ mg/kg/day}$  is equivalent to a LADD of,

$$\frac{1 \text{ ug}}{\text{kg day}} \times \frac{\text{mg}}{10^3 \text{ ug}} = \frac{0.001 \text{ mg}}{\text{kg day}}$$

and the corresponding risk would be,

$$R = (P) \text{ LADD} = 7.7 \frac{(\text{kg day})}{\text{mg}} \times \frac{0.001 \text{ mg}}{\text{kg day}} = 0.0077$$

Now, given these estimates, the number of additional cases of concern in a population of 10,000 people would be  $0.0077 (10,000) = 77$  people, not 770 people

as presented in the ATSDR PCB draft (p. 3). A similar order-of-magnitude error is made assuming a population of 10 million people; the correct numerical answer given the potency assumption is 77 thousand, not 770 thousand. (For reasons discussed later the actual number is likely to be much lower.)

- Second, the charts given in Figures 1.1 to 1.3 of the ATSDR PCB are difficult to interpret, particularly for a lay audience. Axes given have "break points" to span orders of magnitude, and the units chosen for several of these axes (i.e., mg/kg/day) do not relate to a lay person's experience. Some careful thought is appropriate to design more useful graphics.
- Third, although the introductory section does qualify assertions regarding the carcinogenicity of PCBs and indicate that, because "upper-limit" risk estimates are quoted, that "actual risk levels are unlikely to be higher and may be lower," the summary discussion is overly simplified and arguably misleading. It is overly simplified because no mention is made in this summary of the problems occasioned by the fact that Aroclors are mixtures of congeners of varying biological activity -- even though this is discussed in generally balanced although incomplete terms later in the document (pp. 49 et seq.). It is misleading, because the EPA risk estimates cited are the most conservative to date and no mention is made of other plausible alternative estimates that are orders-of-magnitude lower. Moreover, the report generally, and the introduction particularly, fail to note that some prominent PCB researchers, such as Dr. Renate Kimbrough (whose works are cited among the references) have concluded in recent reviews<sup>1</sup> that "the only observed acute health effects

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<sup>1</sup>Kimbrough, R. D., "Human Health Effects of Polychlorinated Biphenyls (PCBs) and Polybrominated Biphenyls (PBBs)," Ann. Rev. Pharmacol. Toxicol. Vol. 27, 1987, pp. 87-111.

have generally been minor" and that "so far, no significant chronic health effects have been causally associated with exposure to PCBs."

- Fourth, in citing standards and recommendations, the ATSDR PCB draft omits the fact that some of the standards/recommendations specifically distinguish among the Aroclors. The American Conference of Governmental Industrial Hygienists<sup>2</sup> (ACGIH), for example, recommends different TLVs for Aroclor 1242 and 1254.<sup>3</sup> As a second example, the list of carcinogens recently promulgated by the State of California under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) includes only polychlorinated biphenyls containing 60% or more chlorine by weight.<sup>4</sup>
- Fifth, it is appropriate to revise the wording of the statement in the ATSDR PCB (p. 1) that "Fish become contaminated with PCBs in water, which results in very high accumulation of PCBs in the fish tissue." This statement is overly simplistic and not correct in general. An improved text might read:

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<sup>2</sup>Incorrectly classified as a federal agency (p. 3). Actually ACGIH is a not-for-profit corporation.

<sup>3</sup>This is correctly shown on page 93 of the ATSDR draft, but it is sufficiently important to be noted in the summary. Incidentally, international data (noted as absent on p. 93) are available in the ACGIH.

<sup>4</sup>State of California, Health and Welfare Agency, "Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65), Chemicals Known to Cause Cancer or Reproductive Toxicity," January 1, 1988.

"Fish bioaccumulate PCBs from water, sediment, PCB laden particulates, and via the ingestion of PCB-contaminated prey. The PCB accumulation varies with, inter alia, fish species (lipid content, dietary and other habits, etc.), frequency of exposure, and the concentration of individual PCB congeners. Accumulated PCBs are not evenly distributed in all fish tissue, but rather are generally concentrated in the liver, gall bladder, and other nonedible portions of the fish."

The rationale for this rewording is as follows.

There exists substantial controversy as to whether the major route of exposure to PCBs for fish is via the water, or via the diet. Present understanding of the relationship between PCB adsorption on suspended particulates in the natural environment would suggest that fish are not exposed to high concentrations of PCB dissolved in the water column. Rather, the primary route of PCB exposure is through the ingestion of food organisms that have accumulated PCBs either from the sediment, by the ingestion of PCB-laden particulates, or via the ingestion of PCB-contaminated prey.

Unlike the assertion in the ATSDR PCB draft, PCB exposure need not result in very high accumulation by fish. Accumulation has been studied in depth, and the kinetics of PCB accumulation by fish is well understood. Accumulation depends upon the concentration of PCB to which the fish are exposed, the frequency with which they are exposed, and the species-specific tendency for a fish to accumulate PCB compounds. Not all exposures result in

". . . very high accumulation. . ." Indeed, if fish are exposed to PCBs at long intervals, overall accumulation may be quite low. If fish are exposed to low concentrations of PCBs -- in the water or in the food -- overall accumulation will be quite low. If the fish species of concern is one that has the capacity to either metabolize or excrete PCBs rapidly, then overall PCB accumulation will be quite low.

Third, the statement refers to ". . . the fish tissue." as though accumulation of PCBs in fish was uniform among tissues. It is not. Gross analysis of the distribution of Aroclor PCBs among fish tissues shows that the major sites for PCB accumulation are not in the edible fish; rather, the highest concentrations of PCBs are accumulated in the liver and in the gall bladder. Concentrations accumulated in somatic muscle tissue -- the edible portions of fish -- are generally lower than the concentrations in liver by a factor of from 4 to 10. The pattern of accumulation of specific PCB congeners is approximately the same in liver and muscle.

These comments can easily be incorporated in the public health statement section of the ATSDR PCB draft. Such changes would not only correct factual errors but also would provide useful perspective on the possible health effects of PCBs.

Carcinogenicity (pp. 66 et seq., 94 et seq.)

The ATSDR PCB draft places undue emphasis on EPA estimates of carcinogenic potency. To be sure, such estimates should be discussed. But a balanced appraisal should include a discussion of the conservative nature of EPA's assumptions employed in calculation of carcinogenic potency together with a presentation of alternative potency

estimates. As shown below, the often used phrase "plausible upper-limit estimate" to describe EPA's calculation of potency greatly stretches the meaning of the word "plausible."

#### —General Remarks on EPA's Conservatism

At the outset, it is important to note that EPA's fundamental conceptual approach to estimation of potency employs highly conservative assumptions. This is not merely a partisan assertion, but rather one that is acknowledged by the federal government. Unfortunately EPA policy in calculation of carcinogenic potency muddles risk analysis (the calculation of best estimates based upon all scientific evidence) with risk management (the judgmental resolution of regulatory matters considering all relevant aspects of a decision). The place for conservatism (if at all) should be in the risk management rather than the risk analysis phase of regulatory action. Indeed, "improving coordination and consistency in risk reduction" was one of the principal themes in the recent Executive Office of the President, Office of Management and Budget (OMB) 1986-1987 Regulatory Program.<sup>5</sup> OMB was strongly critical of the conservative assumptions often employed in carcinogen risk and exposure assessment (see Table I), and highlighted the reasons why such practices were flawed<sup>6</sup>:

"Risk Assessments with such extreme conservative biases do not provide decisionmakers with the information they need to formulate an efficient and cost-effective regulatory strategy. Furthermore, the inconsistency of these assumptions makes it virtually impossible to compare risks from different

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<sup>5</sup>Executive Office of the President, Office of Management and Budget, Regulatory Program of the United States Government, April 1, 1986 - March 31, 1987, Washington, D.C., 1986.

<sup>6</sup>Federal Register, Volume 49, Number 100, 22 May 1984, p. 21514.

TABLE I.  
OMB CHARACTERIZATION OF CANCER ASSESSMENT MODELS  
EMPLOYED BY EPA AND OTHER FEDERAL AGENCIES

"A few examples of these cautious or conservative assumptions are: (1) treating all benign tumors as malignant, (2) using data about only the most sensitive animal species and sex, and (3) using conservative mathematical models to extrapolate from high to low doses. Each of these three kinds of assumptions is discussed briefly below.

**All benign tumors treated as malignant.** In interpreting animal studies, agencies frequently interpret both benign (noncancerous) tumors and malignant (cancerous) tumors to be equally strong indications that a substance is a carcinogen. Scientists know, however, that not all benign tumors evolve into malignancies. Studies that treat benign tumors the same as malignant tumors can overstate the real risk present. Some risk assessments based on animal studies have concluded that a chemical is carcinogenic solely because of an increased number of benign tumors. Assuming that all benign tumors will become malignant will not produce a best estimate of the risk.

**Use of most sensitive species and sex.** Even though the results of several animal studies may be available for a particular suspected carcinogen, it is not unusual for the risk estimate to be derived only from the data for the most sensitive exposed species and sex. This conservative approach tends to overpredict the risk to humans, because it assumes that humans are as sensitive as the most sensitive animal tested even when the most sensitive animal tested is hundreds of times more sensitive than any other animal tested. Furthermore, by using the same data to derive the risk estimate and to determine the most sensitive species, the chance is increased that statistical anomalies will lead to overestimates of the risk. (If a statistical anomaly causes an upward bias in the estimated risk for a particular species, it will also increase the chance that that species will be selected as the most sensitive.) A more accurate estimate could be derived from a weighted average of all the scientifically valid, available information.

**Conservative extrapolation from high doses to low doses.** To determine the risks to humans from exposure to a substance, scientists must extrapolate (or estimate) from the results of high doses in animal experiments to the comparatively low doses of human exposure. This extrapolation relies upon statistical models. The risk from exposure to low doses cannot be determined with certainty. In making the extrapolation, the common practice is not to make a best estimate of the risk from human exposure to low doses, but to determine what a maximum risk would be. Often, such an extrapolation has a 95 percent chance of overstating the true risk. Usually, the explanation for using these conservative assumptions is to ensure that the actual risk is not underestimated. However, the resulting risk estimate can be over one hundred times greater than the best estimate of the risk."

Source: Executive Office of the President, Office of Management and Budget, Regulatory Program of the United States Government, April 1, 1986 - March 31, 1987, Washington, D.C., p. xxiv.

sources. It is particularly difficult to compare safety risk estimates, which are usually best estimates, with health risk estimates, which usually are not best estimates, because the latter embody a series of conservative assumptions. Even different estimates of health risks may not be comparable because of the different degrees of conservatism built into them. Where risk estimates for two different risks cannot be compared, it will be impossible to compare the effects of regulations controlling them.

