

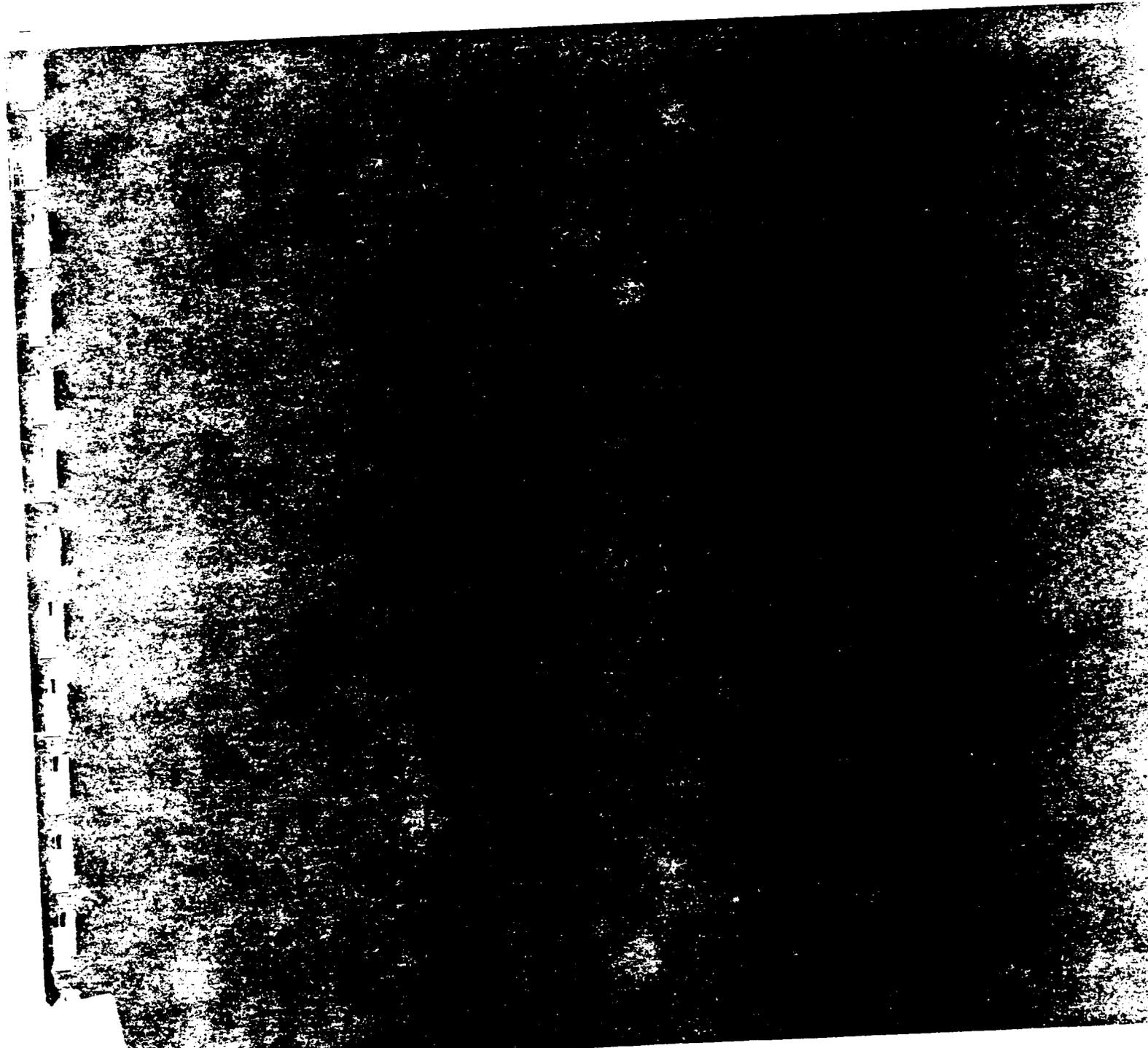
COMMENTS OF AVX CORPORATION

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on

ATSDR's Draft PCB Profile:

"Toxicological Profile for Selected PCBs"
(Aroclor 1260, -1254, -1248, -1242, -1232, -1221, and -1016)



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Ms. Georgi Jones, Director
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Department of Health & Human Services
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Re: Docket Control No. ATSDR-2: Comments on ATSDR
Draft Toxicological Profile for Selected PCB's

Dear Ms. Jones:

Five copies of comments on the ATSDR Draft Toxicological Profile for Selected PCB's ("PCB Profile") are submitted herewith on behalf of AVX Corporation. As our comments make clear in greater detail, the PCB Profile in its present form has misinterpreted and failed to cite important data and mistakenly makes unsupportable and unfounded assumptions. Moreover, the draft PCB Profile is so poorly presented and edited that its effect will be to confuse and mislead, rather than inform, the general public.

We have five particular areas of concern that we wish to stress, although many other problems are noted in the comments. First, an approach that is used throughout the document is its treatment of all PCB Aroclors as having the same toxicity. This assumption is scientifically invalid because it is contradicted by research on this subject, and the result of ATSDR's reliance on this assumption can only be that the public will be misinformed. Second, the draft PCB Profile erroneously describes fish consumption as the major source of

Ms. Georgi Jones, Director
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exposure of the public to PCBs. This error is shown by the PCB Profile's own data, in Table 2.3, and must be corrected to avoid creating unnecessary alarm in the readers of the PCB Profile.

Third, the draft PCB Profile in three places erroneously describes the EPA estimates of risk from PCB exposure. Because the basis, use and limitations of EPA's cancer risk estimates, which are derived from animal studies, are not explained, the draft PCB Profile gives the impression that the EPA risk numbers represent actual human risk, which they do not. Again, the result of these errors will be to create unnecessary alarm in the public.

The PCB Profile also misrepresents the potential carcinogenicity of PCBs. ATSDR appears to have selectively avoided both data that does not support its conclusions and also data that limits the human relevance of the animal data that ATSDR relies upon. In addition, ATSDR has misrepresented the findings of several studies and articles. Given the pervasive presence of PCBs in our environment, ATSDR's apparently intentional exaggeration of qualitative cancer risk is a disservice to the public.

The draft PCB Profile's treatment of studies on developmental toxicity reveals a bias that again leads to unwarranted and erroneously alarming conclusions. ATSDR relies upon inconclusive studies, and in other instances, studies that ATSDR itself, its peer review group, and our experts view as seriously flawed. This reliance is indefensible in light of this unanimous opinion.

As a result of the many inadequacies of the PCB Profile that we note in our comments, the usefulness of the draft PCB Profile is extremely limited. We urge ATSDR to revise the draft to incorporate our comments and other constructive criticism. Unless the draft is thoroughly and accurately revised, the PCB Profile cannot be used as a basis for clean-up decisions at Superfund sites, including the New Bedford Harbor site, at which AVX Corporation has been named as a potentially responsible party and sued in a cost recovery action.

Among the most obvious reasons for revising the draft before using it for decision-making, in addition to those set forth in the enclosed comments, is the fact that the draft PCB Profile itself states that the human data it relied upon is inadequate. In addition, the scope of ATSDR's assignment has necessarily caused ATSDR to reach conclusions on subjects

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beyond ATSDR's and its contractor's expertise, such as the environmental behavior and fate of PCBs. As explained in more detail in our comments, the PCB Profile's simplistic and sweeping statements on the subjects of fate and transport, bioavailability, transformation, and degradation of PCBs in the environment are belied by both scientific research and the multimillion dollar studies that are currently being performed in New Bedford Harbor and elsewhere. ATSDR itself states that a better understanding of environmental cycling of PCBs, especially in sediments, is needed in order to assess exposure. This draft PCB Profile therefore cannot be used with any validity to resolve questions concerning human exposure to PCBs in sediments or effects of PCBs on humans.

Another flaw in the PCB Profile is that the authors either ignored or were ignorant of the results of the Greater New Bedford Public Health Study ("New Bedford Study"). The PCB Profile describes the New Bedford Study as ongoing when in fact it was completed and released three months before the release of the PCB Profile. The New Bedford Study showed that "exposure" to PCBs in fish caused neither elevated blood serum PCB levels nor adverse health effects in the area addressed by the New Bedford Study (blood pressure). Obviously the results of the New Bedford Study are of great significance to the PCB Profile, and the PCB Profile must be revised to take account of the New Bedford Study.

Last but certainly not least, the public has not received meaningful opportunity to comment on the draft PCB Profile. As you know, despite our (and others') repeated verbal and written requests for the PCB Profile, we did not receive the draft PCB Profile until early December, 1987, approximately six weeks after the Profile's purported availability to the public on October 29, 1987. Half of the comment period had elapsed before we received the document. Obviously our intention is to provide thorough and constructive criticism. Because ATSDR's delay cut the comment period in half, we have been prevented from addressing all the problems we see in the draft PCB Profile; and therefore our submission of comments should not be viewed as a waiver of our rights to challenge the contents of the PCB Profile at a later date.

The reasons for ATSDR's delay are inexcusable given the importance of the PCB Profile. Despite many advance requests for the document, ATSDR made only forty-five copies for public distribution and therefore ran out of copies almost immediately. In addition, your office lost our written request for the draft PCB Profile. When we eventually learned, through

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a telephone inquiry, that we had not received the PCB Profile because ATSDR had lost our request for a copy, we were required to submit a new written request and then wait for a new printing of the draft PCB Profile.

Faced with the loss of half of the comment period because of ATSDR's errors, we promptly requested an extension of the comment period until April 7, 1988 to enable our consultants to develop the "comment and feedback" that ATSDR had stated was welcome (52 Fed. Reg. 38341, October 15, 1987). ATSDR denied the extension, and the consequence of this denial is that our comments were developed in a very short time period and are not as thorough as we would have wished. ATSDR's actions -- failing to meet its own statutory deadline, cutting short the comment period through its own administrative inefficiency, and refusing to extend the comment period to ensure that the public could submit thoughtful and fully researched comments -- strongly suggest that ATSDR is not interested in receiving thorough comments from the public.

We hope that AVX Corporation and other members of the public who comment on the PCB Profile will not receive the same short shrift ATSDR's peer review group received. ATSDR's actions and public statements by ATSDR representatives indicate that it is doubtful that ATSDR will perform a meaningful revision of the PCB Profile for at least three years. We strongly urge ATSDR to take the time necessary to fulfill its statutory mandate to prepare a toxicology profile that will provide the public with a meaningful and accurate presentation of all of the significant scientific research on PCBs. In the meantime, however, ATSDR's hurried and incomplete work on this draft PCB Profile, coupled with the shortened comment period that has resulted in depriving the public of meaningful input, are compelling reasons for not using the current PCB Profile in connection with the evaluation and decision-making processes in the Superfund program prior to the revision of the PCB Profile.

If you have any questions on our comments, please direct them to me at the above address. Thank you for your attention to this matter.

Sincerely,



Anne Rogers

AR/jas

COMMENTS OF AVX CORPORATION

on

ATSDR's Draft PCB Profile:

"Toxicological Profile for Selected PCBs"

(Aroclor 1260, -1254, -1248, -1242, -1232, -1221, and -1016)

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EXECUTIVE SUMMARY

The Superfund Amendments and Reauthorization Act of 1986 directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles of the 100 chemicals determined by EPA and ATSDR to pose the most significant potential threat to human health. The purpose of each toxicological profile, as stated in the forward of the draft Toxicological Profile For Selected PCBs (PCB Profile), is to identify and review the key literature that describes the hazardous substance's toxicological properties. The forward notes that it is not the intent of ATSDR to generate a profile that is an exhaustive, comprehensive source of specialty information because the principal audience of these profiles includes private sector organizations and members of the general public. It is, however, the acknowledged intent of ATSDR to revise these toxicological profiles, either in response to public comments or as additional data becomes available. This review and critique of the draft PCB Profile was performed with the intent of improving a document whose principal audience may be non-scientist members of the general public or private sector organizations. The general and specific comments which follow this executive summary point out the most serious flaws in this draft document so that the public might be more accurately informed.

The chief criticism of the current draft of the PCB Profile is that it misinterprets and fails to cite important data, mistakenly makes insupportable and unfounded assumptions, and is poorly prepared and edited. It is the opinion of this review group as well as the opinion of ATSDR's own peer review group that the general public will be confused, seriously misled, and misinformed by the contents of the current draft. Clearly half of the specific comments made about the draft PCB Profile fall under the general category of criticizing biased or misleading statements. Given the fact that the heart of this draft document (i.e. public health statement, health effects summary and toxicological data) is approximately 60 pages in length, it is disconcerting to find some 60 specific comments have been listed in this critique, each of which, in the opinion of the reviewers, represents a serious

technical error. It is also troubling that the general and specific comments, while intentionally kept brief, are as long as the draft PCB Profile itself. It is important that ATSDR revise this toxicological profile so that a more accurate presentation of the existing toxicological information concerning PCBs will be provided to the public and health professionals who may choose to rely solely upon this document. The major problems, which are discussed in more detail in the general and specific comments section of this report, are summarized only briefly in the following paragraphs.

ATSDR repeatedly misleads the reader by stating that contaminated fish is the major source of PCB exposure for the general population. This unsupported assumption made by the contractor (Syracuse Research Corporation) simply is not true, and ATSDR should remove all such statements from the draft PCB Profile. Calculations based on estimates of PCB levels generally found in fish and other food items show that the amount of PCBs ingested each day is much less than the daily exposure to PCBs from breathing indoor air and touching indoor surfaces. Breathing indoor air contributes 5-6 μg of PCBs to our total daily PCB exposure while, as stated on pages 85-86 of the ATSDR document, it is estimated that food contributes only about 0.21 μg of PCBs each day. Additionally, studies of fish-eating populations such as those listed in Table 2.3 of the draft PCB Profile itself and the recently completed study of residents from Greater New Bedford, MA, clearly indicate that the "average" fish-eater has a serum PCB level that does not differ from the 1-40 ppb levels typically reported for the general population.

The draft PCB Profile's discussion of the EPA's estimate of risk associated with PCB exposure is inappropriate, inaccurate, and misleading. While the draft PCB Profile reports that no adverse effects other than chloracne and minor liver changes have been found in capacitor workers experiencing daily PCB exposures far greater than that of the general public, ATSDR proceeds to cite the EPA's risk numbers derived from animal data without any discussion of the basis, the use, or the limitations of estimating human risk on the basis of animal test data. It should be obvious to ATSDR

that the general public and many of the health professionals reading this document will not understand why or how these numbers were derived, how they might be used, and the many limitations inherent in the current risk assessment process. For this reason, the reader may be easily misled into believing these numbers represent the actual human risk when in fact they do not.

There are several other problems with the manner in which the ATSDR document handles the subject of cancer risk. For example, ATSDR has miscalculated the risk associated with a 1 $\mu\text{g}/\text{kg}/\text{day}$ dose on page 3 of the "PUBLIC HEALTH STATEMENT" section. To make matters worse this miscalculation was based on the wrong cancer potency number. ATSDR also fails provide the reader with any information or discussion of relative risk factors, i.e. those risks associated with the regulation of other chemicals or with common, daily activities that every person assumes are virtually risk free. Without this perspective, the average reader cannot reach an informed decision on whether the risk associated with some degree of PCB exposure is an acceptably small risk.