A perverse and unfortunate outcome of using upper-bound estimates based on compounded conservative assumptions is that it may lead us to regulate insignificant risks and ignore more serious risks. Furthermore, the more uncertain we are about the risk posed by a particular hazard, the higher the upper-bound risk estimate will be. Therefore, the less information we have on the risk posed by a potential hazard, the more likely we are to regulate it. Other hazards that pose certain but smaller risks are not considered as dangerous and may not be regulated. Yet, hazards with better understood risks may be more serious.

All the problems we have discussed resulting from compounding conservative assumptions can be addressed by developing best estimates at each stage of the risk assessment process. Estimates of the uncertainty and the outer ranges of potential risk can be developed to supplement the best estimate. Both the best estimate and these supplementary risk indicators should be made available to decisionmakers. Then, if regulatory decision makers want to choose a very cautious strategy of risk control, they could do so and a margin of safety could be applied at the final decision and would be based on all the available information about its consequences and those of alternative strategies. The public and affected parties would also benefit from knowing both the expected risk and the margin of safety rather than being given only alarming and inconsistent estimates that are likely to be very different from actual risks.

Only when best estimates of risks and other information on the likely level of risks are presented to the decision maker, rather than hidden in the assumptions, can we be sure that we are issuing regulations that will make society as well off as possible. Fortunately, more review by regulating departments and agencies and by the Executive Branch has already begun to improve consistency in risk assessment and risk management and, thereby, improve societal welfare. Executive Order No. 12291 provides a mechanism to help ensure consistency." (Emphasis added.)

Seen in this perspective, the conservative assumptions used by EPA in estimation of PCB potencies are potentially counter-productive rather than simply "prudent."

All of the concerns expressed in Table I are legitimate in the case of PCBs, as are others. Key points are highlighted below.

### -Treatment of all PCBs as identical

As the ATSDR PCB draft correctly states (p. 94), "EPA . . . recommended that all commercial PCB mixtures be considered to have a similar carcinogenic potential." This assumption is at variance with an extensive body of scientific knowledge and differs from the approach taken by other regulatory bodies (e.g., the State of California).

As the ATSDR PCB draft notes correctly, commercial PCB preparations (marketed under various trade names by different manufacturers in different countries) are mixtures of various congeners (in all some 209 molecular possibilities, see Figure 1). The approximate composition of several commercial mixtures in terms of the number of chlorine atoms on the biphenyl moiety are shown in Table 2.

To begin, it is important to note that there are no data suitable for direct estimation of PCB cancer potency in humans. Indeed, there is insufficient evidence on which to base any conclusion that PCBs are carcinogenic in humans.<sup>7</sup> Rather, indirect (and mixed) evidence is furnished from experiments with rats and mice. These experiments were conducted at elevated doses (e.g., 25 ppm to 300 ppm in feed) so as to increase response rates and lower requisite animal sample sizes, as is common in studies of this type. The NCI study on Aroclor 1254 used, inter alia, as a basis for EPA's risk estimates and referenced in the ATSDR PCB draft actually stated,<sup>8</sup>

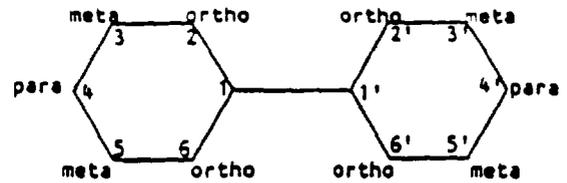
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<sup>7</sup>Drill, Friess, Hays, Loomis, and Schaefer, Inc., Potential Health Effects in the Human From Exposure to Polychlorinated Biphenyls and Related Impurities, Arlington, Virginia, February 1982. See also related report from the same firm, dated 12 February 1982. PCBs are classified 2B in the IARC weight-of-evidence designation (probably carcinogenic in humans; evidence inadequate in humans and sufficient in animals). This is similar to the EPA designation "B2." See also U.S. Environmental Protection Agency, Development of Advisory Levels for Polychlorinated Biphenyls (PCBs) Cleanup, prepared by Exposure Assessment Group, Office of Health and Environmental Assessment, Washington, D.C., OHEA-E-187, May 1986, Final p. D-16.

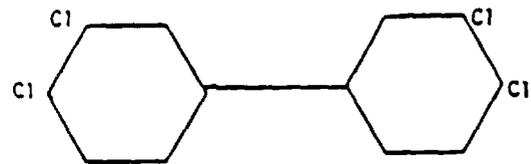
<sup>8</sup>National Cancer Institute Bioassay of Aroclor 1254 For Possible Carcinogenicity, NCI Carcinogenesis Technical Report, Series No. 33, CAS No. 27323-18-8, NCI-CG-TR-38, 1978.

FIGURE 1.  
STRUCTURE, SUBSTITUTION NOMENCLATURE,  
AND NUMBERING SYSTEM FOR PCBs

Substitution Nomenclature  
and Numbering System for PCBs



A Specific Example



3, 3', 4, 4' Tetrachlorobiphenyl

		Chlorine Atoms On First Ring					
		0	1	2	3	4	5
Chlorine Atoms On Second Ring	0	1	3	6	6	3	1
	1		6	18	18	9	3
	2			21	36	18	6
	3				21	18	6
	4					6	3
	5						1

Possible distribution of chlorine atoms in the two rings of biphenyl.

**TABLE 2.**  
**APPROXIMATE PERCENT COMPOSITION OF SOME COMMERCIAL PCB PRODUCTS**

Chlorobiphenyl	Aroclor Type or Grade							Kanechlors			Clophens	
	1016	1221	1232	1242	1248	1254	1260	KC-300	KC-400	KC-500	A 30	A 60
C <sub>12</sub> H <sub>10</sub>	0.1	11	6	0.1	-	0.1	-	-	-	-	-	-
C <sub>12</sub> H <sub>9</sub> Cl	1	51	26	1	-	0.1	-	-	-	-	1	-
C <sub>12</sub> H <sub>8</sub> Cl <sub>2</sub>	20	32	29	16	2	0.5	-	17	3	-	21	1
C <sub>12</sub> H <sub>7</sub> Cl <sub>3</sub>	57	4	24	49	18	1	-	60	33	5	57	2
C <sub>12</sub> H <sub>6</sub> Cl <sub>4</sub>	21	2	15	25	40	21	-	23	44	27	17	3
C <sub>12</sub> H <sub>5</sub> Cl <sub>5</sub>	1	0.5	0.5	8	36	48	12	0.6	16	55	2	20
C <sub>12</sub> H <sub>4</sub> Cl <sub>6</sub>	0.1	-	-	1	4	23	38	-	5	13	-	43
C <sub>12</sub> H <sub>3</sub> Cl <sub>7</sub>	-	-	-	0.1	-	6	41	-	-	-	-	25
C <sub>12</sub> H <sub>2</sub> Cl <sub>8</sub>	-	-	-	-	-	-	8	-	-	-	-	5
C <sub>12</sub> H <sub>1</sub> Cl <sub>9</sub>	-	-	-	-	-	-	1	-	-	-	-	-
C <sub>12</sub> Cl <sub>10</sub>	-	-	-	-	-	-	-	-	-	-	-	-
Average % Chlorine	42%	21%	32%	42%	48%	54%	60%	42%	48%	54%	30%	60%

Sources: Polychlorinated Biphenyls, The National Research Council, National Academy of Sciences, Washington, D.C. 1979.  
Hutzinger, O., S. Safe, and V. Zitko, The Chemistry of PCBs, CRC Press, Boca Raton, Florida, 1980, p. 8.,  
Michael, D. N. Paul, Monsanto, personal communication, and Schaeffer et al., Op. Cit. The figures cited here are for the Clophens taken from Schaeffer.

"It is concluded that under the conditions of this bioassay, Aroclor 1254 was not carcinogenic in Fischer 344 rats,"

a finding that can hardly be termed supportive of EPA's conclusions and which is potentially important in terms of emerging knowledge of the differential toxicity among the various Aroclors.

This observation aside, such a protocol necessitates conversion of results between species (e.g., from mice to humans) and extrapolation of results from the high experimental doses to lower doses more commonly found in environmental exposure. The mechanics of this conversion and extrapolation are subject to much uncertainty and are ultimately contentious. A partial listing of relevant factors includes,<sup>9</sup>

- (i) choice of extrapolation model,
- (ii) background adjustments,
- (iii) statistical fitting procedures used,
- (iv) type of estimate (expected value or upper confidence level)
- (v) dose and exposure assumptions (e.g., effects of cooking, congeners of interest, levels over time)
- (vi) species to human extrapolation basis,
- (vii) response variable measured, and
- (viii) animal experiment used for estimation of the dose-response curve and the specific health effect and endpoint used.

Additionally, with respect to complex mixtures such as PCBs, it is important to identify precisely the composition of the compounds at issue. EPA's own Science Advisory Board (SAB) in reviewing the EPA drinking water document (cited as the source of the potency estimate given in the ATSDR PCB draft) was highly critical of EPA's assumption that all

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<sup>9</sup>Maxim, L. D., and L. Harrington, Everest Consulting Associates, Inc., "A Review of the Food and Drug Administration Risk Analysis for Polychlorinated Biphenyls in Fish," Regulatory Toxicology and Pharmacology, Volume 4, Number 2, June 1984.

PCB mixtures were identical and recommended instead the identification and characterization of congener-specific potency factors.<sup>10,11</sup> This recommendation is potentially important because PCBs found in environmental media could have a congener distribution substantially different from any of the "parent" Aroclor mixtures as a result of environmental exposure (e.g., selective volatilization, soil-water partitioning, photo-degradation, bio-degradation, etc.).

All of this presents a dilemma in terms of formulating a regulatory approach to PCBs. On the one hand normative considerations would appear to argue for a congener-specific approach. But, on the other hand, most of the experimental toxicity data -- at least as regards carcinogenesis -- is based upon results with commercial mixtures. Thus, in a practical sense, it is unclear whether or not a congener-specific approach is warranted. However, it is absolutely clear that all Aroclors should not be regarded as identical. EPA and ATSDR appear to miss this point entirely and to virtually disregard the scientific literature.

For example, the study generally regarded as providing the most convincing evidence of the carcinogenicity of PCBs in rats<sup>12</sup> is that conducted by Kimbrough et al.<sup>13</sup> This Kimbrough study used Aroclor 1260, a mixture containing approximately 60%

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<sup>10</sup>"Major Problems in Drinking Water Document; SAB Recommends EPA Judge PCBs by Isomer Toxicity, Focus on Risky Ones," Inside EPA, Vol. 9, No. 5, Feb. 5, 1988.

<sup>11</sup>"PCB Congener Hazard Ranking Attempt Sought by EPA Advisory Group," Pesticide & Toxic Chemical News, Vol. 16, No. 12, Jan. 27, 1988.