ATSDR's discussions of the potential carcinogenicity of PCBs is also inappropriate, inaccurate, and misleading. The ATSDR summary of the animal studies selectively avoids reporting key data, for instance that only mixtures of 60% chlorine content are clearly animal carcinogens, that PCBs decrease the incidence of extra-hepatic tumors resulting in either a normal or lower than expected total tumor incidence, that PCB-induced tumors lack the characteristics of malignant tumors, and that chronic PCB exposure does not shorten the lifespan of animals. These findings are definitely contradict the public perception of the malignant, life-shortening human cancer that we all try to prevent by reducing our exposure to known human carcinogens. By ignoring such important information it appears that ATSDR misleads the reader by exaggerating the qualitative cancer hazards of PCBs to humans, especially for those PCB mixtures of less than 60% chlorine. In contrast to the misplaced emphasis on the animal data, ATSDR fails repeatedly to make clear that no association between PCBs and human cancer has been observed in occupationally exposed persons with PCB exposures 3-4 orders of magnitude greater than those commonly found

in the environment.

ATSDR should adopt the advice of one of its peer reviewers, Dr. Que Hee, and abbreviate its constant referral to the inconclusive and poorly controlled studies it has listed under the heading of developmental toxicity. None of the studies attempting to correlate serum PCB levels or environmental exposures to effects in newborn infants has demonstrated any adverse effects. Most of these studies suffer innumerable deficits in experimental design. For example, failing to properly control for important confounding variables in the normal population, such as smoking or alcohol ingestion. Each has tended to study women whose serum PCB levels are not elevated or significantly different from the general population. ATSDR, its peer review panel, and the present critique all find these studies to be inconclusive and incapable of attributing the subclinical changes to PCBs (or to any chemical for that matter). Reference to these studies therefore, should be either deleted or mentioned only briefly with an explanation of the severe limitations of these studies.

ATSDR should change its inconsistent discussion of the clinical studies of capacitor workers. As stated by Smith and others, none of the published occupational or epidemiologic studies has demonstrated any adverse health effects in humans exposed to high levels of PCBs except for a reversible skin condition, chloracne. In several instances ATSDR has incorrectly cited studies as evidence that liver injury was found, only later to state correctly that the studies in question actually found no such evidence. These contradictions must be removed. Such obvious contradictions indicate that some areas of the document were written by inexperienced or unknowledgeable persons. This criticism was also lodged, in a slightly different manner, by one of the members of the peer review group who noted that frequently only the abstracts of the papers were cited rather than the actual contents of the article being discussed. Regardless of the actual reasons for these misstatements, ATSDR should re-evaluate its discussions of the clinical studies because no evidence of liver injury has ever been observed.

In several instances the draft PCB Profile has attempted to portray all commercial PCB mixtures (i.e. the different Aroclors) as though they have equivalent toxicities. Both the draft PCB Profile and the scientific literature ignored by ATSDR are replete with contrary evidence. The fact that different PCB mixtures should be treated separately has been noted by federal regulatory agencies (e.g. OSHA has promulgated separate PELs for PCB mixtures of different chlorine content), by state regulatory agencies (e.g. the Science Advisory Panel differentiated by chlorine content for the "Safe Drinking Water and Toxic Enforcement Act of 1986" in California), and by the EPA itself (e.g. the incidental generators rule and in recent recommendations made by EPA's Halogenated Organics Subcommittee of the EPA Science Advisory Board). Seven different commercial PCB mixtures, i.e. Aroclor-1260, -1254, -1248, -1242, -1232, -1221, and -1016 were listed in the announcement on the PCB Profile in Volume 52 of the *Federal Register*, page 12869, April 17, 1987. ATSDR's list of different PCB mixtures, coupled with the prevailing regulatory attitude, led many to assume, and rightly so, that ATSDR's draft PCB Profile would treat the different commercial PCB mixtures separately. ATSDR is well aware that important differences do exist between PCB mixtures as well as PCB congeners. Because its current approach is both scientifically indefensible and contrary to the view held by the scientific community, ATSDR must abandon its approach of treating all PCBs as having equivalent toxicities and toxic potencies.

A major deficiency in the draft PCB Profile is that it contains clear and unequivocal evidence of bias, exaggeration, and inconsistency in the interpretation of data. All of these problems will contribute significantly to the mistaken impression the general public will receive as a result of reading this document. Many examples of these types of problems could be discussed, indeed most of the specific comments address questions of bias, exaggeration, inconsistency, and poor public understanding. In this executive summary, however, only one representative example will be mentioned. After stating on page 42 that the Yusho incident would not be reviewed in the ATSDR report because the effects cannot be specifically ascribed to PCBs, the report proceeds to discuss Yusho in three different areas of toxicology (pages 56, 65 and 69). The

difference between what ATSDR concludes and what it does underscores the need to revise the draft PCB Profile so that such inconsistencies will not undermine the credibility of both ATSDR and this document.

A related criticism of this report is that the contractor, SRC, has in several instances made totally unfounded assumptions or conclusions which ATSDR has failed to recognize. Two such examples occur within the first two pages of the document, the first, when fish is assumed to be the major source of PCB exposure in the environment, and the second, when ATSDR states that serum PCB levels reflect acute exposure to PCBs. ATSDR was not tasked to provide speculation where the amount of available data was so inadequate that informed judgments could not be made. Rather, ATSDR was tasked to provide accurate summaries of actual data in a clear, concise, and informative manner.

ATSDR has chosen a very poor and confusing format for this document. This is the opinion not only of this review group but also of the senior member of ATSDR's own peer review group. A common complaint of both review groups is the separation of toxicological data by route of exposure. This approach only fragments the information, provides no obvious advantage, and serves no useful purpose. We agree with the peer review group that the *"reviewed document is absolutely unacceptable in its present form."*

Finally, this review strongly urges ATSDR to honor the commitment made in the forward of the draft PCB Profile to revise this draft document as public comments or additional data become available. It is disturbing to find that a number of the criticisms of the present draft were also submitted to SRC by the peer review group assigned to review an earlier draft. The present reviewers feel that SRC's failure to incorporate those comments circumvented the peer review process, a process which provides the basis for obtaining an opinion representing the consensus of the scientific community. Despite scientific controversy on specific issues, ATSDR should realize that the public is most interested in understanding the consensus of scientific opinion, not just

opinions that may be skewed to support some preconceived regulatory point of view.

In conclusion, we have tried to point out the most serious flaws in this draft document so that the public might be more accurately informed about PCBs. We wish to reiterate that the PCB Profile as currently drafted has misinterpreted and failed to cite important data, and is so poorly prepared and edited that the general public will be seriously misled and misinformed. This unfortunate result is not in the best interests of the general public or ATSDR, which seeks to serve the general public. With the best interests of all in mind, it is sincerely hoped that these comments will be incorporated into a revision of the current draft so that the final version will be a report that can be relied upon by the lay audience for which it was intended.

GENERAL COMMENTS

1. ATSDR has assumed that fish is a major source of PCB exposure from the environment. This assumption is incorrect and ATSDR must admit it cannot defend it.

On the second page of the PCB Profile, and in several other places, ATSDR has told the reader that consumption of fish is the major source of PCB exposure for the general public. This assumption simply is not true and ATSDR should remove all such statements from this document. The following can easily be cited as evidence that fish consumption does not significantly impact the PCB body burdens of the general population:

- a) When the dose of PCBs coming from indoor air is calculated, ignoring dermal contact with contaminated indoor surfaces, it is clear that this source contributes about 5-6 micrograms of PCBs per day (see specific comment #1 for details). In contrast, the concentration of PCBs coming from the types and sources of fish eaten by most of the general U.S. population is surely less than 0.1 ppm. ATSDR also ignores the fact that fish are generally filleted prior to cooking (e.g. tuna, and fillets of large trout or saltwater varieties). Both this procedure and cooking have been shown to reduce dramatically the content of PCBs found in the edible portion of the fish. Thus, even though the average person might consume about 6.5 grams of fish each day, the intake of PCBs would still be ≤ 0.65 micrograms of PCBs per day. In short, the amount of PCBs coming to the general population via fish is probably less than 10% of the amount encountered in our general indoor environment. [Note: On p.86 of the PCB Profile ATSDR indicates food constitutes a 0.003 $\mu\text{g}/\text{kg}/\text{day}$ exposure which represents a 0.21 $\mu\text{g}/\text{day}$ intake for a 70 kg man.]
- b) In support of the above calculations, it is clear that most "fish-eaters" do not contain more PCBs than are found in the general population. This fact was clearly demonstrated in the recently published study of residents in Greater New Bedford, MA. This finding is also supported by Table 2.3 of

the ATSDR document itself. When one compares pages 24 and 25, it is clear that although some fish-eaters have higher PCB levels, the mean values of these study populations fall within the ≤ 40 ppb serum PCB level that has generally been observed in nonoccupationally exposed persons (see specific comment #18). Since Table 2.3 and the New Bedford study clearly indicate that persons eating fish from PCB contaminated waters tend to have normal PCB levels, fish cannot represent a major source of PCB exposure for the general population.

2. The manner in which the PCB Profile has handled the text describing the EPA's estimate of risk associated with PCB exposure is inappropriate, inaccurate, and misleading.

The ATSDR makes mention of the EPA's cancer risk estimates for PCBs (based on animal data) on pages 3, 19, and 95. It should be obvious to ATSDR that the general public and many of the health professionals reading this document will have little, if any, understanding of how these numbers have been derived, how they might be used, and the limitations inherent to these risk estimates. For this reason, the reader may be misled into thinking that they represent the actual human risk when in fact they do not. Since the intent of this document is to provide a summary of the key information pertinent to PCBs, a discussion of the basis, the use of, and the limitations of any estimates of risk provided in this document is necessary. As demonstrated in specific comment #3, ATSDR has miscalculated the risks associated with a $1 \mu\text{g}/\text{kg}/\text{day}$ exposure. As revealed in the Syracuse Research Corporation's own report of the peer review group's comments, the $7.7 (\text{mg}/\text{kg}/\text{day})^{-1}$ unit cancer risk was mistakenly used in the ATSDR PCB document and should be replaced by the EPA's $5.7 (\text{mg}/\text{kg}/\text{day})^{-1}$ unit cancer risk estimate which was derived from the actual tumor incidence observed in the Norback and Weltman (1985) study. Finally, even when the actual EPA cancer potency is used, it can be demonstrated that the current epidemiologic evidence indicates the EPA number is several orders of magnitude too conservative even if it is assumed that PCBs have some cancer potency in humans that has not yet been observed.

The above comments notwithstanding, an issue which the reviewers also wish to take exception to is the EPA's and ATSDR's practice of providing risk numbers for the general public without any discussion of relative risks or the risks associated with current regulatory standards for carcinogenic substances. This practice tends to distort the risk at hand because the lowest risk usually portrayed is one of 10^{-4} for a lifetime exposure. This gives the general impression that this level of risk is the lowest acceptable level of risk for chemical exposures when in fact there is no level of risk that EPA and other agencies must meet when regulating chemical exposures. The best example of the disparity between the risks portrayed as acceptable in the ATSDR document and actual agency practice is arsenic. According to the EPA's own potency factors, the cancer risk associated with drinking water containing the legal arsenic concentration promulgated by EPA is about 10^{-2} . The disparity between this level and that implied in the ATSDR document is even greater as arsenic is a known human carcinogen while PCBs are not. Therefore, even if the readers obtain a rudimentary understanding of what these numbers are intended to represent, it is still likely that they would have no idea what type of hazard a specific level of risk represents. Because risks estimated for chemical exposures are never compared to the large number of other risks that persons accept daily, the reader cannot reach an informed decision as to the relative undesirability of the risk that a chemical might represent if found at a certain concentration in their environment.

In summary, the ATSDR document attaches an inaccurate risk estimate to a specific PCB dose. Yet the carcinogenicity of certain PCBs in animals cannot be attributed to all PCB mixtures, and the human relevance of the current animal data is of a highly controversial nature (see general comment #3). Because there is clear speculation regarding the human cancer hazard associated with a particular dose of PCBs, from both a qualitative and quantitative standpoint, ATSDR is strongly urged to either move this discussion (so that it occurs later in the document where it can be placed in proper perspective) or delete it.

3. The manner in which the ATSDR document has handled the potential carcinogenicity associated with PCB exposure is inappropriate, inaccurate and misleading.

Concerning the animal carcinogenicity of PCBs, the summaries provided in the ATSDR document selectively avoid negative data and other information provided in the cited studies that limits the human relevance of the animal test data. In other instances ATSDR has incorrectly reported the actual findings of these studies. Both of these factors, when combined with the simplistic assumptions made by ATSDR, act to misinform and mislead the reader concerning the actual findings of these studies. For example, on page 94 ATSDR states that there is positive evidence for the carcinogenicity of Clophen A-30 when the only study reported to date found no evidence of cancer in Clophen A-30 treated animals, and in fact, the total tumor incidence in these animals was significantly lower than that observed in the control animals. As discussed in specific comments #3, #8, #12, #21, #47-55, #62 as well as in other sections of this critique, animal evidence of carcinogenicity has not been demonstrated for many commercial PCB mixtures, in fact, the evidence seems clear only for those of 60% chlorine content.

The ATSDR document ignores the article by Young (1985), certain data provided in Kimbrough et al. (1975), and statements made by Norback and Weltman (1985), all of which clearly indicate that the liver tumors observed in rats fed PCB mixtures of 60% chlorine do not act like malignant tumors. ATSDR also ignores evidence in these citations demonstrating that even the carcinogenic mixtures of 60% chlorine do not tend to shorten the lifespan of the animal, but instead appear to have important antitumorigenic effects on extra-hepatic tumors which are of a more serious in nature. These findings are definitely contrary to the public's conception of the truly malignant lesions we all wish to prevent.

By ignoring the above information, ATSDR apparently intentionally leads the reader to inevitable conclusions which exaggerate the likely qualitative cancer risk that PCBs pose to humans. The reviewer's had no choice but to reach this conclusion in light of the fact that ATSDR has failed to cite a single

epidemiologic study which links PCB exposure to human cancer. In contrast, the largest epidemiologic study cited, that of Brown and Jones (1981) found less cancer in capacitor workers than would normally be expected in this population (39-vs-44).

4. ATSDR should carefully re-evaluate both its interpretation of and repeated reference to those studies listed under the heading of developmental toxicity.

On page 64 ATSDR describes studies by Taylor et al. (1984) and Fein et al. (1984) as inconclusive. If these studies provide no clear or conclusive evidence of toxicity, why does ATSDR repeatedly cite them? More to the point, since a goal of this profile is to cite key literature, why does ATSDR bother to cite them at all? The study by Taylor found no significant effects in spite of the fact that the infants examined in this study were born to women receiving the greatest PCB exposure of any group of women so studied. A recent study by Rogan et al. (1987; see Am. J. Public health 77:1294), which attempted to determine whether or not exposure to PCBs and DDE via breastmilk was associated with any adverse health consequences, likewise found no evidence of harmful effects. In spite of these negative findings, ATSDR repeatedly cites several studies it and its peer review group consider flawed (i.e. Fein et al., 1984; Fein 1984; Jacobsen et al, 1985; Rogan et al., 1986). We agree that these studies are flawed and several of our specific comments address the obvious shortcomings of these studies. In summary, the problems associated with these studies are:

- a) Each study attempts to correlate developmental changes to PCB serum or breastmilk concentrations that are normal for and indicative of the general population. As there is no clear elevation in PCB exposure, each study fails a basic criterion for establishing causation, that of showing a dose-response relationship exists.
- b) These studies often failed to control for factors that are well known to affect human development. These factors include alcohol consumption, serum lead levels, smoking, a

history of low birth weight, the economic status of the mother, and the other organochlorine compounds (DDE, chlordane, heptachlor etc.) common to the mother's environment or diet.

c) In several instances the authors themselves indicated their results could not be relied upon. For example, in the article by Taylor et al. (1984) the authors state "The small number of observations, lack of information on important influencing factors, binary exposure measure, and uncertainty in assigning biological significance to birthweight and gestational age differences of this magnitude mandate that such a conclusion be considered tentative."

d) Both the study by Taylor et al. (1984), which examined mothers and infants with the largest PCB exposure, and the recent follow-up of infant health by Rogan et al. (1987) contradict the weak, subclinical and unsubstantiated changes reported in studies by Fein, Jacobsen and others.

5. ATSDR should carefully re-evaluate its interpretation of the literature reporting clinical measurements taken from capacitor workers.

Despite the contradictory and incomplete review performed by ATSDR, there is no evidence that chronic PCB exposure results in liver injury or elevates serum lipid levels (see specific comments #2, #19, #20, #27, #32, #33 and #38 for examples). The absence of overt clinical dysfunction in the capacitor worker data is perhaps best summarized by Smith et al. (1982) who stated :

"These correlations occur in the absence of overt clinical dysfunction identifiable on physical examinations. The simultaneous changes in SGOT, GGTP, plasma triglyceride, and HDL-cholesterol are evidence of an effect on the liver and exposure to PCB, the biological significance of which is not clear. A positive correlation between serum GGTP and triglyceride has been described as has the rise of serum GGTP

in the presence of drugs known to induce liver microsomal enzymes.

Therefore, alterations in liver enzyme tests in association with increasing serum PCB concentrations may not themselves be predictive of future chronic disease but may reflect liver microsomal enzyme induction.

In general, a lack of clinically apparent illness among workers with high levels of exposure to PCB and high serum PCB concentrations seems to have been the rule. ...

One would expect the adverse human health consequences from exposure to PCB, if they exist, would most readily be identified in groups with the greatest exposures (excluding poisoning attributable to accidental contamination of food). None of the published occupational or epidemiological studies (including ours), however, have shown that occupational exposure to PCBs is associated with any adverse health outcome, to be distinguished from demonstrable subclinical biochemical alterations. An exception to this is the occurrence of chloracne during the early years of its use, and possibly currently as well, depending on circumstances of its use and exposure. "

6. In several instances the PCB Profile has attempted to portray all commercial PCB mixtures as having equivalent toxicities and potencies. There is, however, considerable evidence that PCB mixture may be quite dissimilar in the effects they evoke, particularly when administered at equivalent doses (see specific comments #6, #9, #11, #13, #30, #35, #60, and #62).

The ATSDR document states on the top of page 50, "it is assumed that effects resulting from exposure to a specific Aroclor are representative of effects which may be produced by the other Aroclors," and yet it is clear from its own document that ATSDR cannot defend this approach. For example, ATSDR cites and is therefore aware of:

- a) The very different results obtained by Treon et al. (1956) regarding the inhalation toxicities associated with various Aroclors (page 54, section 4.3.2.1 of draft PCB Profile).
- b) The potency differences in reproductive toxicity for various Aroclors that have been observed in mink (Aulerich and Ringer, 1977; Bleavins et al., 1980).
- c) The different tumorigenic responses produced in the rat by PCB mixtures of 42%, 54% and 60% chlorine (Kimbrough et al. 1975; NCI, 1978, Schaeffer et al., 1984; Norback and Weltman, 1985).
- d) The different tissue accumulations and hepatotoxicities produced by difference hexachlorobiphenyl isomers (Biocca et al., 1981).

Since ATSDR is well aware that important differences between PCB mixtures do exist, the agency must abandon as scientifically indefensible its assumption that all PCBs represent equivalent hazards. In fact, given the considerable number of internal contradictions to the assumption made on page 50, one wonders why ATSDR made this assumption at all. Finally, because this approach is so clearly contradicted by the scientific literature, it only serves to give the knowledgeable reader the distinct impression that ATSDR lacks the understanding and depth of knowledge required to accurately summarize the PCB data. In short, this approach seriously undermines what must be one of the intended purposes of the document, i.e. that of accurately informing the public of potential PCB health hazards.

In stark contrast to the approach taken by ATSDR, it is should be noted that the U.S.E.P.A. has outlined a specific methodology for the evaluation of toxicological data describing the effects of chemical mixtures (51FR34014). This methodology is one ATSDR should consider when evaluating the toxicity data of PCBs. An outline of this basic procedure is provided below for the interested reader. (Note : Since the answer to Step 1 is yes, one proceeds directly to step 5.)

OUTLINE OF THE RISK ASSESSMENT APPROACH SUGGESTED BY
THE U.S.E.P.A WHEN HANDLING CHEMICAL MIXTURES

1. Health effects information is available on the chemical mixture of concern.
 - a. If yes, proceed to Step 5.
 - b. If no, proceed to Step 2.
 2. Assess the similarity of the mixture on which health effects data are available to the mixture of concern, with emphasis on any differences in components, proportions of components, and environmental partitioning.
 - a. If sufficiently similar, proceed to Step 5.
 - b. If not sufficiently similar or if no such data exist, proceed to Step 3.
 3. Derive appropriate indices of acceptable exposure and/or potency factors for carcinogenicity on the individual components in the mixture and proceed to Step 4.
 4. Assess data on interactions of components in the mixture.
 - a. If sufficient quantitative information is available on the interactions (including mechanisms) of two or more toxicants from subchronic or chronic studies, proceed to Step 6.
 - b. If qualitative information is available on acute interactions, attempt to qualitatively indicate the nature of potential interactions and proceed to Step 7.
 5. Conduct risk assessment on the mixture of concern based on health effects data on the mixture, using the same procedures as those for single compounds. Proceed to Step 8.
 6. Use an appropriate interaction model to combine risk assessment on compounds for which the data are adequate and use assumption of dose addition for remaining toxicants. Proceed to Step 8.
 7. Use an additivity assumption for all compounds in the mixture. Proceed to Step 8.
 8. Develop an integrated summary of the qualitative and quantitative assessments with special emphasis on uncertainties and assumptions.
7. The PCB Profile contains a number of the statements that are either biased, exaggerated, or redundant. These flaws can only lead to a poor public understanding of PCBs and their potential health hazards.

In 1983 a panel of the National Research Council (NRC) of the National Academy of Sciences was asked to conduct a study of the institutional means for risk assessment. Their report was completed and published in 1983. The book describing the findings of this panel is entitled "Risk Assessment in the Federal Government : Managing the Process." In this book the NRC panel outlined the perceived criticisms of the risk assessment process as currently performed by federal regulatory agencies. The majority of these criticisms were :

- Bias - that agencies approach risk assessments with attitudes that preclude objectivity, and that regulators may skew their assessment of risk to support a particular preference.
- Exaggeration - that regulatory agencies are accustomed to operating in an adversarial mode, and because they expect to be challenged, regulators typically overstate risks associated with chemicals they intend to regulate and understate the risks associated with those chemicals that they decide not to regulate. The instinct to support a position with every available argument may distort interpretation of scientific data, selection of the extrapolation procedure, and assumptions about human exposure.
- Poor Public Understanding - if risks are misdescribed, the public perception of risk will be inaccurate.
- Inconsistency - agencies have applied inconsistent criteria and reached inconsistent results in assessing the risks posed by the same hazards.
- Redundancy - that each agency has often been tasked to make the same or similar efforts; therefore a duplication of agency efforts does exist.

Although several federal regulatory agencies have improved their risk assessment procedures since 1983, a review of ATSDR's PCB Profile reveals that it suffers from the same problems NRC cited in its 1983 review of the risk assessment process. For example, the following illustrations of these problems have been noted in the specific comments of this critique of the PCB profile.

- Bias - In several instances ATSDR either omits critical data or fails to cite studies reporting a No Observed Adverse Effect Level. For example, on page 18 ATSDR cites the toxicity produced by Aroclor 1254 in the Aulerich and Ringer

(1977) study while ignoring the NOAEL also provided in this study for Aroclors 1016, 1221, and 1242. Later, ATSDR cites the NCI chronic study as evidence of decreased survival in rats fed diets > 25 ppm of Aroclor 1254 while ignoring the fact that chronic consumption of diets containing 100 ppm of Aroclor 1260 and Clophen A-60 and A-30 actually increased the longevity of the treated rats (see specific comment #9).

The first ATSDR citation of epidemiologic data is the weakest epidemiologic study to date (Bahn et al, 1976), and it is cited because it suggested positive findings. Even though this study has been withdrawn, it has been cited in the ATSDR document at the expense of much stronger and more convincing human studies in which no increase in cancer was observed.

- Exaggeration - In the second and third paragraphs of page 27 the PCB Profile states "possible hepatocellular damage has been demonstrated only in occupationally exposed groups with higher PCB levels (Kreiss, 1985).... Maroni et al (1981a) examined the health condition and PCB blood levels of 80 electrical workers..... The abnormal liver findings include hepatomegaly and altered liver enzyme levels, with well-defined liver failure noted in a few cases" (emphasis added by reviewer). In the first statement ATSDR has exaggerated and distorted Kreiss's conclusion by omitting a subsequent qualifying statement. What Kreiss actually stated was "Only occupationally groups with a higher range of PCB levels have been shown to demonstrate associations with indicators of possible hepatocellular damage such as SGOT and SGPT. Indices of obstructive liver disorders have not been demonstrated even in occupationally exposed groups.
.....Some questions regarding subclinical biochemical associations with PCB concentrations require further understanding of serum-adipose partition. (emphasis added by reviewer) In this regard the findings of Chase et al. (8) that plasma PCB level, but not adipose concentration, correlated with plasma triglycerides suggests the association may be unrelated to body burden. Rather,

persons with higher fat content in the blood may simply partition their body burden of PCBs to favor higher PCB concentrations in blood."

In its statement of the Maroni study, ATSDR has misinterpreted the study and attributed a finding to that study that does not exist. Maroni et al. (1981a) did not find "well-defined liver failure." Maroni et al. (1981a) found only asymptomatic hepatomegaly (liver enlargement). ATSDR by this error has not only misstated the Maroni et al. (1981a) findings, but also has made those findings appear more serious than they were. ATSDR states the findings correctly (and thereby contradicts its error on page 27) on page 52 by stating, "Epidemiologic studies and clinical surveys indicate that occupational exposure to can produce alterations in liver enzymes that are inconsistent and not clearly associated with clinically detectable liver disease. Asymptomatic hepatomegaly was reported in one study (Maroni et al. 1981a)" (emphasis added by reviewer).

In addition, the above exaggerations contrast sharply with comments made by one author cited in the review article by Kreiss (1985). Fischbein et al. (1979) made clear note of the "paucity of abnormal results" observed in their study of capacitor workers. The ATSDR exaggerations are also contradicted by an earlier opinion of Smith et al. (1982), in a paper not reviewed by Kreiss (1985), who stated, "None of the published occupational and epidemiological studies (including ours), however, have shown that occupational exposure to PCBs is associated with an adverse outcome, to be distinguished from demonstrable subclinical biochemical alterations."

Finally, it is disturbing to note that in addition to misinterpreting the Kreiss (1985) paper the PCB Profile (ATSDR) failed to cite two additional papers that preceded the Kreiss article in volume 60 of Environmental Health Perspectives (1985). The first paper, by Dr. Guzelian (1985), states "Initial enthusiasm for the γ -GTP test may be

subsiding because of the realization that γ -GTP (36) activity in human serum is increased in association with so many physiologic conditions. . . . A most troublesome confounding factor that may complicate the usefulness of γ -GTP in epidemiologic studies is that consumption of alcohol even in moderate amounts may elevate the γ -GTP activity in as much as 70% of the subjects. . . . In summary, environmental agents produce subtle yet statistically demonstrable changes in human liver at least judged by routine chemistry evaluation. There is no evidence that these subtle changes are likely to lead to clinically significant liver disease."

The second paper located in the same journal volume as the Kreiss paper and which ATSDR also failed to mention was one by Dr. Lawton who after his examination of capacitor workers stated "No evidence for health impairment related to PCBs was found, despite the high serum levels of PCBs in the study population." The unexplained failure on the part of ATSDR to cite two articles taken from the same volume of the journal as the Kreiss article suggests an intent on the part of SRC to bias and exaggerate the data finally reported in this draft of the PCB Profile.

- Poor Public Understanding - Evidence of this problem has already been cited in previous general comments. For example, as discussed in comment #2, this document will mislead and confuse the public concerning the perceived cancer risks associated with PCB exposure. As discussed in comment #4, the reader will be confused concerning the reported developmental effects because even though ATSDR notes that "no effects can be attributed to PCBs," it repeatedly cites the developmental studies elsewhere without these necessary qualifiers. This practice gives the impression that ATSDR attributes some validity to these poorly designed studies.
- Inconsistency - On page 42 ATSDR states "Although there is an historical linkage between Yusho and PCBs and some

regulatory documents ascribe health effects from these incidents to PCBs, effects from these incidents are not reviewed in this report because the effects cannot be ascribed specifically to the Kanechlors." (emphasis added by reviewer). After making this disclaimer, one which is strongly supported by scientific evidence, the ATSDR proceeds to discuss Yusho on pages 56, 65 and 69 as though it reflects the toxicity of PCBs. This clear contradiction and inconsistency should be removed.

As mentioned in general comment #4, the studies of Fein, Jacobsen and others are referred to as "inconclusive" and with disclaimers such as "these effects cannot be attributed to PCBs" on pages 32 and 64, and yet these same studies are cited in at least four other places in the ATSDR document without these caveats.

- Redundancy - While it is understood that ATSDR has been tasked by Congress to develop these toxicological profiles, one must question the purpose and poor quality of the PCB document in light of the fact that USEPA just released a new summary of the toxicological properties of PCB in late 1987 (1987 draft drinking water criteria document). When compared to the water quality criteria document, the shorter and mistake-ridden ATSDR document serves little purpose.

8. ATSDR makes several completely unfounded and inaccurate conclusions or assumptions in the PCB Profile.

As discussed in general comment #1, ATSDR begins the PCB Profile by stating that the consumption of fish is the major source of PCB exposure while exposure via inhalation is considered negligible. As shown convincingly in our specific comments # 1 & #26, indoor air is the major route of exposure for most U.S. citizens. This fact explains why most persons in the U.S. have the same PCB body burdens, and why most fish-eaters do not have serum PCB levels that are significantly higher than persons who do not eat PCB contaminated fish.

On page 2 of the PCB Profile, ATSDR makes the indefensible statement that serum levels reflect recent exposures while fat levels are indicative of chronic exposures (see specific comment #2). On page 52, ATSDR states, "The cause of death was unspecified but may have been related to the development of nodular hyperplasia in the liver." The task of ATSDR is not to speculate but to provide summaries that are as accurate as possible in a clear and informative context.

9. The format of the PCB Profile is cumbersome and confusing.

ATSDR has chosen a confusing format for this document, making any attempt to understand the information a cumbersome task. The constant division of each area of interest into three categories depending on whether or not the exposure occurred via an inhalation, oral or dermal route, fragments the PCB Profile. This format has also received severe criticism from Dr. Hartung of ATSDR's PCB Profile peer review group. ATSDR should simply admit that like most chemicals, the toxicity of PCBs has been examined in most cases by using routes of exposure other than inhalation or dermal. This is not to say that the information provided in studies using these routes of exposure are not important, but rather that if these data were noted when discussing the toxicity of interest, the presentation of information would be cohesive and a much simpler task to review. In other words, to make the information understandable ATSDR should divide the profile into sections discussing specific toxicities so that the reader can find all studies dealing with that particular toxicity in one place. By separating the discussion by routes of exposure one has to scan all three exposure sections to find all of the information for a specific toxicity.