<sup>12</sup>Crump, K. S., and M. D. Masterman, Assessment of Carcinogenic Risks From PCBs in Food, prepared for United States Congress, Office of Technology Assessment, April 1979, p. 24.

<sup>13</sup>Kimbrough, R. D., et al., "Induction of Liver Tumors in Sherman Strain Female Rats by Polychlorinated Biphenyls Aroclor 1260," Journal of the National Cancer Institute, Volume 55, 1975, pp. 1453 et seq.

chlorine (q.v., Table 2). Moreover, the Norback and Weltman study<sup>14</sup> (used as the basis for EPA's recent potency estimate) also used Aroclor 1260 (of unreported purity) for its feeding studies. (Critical remarks on this study are given below.) That these studies used only Aroclor 1260 is important because there is strong evidence from numerous studies that the biological activity of PCBs is a function of the degree of chlorination:

- (i) Feeding experiments over 224 days with Kanechlor 300, 400, and 500 in mice were conducted by Ito et al.<sup>15</sup> Hepatocellular carcinomas were induced only by the highest chlorinated compound, Kanechlor 500 (q.v. Table 2).
- (ii) A study by Schaeffer et al.<sup>16</sup> indicated that at the end of an 800-day feeding experiment, the incidence of hepatocellular carcinoma in mice fed Clophen A 60 (similar to Aroclor 1260 q.v., Table 2) reached 48%, whereas only 3% of those fed Clophen A 30 and 0.8% of the controls were similarly affected. It is unfortunate that ATSDR remarked (p. 72) only that the Schaeffer study "demonstrates that PCB mixtures free from contamination with furans elicit a carcinogenic response." (The study reported that the Clophens were free of chlorinated dibenzofurans, but test method, level of detection, and actual results were not specified.) In fact, the Schaeffer study has much broader implications. Table 3 shows the Schaeffer data. The incidence of hepatocellular carcinoma was elevated (in a statistically significant manner) only for Clophen A60. Thus, the results of this study not only supported other findings that PCB mixtures containing 60% chlorine by weight were associated with hepatocellular carcinoma in rats, but also indicated that PCBs containing lesser amounts of chlorine were not proven to be carcinogenic. Even if it is argued that Clophen A30's lack of significance was solely an artifact of sample size, the raw data is consistent with the finding that the potency of A30 is at most 1/16 that of A60! This finding is absolutely at variance with the EPA presumption that "all PCBs have equal potency," and should be

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<sup>14</sup>Norback, D. H., and R. H. Weltman, "Polychlorinated Biphenyl Induction of Hepatocellular Carcinoma in the Sprague-Dawley Rat," Environmental Health Perspectives, Vol. 60, 1985, pp. 97-105.

<sup>15</sup>Ito, N., et al., "Histopathologic Studies on Liver Tumorigenesis Induced in Mice by Technical Polychlorinated Biphenyls and its Promoting Effect on Liver Tumors Induced by Benzene Hexachloride," Journal National Cancer Institute, Volume 51, 1973, pp. 1637 et seq.

<sup>16</sup>Schaeffer, E., et al., "Pathology of Chronic Polychlorinated Biphenyls (PCB) Feeding in Rats," Toxicology and Applied Pharmacology, Volume 75, 1984, pp. 278-288.

**TABLE 3**  
**Frequency of Hepatocellular Alterations Induced by**  
**Chronic Feeding Studies with**  
**Clophen A30 and Clophen A60**

	# of Foci	Neoplastic Nodules	Hepatocellular carcinoma
Controls (group 1)	6/131 (4.5%)	5/131 (3.8%)	1/131 (0.8%)
Clophen A30 (group 2)	63/130* (48%)	38/130* (29%)	4/130 (3%)
Clophen A60 (group 3)	3/126 (2.4%)	63/126* (50%)	61/126* (48%)

\* denotes a significant difference from the control value ( $P < 0.05$ )

Source: Schaefer, et al., as cited in Harbison et al.

explicitly noted in the ATSDR PCB draft.

(iii) Schaeffer, et al.,<sup>17</sup> also note,

"Both the DHEW Subcommittee on Health Effects of PCBs and PBBs (1978) and Ecobichon (1975) have reported that the toxic potency of PCBs (hepatic enzyme induction, hepatocarcinogenic effect) increases with increasing chlorination and chlorine substitution in the para, ortho, meta positions, respectively."

These and other results support the notion of increasing biological hazard with increasing average degree of chlorination of PCB mixtures. Thus, Kimbrough's and Norback and Weltman's results with Aroclor 1260 have to be viewed as a "worst case," and moreover, an "unlikely worst case" as production of 1260 only accounted for a minority of total domestic PCB production,<sup>18</sup> an important fact that is not given in the ATSDR PCB draft. (Indeed, according to Monsanto, production of Aroclor 1260 accounted for only 10.6% of total Aroclor production over the period 1957-1977.)

#### --Concerns Regarding the Norback and Weltman Study

As noted, the potency estimate cited in the ATSDR PCB draft is based on an EPA analysis of the Norback and Weltman study. Aside from the fact that this study used Aroclor 1260 -- and thus results are not applicable to other Aroclors -- there are other factors which make direct use of this study problematic.

Perhaps chief among these is a feature of the protocol which, ironically, was regarded by EPA as being desirable. That is, some of the animals used in this study had

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<sup>17</sup>Schaeffer, E., et al., "Pathology of Chronic Polychlorinated Biphenyls (PCB) Feeding in Rats," Toxicology and Applied Pharmacology, Volume 75, 1984, pp. 286.

<sup>18</sup>Hutzinger, O., S. Safe, and V. Zitko, The Chemistry of PCBs, CRC Press, Boca Raton, Florida, 1980, p. 9, also personal communication from Dr. Paul Michael, Monsanto Corporation. In the last 20 years of production (1957-1977) the approximate production share for each of the Aroclors was 1221; 0.9%, 1232; 0.2%, 1242; 51.8%, 1248; 6.8%, 1254; 15.7%, 1260; 10.6%, 1262; 0.8%, 1268; 0.3%, 1016; 12.9%.

been partially hepatectomized. This procedure involves anesthetizing the animal with ether and surgically removing the medial left lobe of the liver -- a treatment applied to ten animals (two control and three PCB-treated animals of each sex) at various times. In this way the progressive development of pre-neoplastic conditions leading to tumors could be followed -- a key feature from EPA's perspective. However, this unfortunately introduces a potential bias to the quantitative estimates of potency.

This is because the treated (i.e., hepatectomized) animals appear to have been included in the cancer incidence rate calculation. If so, it is impossible to separate out the effects of the hepatectomy from the effects of the PCBs. It is well known that partial hepatectomy and subsequent treatment with a material that can also promote carcinogenesis can play a synergistic role in the increase in incidence of liver nodules and tumors.<sup>19,20</sup> Since experimental evidence supports the promotional effect of PCBs and agents that are promoters are considered to be different than initiators in the process of carcinogenesis, a synergistic action with hepatectomy cannot be ruled out.

The progression of neoplastic nodules to hepatocellular carcinoma was regarded by EPA as a basis to include these lesions in its estimate of total tumor incidence. Since not enough of the raw data is presented in the original paper and neither the EPA nor ATSDR chooses to provide the needed information, the exact role that the partial hepatectomy may have played in the development of these tumors cannot be

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<sup>19</sup>Pitot, H.C., et al., "A method to quantitate the relative initiating and promoting potencies of hepatocarcinogenic agents in their dose-response relationships to altered hepatic foci." Carcinogenesis, Vol. 8, 1987, pp. 1491 et seq.

<sup>20</sup>Craddock, V. M., "Liver Carcinomas Induced in Rats by Single Administration of Dimethylnitrosamine After Partial Hepatectomy," Nat. Cancer Inst. Vol. 47, 1971, pp. 889-907. See also Kauffman, W. K., Rahija, R. J., MacKenzie, S. A., and Kauffman, D. J., "Cell-cycle Dependent Initiation of Hepato Carcinogenesis in Rats by (+/-)-7R, 8T-dihydroxy 9T, 10T- exoxy - 7, 8, 9, 10 - tetrahydrobenzo (A) pyrene." Cancer Research, Vol. 47, 1987, pp. 3771-3775.

determined. This bias has been noted by other reviewers.<sup>21</sup>

The ATSDR document summarizes the calculation made by the EPA Cancer Assessment Group in their development of a quantitative potency estimate for PCBs, the so called  $q_1^*$  which was stated to be  $7.7 \text{ (mg/kg/day)}^{-1}$ . The previous estimate was based on the study of Kimbrough et al. (cited earlier) and the calculated potency value was less than that calculated for the Norback and Weltman study. This earlier value, namely  $4.3 \text{ (mg/kg/day)}^{-1}$ , is based on a similar dietary exposure concentration of Aroclor 1260, and nearly similar exposure time. The sacrifice times differed and, as a consequence, a greater tumor incidence was found in the study with a later sacrifice time. The appearance of tumors is frequently a function of age at death, by natural causes or sacrifice. Norback and Weltman's use of a test species with low background incidence of disease, the longer period of observation and the arbitrary reduction of dietary PCB feeding led to an outcome where the tumor incidence was nearly 100% in treated females but almost 0% in surviving controls -- apparently an enviable situation from a calculation standpoint.

Unfortunately, the choice by the Agency of an amortised lifetime dose may lead to an inflation of the potency compared to an experiment in which the dose were held constant. By combining nodules with tumors, the nearly 100% occurrence of total tumors at 29 months of age plus the single tested dietary dose allows a simplified calculation that depends almost totally on the choice of values for average daily dose. Had Norback and Weltman allowed the PCB feeding to continue with no reduction in dose, no amortization would have been needed and the resulting potency value would have been

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<sup>21</sup>Harbison, R. D., et al. "Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans," Prepared for Scientific Advisory Panel, Safe Drinking Water and Toxic Enforcement Act, State of California, August 1987.

lower. Because cancer has an appreciable latency, the initial daily dose may be more important in carcinogenesis. The protocol did not permit such a contrast to be drawn, and the dose-response models employed by EPA do not have this feature.

Another important aspect of the Norback and Weltman study results that should be included in the ATSDR PCB draft report was detailed (in another context) by Harbison et al.<sup>22</sup>

"Another important factor to consider, is that almost all of the tumors reported in this study were very late-developing tumors. In their paper, only 4 trabecular carcinomas and only 2 adenocarcinomas had developed between the 18- and 24-month sacrifices. Thus, 35/41 or some 85% of the liver tumors observed in this study developed in the last 25-29 month period of the study. These tumors had not metastasized to other organs, and none appear to have been life-shortening. Concerning this last aspect, unfortunately no information is given concerning the cause of death for any animals dying early, or concerning the number of animals lost. But from the data supplied it would appear that a number of early deaths occurred only in the group of male control animals. These same observations were also noted by the authors, who stated in the discussion of this paper:

"Although the tumors met the morphological criteria for malignancy, their biologic behavior was relatively unaggressive. The neoplasms did not metastasize to distant organs nor invade blood vessels. Mortality of the animals was not increased. The lack of greater morbidity or mortality is likely due to slow progression of the neoplastic process and late appearance and slow growth of the hepocellular carcinoma."