A second problem stems from the use of the thermometer graphs as a means of listing LOELs and NOAELs and the use of the bar graphs to depict the adequacy of the data base. These graphs are not particularly informative, and both types are misleading. For example, the data in Figures 2.1 and 2.2 cannot be compared because the first merely reports the air concentration while the second

presents the actual dosage. Since the dosages the animal ultimately received are not provided in Figure 2.1, these data cannot be compared to data in other figures and therefore are of limited use. Further, as the respiration rate of small animals, e.g. rodents, is significantly greater than that of humans, and because the type of animal toxicity observed is not provided, the comparisons made in Figure 1 are, in the opinion of the reviewers of this draft, to be deliberately misleading. In Figures 2.2 and 2.3, as in other figures, ATSDR is more than willing to cite the results of a single observation without the context of other studies which were negative. In addition, Figures 2.3 and 2.3 lack human data which ATSDR states is not available. However, the study of Maroni et al. (1981a), which it cites, can be used to calculate dermal doses in capacitor workers, and the studies reported by the FDA (Kolbye, 1972) have estimated the daily intake of PCBs from foods. Finally, the fact that throughout these graphs the effects observed at the LOEL value have not been provided can be very misleading. For example, the liver effects portrayed in Figure 2.5 refer to liver induction rather than toxicity. This same change is associated with hundreds of medications used daily in the United States and should not be construed as some sort of toxicity.

The bar graphs on pages 30 and 31 should be removed from this document. They are inaccurate and provide information that should be discussed in the text of the document where the adequacy of the data base can be better described and where the shortcomings and strengths of the available data can be clearly demonstrated. The problems with figures 2.7 and 2.8 can be seen clearly when one realizes that for the human data ATSDR has listed some data under inhalation and oral developmental toxicity while in fact ATSDR has stated these studies are "inconclusive" (p.64) and "that the effects cannot be attributed to PCBs" (p.32). Studies that are inconclusive should not be considered as representing some data. Data from which concrete and reliable conclusions cannot be drawn are the same as having no data at all. This same categorization (i.e. some data) is given to the epidemiologic evidence of Brown and Jones (1981) which is a much stronger study than all of the studies cited under developmental toxicity. Last, Figure 2.7 contains four bars which contain unexplained asterisks.

10. ATSDR has ignored valuable criticisms from its peer review group.

A copy of the comments made by the PCB document peer review group, i.e. Dr. Hartung, Dr. Que Hee, and Dr. Olson, raises disturbing questions concerning ATSDR's willingness to incorporate appropriate comments made about this document. In the foreword ATSDR encourages peer review and public comment and further states that it plans to revise this document in response to comments and new data. However, a review of the comments made by ATSDR's own peer review group reveals that in many instances appropriate and important comments were completely ignored by ATSDR without justification.

For example, in the previous general comment the format of this document and its separation of routes of exposure was criticized. Yet Dr. Hartung had already made a similar comment which ATSDR has clearly ignored. For example, Dr. Hartung stated :

"ORGANIZATION:

The organization of the report is not acceptable. The general outline in which the information is presented does not provide a logical flow of the information. The separation of health effects and toxicological data by route of exposure provides few advantages, and may in fact obscure potential effects to a reader who uses only portions of the document without being familiar with its entirety. Conclusions in the form of the public health statement and the health effects summary precede the presentation of the toxicological information or the information that is required to estimate the likelihood of exposure. The present organization became an obstacle during the in-depth review, because the report had to be read in a different sequence than that provided in its presentation. Thus it is important to have an understanding of physical and chemical properties plus uses and potential for exposure, before the assessment of toxicity data, so that the realism of an exposure can be judged. Toxicity data should be presented before occupational data and before concluding health assessments.

CONCLUSIONS:

The reviewed document is absolutely unacceptable in its present form. The major reason for unacceptability is the obtuse and illogical organization of the report. This report is more complex than the first one which I evaluated for Syracuse Research Corporation. In comparison, the first report was relatively simple. As the complexity of the subject increases, the adverse effects of poor organization are compounded. Repeated use of this organizational scheme is not likely to generate fondness through familiarity. This entire

series of reports should NOT be released until the sponsoring Agency changes the format to a logical one.

Aside from the organizational disaster, a number of deficiencies requiring revisions have been identified in this report. Once those deficiencies have been assessed and acted upon, the report should be acceptable."

Or as this critique has stated in a number of places, the studies which attempt to suggest development toxicity in infants born to women with normal serum PCB levels provide no useful information. While the ATSDR document has noted some of the limitations of these studies, we agree with Dr. Que Hee who apparently suggested that ATSDR handle this subject in the following manner (this quote is taken from p. 10 of SRC's report of the peer review group's comments):

" • On pages 74-75, Dr. Que Hee indicates that the effects on infants born to women who consume Lake Michigan fish contaminated with PCBs may not be specific to PCB contamination because the fish are also contaminated with numerous pollutants. He further states that correlations between serum levels of PCBs with effects in these studies do not necessarily mean that the effects were caused by PCBs. He suggest condensing these studies into one paragraph and deemphasizing the cause and effect implications. SRC will comply."

It is the opinion of this critique of the PCB profile prepared by SRC and accepted by ATSDR, that this change is not evident in the document in this draft even though SRC had previously stated it would comply. Further, on p. 7 of the SRC's Report of the Peer Review Evaluation of the Toxicological Profile on PCBs, SRC states:

"SRC noticed that the q_1^* is also incorrect on page 115. It will be changed to $5.7 \text{ (mg/kg/day)}^{-1}$ as stated in the U.S. EPA (1987a), and a statement will be added to indicate that this q_1^* has been verified by the CRAVE Work group."

It is clear that this change was not made in the last draft of the document that SRC submitted to ATSDR.

Given the above, it does not appear that ATSDR, or its contractor Syracuse Research Corporation, will seriously consider or incorporate comments made by outside reviewers. This is in direct contrast with the stated intentions of ATSDR, and this critique requests that ATSDR honor this commitment to the general public it is supposed to be serving. To do otherwise is to

circumvent the peer review process and to admit that the document is not provided to inform others, but rather is provided to support a preconceived point of view that is currently held by at least ATSDR and apparently EPA.

SPECIFIC COMMENTS

1. Page 1, section 1.2, p 2, "Consumption of fish is a major source of PCB exposure to humans. Compared to the intake of PCBs through consumption of contaminated fish, exposure to PCBs as a result of breathing air containing PCBs is negligible."

In addition the comments made regarding the manner in which PCBs are released into the environment are sweeping generalizations which deserve further clarification.

Response : The first statement made by ATSDR is incorrect. The typical amount of PCBs inadvertently ingested via fish by the average individual is not sufficient to make this the dominant route of exposure for the general population. While there are certainly waters within the U.S. containing fish with substantial PCB contamination, the bulk of the commercial fish in the U.S. food supply contains well below the 2 ppm FDA maximum permissible PCB level. Consequently, the average PCB exposure from fish consumption is thought to be considerably less than one microgram per day. Even in populations known to ingest fish with PCB levels above the FDA limit, significant increases in PCB body burdens cannot always be demonstrated. For example, no significant elevations in blood PCB levels could be detected among those who ate contaminated fish in major studies by Smith, 1984; and the Greater New Bedford PCB Health Effects Study showed such individuals in New Bedford to be well within CDC estimates for non-exposed U.S. residents who participated in other studies. Therefore, it would appear that fish consumption is hardly the single major source of PCBs found in the general population.

The statements made in ATSDR's PCB Profile are also misleading in that they grossly underestimate exposure from ambient air. Oatman and Roy (1986) have reported airborne PCB concentrations in public buildings with means ranging from 117 to 653 ng/m³; the EPA (1979) has found PCB air concentrations ranging from 110 to 240 ng/m³ in commercial buildings; and MacLeod (1981) has reported airborne PCB levels in homes with average concentrations up to 580 ng/m³.

Even if one makes the following conservative assumptions:

- 1) that while indoors the time weighted average airborne PCB concentration for home and office is approximately 250 ng/m³,
- 2) that the average adult leads a rather sedentary life and is only inhaling 20-24 m³ of air/day, and
- 3) that inhaled PCBs are completely absorbed,

then the amount of PCBs absorbed from ambient, indoor air in the United States is about 5-6 µg/day. By comparison, the estimated dietary intake of PCBs is only 0.21 µg/day (see table 7.2, p.86 of the PCB Profile). Therefore, air is not a negligible route of exposure. Indoor air, as a source of PCBs, is not only greater than that coming from contaminated fish, but the amount of PCBs contributed by indoor air can be expected to exceed that stemming from the consumption of fish in all but a limited number of instances. This explains why persons throughout the U.S. tend to have similar PCB body burdens and why persons consuming some fish from waters containing PCBs do not have higher than normal PCB serum levels.

Finally, the PCB Profile is also somewhat misleading in its presentation of ways that PCBs can be released into the environment. Disposal of the consumer products listed on page 2 is very likely to release PCBs into the environment because these products typically end up in sanitary landfills rather than in a secure facility.

2. Page 2, section 1.5, "Blood PCB levels are the best indicator of recent exposure to PCBs, and levels in the fat are the best indicators of long-term exposure."

Response : The distinction between blood and fat levels as indicators of exposure in this statement is presumably related to the delayed distribution phase following the absorption of PCBs. PCBs are first absorbed by and distributed to the most highly perfused tissues, e.g. muscle and liver tissue. Within about 48 hours, however, the PCBs

have re-distributed to and accumulated in those tissues with the highest lipid content (and therefore affinity for PCBs), e.g. adipose tissue. Therefore, while a relatively large and very recent exposure to PCBs might be best reflected by serum PCB levels (i.e. an exposure occurring less than 24 hours before the time of measurement), the draft PCB Profile ignores the fact that some 48 hours after exposure the redistribution phase is complete and blood samples now offer few advantages over samples taken from other tissues. (Note: We do recognize, of course, that blood/serum remains the easiest and safest type of tissue sample to collect.) Although it is true that once the distribution phase is complete and an equilibrium between tissues has been established, it may be stated that serum PCB levels reflect tissue PCB levels (serum to fat partition coefficients have been reported for various PCB isomers, Wolf et al., 1982a&b), there is still one serious drawback to sampling blood rather than fat. Recent studies by Emmett (see comment #24 for details) have shown that, as might be expected, serum lipid levels dramatically alter serum PCB levels. Thus, as Emmett has demonstrated, when serum PCB levels are not corrected for lipid content they may be a poor and overstated index of the PCB tissue levels and PCB body burdens resulting from acute or chronic exposures.

Finally, ATSDR should recognize that the typical or predominant level of environmental exposure to PCBs is characteristically not to occasional, large amounts of PCBs, but to continuous small amounts. Under these conditions, ATSDR's stated advantage of sampling blood versus fat would not hold true even if serum lipids did not distort serum PCB levels. At this point in the document, ATSDR should merely state that nearly everyone has been exposed to PCBs, and that worldwide nearly all persons are likely to have detectable levels of PCBs in their body fat and blood. These exposures are derived primarily from indoor air, are unavoidable, and do not represent an unusual or excessive risk.

3. Pages 2-3, section 1.6, concerning the information conveyed to the general public in this subsection entitled - WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Response : A discussion of PCB carcinogenicity has no place under this heading. The heading implies that carcinogenic effects are clearly known to result from human PCB exposure, an implication that has already been contradicted on page 2, section 1.4, which states that skin rashes and liver effects are the only significant health effects that have been observed in occupationally exposed persons. This subsection further states that the occupational exposures are much higher than environmental exposures affecting the general population and that adverse health effects have not been observed in people following nonoccupational exposures.

As ATSDR should admit, animal carcinogenicity studies, the relevance of these studies to humans, and the manner in which risk estimates are derived, are topics of toxicology that will be poorly understood, if at all, by the general public. Further, certain aspects of each topic are considered to be controversial issues in the scientific community itself (see Appendix A, for additional discussion regarding PCB animal carcinogenicity studies). Therefore, this subject matter has no place under a summary heading which fails to explain the complexity of the subject, especially since it is contradicted by or inconsistent with the text on the previous page. Because this paragraph will no doubt mislead many readers into believing that a causal link between PCB exposure and cancer has been conclusively established when it clearly has not, this paragraph should be either deleted or moved to a separate section where this subject can be placed in the proper context.

There are other problems with this paragraph as well. First, the risk estimate provided in this paragraph (i.e. 770 additional cancers per 10,000 persons exposed to 1 µg/kg/day) is incorrect. On page 19 the risks associated

with certain daily doses have been correctly calculated using the EPA's new potency factor (q_1^*) while the numbers provided on page 3 are one order of magnitude too high. However, in neither instance has SRC used the proper and lower q_1^* of $5.7 \text{ (mg/kg/day)}^{-1}$ as SRC stated it would in its response to comments made by the PCB Profile peer review group concerning an earlier draft of this document.

Second, any of the risk estimates or potency factors that the EPA has calculated from animal studies can be shown to be excessive. The Brown and Jones (1981) study can be used to illustrate the lack of the validity of the risk analysis put forth in this section as well as that provided on page 19. Although the EPA may consider a $1 \text{ } \mu\text{g/kg/day}$ lifetime exposure level to be associated with 77 additional cancers in 10,000 people (using the correct estimate listed on p.19), studies in occupationally exposed persons show this cannot be the case. In the Brown and Jones study, no excess incidence of cancer was noted. Interestingly, even if the 2567 persons in the Brown and Jones cohort were only exposed at the level of $1 \text{ } \mu\text{g/kg/day}$, some 20 excess cancers should develop in this group. Should these 20 additional cancers occur in a tissue in which the human cancer incidence is low, e.g. the liver, the observed cancer incidence would be about one order of magnitude greater than expected. Yet in the Brown and Jones (1981) study the total cancer incidence was lower than expected (i.e. 39 observed-44 expected), and no specific type of cancer was significantly elevated when all exposed persons were considered.

A closer examination of the Brown and Jones (1981) study suggests that if EPA's risk estimates were correct, the incidence of cancer in these occupationally exposed persons should have been even greater than assumed in the previous paragraph. Air samples were taken in 1977, a time when more recent industrial hygiene practices kept PCB air concentrations low compared to the work practices of previous decades, showed personal air samples ranged from

24-343 $\mu\text{g}/\text{m}^3$ in plant #1 and 170-1260 $\mu\text{g}/\text{m}^3$ in plant #2. Ignoring the evidence provided in Maroni et al. (1981a) and Ouw et al. (1976) which suggests that dermal exposure was possibly the largest route of exposure {see comment #13 where the dermal exposure may have provided an additional 26-326 $\mu\text{g}/\text{kg}/\text{day}$ }, the estimated average air concentration for these employees was 208-715 $\mu\text{g}/\text{m}^3$. Even if the workers did not work strenuously, they would have inhaled at least 10 m^3 of PCB laden air each day of work. This suggests that via inhalation these workers received daily dosages in the neighborhood of 30-102 $\mu\text{g}/\text{kg}/\text{day}$. If dermal exposure is also considered then the exposure ranges from about 56-428 $\mu\text{g}/\text{kg}/\text{day}$. Applying the EPA risk estimate to these daily doses, the risks associated for a lifetime exposure would range from a low of 1107 additional cancer cases in this cohort to as high as 8,460 additional cancer cases. While no one in this cohort did work their entire lifetime, some 780 workers in the cohort had greater than 3 years of exposure (558 had 3-10 yrs, 222 had greater than ten years). For this group alone the number of additional cancers would be expected to range from 14-110. In fact, in those 222 persons working more than 10 years some 14-105 additional cancers would be expected. In other words, according to the EPA's risk estimate an increase in the cancer incidence in the Brown and Jones study should have been obvious and easily detected. In contrast to this prediction, however, the Brown and Jones (1981) study failed to find any statistically significant increase in cancer incidence.