The authors future noted that it remains to be established whether PCBs have an initiating effect or whether the neoplasms observed result from the promotion of a background incidence of initiated cells."

Finally, it is unfortunate that, unlike the NCI study, the Norback and Weltman study used only one progressive dose level of PCB. Use of multiple constant levels could have enabled a wider variety of dose-response models to be fit to the data.

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<sup>22</sup>Harbison, R. D., et al. "Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans," Prepared for Scientific Advisory Panel, Safe Drinking Water and Toxic Enforcement Act, State of California, August 1987.

For all these reasons, the ATSDR should consider carefully how to describe the significance of the results of the Norback and Weltman study, and the resulting potency factor calculated by EPA.

#### —Models Used for Calculation

For the purposes of these comments on the ATSDR document, a carcinogen (or carcinogenic treatment) can be defined as any substance or treatment which causes an increased incidence in the numbers of tumors found in the organism of interest. This statement is consistent with, but is more general than, similar definitions in recent EPA documents.<sup>23</sup> It may be further assumed that carcinogens act in more than one way and likely many different ways to produce lesions or conditions that advance cells on the pathway to cancer. These may be:

1. by directly causing lesions in the genetic information of the cell, namely in the cellular DNA (Initiation).
2. by indirect action, eg., by stimulating cell proliferation as a consequence of repeated injury (Promotion).
3. by oncogene activation not related to genetic damage.
4. by hormonal and receptor mechanisms.
5. by other than the above.

A chemical or a treatment regimen may be an initiator, a promotor, or a complete carcinogen, namely one possessing both actions. Agents that are initiators directly cause lesions in the genetic material, i.e. the cellular DNA (genes and chromosomes) and thus,

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<sup>23</sup>EPA Guidelines for Carcinogen Risk Assessment (August 1986).

are said to exhibit a genetic (or genotoxic) mechanism. The ATSDR implies that this appears not to be the case for PCBs.

If the agent acts indirectly, such as by stimulating cellular proliferation (increase in number of cells) of the population of previously initiated cells (genetically damaged or otherwise activated), the process is more accurately termed promotion. Promotion is one type of indirect mechanism that does not directly affect genes and chromosomes and a chemical which is classified as a promoter is, by definition, an epigenetic carcinogen. In general, epigenetic refers to any carcinogenic mechanism other than the usual genotoxic mechanisms. EPA's use of the linearized multi-stage model for such compounds may be inappropriate and a threshold method of potency estimation might be better applied. In this regard, the 1987 EPA document acknowledges this and says that lacking evidence to support a threshold, the regulatory authority and requirement exists to apply the linearized model.

However, EPA has recently reassessed and lowered risk estimates for, inter alia, dioxins<sup>24</sup> based upon the same promoter versus initiator argument. ATSDR should take a similar approach and recalculate PCB risks.

#### —Significance of the Above

To lend perspective to the above, it should be noted that differences of orders-of-magnitude in the resulting risk estimate can result from, inter alia, differing assumptions as to the appropriate model for calculation, the clinical data set and biological end point used, and the basis for animal-to-human conversion. Table 4 shows illustrative potency calculations -- expressed as the incremental health risk associated with the consumption

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<sup>24</sup>U.S. EPA, Office of Research and Development, "A Cancer Risk-Specific Dose Estimate for 2, 3, 7, 8 TCDD," EPA-600 Review Draft, Nov. 1987.

TABLE 4  
PCB POTENCY — LIFETIME INCREMENTAL HEALTH EFFECTS  
ASSOCIATED WITH A LIFETIME CONSUMPTION OF 1 GRAM OF PCB

<u>RISK PROBABILITY</u>	<u>MODEL</u>	<u>BASIS FOR ANIMAL TO HUMAN CONVERSION</u>	<u>USES UPPER CONFIDENCE BOUND</u>	<u>AROCLOR</u>	<u>BIOASSAY DATA</u>	<u>CALCULATION</u>
less than $10^{-10}$	Probit	ppm	no	1254	NCI Liver Carcinoma Adenomas and Hematopoietic System	Maxim and Harrington
$3.4 \times 10^{-8}$	Logistic	ug/kg	no	1254	NCI Liver Carcinoma and Adenomas	Maxim and Harrington
$2.3 \times 10^{-7}$	Logistic	ppm	no	1254	NCI Liver Carcinoma and Adenomas	Maxim and Harrington
$3.6 \times 10^{-7}$	Extreme Value	ppm	no	1254	NCI Liver Carcinoma and Adenomas	Maxim and Harrington
$3.2 \times 10^{-6}$	Logistic	ppm	no	1254	NCI Hematopoietic System	Maxim and Harrington
$8.7 \times 10^{-6}$	Multistage	ppm	no	1254	NCI Liver Carcinoma and Adenomas	Maxim and Harrington
$1.5 \times 10^{-5}$	One-Hit	mg/kg/day	no	1260	Kimbrough hepatocellular carcinoma	OTA (Crump, see Appendix)
$1.5 \times 10^{-5}$	One-Hit	Unstated	no	1260	Kimbrough hepatocellular carcinoma (see Appendix)	Decision Focus, Inc., Based on EPA-OTS
$3.2 \times 10^{-5}$	Multistage	ppm	no	1254	NCI Hematopoietic System	Maxim and Harrington
$3.6 \times 10^{-5}$	One-Hit	ppm	no	1260	Kimbrough hepatocellular carcinoma	OTA (Crump, see Appendix)
$4.2 \times 10^{-5}$	One-Hit	ppm	99%	1254	NCI Liver Carcinoma and Adenoma	FDA (see Appendix)
$4.2 \times 10^{-5}$	Multistage	mg/kg/day	no	1254	NCI Total Malignancies	EPA-OTS
$6.0 \times 10^{-5}$	One-Hit	ppm	99%	1260	Kimbrough liver carcinoma	FDA (see Appendix)
$6.8 \times 10^{-5}$	Multistage	mg/kg/day	95%	1254	NCI Total Malignancies	EPA-OTS
$1.9 \times 10^{-4}$	One-Hit	ppm	99%	1254	NCI Total Malignancies	FDA (see Appendix)
$2.5 \times 10^{-4}$	Multistage	ug/(kg) <sup>2/3</sup>	no	1254	NCI Total Malignancies	EPA-OTS
$3.2 \times 10^{-4}$	Multistage	mg/kg/day	no	1260	Kimbrough Hepatocellular carcinomas and neoplastic nodules	CAL-Health (see Appendix) Recomputed
$4.1 \times 10^{-4}$	Multistage	ug/(kg) <sup>2/3</sup>	95%	1254	NCI Total Malignancies	EPA-OTS
$1.9 \times 10^{-3}$	?	surface area	no	?	?	CAL-Health (see Appendix)
$2.2 \times 10^{-3}$	?	surface area	?	1260	Kimbrough	EPA-OHEA (see Appendix)
$2.7 \times 10^{-3}$	?	surface area	95%	?	?	CAL-Health (see Appendix)
$4.3 \times 10^{-3}$	Multistage	surface area	95%	1260	Norback and Weltman	EPA cited in ATSDR

of one gram of PCBs over a lifetime. The risk estimates range from less than  $10^{-10}$  to  $4.3 \times 10^{-3}$ , more than seven orders of magnitude. Yet the only result given in the ATSDR document is the EPA estimate which is the largest value among all the estimates. Although not all the above estimates may be regarded as equally likely, all would have some credence in the scientific community. By citing only the largest potency estimate in this list, ATSDR does the reader a disservice. At best, the latest EPA estimate can be characterized as a "worst case" estimate applicable to only one Aroclor formulation -- and one that (as noted) accounted for only a minority of total PCB production.

### New Sections to be Added

Turning now to other matters, there are three sections that should be added to the ATSDR PCB draft. The first is a review of the literature concerning health effects in animals versus humans. Although limited data are available on human exposure, most studies fail to identify significant adverse effects, while the toxicity in animals such as rats, mice, and monkeys has been studied fairly thoroughly. It is unknown whether such a marked difference in effects is the result of dosing, relative resistance, or both. Significantly, morbidity and mortality studies on humans with high exposure levels remain nonrevealing.

Aerovox Incorporated also proposes adding a section to review quantitative and qualitative differences among Aroclors for various toxic parameters including carcinogenesis. This was discussed above.

A section summarizing the scientific literature in the context of the strength of associations should also be added. For example, a table might be devised with three columns identifying the organ system investigated, the reported finding and the strength of the evidence. The basis for the evidence might also be cited, such as clinical Table 4

description, epidemiological study or anecdotal report. The method for determining relative strengths should be described. Table 5 provides an illustration:

**TABLE 5. EVIDENTIAL BASIS**

<u>Organ System</u>	<u>Reported Finding</u>	<u>Strength of Evidence</u>
Skin	Chloracne	Sufficient (several clinical descriptions)
	Malignant Melanoma	Weak (single report)
Liver	Elevated mean SGOT in groups of workers	Strong (several reports)
	Hepatomegaly	Suggestive (single report many negative)
Cancer	Weak	(single study with questionable reliability, several negative)

Finally, it would help the readers of the ATSDR PCB draft to learn how ATSDR critically reviews the literature and what the agency feels the important features of a study to be. This would probably be best accomplished within the body of the document as studies are cited rather than as a separate section.

### Systemic Organ Toxicity

The comments below relate to systemic/target organ toxicity.

### —Developmental Toxicity

Section 2.2.1.1 (p. 15) et seq. of the ATSDR PCB draft reviews inhalational exposure as it relates to developmental toxicity. We are not aware of any animal studies

that investigate such effects. Human data is limited to Taylor<sup>25</sup> who reported a shortened gestation period by 6.6 days for 51 women with presumed direct exposure to PCBs, compared to 337 with presumed indirect exposure. Birthweights were reported to be dependent on gestation period with a difference of 58 gms. As noted in the profile, these differences were quite small. However, the ATSDR PCB draft fails to record that in the same article, Taylor also compared the directly exposed population with community-matched controls. Although not clearly reported, the mean birthweight for the community controls was closer to the directly-exposed group than the indirectly-exposed group, thus making the findings questionable. Further, no confounding factors such as prenatal care, tobacco use, or alcohol use were evaluated.