In summary, the ATSDR document attaches an inaccurate risk estimate to a specific PCB dose. As will be demonstrated in subsequent specific comments, the carcinogenicity of PCBs in animals cannot be attributed to all PCB mixtures, and the human relevance of the current animal data is, to say the least, controversial. Therefore, the EPA is obviously speculating when it attaches a specific human cancer risk to a particular dose of PCBs, and this speculation is both qualitative and quantitative in nature.

Because this risk estimate is of such a speculative nature, ATSDR should either move this discussion to a section in the document where it can be placed in a more accurate perspective, or delete it.

4. Pages 2-3, section 1.7, concerning the information conveyed to the general public in this subsection entitled - WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

Response : The PCB Profile simply lists the regulations promulgated for PCBs. There is no attempt to explain or discuss the disparity in the "acceptable dose" allowed by each standard or guideline. The basis for the disparity in the level of PCB exposure allowed by ACGIH and NIOSH, as well as the different limits and "allowable doses" set by the Food and Drug Administration and Environmental Protection Agency should be addressed. By using commonly accepted exposure assumptions, the human daily exposure allowed by these various regulations could be calculated and presented in tabular form. The large differences in human exposure allowed by these regulations would then be very apparent. For example, the ACGIH limit is 500-1000 times higher than the exposure limit recommended by NIOSH. This presentation would promote a critical look at PCB regulations and provide the opportunity to explain that little general agreement has been reached on an acceptable level of PCB exposure.

In addition, ATSDR might demonstrate that the NIOSH limit would "allow" for a workplace dose that corresponds to a cancer risk, based on EPA risk estimates, that is on the order of 100 additional cancers per 10,000 persons exposed, and that the OSHA limit would allow a dose or exposure that is three orders of magnitude higher (i.e., a cancer risk greater than 100%). As stated in the previous comment, these comparisons would provide readers unfamiliar with the risk assessment process an opportunity to realize that each standard carries a significantly different mathematical risk. It would also clearly demonstrate that among

scientific and regulatory groups there exists a considerable difference in opinion as to what level of PCB exposure represents an acceptable risk.

5. Page 8, section 2.2 concerning the information conveyed in the subsection entitled "LEVELS OF SIGNIFICANT EXPOSURE " and the use of thermometer graphs to depict information.

Response : As stated in paragraph 2 under Section 2.2, no adjustments were made to account for differences in exposure duration or for intermittent exposure. Failure to separate results of studies of varying exposure duration runs counter to the general principles of toxicology, since the dose-response relationship is often determined, in part, by the duration of exposure. In the case of PCBs and other persistent chemicals, the exposure duration has a dramatic effect on this relationship. A more traditional (and instructive) toxicological approach would be to express oral data from acute, subchronic, and chronic studies in Figure 2.2 in the same way that data are presented in Figure 2.4. Additionally, more information regarding the duration of human exposure should be included in these thermometer graphs. As has already been stated, ATSDR should always give as much perspective as is possible to the information that is provided in this document.

6. Page 15, section 2.2.1.1 Inhalation exposure (Target organ/systemic toxicity) - concerning the last sentence of paragraph 3. "Since the FEL for Aroclor 1254 is lower than the NOAEL for Aroclor 1242, a minimal risk cannot be derived."

Response : This statement clearly differentiates the toxicity of the two Aroclor mixtures and supports the argument that separate toxicological consideration be given these two Aroclor mixtures. Because the potency of each mixture varies, the statement as written is false.

7. Page 15, section 2.2.1.1 Inhalation exposure (Developmental toxicity) - concerning the last sentence of this subsection.

Response : This subsection implies that the Taylor et al. (1984) study provides evidence that PCBs cause developmental deficits in humans. However, important limitations to this study are not discussed. These limitations are listed below.

- The study failed to account for tobacco use among the mothers.
- The study failed to account for underlying medical conditions and maternal height.
- The study failed to consider a previous history of low birth weight.
- The study did not consider economic status as a possible confounding factor. As was indicated in the Taylor paper, mothers bearing low birth weight infants tended to have less education and be members of the high PCB exposure group. If the level of education is well correlated with economic status, a lower economic status in the less educated, high exposure group could account for the small difference in birth weights between high and low exposure groups of mothers. This stems from the fact that mothers from low income families tend to receive less prenatal care than mothers from high income families. Less prenatal care would likely cause lower birth weights.

Besides the above problems, the Taylor et al. (1984) study suffers from two additional, fatal flaws. First, this study failed to observe a statistically significant difference in birth weights between the high and low exposure groups. Thus, Taylor et al. (1984) provides no real evidence of any association between PCB exposure and low birth weight. Second, the published article has no control group. Thus, there is no evidence to demonstrate that either exposure group is significantly different from nonoccupationally exposed persons. Without a control

population providing reference values, attempts by Taylor et al. (1984) to study capacitor workers with assumed different exposure levels provides no information useful to those persons not occupationally exposed. (see Appendix B for a more detailed discussion of this issue)

8. Page 16, section 2.2.1.1 Inhalation exposure (carcinogenicity) - concerning the use of the Bahn study to the exclusion of other, more pertinent information.

Response : Carcinogenicity- This subsection ignores the studies of Brown and Jones (1981), or Gustavvson et al. (1986) and instead focuses on the results of a small study by Bahn et al. (1976). The Bahn et al. study not only involves fewer workers than the other above-mentioned studies, but the workers in the Bahn et al. study were also exposed to epoxides, as noted by Lawrence (1977). Several epoxides are known to be carcinogenic in animals, and since epoxides composed 0.5% of the capacitor fluid being used at the plant, the concomitant exposure to epoxides must be considered to be a serious confounder to any interpretation of these results which proposes PCBs might be the causal agent. In response to the criticism of Lawrence (1977), Bahn et al. (1977) did agree that further information was essential, and apparently withdrew this study for revision (Gaffey, 1981); but as yet no follow-up has ever been re-released. In light of the above limitations, there is no reason to consider the study of Bahn et al. (1976) above any of the other occupational PCB exposure studies, and in fact it has less validity than the other studies. Therefore, it should not used as a key paper in subsection 2.2.1.1 and ATSDR should delete it. (see Appendix C for additional discussion on this issue)

9. Page 16, section 2.2.1.2 Oral exposure (Lethality and decreased longevity) - concerning paragraph 3.

Response : Although the NCI study (1978) was cited in the ATSDR document as evidence of decreased animal survival due to Aroclor 1254 treatment, two other chronic studies using

Aroclor 1260 (Kimbrough et al., 1975) or Clophen A60 and Clophen A30 (Schaeffer et al., 1984) actually indicated that PCB exposure decreases mortality. Young (1985) has re-analyzed the Schaeffer et al. (1984) study and the improvement in the longevity of these animals is obvious. Because the findings of two chronic studies contradict the findings cited by ATSDR (and one was of considerably longer duration), it is not appropriate that the ATSDR document states that chronic PCB levels greater than 25 ppm reduce survival. This statement is not true and therefore should be deleted from the document.

10. Page 17, section 2.2.1.2 Oral exposure (developmental toxicity) - first paragraph of this subsection. Studies by Fein, 1984, Fein et al., 1984, Rogan et al., 1986, and Jacobson et al., 1985 are cited as evidence of the possible association of developmental problems in newborns with maternal ingestion of fish containing PCBs or with ingestion of PCBs in mothers' milk.

Response : Close scrutiny of these articles does not support the contention made in the ATSDR document. Fein et al. (1984) reported that newborns born to mothers who ate fish containing PCBs had significantly decreased birth weight, head circumference, and gestational age. However, in this study several statistically significant differences between the control and exposed populations were observed including the fact that the incidence of mothers ingesting alcohol during pregnancy was 3 fold higher in the exposed population. Alcohol is well known to produce a number of birth defects. For example, Mills et al. (1984) found that mothers consuming one or two drinks a day were at substantially increased risk to produce a growth retarded infant, and Jones et al. (1973) have described microcephaly and small birth weight as being characteristics of the Fetal Alcohol Syndrome infant. As the changes in birth weight and head circumference described by Fein et al. (1984) in the newborns of "PCB exposed mothers" were small, the increased alcohol consumption by these women could easily explain the observed changes. In addition, the use of cough and cold preparations and caffeine was also higher in the group listed as the PCB exposed population. Furthermore, the

authors of this study failed to account for the possible effects of other persistent environmental contaminants (such as DDT) which may be present in Great Lakes fish. Therefore, because several confounders (including alcohol) were not controlled for in the Fein et al. study, and because the difference in alcohol consumption was significantly greater in the PCB exposed group, the Fein et al. (1984) study can not be relied upon and the effects described in this paper cannot be unequivocally attributed to PCBs.

Rogan et al. (1986) examined the relationship between problems identified in newborns using the Brazelton Neonatal Behavioral Assessment Scale (NBAS) and the level of DDE and PCBs in mothers' milk fat. PCB levels were associated with less muscle tone and activity, but only at the highest PCB concentrations. Hyporeflexia was also associated with only the highest PCB concentration. DDE levels also correlated with hyporeflexia, indicating that it is impossible to determine whether hyporeflexia is due to either PCB or DDE exposure, or perhaps to some other chemical which was also elevated in this group but which was not measured in this study. It should also be noted that the NBAS technique is generally only applicable to newborns, and it cannot distinguish between transient abnormalities and those of a more lasting nature. For these reasons, the findings of Rogan et al. (1986) are difficult, if not impossible, to interpret with respect to the causal agent and the permanence of the observed changes. Last, the findings of Rogan et al. (1986) also contradict the study by Fein et al. (1984) as Rogan and coworkers failed to observe a relationship between birth weight or head circumference and PCB levels. Thus, in addition to the numerous inadequacies listed in the preceding paragraph, the findings of Fein study are not supported by subsequent studies.

Jacobson et al. (1985) examined children born to mothers in Grand Rapids, Michigan to study the possible association of umbilical cord PCB levels with the occurrence

of subtle neurological changes. The test population consisted of 123 white, predominantly middle-class infants. Approximately 75% (92/123) of the mothers of these infants were considered to be moderate to heavy consumers of PCB-contaminated Lake Michigan fish. The other mothers did not eat these fish. The seven-month old infants were tested for their ability to recognize visual stimuli. In this test, the children were exposed to a visual target, and later during the procedure were simultaneously re-exposed to the same target and a novel target. Visual recognition was defined as the percent of visual fixation on the novel target. The authors stated that there was a statistically significant dose-effect relationship between cord PCB levels and fixation on the novel target. Children born to mothers with cord serum PCB levels of 0.2-1.1 ng/ml fixed their gaze on the novel target approximately 61% of the time. Infants born to mothers with cord serum PCB levels of 1.2-2.2, 2.3-3.5, and 3.6-7.9 ng/ml were reported to have had visual fixation percentages of approximately 60%, 57% and 50%, respectively; and the difference between the fixation times of infants in the high cord serum PCB group and the two low cord serum PCB groups was reported to be statistically significant ($p < 0.05$). Because the possible significance of this test methodology remains to be demonstrated, and because the authors failed to provide any information concerning the range of variation within groups tested or the standard deviations of the percentages reported, serious concern must be expressed for the significance the ATSDR document attempts to attach to this article. Because the authors themselves indicated that the results of this study cannot be extrapolated to suggest that any permanent PCB-induced damage had occurred, the ATSDR should not use this study to imply that PCBs cause developmental toxicity.

Although the authors did attempt to account for a number of confounding variables in their analysis, one obvious oversight was the failure to include an evaluation of serum or cord lead concentrations. Considerable evidence suggests that lead may induce subtle changes in learning and

behavior in children born to mothers with slightly elevated blood lead concentrations, and the study of Jacobson et al. (1985) should be considered flawed for failing to consider the potential effect of this important environmental contaminant.

It is disturbing that the ATSDR fails to discuss the aforementioned uncertainties and contradictions that are associated with these articles, particularly in light of the fact that in some instances the authors themselves point out some of the inadequacies of these studies. If the ATSDR document intends to cite these studies, it should qualify its discussion with a brief summary of their weaknesses and the fact that no conclusions can be reached from these studies. The ATSDR should further note the study by Taylor et al. (1984) was negative and that it examined a population of women with the greatest PCB exposure, i.e. the population was composed of capacitor workers. It is therefore requested that the paragraph on page 17 of the ATSDR be deleted completely or moved to a portion of the document where the limitations of each study can be adequately addressed.

11. Page 18, section 2.2.1.2 Oral exposure (reproductive toxicity) - concerning the statement - "Diets that provide > 2 ppm of Aroclor 1254 for 4 months prior to mating and during gestation were lethal to the fetuses and caused reproductive failure in mink (Aulerich and Ringer, 1977; Bleavins et al., 1980). Assuming mink consume 150 g of feed per day and weigh 800g (Bleavins et al., 1980), then the 2-ppm FEL provided 0.38 mg/kg/day."

Response : This statement deliberately misleads the reader. As can be seen in the table following this comment, Aulerich and Ringer (1977) found no reproductive toxicity after feeding mink diets containing 2 ppm of Aroclors 1016, 1221, and 1242 for 10 months. Thus, the Aulerich and Ringer (1977) study is useful not only for the identification of a FEL for Aroclor 1254 but also a NOAEL for Aroclors 1242, 1221, and 1016. The obvious disparity between Aroclors in this study again underscores the need for ATSDR and EPA to recognize the fact that a study with a single PCB mixture will not necessarily be representative of the responses

produced by other PCB mixtures. Therefore, the practice of treating all Aroclors as equivalent mixtures is scientifically incorrect and cannot be defended.

**Reproductive Performance and Mortality of Female
Minks Fed Diets Containing 2 ppm PCBs**

PCB	Adult Females	Kits		
	percent mortality	No. whelped per female mated	percent kits whelped still alive at 4 weeks	average birth weight
Control	0%	4.1	64%	9.9 ± 0.3
Aroclor 1016 (2 ppm)	0%	4.5	57%	9.2 ± 0.3
Aroclor 1221 (2 ppm)	12%	6.3	86%	9.6 ± 0.3
Aroclor 1242 (2 ppm)	12%	5.6	91%	9.3 ± 0.3
Aroclor 1254 (2 ppm)	12%	0.3	0%	5.4

Adapted from Aulerich and Ringer (1977)

12. Page 18, section 2.2.1.2 Oral exposure (Carcinogenicity) - concerning the proposed unit cancer risk.

Response : Although a unit cancer risk may be calculated from these numbers, the ATSDR document fails to mention the shortcomings associated with this risk estimate (see specific comments #3 & #4). It also fails to provide any justification for only using the data pertinent for female animals in this study and dismissing data derived for the male or female animals in studies by Norback and Weltman (1985), Schaeffer et al. (1984), or Kimbrough et al. (1975). As discussed elsewhere, a cancer risk estimate cannot be derived for PCB mixtures of less than 60% chlorine, and the cancer estimate derived is obviously inaccurate when the possible risk to capacitor workers is considered (see comment #3). Since the ATSDR document recognizes (in the last paragraph of this same page) that "Occupational exposure to PCBs, which involves inhalation as well as

dermal exposure, provides inadequate evidence of carcinogenicity in humans," it seems clear that the authors of this document should be cognizant of the limited applicability of the unit cancer risk derived from animal data. Therefore, this risk estimate should be qualified and placed in the context of the caveats that are associated with its use before it is provided to the unknowledgeable general public as if it were a statement of fact.