Writers of the ATSDR PCB draft need to obtain Taylor's expanded data of this same population. Currently in draft form, this paper reports reproductive outcomes for 200 women with direct exposure to PCBs versus 205 without direct exposure. Air monitoring data, correlations with blood PCB levels (higher homologues), tobacco use, alcohol use, medical conditions, pregnancy complications, history of low birth weight prior to exposure, and prenatal care were reported. Unadjusted mean birth weight was 96 gms less in the directly exposed versus the indirectly exposed. However, when adjustments were made with a model incorporating exposure on a continuous scale, a significant difference between groups was not found.

Section 4.3.3.2 (pp. 62 et seq.) of the ATSDR PCB draft reviews studies on environmentally exposed persons (nonoccupational) with presumed oral exposure to PCBs

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<sup>25</sup>Taylor, P. R., Lawrence, C. E., Hwang, H. L., Paulson, A. S., "Polychlorinated Biphenyls: Influence on Birthweight and Gestation. AJPH 74(10), 1984, 1153-1154.

and developmental toxicity. The Fein<sup>26</sup> and Jacobsen<sup>27</sup> series provides data on infants born to 242 women reporting moderate Lake Michigan fish consumption versus 71 who deny fish consumption. The authors report a statistically significant association with fish consumption and birthweight (190 mg), head circumference (0.56 cm), gestational age (4.9 days), and Brazelton Neonatal scale for behavior. These same parameters also correlate with cord serum PCB level. As noted in the ATSDR PCB draft, these differences are minimal and, although reaching statistical significance, are probably only statistical phenomena lacking clinical significance. It should be noted that there are some inconsistencies in the data. Gestational age by one scale (based on last menstrual period) is correlated with self-reported fish consumption but, as measured by another scale (Ballard examination), no correlation exists. The converse is true for cord serum PCB level. A major flaw in these publications is the failure to report maternal and cord serum PCB levels based on consumption. This information is necessary to assess effects and confirm oral exposure. Correlation coefficients are provided but the mean values for each group are not. Indeed, the data in Table II of Fein (1984) show that 71 women deny fish consumption while 242 report eating moderate amounts, but 166 infants had a level less than 3 ng/dl while 75 had levels greater than 3 ng/dl. Finally, there were substantial differences among the groups for alcohol consumption (prior and during pregnancy) and use of cold medications. While these variables were adjusted for, the probability that either of these confounders influenced small differences in gestational age, head

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<sup>26</sup>Fein, G. G., Jacobsen, J. L., Jacobsen, S. W., Schwartz, P. M., and Dowler, J. K., "Prenatal Exposure to Polychlorinated Biphenyls: Effects on Birth Size and Gestational Age," J. of Ped. 105(2), 1984, 315-320.

<sup>27</sup>Jacobsen, J. L., Jacobsen, S. W., Schwartz, P. M., Fein, G. G., Dowler, J. K., "Prenatal Exposure to an Environmental Toxin: A Test of the Multiple Effects Model." Dev. Psycho., 20(4), 1984, 523-532.

circumference, or birthweight remains high. Finally, Jacobsen (1984) was not correctly cited in section 4.3.3.2 as the investigators did not find a statistically significant association between fish consumption and autonomic maturity ( $p < 0.10$ ).

Rogan<sup>28</sup> investigated results of the Brazelton Neonatal Behavioral Assessment Scale, serum PCB levels and PCB milk fat levels. They reported an association with less muscle tone, decreased activity, and abnormal reflexes in neonates, but only at the highest PCB level. On the other hand, there was a more gradual dose-response effect for serum levels of DDE, indicating yet another confounding factor or causative agent.

The Brazelton Scale is a screening tool for detecting developmental abnormalities in neonates. The clinical significance of an abnormal score, and how it relates to problems in early childhood or adulthood, is unknown. In fact, Rogan<sup>29</sup> recently reported a follow-up of those same children assessing number of physicians visits, frequency of infection, and body weights. No adverse effects were found.

The general discussion of developmental toxicity in section 4.3.3.4 of the ATSDR PCB draft should note that Rogan's (1986) findings are not consistent with Fein's (1984), as he did not find associations between decreased birth weight or head circumference and serum PCB levels.

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<sup>28</sup>Rogan, W. J., Gladen, B. C., McKinney, J. D., Carreras, N., Hadry, P., Thullen, J., Tinglestad, J., and Tully, M., "Neonatal Effects of Transplacental Exposure to PCBs and DDE." J. of Ped., 109(2), 1986, 335-341.

<sup>29</sup>Rogan, W. J., Gladen, B. C., McKinney, J. D., Carreras, N., Hardy, P., Thullen, J., Tigelstad, J., and Tully, M., "Polychlorinated Biphenyls (PCBs) and Dichlorodiphenyl Dichloroethene (DDE) in Human Milk: Effects of Growth, Morbidity, and Duration of Lactation." AJPH, 77(10), 1987, 1294-1298.

## -Cutaneous Tissues

An inhalational LOAEL of  $0.07 \text{ mg/m}^3$  is offered by ATSDR for skin effects and based on Fischbein<sup>30</sup> (1979). Reliable information on the primary route of absorption in occupationally exposed persons is lacking. Exposure probably occurs via an inhalational and dermatological route. As is noted in the Toxicological Profile, PCB exposure in the occupational setting is associated with minimal alterations in liver-associated enzymes and chloracne. Fischbein (1979) reports an exposure range of  $0.07$  to  $11 \text{ mg/m}^3$  but does not provide data for the distribution of workers' exposures nor for the prevalence of symptoms. Thus, we do not know the LOAEL for this population. More importantly, Fischbein's (1979) study does not compare prevalence of disease in exposed workers to controls, nor are confounding variables such as other chemical/metal exposures investigated. Thus, we do not even know if the incidence of reported symptoms is truly elevated. The reliance on worker self-reported questionnaires further weakens the findings. Fischbein<sup>31</sup> (1982) reported the dermatological findings in further detail and attempted to find a correlation with blood PCB levels. Workers who were thought to have PCB-related skin effects were compared with an unspecified population, presumably workers without dermatological findings. No statistical differences were found for female workers. A statistically significant difference at the  $p=0.03$  level was reported for males using a Student t-test adjusting for unequal variances but not for

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<sup>30</sup>Fischbein, A., Wolff, M. S., Lilis, R., Thornton, J., and Selikoff, I. J., "Clinical Findings Among PCB-Exposed Capacitor Manufacturing Workers." Ann. NY Aca. Science, 1979, 703-715.

<sup>31</sup>Fischbein, A., Wolff, M. S., Berstein, J., Selikoff, I. J., "Dermatological Findings in Capacitor Manufacturing Workers Exposed to Dielectric Fluids Containing Polychlorinated Biphenyls (PCBs)." Arch. Env. Health, 37(2), 1982, 69-74.

nonparametric tests. Thus, the Fischbein series does not provide sufficient data for estimating inhalation effects of PCBs in humans.

Ouw<sup>32</sup> (1976) is also cited in the context of skin problems caused by PCBs. This study did not utilize a control group either, and symptoms did not correlate with PCB blood levels. Like Fischbein (1979), Ouw (1976) does not provide sufficient data for estimation of symptom prevalence.

Chloracne has been reported in several morbidity studies. As is stated in the Toxicological Profile, correlations between chloracne and duration of exposure or blood PCB level are lacking. It should also be noted that while we do not know the true incidence of chloracne, it appears to be very low.

#### -Liver

A LOAEL of 0.9 mg/m<sup>3</sup> has been reported in the Toxicological Profile for liver effects. Fischbein (1979), the cited reference, is not a reliable reference for establishing a LOAEL, as explained above.

PCB exposure has been associated with alterations in liver-associated enzymes. A distinction should be made between alterations in liver-associated enzymes, liver function tests, and adverse health effects. Blood measurements used in routine clinical practice, such as SGOT, SGPT, and GGT, do not reflect the liver's ability to function as they are not products of liver function per se. True liver function studies are measurements of albumin, prothrombin time, bilirubin, dye clearance, or drug

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<sup>32</sup>Ouw, H. R., Simpson, G. R., Davinders, S., "Use and Health Effects of Aroclor 1242, a Polychlorinated Biphenyl, in an Electrical Industry." Arch. Env. Health, 1976, 189-194.

metabolism. With the exception of Alvares<sup>33</sup> (1977) and Ouw (1976), none of the cited references in the Toxicological Profile measure liver function. Further, elevation of these liver-associated enzymes do not necessarily indicate an adverse health effect. Such an assessment would depend on the degree of elevation. Also, many elevations are reversible (i.e., alcoholism or infectious hepatitis).

Letz<sup>34</sup> (1983) is cited as a reference for evidence of metabolic enzyme induction in organs other than the liver and to support the implication that altered liver enzyme induction can be associated with disease or interference with medical therapy. Letz (1983) is a review study that does not provide original data. The referenced articles from Letz (1983) do not support his claim. For example, Letz (1983) states that altered liver metabolism in humans continues after cessation of exposure. The article cited, Alvares (1979), actually investigates antipyrine half-life in workers with ongoing exposure. In addition, no reference is provided for citing adverse effects on medical therapy or disease. These effects are speculative; while theoretically plausible, the reverse can also be true. The metabolism of toxic chemicals or metabolites can be speeded up with resultant decreased levels of toxic metabolites.

### —Immunological Effects

Data for immunological competence testing in humans exposed to PCBs is quite limited. In addition to the studies measuring globulin levels cited in the ATSDR PCB

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<sup>33</sup>Alvares, A. P., Fischbein, A., Anderson, K. E., and Kappas, A., "Alterations in Drug Metabolism in Workers Exposed to Polychlorinated Biphenyls." Clin. Pharma. and Thera., 22(2), 1977, 140-146.

<sup>34</sup>Letz, G., "The Toxicology of PCBs -- An Overview for Clinicians." West J. Med., 1983, 138-534-540.

draft, the studies by Emmett<sup>35</sup> (1983) and Lawton<sup>36</sup> (1985) should be cited. Emmett (1983) performed delayed hypersensitivity skin testing with mumps and trichophyton in switchgear workers. No significant difference was found between workers with high exposure and those with low exposure. Lawton (1985) performed differential white blood cell counts in capacitor workers and reported a reversible increase in the number of lymphocytes and total white blood cells. Monocyte levels correlated inversely with the log of highly chlorinated blood PCB levels. However, the magnitude of the decrease was quite small. Whether or not these altered monocyte levels influence the immune system is not known but unlikely.

There has been much speculation on the role of PCBs in altering the immune system and changing the incidence of infection or cancer. ATSDR should acknowledge that there is currently insufficient data to support this speculation. The Toxicological Profile notes that immune system function has not been evaluated adequately. However, several morbidity studies (using self-reported questionnaires or interviews by medical personnel) lend themselves to the probable identification of significant effects. As yet, no such effects have been reported.

Regarding cancer, there is insufficient evidence to support the role of PCBs in a defect of immunosurveillance associated with carcinogenesis. Persons with immunodeficiency syndromes are at increased risk for specific types of tumors. However, it is unknown whether immunodeficiency per se is a cause of cancer or a result

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<sup>35</sup>Emmett, E. A., Agnew, J., Bleecker, M. L., Ferrara, J. M., Levin, B. K., Jefferys, J., Maroni, M., "Health Effects of PCB Exposure of GSA Switchgear Employees," NIOSH Health Haz. Eva. Prog. Med. Rep.; Technical Assistance Request #80-7, 1983.

<sup>36</sup>Lawton, R. W., Ross, M. R., Feigold, J., and Brown, J. F., Jr., "Effects of PCB Exposure on Biochemical and Hematological Findings in Capacitor Workers." Env. Health Persp., 60, 1985, 165-184.

immunodeficiency syndromes. In addition, the ATSDR PCB draft correctly states that the available data does not associate a tumorigenic effect with PCB exposure regardless of immune system effects. There is also no evidence that PCBs are associated with autoimmune diseases.

### —Porphyria

The Toxicological Profile states that porphyria has not been noted in Aroclor-exposed persons. Although not cited in the Toxicological Profile, Colombi<sup>37</sup> (1982) performed urinary porphyrin analysis on 67 occupationally exposed persons. They reported an increase in total porphyrin levels but not disturbance in ratios. The authors concluded that this was indicative of the first stage of chemical porphyria. However, as Strik<sup>38</sup> (1980) points out, there needs to be an alteration of copro- to uroporphyrin ratio with values no greater than controls for coproporphyrin, uroporphyrin, or heptacarboxylic porphyrin. Thus, the findings of Colombi (1982) do not provide evidence for abnormal porphyrin metabolism. The significance of an elevated porphyrin level without alterations in individual levels or ratios remains unknown.

Drill<sup>39</sup> (1981) is cited in the Toxicological Profile as speculating that exposure to PCBs can cause an attack of porphyria in patients suffering from acute intermittent

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<sup>37</sup>Colombi, A., Maroni, M., Ferioli, A., Castoldi, M., Jun, L. K., Valla, C., and Foa, V., "Increase in Urinary Porphyrin Excretion in Workers Exposed to Polychlorinated Biphenyls." J. Appl. Tox., 2(3), 1982, 117-121.

<sup>38</sup>Strik, J. J. T. W. A., Debets, F. M. H., and Koss, G., Chemical Porphyria in Halogenated Biphenyls, Terphenyls, Dibenzodioxins, and Related Products. North Holland Biomedical Press, 1980.

<sup>39</sup>Drill, V. A., Freiss, S. L., Hays, H. W., Loomis, T. A., Schaeffer, C. B., Potential Health Effects In the Human From Exposure to Polychlorinated Biphenyls (PCBs) and Related Impurities. Unpublished Report, Arlington, VA: Drill, Freiss, Hays, Loomis, and Schaeffer, Inc., 1981.

porphyria. We know of no PCB morbidity study, mortality study, or even anecdotal case studies reporting acute intermittent porphyria in humans. If such data exists, it should be cited and reviewed. The data from Colombi (1982) suggests that the converse may be true.

#### —Human Studies on Carcinogenicity

Several studies investigate the mortality patterns of persons occupationally exposed to PCBs. The ATSDR PCB draft cites Bahn<sup>40,41</sup> (1976, 1977) for evidence of an increased incidence of malignant melanoma in petrochemical workers. This study is generally not accepted as sufficient evidence because of a very small number of tumors and the small cohort from which they come. In addition, no attempt was made to identify and eliminate potential confounding factors. No other mortality study has been able to reproduce Bahn's (1976) findings.

The Brown and Jones<sup>42</sup> (1981) data has recently been updated. Brown<sup>43</sup> (unpublished - May 1987) includes a larger cohort followed for a total of 55,545 person-years. The overall SMR for malignancy was lower than expected (statistical significance was not reached) and SMRs for individual tumors such as melanoma were not elevated. Brown (May 1987) reported that the SMR for liver, gall bladder, and biliary tract was

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<sup>40</sup>Bahn, A. K., Rosenwaik, I., Hermann, N., Grover, P., Stellman, J., O'Leary, K., "Melanoma After Exposure to PCBs," N. E. J. of Med., Letter to Editor, 1976, p. 450.

<sup>41</sup>Bahn, A. K., Grover, P., Rosenwaik, I., O'Leary, K., Stellman, J., "PCB and Melanoma," New England Journal of Medicine, 296:108. (Cited in EPA 1987a) 1977.

<sup>42</sup>Brown, D. P., Jones, M., "Mortality and Industrial Hygiene Study of Workers Exposed to Polychlorinated Biphenyls," Arch. Env. Hlth, 36 (3), 1981, 120-129.

<sup>43</sup>Brown, D. P., "Mortality of Workers Exposed to Polychlorinated Biphenyls -- An Update," Natl. Inst. Occ. Safety and Hlth, 1987, 1-25.

statistically significantly increased over expected (5 versus 1.9). However, review of the data shows that there was only one liver cancer (adenocarcinoma); the other four included two from the biliary tree and two of unclear origin (although one labeled as metastatic and one as bile duct cancer). Thus, no single type of tumor is elevated, and it was incorrect to group these tumors together from an etiological standpoint as they have very different characteristics (liver tumors are thought to be toxicant or virally related while biliary tumors are not).

Bertazzi<sup>44</sup> (1987) was not reviewed by ATSDR. This study presented mortality data on Italian workers exposed to both Aroclors and Pyralenes. An increased incidence of gastrointestinal tumors in males and hematological neoplasms in females was found. However, data comparing local versus national rates was not consistent. More importantly, there were very liberal inclusion criteria (exposure for as little as three weeks) and a very short latency period for some of the tumors (2.4 months). Finally, there was no consistent type of gastrointestinal malignancy found. Clearly, this study does not indicate an increased SMR for some types of tumors in this cohort.

Yusho data is presented in the Toxicological Profile as evidence for cancer mortality. This is inconsistent with the rest of the ATSDR PCB draft which eliminates such data because of confirmed coexposure to PCDFs and exposure to PCB mixtures other than Aroclors. In addition, there are several methodological flaws in the Amano<sup>45</sup> (1984) study such as poor substantiation of causes of death (identified by questionnaires of deceased relatives), no differentiation of primary from metastatic lesions and no

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<sup>44</sup>Bertazzi, P. A., Riboldi, L., Pesatori, A., Poce, L., and Zocchetti, C., "Cancer Mortality of Capacitor Manufacturing Workers," Am. J. Ind. Med., 11, 1987, 165-176.

<sup>45</sup>Amano, M., Yagi, K., Nakajima, H., Takehara, R., Sakai, H., Umeda, G., "Statistical Observations about the Causes of the Death of Patients with Oil Poisoning," Japan Hygiene, 39(1), 1984, 1-5 (Translated by EPA).

attempt to identify confounding factors. Limited conclusions can be made from Kuratsune's data<sup>46</sup> (1986). He specifically included all liver tumors (metastatic and primary). There are inconsistencies within the tables. Finally, there was no pathological confirmation or medical record review to substantiate the cause of death.

Several animal studies report an increased incidence of hepatocellular carcinoma in rats fed high doses of PCBs (Kimbrough, 1975; Schaeffer, 1984; Norback and Weltman, 1985; and Ito, 1974). In none of these studies were the tumors shown to be aggressive or to have metastasized. Animals studied by Norback and Weltman (1985) had a similar mortality experience as controls. Animals studied in Schaeffer (1984) had a longer survival than controls. There was also a decreased incidence of thymomas and spontaneously occurring glomerulonephritis.

Many animal studies report both a cancer promoting ability of PCBs and a cancer inhibiting ability. For example, Diethylnitrosamine (DEN)-initiated hepatocellular carcinoma was reportedly promoted by very high doses of PCBs (Nishizumi,<sup>47</sup> 1979; Oesterle and Deml,<sup>48</sup> 1983; and Preston,<sup>49</sup> 1981). However, PCB inhibition of DEN-

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<sup>46</sup>Kuratsune, M., 1986. Letter to A. Chiu and D. Bayliss. Carcinogen Assessment Group, Washington, D.C.: EPA. June 30. (Cited in EPA 1987a)

<sup>47</sup>Nishizumi, M., "Effect of Phenobarbital, Dichlorodiphenyltrichloroethane, and Hepatocarcinogenesis," Gann, 70, 1979, 835-837.

<sup>48</sup>Oesterle, D., and Deml, E., "Promoting Effect of Polychlorinated Biphenyls on Development of Enzyme-Altered Islands in Livers of Weaning and Adult Rats," J. Cancer Res. Clin. Oncol., 105, 1983, 141-147.

<sup>49</sup>Preston, B. D., Van Miller, J. P., Moore, R. W., and Allen, J. R., "Promoting Effects of Polychlorinated Biphenyls (Aroclor 254) and Polychlorinated Dibenzofuran-Free Aroclor 1254 on Diethylnitrosamine-Induced Tumorigenesis in the Rat," J Natl. Cancer Inst., 66(3), 1981, 509-515.

initiated tumors has also been reported (Nishizumi,<sup>50</sup> 1980; Makiura,<sup>51</sup> 1974). PCBs have also been reported to inhibit tumor formation from other carcinogens (Kimura,<sup>52</sup> 1976) or inhibit growth of transplanted tumor cells (Kerkvliet,<sup>53</sup> 1977).

#### Comments on Physical/Chemical Properties and Environmental Fate/Transport

Shown below are Aerovox Incorporated's comments on portions of the ATSDR PCB draft that relate to physical/chemical properties and environmental fate/transport of PCBs. These comments are groups under the section headings in the ATSDR PCB draft. Page citations are:

#### -Human Exposure Potential (p. 28. Sect. 2.2.3.2. lines 3-5.)

Experimental monitoring data. . ." The statement in the ATSDR document is a gross oversimplification of the true situation. In fact, PCB concentrations on sediments and suspended particulate matter are not necessarily higher than in the associated water column. As for sediments, it has been demonstrated time and again that the PCB concentration in sedimentary deposits depends upon two factors; 1) particle size-

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<sup>50</sup>Nishizumi, M., "Reduction of Diethylnitrosamine-Induced Hepatoma in Rats Exposed to Polychlorinated Biphenyls Through Their Dams," Gann, 71, 1980, 910-912.