13. Page 19, section 2.2.1.3 - Dermal, paragraph 1.

Response : This paragraph fails to consider information regarding the dermal absorption of PCBs in animals. For example, Wester et al. (1983) examined the dermal absorption of two PCB mixtures (42% chlorination and 54% chlorination) in guinea pigs and found that only 56% of the 54% chlorine PCB mixture was absorbed during the first 24 hours; and only 33% of the 42% chlorine mixture was absorbed during this same interval. These authors also found that 15%-34% of a 42% chlorinated PCB mixture applied to the skin of monkeys was absorbed in 24 hours. So, while this paragraph places importance on the dermal route by stating that the dermal route may be a "major route of exposure," the study by Wester et al. (1983) provides PCB skin absorption values that could be used to provide quantitative estimates of human PCB uptake from dermal exposures. Therefore, the Wester et al. (1983) study should be discussed in this paragraph regarding dermal exposure to PCBs.

In the next paragraph, the PCB dermatotoxicity study by Vos and Beems (1971) is cited as evidence that dermally-administered PCBs produce frank toxic effects in rabbits. A 43.7 mg/kg/day dermal dose of PCBs caused liver and kidney degeneration in rabbits. This dose can be compared to that which workers in the Maroni et al. (1981a, 1981b) study may have experienced from handling PCB-contaminated tools. PCB levels on the hands of workers ranged from 2-28 $\mu\text{g}/\text{cm}^2$. If it is assumed that the hands are uniformly soiled and have a surface area of 910 cm^2 and

that the average adult weighs 70 kg, the exposure of the workers to PCBs from the dermal route in the Maroni studies ranged from 0.026-0.364 mg/kg/day, and none of the workers in these studies had any clear evidence of liver disease. While the exposure to the workers was 120-1700 times lower than that experienced by the rabbits on a mg/kg basis, this comparison illustrates that dermal exposure to PCBs in the general environment (which is several orders of magnitude lower than that experienced by capacitor workers) is not likely to result in any risk of acute or subchronic effects.

14. Page 19, section 2.2.1.3 - Dermal (Carcinogenicity) concerning the suggestion that PCBs are initiators as shown in skin painting experiments.

Response : The authors discuss information regarding the initiating ability of Aroclor 1254 in the mouse skin model. Presumably (since this discussion contains no citations), the study relied upon was that conducted by DiGiovanni et al. (1977). In this study, Aroclor 1254 was examined for its ability to initiate skin tumors which could be promoted by 12-O-tetradecanoylphorbol-13-acetate (TPA). Although the authors stated that Aroclor 1254 had "weak tumor initiating capacity" in the presence of TPA-induced promotion, the authors failed to include a TPA-only control. The failure to include a TPA-only control weakens the conclusion that PCBs have weak initiating properties, since Van Duuren (1982) found that TPA alone also produces a low incidence of skin cancer. Thus, it is impossible to separate any possible weak carcinogenic effect of PCBs from the known, weakly carcinogenic effects of TPA. Since the discussion in this paragraph is not supported by a thorough, well-conducted study, it should be deleted from the document.

15. Page 20, section 2.2.2.1 - Biological Monitoring - Exposure - concerning paragraphs 2 and 3 and the levels of PCBs in human tissues.

Response : The authors should search the literature for other informative studies of human adipose levels in the

United States and other countries rather than relying upon the statistical analysis from a single data source for illustrating the important trends of PCB levels in human adipose tissue. For additional perspective on this issue we suggest the following investigations which include a variety of PCB levels in various populations: Price and Welch (1972), Yobs (1972), Kutz and Strassman (1976), Lucas (1982), Grant et al. (1976), Mes et al. (1982), Hattula et al., (1976), IARC (1978), and Tatsukawa (1976). For example, these studies suggest that overall the adipose tissue PCB levels in the U.S. population gradually increased from 1972 to 1981, but the percentage of individuals with greater than 3 ppm reached a peak in 1977 (10%) and decreased steadily to become 1% by 1981 (Lucas, 1982). Several of the above references will also give adipose PCB levels in foreign populations which may serve as a relative reference for U.S. exposure levels.

We also suggest that the text and tables in this section should be labeled in a consistent fashion such that the untrained reader can easily realize the frequent 1 to 2 order-of-magnitude difference observed between blood and adipose tissue PCB levels in relative terms (i.e. ppm in adipose and ppb in blood, or a reference to what conversion factor one might use to put these two tissue levels in directly comparable terms).

16. Pages 20-22, section 2.2.21. Biological Monitoring - Exposure

Response : The data presented from the Wolff (1985) study (Tables 2.1 and 2.2) illustrates the imperfect relationship between exposure to various levels of PCBs and the resulting blood and/or adipose tissue levels found in these same workers. Also, the "nonexposed" blood levels are quite high in comparison to the PCB blood levels in the majority of general population as listed in Table 2.3. It should be clearly stated that, although the analysis of blood and adipose tissue for PCBs may "generally" correlate, much further study is needed to refine the methods and

qualify the assumptions (i.e., pharmacokinetic disposition of PCBs in human tissues and establishing specific and carefully controlled background tissue levels for statistical comparisons) involved in the determination of these tissue levels before the utilization of blood/adipose PCB levels can be considered accurate estimators of PCB exposure or body burden.

The authors should note that Sahl et al. (1985) is another blood PCB level reference (738 persons, 1982-1984) for comparison to the Kreiss (1985) data. Sahl et al. showed a mean PCB blood level of 4 ng/ml for workers in California, and should be added to Table 2.3 because it represents a timely and large "nonexposed" population which is useful to compare to the findings of the other studies shown.

The authors' reference to the Kimbrough (1987) study is somewhat misleading and should be qualified as to the actual relevance of the milk fat PCB measurement. The statement that adipose and milk fat PCB levels are 100-200 times serum levels sounds alarming in this context, yet, if explained earlier in this section when its relevance was revealed, it could have been considered more objectively. The milk fat percentage in breastmilk is most relevant when PCB levels are reported as a concentration relative to milk fat, and should be included along with some mention of the PCB levels measured in whole breastmilk (in the Michigan study and for the general U.S. population).

In addition, the authors state that PCB breastmilk levels measured in a Michigan population (Wickizer et al. 1981) are high and result from the consumption of PCB-contaminated fish. However, contradicting this implication by ATSDR is the fact that Rogan et al. (1986) reported a breastmilk PCB concentration at birth of 1.8 ppm among 733 women in North Carolina. While other studies have presented lower reference values from which a more objective presentation of breastmilk PCB levels in the U.S. might be constructed (see

Bush et al., 1985; Slorach and Vaz, 1985), and as several other studies are available to provide exemplary PCB levels found in foreign countries for comparison to the U.S. levels, the ATSDR is urged to include these studies for comparison and to delete the misconception that PCBs in breastmilk result primarily from the consumption of PCB-contaminated fish.

17. Page 22, section 2.2.2.2. Biological Monitoring - Effects

Response : Regarding the Triana, Alabama study, some additional comments are also in order. None of the following indices of health were associated with PCB levels: weight loss, prevalence of disease, use of medications or medical care, miscarriage, stillbirth, or infant death or heart disease. The association between log PCB concentrations and diastolic blood pressure were small and of borderline significance. And the authors noted that the strongest correlation was between log DDT and log PCB serum levels, a fact which eliminates the possibility of attributing a significant finding solely to PCBs.

18. Page 25, Table 2.3

Response : ATSDR fails to note in its document that the data in table 2.3 suggests that fish consumption may have no significant impact on a person's PCB body burdens. The last three studies on page 25 report mean serum PCB values that are well within the normal range for persons living in the U.S. For example, in the first part of this table, six of the "control" populations have serum PCB values that range from about 1 ppb to ≥ 40 ppb. In addition, the recently reported New Bedford, Massachusetts study concluded that persons eating fish taken from contaminated areas did not have elevated serum PCB levels. ATSDR should also recognize that studies using "volunteers" may report mean values that are considerably skewed as the volunteers may over-represent the category containing those persons which

consume large amounts of highly contaminated fish; and therefore are not representative of the average fish eating population.

19. Page 27, section 2.2.2.2. Biological Monitoring (Effects) - concerning the discussion in the 2nd paragraph, last sentence

Response : The references used in the second complete paragraph on this page to indicate that occupational PCB exposure is associated with changes in serum enzyme and other clinical chemistry values do not unequivocally support the contention that liver damage has been found in capacitor workers. For example, the study of Ouw et al. (1976) is indicated as evidence of a significant correlation between PCB exposure and elevated SGPT. Ouw stated in this paper "Despite some individual abnormal results, however, the mean of each hepatic function test for the whole group is within normal limits." This study cannot be construed as significant evidence of PCB-induced changes in hepatic enzyme levels in serum. Likewise, the study of Fischbein et al. (1979) is cited as evidence of PCB induced increases in serum GOT in exposed workers. The SGOT values from PCB-exposed workers actually are within a range which would normally be expected in the general population. Of the exposed population, 97.8% had SGOT values equal to or below 50 I.U./l. This was considered the normal range by the authors. Only 2.4% of the exposed workers had SGOT values higher than 50. Even if it is assumed that a "normal" value includes a span of SGOT values that are two standard deviations about the mean value (i.e., encompassing only 95% of the general population not suffering liver injury if SGOT activity is normally distributed), then the small percentage of the exposed worker population (2.4%) which were reported to have an "abnormally high SGOT" is a percentage of persons that is no higher than would be expected in the general population. If the data relied upon by Fischbein et al. (1979) reports a range for only one standard deviation above the mean for normal values, then the 2.4% of the capacitor workers observed above this range is considerably lower than

the expected 16% or more of normal persons that might also fall above this range.

The study by Chase et al. (1982) is improperly cited as evidence of a correlation between plasma PCB levels and increased SGOT. The non-exposed (plasma PCB level less than 10 ppb), nominally exposed (plasma PCB level 10-30 ppb), and exposed (plasma PCB level 10-312 ppb) workers had SGOT values of 19.4, 19.1, and 19.6 I.U./l, respectively. It is apparent from these results, in contrast to the opinion stated in the ATSDR document, that this study actually reports NO significant correlation between plasma PCB levels and SGOT values.

In summary, the papers in this paragraph which supposedly support the association between plasma PCB values and subclinical alterations in biochemical indicators of potential organ injury are either misinterpreted or misrepresented by ATSDR. These studies should be re-evaluated in a more critical fashion and reported in a manner that is consistent with the observed findings reported in each study.

20. Page 27, section 2.2.2.2. Biological Monitoring (Effects) - concerning the discussion of the Maroni et al. 1981 study in the 3rd paragraph, last sentence

Response : Of the 80 workers studied, 16 of the workers were reported to have hepatic involvement as determined by hepatomegaly or an elevation in a liver function test value. There was, however, no correlation of hepatic findings to duration of exposure or to total PCB blood levels (see following table). There was no specific pattern to the liver function tests reported as being outside the normal range, and none of the elevations were of a magnitude sufficient to indicate a significant liver function problem (e.g. all alkaline phosphatase, serum electrophoretic patterns, bilirubin, and urinalysis values were normal). The subjective reference in the ATSDR document to a "few cases" (cases which were not clearly identified) of

"well-defined liver failure" is a completely false statement. The results of the Maroni et al. (1981a) study did not report any liver failure, and this study provides no convincing evidence of liver injury. Furthermore, an age-paired control group comprised of persons from the area was not included in this study, a deficiency further complicating any attempt to interpret the significance of the minor changes reported in this study. None of the workers diagnosed as having liver abnormalities had ever suffered chloracne, and a number of unrelated health problems were described in these workers that may have contributed to the minor, subclinical findings reported in this study. Thus, it appears evident upon review of these data that the changes noted were not remarkable and do not appear to be related to PCB exposure.

**Clinical Findings in Capacitor Workers
Exposed to Pyralene or Apirolio**

Age (yrs)	Exposure index (yrs)	Hepato- megaly	Clinical tests					Blood PCB levels (ppb)
			AST <12	ALT <12	SGGT 6-28	SOCT 0.5-10	SPCH 18-36	
Plant A								
52	10.9	++				11	691	
50	13.7	+					1319	
44	6.2	++			34		611	
51	2.6	+++				10.2	672	
39	2.5	+	20	13	49	17.2	39	643
26	0.3	+				15		1259
31	1.3	-			39	11.7		277
38	3.1	-	13			13.7		438
Plant B								
30	4.0	+		21.8	33			470
30	2.5	++			53			377
56	11.0	++		20				180
24	2.5	++						131
26	2.5	++		23.6	49			376
30	4.0	+		18.2	48			290
31	2.0	+	25.4	36.4	91			152

AST = serum aspartate aminotransferase; ALT = serum alanine aminotransferase;
 SGGT = serum gamma glutamyltranspeptidase; SPCH = serum pseudocholinesterase
 SOCT = serum ornithine-carbamoyltransferase;
 - = absent, + = mild, ++ moderate, +++ = pronounced
 Adapted from Maroni et al. (1981a)

21. Page 28, section 2.2.3.2. Human exposure potential - concerning the last line in the first paragraph, and paragraph 2.

Response : The last line in the first paragraph perhaps should read "The exposure to" rather than "The exposure of". Also, references to filtration in this sentence indicate that water treatment will be discussed. Since it is not, the last line of this paragraph should be removed.

In the second paragraph, inhalation is identified as the principal route of human exposure to PCBs from a spill in soil at a restricted outdoor site. No exposure estimates or relative risks are supplied to support this statement, which leads the reader to ask whether this statement is merely an intuitive guess. The "Polychlorinated Biphenyls Spill Policy" referenced as EPA, 1987b states the following:

"The principal route of human exposure to PCBs from a spill in soil is through the inhalation route. Soil ingestion and dermal contact with soil would not be expected to be significant routes of exposure at a restricted access site. PCB levels in soil of 25 ppm would present less than a 1×10^{-7} risk to people on-site who work more than 0.1 km from the actual spill area (assuming that the spill area is less than 0.5 acre)."

The above statement would add to the ATSDR discussion by clearly indicating the risk associated with exposure to airborne PCBs from a limited access site, and would serve to allay public fears concerning the risks from PCB spills at sites with restricted access.

22. Page 32, section 2.3.2.2. in section 2.3 "Adequacy of Database", line 5 on this page.

Response : The occurrence of developmental effects in children born to mothers consuming PCB-contaminated fish is discussed at the top of this page where the document states, "but the effects cannot be directly attributed to PCBs...." If these effects cannot be "directly attributed to PCBs," two problems arise. First, if these effects cannot be attributed to PCBs, and we agree they cannot (see comments #7 & #10), ATSDR must admit that its discussion of these citations is misleading and should be either corrected or

removed. Second, if the information is inconclusive why is the data graphed as providing "some data"? Inconclusive data provides no information. Rather than graphing the adequacy of the database by whether or not citations were available (as was apparently done), ATSDR should clearly indicate if studies were available that could be relied upon to arrive at conclusions concerning the toxicities of PCBs. This would prevent second guessing by the reader as to whether a study is considered to provide "adequate" data in support of toxicity or "adequate" data which does not support toxicity or "some" data that provides no concrete information at all.

In the first complete paragraph on this page, the data concerning acute oral, inhalation, and dermal studies of the effects of PCBs in animals are described as being inadequately studied. There is a considerable body of literature concerning the effects of orally administered PCBs. What constitutes an "extensively investigated" route of PCB exposure? This is not defined in the ATSDR document, and once again ATSDR does not provide the reader with any perspective or context for conclusions reached in the document.

23. Page 32, section 2.3.2.3. Summary of relevant research

Response : In the ongoing studies by Rogan, children exposed to PCBs and polychlorinated dibenzofurans (Taiwanese children) will be compared to children from North Carolina who are exposed only to PCBs. Though it is implied that the comparison will yield information relevant to high-exposure (Taiwanese children) versus low-exposure (North Carolina children) PCB effects, results from this study will have to be interpreted with extreme caution. The obvious failure to control for concomitant exposure to PCDFs will invalidate the results of this comparative study. The consensus of the scientific opinion on this issue is clear -- the Yu-cheng and Yusho incidents are PCDF poisonings and cannot be used to predict the potential health effects of PCBs. Some of the

arguments which support the role of PCDFs as causal agents in the Yusho and Yu-Cheng incidents have recently been discussed by several Japanese scientists. The conclusions of these studies regarding the role of PCB, PCQ, and PCDF in the Yusho and Yu-Cheng incidents are summarized below.

- Although blood PCB levels of a group of Japanese capacitor workers and Yu-Cheng patients were similar, only Yu-Cheng patients had severe clinical manifestations of disease (Kunita et al., 1984; Masuda et al., 1985). Unlike the workers, Yu-Cheng patients were heavily exposed to PCDF, suggesting that the clinical manifestations of Yusho could best be explained by exposure to PCDF (Kashimoto et al., 1985; Kashimoto and Miyata, 1986).
- PCQ blood levels in workers exposed to used PCB were similar to those of Yu-Cheng patients. Thus, the comparatively severe symptoms experienced by the Yu-Cheng patients are not explained by differences in PCQ exposure.
- In Yusho patients, blood PCB levels declined to near background levels five years after exposure. For this reason, PCB is unlikely to be the cause of the chronic symptoms of poisoning experienced by Yusho patients. In contrast, toxic isomers of PCDF have been shown to persist in the tissues of Yusho victims up to 10 years after exposure (Kashimoto et al., 1981).
- Studies in monkeys have shown that animals fed PCBs with PCDFs and PCQs contaminant levels similar to those found in the Yusho oils produced a symptomatology that was similar to that found in the Yusho victims (Kunita et al., 1984). Monkeys fed PCBs or PCQs alone remained asymptomatic.

As a class, PCDFs are much more toxic than PCBs, and it now appears that even though Yusho and Yu-Cheng victims were exposed to an average of between 600 to 900 mg of PCB over the course of these incidents, the estimated exposure to 3.3 to 3.8 mg of PCDF appears to be responsible for many of the symptoms associated with these poisonings (Kuratsune , 1980; Kashimoto et al, 1981; Drill et al, 1982; Masuda et al, 1982; Masuda and Yoshimura, 1984; Chen et al, 1984; Bandiera et al., 1984; Kunita et al., 1985; Masuda et al., 1985 Miyata et al., 1985; Kashimoto et al., 1985; Kashimoto and Miyata, 1986).

24. Page 33, Section 2.3.3.2 : Monitoring of human biological samples

Response : ATSDR is apparently unaware that the New Bedford study has been completed. This study failed to find any significant increase in the PCB levels of persons eating fish taken from contaminated areas in the harbor. In addition, no association between blood pressure and serum PCB levels was found in this study.

25. Page 33, Section 2.3.3.3: Regarding the PCB Profile's discussion of environmental considerations related to PCB's, relatively broad and sweeping statements are made which deserve additional clarification.

Response : Although a significant amount of information regarding the bioavailability of PCBs from environmental media exists, the determination of bioavailability of PCBs in specific situations requires detailed data describing site conditions, empirical evaluation of these data and subsequent application of these data in a professional manner. As an example, if bioavailability of PCBs were relatively well understood and simple to determine, Battelle Northwest would not be conducting a multimillion dollar food web study for New Bedford Harbor.

Similar arguments can also be made regarding the PCB Profile's statement that the environmental fate and transport of PCBs is fairly well understood. The U.S. EPA

is currently funding significant studies regarding the environmental fate and transport of PCBs in New Bedford Harbor and the Great Lakes in order to develop data related to this issue. Although general atmospheric PCB transport models have been developed, the significance of the components of these models is not yet well understood. Some examples of model components which have only recently been considered are the rate of photolysis of PCBs in ambient air and anaerobic degradation of PCBs in buried sediments.

We note at this juncture that because of the time limitations imposed by ATSDR's delays in issuing the draft PCB Profile, these comments focus primarily on ATSDR's description of the toxicological properties of PCBs. In this and other sections of the PCB Profile, ATSDR has touched on the broad subject of the behavior and fate of PCBs in the environment. ATSDR's treatment of such subjects should be recognized as extremely limited in scope and our failure to discuss such limitations in greater detail, both with respect to this specific section and elsewhere, should not be taken as concurrence in ATSDR's broad and sweeping generalizations.

26. Page 41, Section 4.1: Overview

Response : In the second paragraph of this section, the authors give the impression that PCB contaminated fish are the only important source of dietary PCB intake in the US. This has not always been the case, however, since milk, eggs, cheese, poultry, and other meats have been shown to contain significant PCB residues (Kolbye 1972; Jelinek and Corneliussen 1976; EPA 1980), and many individuals do not regularly consume fish or fish by-products. In addition, relatively high average PCB concentrations measured for indoor air (39-500 ng/m³ versus 4-18 ng/m³ for outdoor air) of homes and public buildings have been indicated as significant sources of potential PCB exposure to the general population via the inhalation route (Macleod 1981). An overview such as this should contain all relevant exposures

to the general population (see specific comment #1).

In paragraph 5, the authors note that "higher PCB levels may reach the offspring through nursing than through placental transfer." This statement should be qualified because although this effect of breast-milk PCB transfer has been demonstrated in at least 3 studies (Kodama and Ota, 1980; Yakushiji et al., 1984; Ando et al., 1985), no human studies exist to suggest an unsafe human milk level of PCBs (Kendrick, 1980). Further, a study by Rogan et al. (1986) suggested that there are a number of variables within a population that can influence the concentrations of PCBs in breast milk, including such variables as alcohol consumption, age, number of children, and time spent breast feeding. Considering that the many studies of breast-milk PCB concentrations have demonstrated that these concentrations are inherently variable in a given subpopulation, this variability supports the existence of many factors that may affect the degree of PCB exposure through breast milk ingestion. More importantly, however, no unequivocal evidence has been put forth to suggest that the low ppm levels of PCBs found in breast milk are necessarily harmful.

Concerning the metabolism of PCBs, some additional comments are needed to give a more complete overview. First, the generalization that PCB metabolites "tend to be produced via an arene oxide intermediate" needs to be qualified in that 3-hydroxybiphenyl formation appears to result from a direct insertion reaction (Billings and McMahon, 1978). Also, the final sentence in this paragraph is somewhat misleading and unclear in suggesting that vicinal unsubstituted carbon atoms "may be helpful but not essential to this process." The requirement for two adjacent unsubstituted carbons for arene oxide formation, coupled with the role of arene oxide formation in the hydroxylation of two of the three possible hydroxylation sites on the biphenyl ring, makes it clear why the position of chlorination is at least as important as the extent of

chlorination in influencing metabolic rate. For example, substitution in the para or 4 and 4' positions affects the favored route of metabolism (Tuey and Matthews, 1977; Matthews and Dedrick, 1984). In addition, when vicinal or adjacent carbons in the ring are chlorinated, the rate of metabolism is further reduced as the preferred mechanism of arene oxide formation is inhibited because both carbons to be involved in epoxide formation are already bonded to chlorine. Thus, at least two adjacent unsubstituted ring carbons, particularly in the 3,4,5 or 3',4',5' positions, are required for the rapid metabolism of PCBs (Tuey and Matthews, 1977; USEPA, 1980; Drill et al., 1982; Matthews and Dedrick, 1984). Conversely, PCB isomers chlorinated in the 3,4,5 and 3',4',5' positions tend to be metabolized slowly and are more likely to bioaccumulate.

27. Page 42, Section 4.1: Overview - In the 2nd and 4th paragraphs

Response : The authors note the apparent half-life of a hexachlorobiphenyl compound but have included only four position designations in identifying the chemical and do not provide the citation for this particular comment. In the fourth paragraph, last sentence, the authors suggest that *"biochemical effects such as increased liver enzyme levels have been associated with Aroclor exposures in workers and in the general population."* To the best of our knowledge, there is no evidence to support the latter claim. Two studies have addressed this purported association in the general population. Baker et al. (1980) showed that plasma triglyceride levels increased significantly with serum PCB level, but this might be an association secondary to the preferred distribution of PCBs into serum containing elevated triglycerides. In the Triana study, serum cholesterol was positively associated with serum PCB levels and a weak correlation between log-transformed PCB and triglyceride levels was shown (an association which disappeared when controlled for cholesterol and GGT_P levels). It is apparent that the authors have drawn the conclusion that Aroclor exposure is associated with GGT_P

increases observed in the Triana study (Kreiss et al., 1981)
yet in the section (2.2.2.2) which discussed this study, the
authors of the ATSDR document also noted that "this effect
has not been validated and has uncertain relevance to PCB
exposure because the fish also contained high concentrations
of DDT residues." Thus, the term "equivocal association"
would be more appropriate in the overview to describe the
relationship between both occupational and environmental
Aroclor exposures and increased liver enzyme levels.
Regarding occupational PCB exposures, we have previously
noted that while the review of Kreiss (1985) has been quoted
as evidence that occupationally-exposed groups with the
higher serum PCB levels are associated with indicators of
possible hepatic damage such as SGOT or SGPT, the studies
relied upon by Kreiss do not support this contention.
Therefore, even among capacitor worker populations this
association remains unproven.

In addition, an increase in liver enzyme level (i.e.
GGTP) is not necessarily a toxic manifestation and is more
likely an adaptation response to the presence of any number
of different chemicals in the liver. Both the ATSDR
document and the articles cited therein fail to note this
possibility. Last, the ATSDR document has failed to review
these occupational studies in the context of the study by
Emmett (1985) which showed that serum PCB levels correlate
to serum lipid levels because lipids increase the water
solubility of PCBs. Thus, the study of Emmett (1985)
demonstrated that serum lipid levels confound serum
measurements and serum levels may be a poor predictor of fat
PCB levels. Because Emmett found that neither serum SGGT nor
serum triglyceride levels correspond to tissue (adipose)
PCB levels, this lack of tissue dose-response suggests that
PCB levels are not responsible for the small serum enzyme
changes that have been occasionally reported. For the
interested reader the Emmett study is summarized below.

Emmett (1985) has published a study of switchgear shop
employees involved with transformer maintenance functions.

Thirty-eight current employees and 17 previously-exposed employees were included in the study, and their measurements were compared to those of 56 non-exposed individuals. Adipose and serum PCBs in the currently exposed workers ranged from 0.2-33.0 ppm and 1-300 ppb, respectively (with a geometric mean of 2.1 ppm adipose and 12.2 ppb serum), while in previously-exposed workers adipose levels ranged from 0.3 to 5.1 ppm and serum ranged from 1 to 30 ppb (geometric means of 0.83 ppm and 5.9 ppb, respectively). By comparison, non-exposed persons had adipose tissue levels of 0.2-3.0 ppm (mean of 0.6 ppm), and serum levels of only 1-15 ppb (mean of 4.6 ppb).

Several clinical biochemical parameters were determined and compared to a non-exposed group (operating engineers). These comparisons revealed small but statistically significant differences in serum albumin, serum LDH, and serum T₄ levels when the values for non-exposed persons were compared to the exposed group (4.66 vs 4.55, 186.8 vs 202.3, and 8.8 vs 8.24, respectively). However, none of these small changes was associated with any clinical symptoms in this study, and as can be seen in Table 1 (on the next page), attempts to correlate log adipose or serum PCB levels to test values found no associations in every instance except for urinary 17-OH steroids and SGGT. Thus, there was no PCB-related trend for any of the variables reported to have small but significant differences in the exposed group, and no significant differences were noted between groups for those two parameters that appear to correlate with PCB levels (borderline significance [p = 0.055] was noted for 17-OH steroids). In contrast to a number of other studies, serum lipids in the PCB-exposed group (current and former employees combined) were not different from those in the non-exposed group (see Table 2), but log serum PCB concentrations did correlate with log triglyceride, cholesterol, and log VLDL (see Table 3).

Table 1

**Pearson Correlation Coefficients for PCB
Concentrations and Laboratory Results***

Liver Function Log of Variable	Log Adipose PCBs		Log Serum PCBs		
	Correlation coefficient	p value	Correlation coefficient	p	value
total protein	0.163	NS	-0.028		NS
abumin	-0.086	NS	-0.022		NS
bilirubin	-0.108	NS	-0.138		NS
alkaline phosphatase	0.140	NS	0.177		NS
SGOT	-0.106	NS	0.096		NS
SGPT	-0.195	NS	-0.053		NS
SGGT	0.086	NS	0.194		0.045
serum T4	-0.109	NS	-0.009		NS
urinary ALA	-0.108	NS	-0.028		NS
urinary 17OH steroids	-0.315	0.002	-0.146		NS
urinary coproporphyrins	-0.099	NS	-0.080		NS
urinary uroporphyrins	0.002	NS	-0.169		NS
antiprene half-life	-0.131	NS	0.023		NS

* results were not corrected for possible confounding variables

**Table 2
Serum Lipid Concentrations**

Variable (mg/dl)	Mean or Geometric Mean	
	Exposed group	Nonexposed group
triglycerides	116	128
total cholesterol	191	197
HDL cholesterol	43	40
LDL cholesterol	120	126
VLDL cholesterol	23	25

* geometric mean used for values with log normal distribution (Note : none of these variables were significantly different at the p < 0.05 level)

**Table 3
Pearson Correlation Coefficients for PCB
Concentrations and Serum Lipid Levels**

Log of Variable	Log Adipose PCBs		Log Serum PCBs	
	Correlation coefficient	p value	Correlation coefficient	p value
triglycerides	0-0.019	NS	0.259	0.007
total cholesterol	0.031	NS	0.202	0.036
HDL cholesterol	0.063	NS	0.053	NS
LDL cholesterol	0.021	NS	0.143	NS
VLDL cholesterol	-0.010	NS	0.270	0.005

All tables were adapted from Emmett (1985)

Based on these observations, Emmert proposed that PCBs may preferentially partition with plasma lipids. Such a phenomenon would explain the positive correlations observed between serum triglyceride levels and serum PCB concentrations in a number of studies. This phenomenon also seriously undermines the assertion that this correlation indicates that PCBs alter lipid metabolism. As can be seen in Tables 2 and 3, rather than serum PCB levels influencing serum triglyceride concentrations through an effect on lipid metabolism, serum triglyceride levels appear to dictate (all other factors being equal) serum PCB concentrations by increasing the serum:adipose partitioning coefficient and shifting PCBs from adipose tissue stores to the blood compartment.

28. Page 42, Section 4.1: Overview - 5th paragraphs

Response : In the last sentence of paragraph six, the authors note that various "fetotoxic effects" have been associated with PCB exposure in humans. Our objections to this conclusion have been elaborated elsewhere in this commentary, but the thrust of our argument is that these effects are not necessarily toxic manifestations and are largely equivocal observations. As mentioned in the authors' own commentary on those studies (section 2.2.2.2), "the effects are not well validated" and those studies based on contaminated fish consumption could not possibly exclude effects induced by other organochlorine contaminants also present in the fish. Again, equivocal evidence such as this should be placed in the proper context, and the reader should be made aware that it cannot be relied upon.

29. Page 46, Sec. 4.2.2.2, π 1. "Results such as these have led some investigators to conclude that transfer through nursing may account for higher exposure of young than does placental transfer. This conclusion may be inappropriate, as it is often based on the fact that the absolute quantity of PCB residues is substantially higher in breast milk than cord serum; relative to fetal body weight, even low-level prenatal exposure can cause substantial concentrations (Jacobson et al., 1985)."