<sup>51</sup>Makiura, S., Aoe, H., Sugihara, S., Hirao, K., Arai, M., and Ito, N., "Inhibitory Effect of Polychlorinated Biphenyls on Liver Tumorigenesis in Rats Treated with 3'-Methyl-4-dimethylaminoazobenzene, N-2-Fluorenylacetamide, and Diethylnitrosamine," J. Natl. Cancer Inst., 53(5), 1974, 1253-1257.

<sup>52</sup>Kimura, N. T., Kanematsu, T., and Baba, T., "Polychlorinated Biphenyl(s) As A Promoter In Experimental Hepatocarcinogenesis in Rats," A. Krebsforsch, 87, 1976, 257-266.

<sup>53</sup>Kerkvliet, N. I., Kimeldorf, D. J., "Antitumor Activity of a Polychlorinated Biphenyl Mixture, Aroclor 1254, in Rats Inoculated with Walker 256 Carcinosarcoma Cells," J. Natl. Cancer Inst., 59(3), 1977, 951-955.

distribution of the sediment and 2) organic carbon content of the sediment. Sediments that are composed of primarily large particles with low organic content (clean sands, fine sands) are generally low in PCB content. Sediments that have a high concentration of organic material are generally higher in PCB content. In addition, it has been demonstrated that the PCB concentration in the sediments from a given water body are generally similar to the PCB concentrations on the suspended particulate matter in the same water body. Since the majority of the PCB in the water column is adsorbed to particulate material, and since the PCB concentration of the sediments is about the same as that of the suspended sediments, the conclusion may be drawn that the PCB concentration in the sediments (dry weight basis) is about the same as the PCB concentration in the water column (dry weight basis of particulates).

(p. 28. Sect. 2.2.3.2. lines 8-10.) This statement comprises an inversion of the actual situation. Lower chlorinated PCBs have a lower octanol-water partition coefficient ( $\log K_{ow}$ ) than higher chlorinated PCBs. However, the  $\log K_{ow}$  values under consideration are very high; 5.3 for dichlorobiphenyls and from 7.0 to 9.0 for pentachloro through octachlorobiphenyls. By any measure, this demonstrates that all PCB congeners partition to particulate matter -- not to water. While it is true that the lower chlorinated PCBs have a higher solubility this does not imply that they partition to water.

(p. 28. Sect. 2.2.3.2. lines 14-16.) "The exposure of lower chlorinated. . ." This statement is inaccurate and based upon a misinterpretation or a misunderstanding of the physical characteristics of PCBs. It is based upon the concept that the lower chlorinated PCBs have a high solubility, and it ignores the fact that PCBs have a substantial vapor pressure. Thus, lower chlorinated PCBs may be present dissolved in filtered water to a slightly greater extent than the higher chlorinated PCBs, unfiltered water with lower

chlorinated PCBs dissolved in it will lose those PCBs to the atmosphere by volatilization. In fact, the ATSDR document mentions PCB volatility in the subsequent paragraph (p. 28. lines 13-16) and in the section on the Environmental Fate of PCBs (p. 77. Section 6.2. Para. 3. lines 5-9.). If volatility is a factor in environmental cycling, volatility must be considered in all aspects of assessing human exposure to PCBs. The final document must take these inconsistencies into account.

--Environmental Considerations (p. 33. Section 2.3.3.3. Para 1.)

Methodology of sufficient sensitivity and specificity to measure PCBs in the environment may exist as "state of the art," if the authors of the report are referring to capillary column Gas Chromatographic analysis for PCB congeners. However, such analysis is certainly not "state of the practice," and is not used routinely in government laboratories at the local, state, and federal levels. Nor, for that matter, is capillary column analysis used routinely in the research community. It is misleading to state that the more common methods used for PCB analysis (packed column Gas Chromatographic analysis) are sufficiently sensitive or specific for fully accurate and meaningful measurement of PCBs in the environment.

It is also misleading to state that the bioavailability of PCBs from environmental media is fairly well understood. Bioavailability studies of PCB transport from the environment to humans, to mammals and to lower vertebrates have been ongoing for relatively few years, and studies completed to date have not yet arrived at a point where it is possible to make accurate prediction of bioaccumulation for other than Aroclor mixtures. The bioavailability -- as well as the metabolism and elimination -- of PCB congeners is not well understood.

Research in which the interaction of PCBs with other pollutants has been studied are quite abundant in the literature, including 1) studies of the adsorption of PCBs simultaneous with other organic pollutants, 2) bioaccumulation of PCBs in parallel with PAHs and organochlorine pesticides, 3) the interaction of PCBs with other pollutants in carcinogenesis, and 4) the relationships that exist between PCB metabolism and the metabolism of pollutants such as PAHs, aflatoxin, and other compounds. It is recommended that additional literature research be undertaken prior to finalization of the ATSDR document on PCBs.

The environmental fate of PCBs is the object of many studies ongoing throughout the nation and the world. ATSDR should make a more thorough literature review before asserting the contrary.

-Toxicity (pp. 49-50. Section 4.3. Para. 1.)

The facts laid out in this summary paragraph are well known to all those involved in the investigation of PCBs and the effects of PCBs on organisms. Their inclusion in this section is testimony to the fact that most studies of the toxicity of Aroclors and PCB mixtures are difficult and challenging to interpret. It is well that the authors have seen fit to include these caveats in the "toxicity" section.

Having made those statements, and having made it clear that assessment of the toxicity of PCB mixtures is difficult due to isomer and congener effects, contamination and other factors, it is incredible that the authors should then proceed to state that ". . . it is assumed that the effects resulting from exposure to a specific Aroclor (a mixture of PCBs) are representative of effects which may be produced by the other Aroclors."

This statement is patently untrue. And for this reason any attempt to derive toxic end points for ALL PCBs based upon results from experiments or observations from a single Aroclor is misleading. It is also probably incorrect.

—Releases to the Environment (p. 77. Section 6.2. Para. 1.)

The list of major sources of PCBs to the environment fails to mention the contribution that has been identified as being from the discharge sewage waste materials, both untreated and treated wastewater effluents. In many systems, particularly in the major urban- industrial areas of the East and West coasts of the U.S. the PCB contribution from sewage may well be the major source of PCBs to aquatic systems.

—Transport and Partitioning (p. 78. Section 6.3.1. Para. 1.)

This paragraph provides, once again, a series of over-generalized statements regarding the environmental fate of PCBs. It is of considerable importance to the adsorption of PCBs to know what the particle-size distribution of adsorbing solids is, as well as the organic carbon content of the particles in question. As stated, the  $\log K_{ow}$  of different PCB congeners vary; thus, the tendency for PCB congeners to adsorb and remain adsorbed to different particles varies. If the particles in question happen to be coarse mineral solids, a very low porportion of any congeners will adsorb. If the particles happen to be organically-enriched, fine detritus particles, as occur in many natural water bodies, all PCBs will be adsorbed quite strongly. The portion of the PCB material that can be desorbed from particles is not a simple function of  $\log K_{ow}$ ; rather, desorption and re-solution of PCB congeners will depend upon the  $\log K_{ow}$ , solubility and vapor pressure of the PCB in question, as well as the size and organic content of the particle(s) to which the material is adsorbed.

It is certainly true that, since PCBs in sediments are present in higher concentrations than dissolved in the water column, they may serve as sinks for environmental distribution. However, this conclusion, stated in such vague terms, fails to present the fact that deep sediments accreted over time retain substantial concentrations (masses) of PCBs. Thus, the "sink" concept must be modified in the sense that PCBs accumulated in deep layers of sediment have been removed from the environmental cycle in proportion to the permanence of the sedimentary deposit. In those instances where PCBs may be detected in sediments that can be dated as having been deposited prior to, say, 1980, one may conclude fairly that those PCBs have been removed from the redistribution process; they have been "sequestered" in sites where their impact on biological and ecological processes will not occur. It is only the PCBs in the very top layers of sedimentary deposits that are available for redistribution.

—Transformation and Degradation (p. 79. Section 6.3.2., Para. 4. lines 1-6.)

This section of the paragraph is rife with over-generalizations and misleading statements. First, the designation of Aroclors as being composed of particular isomer groups of PCBs is too general. For example, Aroclors 1016 and 1242 are not comprised of tetrachlorobiphenyls; Aroclor 1242 contains some tetrachlorobiphenyls, to be sure, but Aroclor 1016 contains far fewer of them than does Aroclor 1242. Aroclor 1016 contains far more di- and trichloro-PCB congeners than does Aroclor 1242. Similarly, Aroclors 1242 and 1254 overlap in their congener distribution in that Aroclor 1254 contains some tetrachlorobiphenyl congeners.

Another over-generalization is the statement that an "Aroclor" may biodegrade "rapidly" or "less rapidly." Rather, some of the congeners that are constituents of

particular Aroclors can be said to be degraded to such an extent that the Aroclor ceases to exist as a conceptual entity on a gas chromatographic tracing.

—Potential For Human Exposure (p. 82. Section 7.2.2. Para 1.)

The paragraph is in complete contradiction with itself. If, in fact, the concentration of PCBs in the ocean is an indication of ". . . the environmental background level. . . ," then one might expect some reasonably consistent concentration of PCBs in oceanic waters. The paragraph itself shows this not to be true. Since PCB concentrations in ocean waters vary tremendously, they reflect local PCB inputs and are not useful as a "background" against which PCB contamination may be measured or evaluated.

In Closing

For all the above reasons, we believe that the ATSDR PCB draft should be substantially revised.

Respectfully Submitted,

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APPENDIX A  
SUPPORT FOR SEVERAL OF THE ESTIMATES  
GIVEN IN TABLE 4

## FDA ESTIMATES

**Source:** FDA as reported in F. Cordle, R. Locke and J. Springer (1982). "Risk Assessment in a Federal Regulatory Agency: An Assessment of Risk Associated with the Human Consumption of Some Species of Fish Contaminated with PCB's, Environmental Health Perspectives, 45, pp. 177-182.

**Statement:** Key facts are contained in Table 4 of this document reproduced on the following page. "50th percentile eaters" consumed an average of 8.46 g/day PCB if no tolerance limit was imposed. The range of risks reported was from 0.9 to 4.1 per 100,000.

**Assumptions:** One-hit model based upon data sets indicated in attached table, 99% confidence limits, ppm in diet, all PCBs in edible material absorbed.

### Computation:

$$\text{Lifetime dose} = \frac{8.46 \times 10^{-6} \text{g}}{\text{day}} \times \frac{365 \text{ days}}{\text{year}} \times \frac{70 \text{ years}}{\text{lifetime}} = 2.16 \times 10^{-1} \text{ grams PCB.}$$

Consider first the  $4.1 \times 10^{-5}$  risk computation,

$$\frac{2.16 \times 10^{-1}}{4.1 \times 10^{-5}} = \frac{1 \text{ gram}}{x} \quad x = 1.9 \times 10^{-4}$$

If the lower risk figure is used corresponding to NCI liver carcinoma and adenomas (male and female rats), then  $x = 4.2 \times 10^{-5}$  is the risk associated with ingestion of 1 gram PCB.

Finally, the FDA analysis of Kimbrough data for liver carcinoma leads to a potency value of  $6.01 \times 10^{-5}$ .

**UPPER CONFIDENCE LIMITS (99%) ON LIFETIME RISKS OF CANCER  
AND PROBLEMS OF REPRODUCTION IN EATERS OF FISH AND SPECIES OF INTEREST**

Study		Lifetime Risks Per 100,000 <sup>a</sup>							
		50th Percentile Eaters				90th Percentile Eaters			
		Assumed no tolerance	Assumed tolerance = 5 ppm <sup>b</sup>	Assumed tolerance = 2 ppm	Assumed tolerance = 1 ppm	Assumed no tolerance	Assumed tolerance = 5 ppm	Assumed tolerance = 2 ppm	Assumed tolerance = 1 ppm
Basis Parameter/Species									
NCI	Total malignancies (male and female rats)	4.1	3.7	2.7	1.6	10.6	9.8	7.2	4.4
NCI	Liver carcinoma and adenomas (male and female rats)	0.9	0.9	0.6	0.4	2.5	2.3	1.7	1.0
NCI	Hematopoietic (male and female rats)	2.7	2.4	1.8	1.1	7.0	6.5	4.7	2.9
Kimbrough	Liver carcinoma	1.3	1.2	0.8	0.5	3.4	3.1	2.3	1.4
Kimbrough	Liver hepatomas (mice)	2.0	1.8	1.2	0.8	5.2	4.8	3.5	2.2

<sup>a</sup>All risks are lifetime risks computed as rates per 100,000 of the population at risk.

<sup>b</sup>For each assumed tolerance, PCB values below tolerance were eliminated.

## OHEA ESTIMATE

Source: Halper, M.P., "Draft TSCA PCB Cleanup Policy," USEPA Office of Pesticides and Toxic Substances, August 23, 1985, p. 14.

Statement: "The OHEA calculation of the human dose associated with a  $1 \times 10^{-6}$  level of oncogenic risk is 0.0175 microgram/day."

Assumptions: Unstated

Computation:

$$\text{Lifetime dose} = \frac{0.0175 \times 10^{-6} \text{ g}}{\text{day}} \times \frac{365 \text{ days}}{\text{year}} \times \frac{70 \text{ years}}{\text{lifetime}} = 4.471 \times 10^{-4} \text{ grams PCB.}$$

Based upon a linear proportionality between lifetime dose and risk,

$$\frac{4.471 \times 10^{-4}}{1 \times 10^{-6}} = \frac{1 \text{ gram}}{x}$$

$$x = 2.237 \times 10^{-3} = \text{lifetime risk associated with ingestion of 1 gram PCB,}$$

$$\text{or rounded} = 2.2 \times 10^{-3} \text{ per gram.}$$

## EPA - DECISION FOCUS

**Source:** Utility Solid Waste Activities Group, Proposed Spill Cleanup Policy and Supporting Studies, Submitted to the United States Environmental Protection Agency, October 15, 1984, p. 28.

**Statement:** "The potential health effects were estimated using PCB dose-response functions developed by the EPA Office of Toxic Substances. For the purpose of this analysis, only major, life-threatening health effects such as cancer were estimated. Converting to a cumulative lifetime deposition basis, these functions estimate the likelihood of an exposed individual incurring cancer as follows:

Base Case -  $1.5 \times 10^{-5}$  X Cumulative PCB Deposition in Grams

Conservative Case -  $4.0 \times 10^{-4}$  X Cumulative PCB Deposition in Grams"

**Assumptions:** "The EPA-OTS document, 'Carcinogenic Risk Assessments of Polychlorinated Biphenyls (PCBs),' reviewed a number of health risk assessments and resulting dose-response relationships. All of the dose-response relationships are conservative, typically assuming surface-area extrapolation from animals, relatively sensitive animal species, and linear extrapolation from high to low doses.

The base case dose-response function used in this analysis corresponds to an OTS analysis of hepatocellular carcinoma based on a one-hit model applied to Kimbrough rat data. The conservative case used the 95 percent upper confidence limit from an EPA-OTS analysis of NCI total malignancies data using a multistage model and conservative rat to human conversions. In both cases, the dose-response functions were based on average daily lifetime doses; for this analysis, they were converted to cumulative lifetime deposition, using an average lifetime of 70 years."

**Note:** It is unclear whether or not this estimate makes any allowance for dermal absorption. If so, the estimate should be adjusted upwards.

## OTA ESTIMATES

**Source:** Crump, K.S. and M.D. Masterman "Assessment of Carcinogenic Risks From PCB's in Food; Prepared for United States Congress, Office of Technology Assessment Under Contract Number 933.1350.0, April 1979, p. 37.

**Key Data:** Following table of best estimates of lifetime extra risk to humans of hepatocellular carcinoma based upon applying a one-hit model to the Kimbrough, et al. (1975) rat study.

<u>Human PCB Dosage</u>	Risks calculated from converting human dose to animal does on the basis of	
	<u>ppm in diet</u>	<u>mg/kg/day</u>
8.7 ug/day (1975 Total Diet Study, Table 2)	1/123,000	1/288,000
3.3 ug/day (1976 Total Diet Study, Table 2)	1/328,000	1/764,000
127 ug/day (Average intake of people consuming more than 24 pounds per year. Lake Michigan fish, Humphrey (1977))	1/8,000	1/20,000

**Assumptions:** Stated above.

**Computation:** Consider first the ppm in diet risk estimate associated with consumption of 3.3 ug/day, resulting in a reported risk of 1/328,000, or  $3.0488 \times 10^{-6}$ .

$$\text{Lifetime dose} = \frac{3.3 \times 10^{-6}}{\text{day}} \times \frac{365 \text{ days}}{\text{year}} \times \frac{70 \text{ years}}{\text{lifetime}} = 8.43 \times 10^{-2} \text{ grams PCB.}$$

Based upon a linear proportionality between lifetime dose and risk,

$$\frac{8.43 \times 10^{-2}}{3.0488 \times 10^{-6}} = \frac{1 \text{ gram}}{x}$$

$$x = 3.616 \times 10^{-5} = \text{lifetime risk associated with ingestion of 1 gram PCB.}$$

Now consider extrapolation based upon mg/kg/day. The same daily intake is associated with a risk of 1/764,000 or  $1.3089 \times 10^{-6}$ .

$$\frac{8.43 \times 10^{-2}}{1.3089 \times 10^{-6}} = \frac{1 \text{ gram}}{x}$$

$$x = 1.553 \times 10^{-5} \text{ or, rounded, } = 1.5 \times 10^{-5} \text{ per gram.}$$

## CAL-HEALTH

Source: D.W. Boyd, et al., Analysis of The Costs and Benefits of Alternative Askarel Transformer Regulatory Options, final report prepared for the Utility Solid Waste Activities Group and Edison Electric Institute, Decision Focus Incorporated, July 1984, pp. A-48, et seq.

**Statement:** "Data on human health effects due to PCBs, other than chloracne, are sparse. It has not been proven that PCBs are a human carcinogen.

CAL-HEALTH: Using a 95 percent (conservative) confidence limit, the average daily for a 50 kg. woman resulting in a  $10^{-6}$  risk of cancer is  $1.46 \times 10^{-8}$  g/day (lifetime). Using a maximum likelihood estimate, the average daily dose for a 65 kg. woman resulting in a  $10^{-6}$  risk of cancer is  $2.05 \times 10^{-8}$  g/day (lifetime)."

**Assumptions:** Surface area extrapolation, other assumptions unstated.

**Computation:** Consider first the maximum likelihood estimate based on a 65 kg woman.

$$\text{Lifetime dose} = \frac{2.05 \times 10^{-8} \text{g}}{\text{day}} \times \frac{365 \text{ days}}{\text{year}} \times \frac{70 \text{ years}}{\text{lifetime}} = 5.238 \times 10^{-4} \text{ grams PCB.}$$

$$\frac{5.238 \times 10^{-4} \text{g}}{1 \times 10^{-6} \text{ risk}} = \frac{1 \text{ gram}}{\text{x risk}} \text{ implies } \text{x} = 1.9 \times 10^{-3}$$

Similar computations for the other case give  $\text{x} = 2.7 \times 10^{-3}$ .

## CAL-HEALTH RECOMPUTED

Source: Gravitz, N., Fan, A., and R.R. Neutra, "Interim Guidelines For Acceptable Exposure Levels in Office Settings Contaminated With PCB and PCB Combustion Products," California Department of Health Services, September 30, 1983, pp. 26 et seq.

Statement: "The maximum likelihood estimate of dose corresponding to a  $1/10^{-6}$  risk level is  $1.72 \times 10^{-6}$  mg/kg/day."

Assumptions: Crump multistage estimate based on Kimbrough data for hepatocellular carcinomas and neoplastic nodules. Species to man extrapolation based on equivalent mg/kg/day figures and average human weight equal to 70 kg. Note that this extrapolation was not used in this Cal-Health document.

Computation:

$$\text{Lifetime} = \frac{1.72 \times 10^{-6} \text{ mg}}{\text{kg day}} \times \frac{1 \text{ gram}}{1000 \text{ mg}} \times 70 \text{ kg} \times \frac{365 \text{ days}}{\text{year}} \times \frac{70 \text{ years}}{\text{lifetime}} = 3.076 \times 10^{-3} \text{ grams}$$

$$\text{Risk} = \frac{3.076 \times 10^{-3} \text{ gr}}{1 \times 10^{-6} \text{ risk}} = \frac{1 \text{ gram}}{\text{x risk}}, \text{ x} = 3.2 \times 10^{-4} \text{ risk/gram.}$$

## EPA MOST RECENT

The most recent potency estimated cited in the ATSDR PCB draft is  $7.7 \text{ (mg/kg day)}^{-1}$ . For units conversion to risk/gm., note that a reference person of weight 70 kg who absorbs a dose of 1 gram PCB over a nominal 70-year-human lifespan would absorb a lifetime average daily dose (LADD) of,

$$\frac{1 \text{ gm PCB}}{\text{lifetime}} \times \frac{1 \text{ lifetime}}{70 \text{ years}} \times \frac{1 \text{ year}}{365 \text{ days}} \times \frac{1000 \text{ mg}}{\text{gm PCB}} \times \frac{1}{70 \text{ kg}} = 5.591 \times 10^{-4}$$

Thus the risk per gram of PCB is  $7.7 (5.59 \times 10^{-4}) = 4.3 \times 10^{-3}$ .