Response: We strongly disagree with the inclusion of the

unsupported speculation by Jacobson et al. (1985) that placental transfer of PCB could be more harmful than the more notable breast milk transfer shown in a number of animal studies. A number of studies can be cited to the contrary which indicate fetal PCB burden relative to body weight or tissue weight. In rats, Baker et al. (1977) showed that induction of fetal livers was not significant, suggesting that PCBs were not crossing the placenta in significant amounts, a finding consistent with the study of Ando (1978) in rats and the studies of Vodicek and Lech (1980a & b) in mice. Measurements of tissue PCB levels confirmed this suggestion, and PCBs were detected in newborn pups in significantly greater quantities than were found in fetal tissues (Baker et al. 1977).

Takagi et al. (1986) showed that the average amount of PCB (Kanechlor 600, administered at 10 mg/kg/week, p.o., for five consecutive weeks) transferred from the dam to the fetus by gestational day 18 was only 0.0031% of the total PCBs accumulated in the dam. The average amount of PCB in fetal tissues ranged from 0.170-0.350 ppm with the highest concentration located in the fetal liver. As in other studies, the largest transfer of PCBs occurred after birth. PCBs transferred postpartum increased gradually from 0.042% on day 1 to 4.9% on day 5. This increased whole-body PCB concentrations in the newborn from 0.6 ppm on day 1 to about 8 ppm by days 11-18. The average concentration of PCBs in rat milk for this period was 1.84 ppm. Considering the low PCB tissue concentrations measured in the fetus and the approximately 23-fold higher PCB tissue level found at about two weeks after parturition, the speculation of Jacobson et al. (1985) is not supported here. It is clear that the majority of the postnatal dose is received from the breast milk and this exposure causes substantially higher tissue levels to be achieved in a shorter period of time. For instance, from these data the comparative rate of PCB accumulation in fetal tissues by gestational day 18 could be estimated at 0.019 ppm/day (0.35 ppm/18 days = 0.019 ppm/day) while the same rate in postnatal rat pups increases

at a rate of 0.41 ppm/day (8 ppm-0.6 ppm/13 days). The postnatal rate of PCB tissue accumulation is 21.6-fold greater than the prenatal rate.

In a review of the toxicology of PCBs in mink, Ringer (1984) points out that, even though there is some placental transfer of PCBs to the fetus, mink kits receive far more PCBs during lactation via breast milk than they do during gestation (a nearly two-fold average PCB/body weight increase from parturition to two weeks of age).

30. Page 49, Sec. 4.3. "Because of these factors and a lack or paucity of data for some of the Aroclors (most of the studies were conducted with the higher chlorinated Aroclors), it is assumed that effects resulting from exposure to a specific Aroclor are representative of effects which may be produced by other Aroclors."

Response: The ATSDR Document indicates here that a lack or paucity of data for some of the Aroclors exists with respect to toxicity. The document, in our opinion, has reached a conclusion that has no reasonable basis and one that cannot be supported (see specific comment #6). In addition, it should be noted that the ATSDR document cites evidence in several places documenting the fact that Aroclors are not equivalent. For example, ATSDR is or should be aware of : 1) the potency differences in reproductive toxicity that have been observed in mink (Aulerich and Ringer, 1977; Bleavins et al., 1980); 2) the different tumorigenic responses produced in the rat by PCB mixtures of 42%, 54% and 60% chlorine; and 3) the different hepatotoxicities produced by different hexachlorobiphenyl isomers (Biocca et al., 1981). Other examples not reported by ATSDR can also be cited, such as the vastly disparate estrogenic activities of various Aroclors (Gellert, 1978). Therefore, ATSDR should abandon its approach of assuming that all PCBs represent equivalent hazards and produce equivalent toxicities. ATSDR's approach is contradicted by the scientific literature, and it indicates a clear lack of understanding and limited knowledge concerning the potential toxicities of PCBs.

31. Page 52, Sec. 4.3.1.2, "The cause of death was not specified but may have been related to development of nodular hyperplasia in the liver. There was no effect on survival of female rats similarly treated. There was no attempt to identify or quantitate impurities."

Response: The document's statement that the cause of death may have been related to development of nodular hyperplasia of the liver is purely speculative and should be removed from the document because it cannot be supported by the data. More appropriately, the document should mention that the decreased survival of the male animals is not a universal finding in chronic studies, since the analysis of the Schaeffer et al. (1984) study by Young (1985) indicated that Clophen A30 (similar to Aroclor 1242) and Clophen A60 (equivalent to Aroclor 1260) actually increased survival in treated rats over that observed in controls. To make this discussion complete, Young (1985), Schaeffer et al. (1984), Kimbrough et al. (1975), and Norback and Weltman (1985) all should be reviewed in greater detail than ATSDR has reviewed them in this document. A careful review of these studies indicates that, in general, no decrease in rat survival or longevity is observed following chronic exposure to dietary levels of 100 ppm PCBs. **{See Appendix A for more discussion}**

32. Page 52, Sec. 4.3.2.1, π 1. "Epidemiological studies and clinical surveys indicate that occupational exposure to Aroclors can produce alterations in liver enzymes (e.g., SGOT, GGTP) that are inconsistent and not clearly associated with clinically detectable liver disease... Asymptomatic hepatomegaly was reported in one study... The subjects of these studies were primarily involved in electrical equipment (e.g., capacitors, transformers) manufacturing and repair, and many had measurable and often high serum levels of PCBs."

Response: This paragraph is a clear example of the inconsistency with which the ATSDR document has been written. For example, an increase in SGOT is described as an indicator of "possible hepatocellular damage" of unspecified magnitude on page 27, but this same clinical measurement is described as "not being associated with clinically detectable liver disease" on page 52. These two descriptions represent two inconsistent and contradictory ATSDR opinions of the same study results. Also, in

describing the Maroni et al. (1981a) study, the discussion on page 27 inaccurately refers to "well defined liver failure" which has been significantly changed and more accurately described as "asymptomatic hepatomegaly" on page 52. Again, the first description implies that a serious disease of a lethal nature was observed in the Maroni study when no such findings were reported. The much more accurate second description implies that a liver enlargement of no consequence was what was actually observed. If the results of the above studies had been described accurately under the previous discussion on page 27, as has already been suggested, this discrepancy would have been avoided. Such major discrepancies in the ATSDR document raise serious concerns for the manner in which this document was developed, the credentials of the persons responsible for the general text, and either the lack of an adequate review by its peer review panel or the failure of ATSDR to consider important comments made by this panel.

33. Page 52-54, Sec. 4.3.2.1. "(Fischbein et al. 1979) Approximately 40% of the workers in this study were employed for > 20 years. There was a correlation between SGOT and serum PCB levels."

Response: The simple statement in the ATSDR document that "There was a correlation between SGOT and serum PCB levels" in the Fischbein et al. (1979) study is inadequate to describe these results. Fischbein and coworkers first examined the correlation between plasma levels of the higher homologues of PCBs and SGOT values and secondly, the correlation of plasma levels of the lower PCB homologues and SGOT values. For the higher homologues comparison, 280 workers were arbitrarily divided into groups having high homologue PCB plasma levels of 0-75 ppb or 75 and greater ppb. For the lower homologues, groups were divided into persons having lower homologue PCB plasma levels of 0-200 ppb or 200 and greater ppb in the plasma. Fischbein and coworkers found that there was an association between the groups with high levels of PCB homologues in plasma and the percentage of persons in that group with SGOT values out of

the "normal range." They did not, however, as the ATSDR document leads the reader to believe, perform any statistical tests to examine the correlation between SGOT values and PCB serum concentrations. Stated more correctly, these results are evidence that high serum PCB levels may be associated with a marginally increased incidence of persons with SGOT values outside of the "normal" range.

In a subsequent study (Fischbein, 1985), Fischbein examined 93 female and 134 male capacitor workers to determine whether there was a statistical correlation between plasma PCB levels of lower and higher homologues and SGOT values. Fischbein was un able to detect any statistically significant correlation between plasma PCB level (of either higher or lower homologues) and SGOT values. This study and the recent studies by Emmett (1985) and Lawton et al. (1985) contradict the statement made by ATSDR. Therefore this statement should be either removed or changed to incorporate a more complete picture of the data available on this subject.

34. Page 54, Sec. 4.3.2.1, π 3. "Serum PCB levels were positively associated with increased GGTP levels and blood pressure in Triana, Alabama, residents that were exposed to contaminated fish (Kreiss et al., 1981)."

Response: The associations between log PCB concentrations and diastolic blood pressure were small and of borderline significance, as admitted by the authors (Kreiss et al. 1981). The authors also noted that the strongest correlation existed between log DDT and log PCB serum levels, a fact which undermines their ability to attribute a significant finding solely to PCB exposure. This is not just our opinion as Kreiss (1985) recently stated, "However, the collinearity of DDT and PCB serum concentrations in this rural population, exposed to both chemical families through consumption of contaminated fish, precludes any certainty regarding which family of chlorinated hydrocarbons may be correlated with blood pressure." (emphasis added by reviewer). The fact that the Kreiss (1985) was cited in the

PCB Profile, and yet her new conclusion regarding the relevance of her earlier reported finding, is yet another example of the biased manner in which much of the data provided in the PCB Profile has been cited.

In contrast to the early study by Kreiss and coworkers (Kreiss et al., 1981), Bumgarner et al. (1973) was unable to detect any association between PCB exposure and blood pressure. In a recent PCB health effects study concerning PCB exposure to residents of New Bedford, Massachusetts, through fish, lobster and eel consumption, it was concluded that 1) the general prevalence of elevated PCB levels among residents of Greater New Bedford is low; 2) even residents at highest risk of PCB exposure from locally caught seafood consumption, for the most part, had levels within the typical range of the US population; and 3) low and moderate serum levels of PCBs in this population do not appear to be associated with elevated blood pressure measurements. These results completely contradict the single, isolated finding of Kreiss et al. (1981). Again ATSDR should either remove or update its statement.

35. Page 55, Sec.4.3.2.1, π2. "The effects of chlorination and chemical composition of PCBs with regard to the dose effects relation of liver toxicity after subchronic exposure are indicated by the data of Biocca et al. (1981)..."

Response: In addition to the data discussed in this paragraph, this study also indicates that more potent PCB isomers tend to accumulate to a greater extent in the fat. This is a point which should be included here, and the relevance of these findings should be considered in re-evaluating the ATSDR document's previous opinion that all Aroclor mixtures should be considered as being equally toxic.

36. Page 56, Sec. 4.3.2.1, π2. "Implications of enzyme induction for human health include the occurrence of disease secondary to the increased metabolism of endogenous or exogenous substances, and the interference with medical therapy due to increased metabolism of administered drugs (Letz 1983)".

Response: For the sake of completeness, ATSDR should also include the fact that prior microsomal enzyme induction by PCBs has been shown to decrease the tumorigenic effects of a number of carcinogens such as 3'-methyl-4-dimethyl-aminoazobenzene (Makiura et al., 1974; Kimura et al., 1976), N-2-fluorenylacetamide (Makiura et al., 1974), diethylnitrosamine (Makiura et al., 1974; Nishizumi, 1980; Anderson et al., 1983), aflatoxin B-1 (Hendricks et al., 1977; Shelton et al., 1984a & b), dimethylbenzanthracene (Berry et al., 1979), and benzo[a]pyrene (Nesnow et al., 1981). **{See also the Table provided in specific comment #57}** Not only do these studies run counter to the statement made by Letz, but ATSDR and Letz should both be aware that microsomal enzyme induction is generally beneficial because it increases the body's ability to eliminate toxic chemicals. While this effect will also result in the need to increase the dose of some medications, this is not an uncommon or difficult problem. Instead this is a rather routine phenomenon experienced in medicine, and a number of important drugs which have been used chronically in humans are potent microsomal enzyme inducing agents. As in other places in this document, ATSDR's failure to critically evaluate the statements of made by others, or its failure to include all the available data relevant to the issue being discussed, shows considerable bias on the part of ATSDR.

37. Page 56, Sec. 4.3.2.2, π3. "Safe et al. (1985) reviewed data concerning the mechanism of PCB induction of liver microsomal enzymes... Support for the receptor mediated mechanism of action was found when..."

Response: The document cites the review by Safe et al. regarding the mechanism of PCB induction of liver enzymes. It should be pointed out that while there is a general agreement as to the role of the Ah receptor in enzyme induction, the role for this receptor in PCB toxicity is much less clear and in fact, this theory has become a controversial issue. The structural attributes of halogenated aromatic hydrocarbon (HAH) molecules which

facilitate Ah receptor binding appear to be associated with toxicity. However, an important confounder in attempting to use these correlations to ascribe PCB toxicity to Ah receptor binding is the fact that the congeners which are most toxic are also the congeners which tend to be most persistent. Increased toxicity for these congeners can therefore be explained on the basis of bioaccumulation and prolonged half-life alone.

Three additional lines of evidence weaken the proposal that Ah receptor binding is the critical event in the development of HAH toxicity:

1) There is a lack of correlation between Ah receptor binding and toxicity of HAHs across species. For example, there are enormous differences among species with respect to sensitivity to TCDD toxicity, covering a 5000-fold range of acute LD50 values. Despite this wide range of sensitivities to TCDD toxicity, the binding affinity of TCDD to the Ah receptor is remarkably consistent among species. This is illustrated by the binding study of Gasiewicz and Rucci (1984);

2) A number of studies have found a dissociation between inductive effects of HAHs and toxic effects. Greig et al. (1984) reported that porphyria induced by tetrachlorodibenzodioxin (TCDD), another HAH postulated to produce toxicity through binding to the Ah receptor, does not correlate with the Ah phenotype, and Seki et al. (1987) made a similar observation with porphyria induced by PCBs. Rifkind et al. (1984) studied HAH toxicity in a chick embryo model and found that benoxypfen can prevent the lethality, pericardial edema, and thymic atrophy induced by 3,4,3',4'-tetrachlorobiphenyl without affecting AHH induction. Holsapple et al. (1986) found that 2,7-dichlorodibenzodioxin, a polychlorinated dibenzodioxin which lacks affinity for the Ah receptor, produced immunosuppression in mice similar to that produced by TCDD; and

3) There is a lack of correlation among HAHs between binding to the Ah receptor and toxicity within a species, e.g. the guinea pig. There are a number of compounds which bind to the Ah receptor in the guinea pig with affinity similar to TCDD. Yet among these compounds, lethal doses can vary from 2 to >10,000 µg/kg. Though there is evidence that the nature of the molecular properties of Ah receptors differs among species (Denison et al., 1986; Romkes et al., 1987), this does not account for the lack of correlation between binding affinity, number of receptors, and sensitivity to toxicity.

38. Page 56-57, Sec. 4.3.2.2. "Inhalation, human... Drill et al. (1981) concluded that individuals with blood levels of ≥ 200 ppb of PCBs have an increased risk of chloracne and that chloracne may occur more frequently in workers exposed to PCBs that have been heated and to PCBs that have >54% chlorination."

Response: Although blood PCB levels greater than or equal to 200 ppb are said to be associated with chloracne, there are little or no data available to suggest that the 200 ppb level represents some type of threshold for chloracne. For this reason the above statement should be changed or carefully qualified until better data relating blood PCB levels and chloracne are made available.

39. Page 62, Sec. 4.3.3.2. "Human. Birth weight, length, head circumference, gestational age, and neonatal behavior were evaluated in 313 newborn infants (Fein 1984, Fein et al., 1984, Jacobson et al. 1984a)...."

Response: These studies (Fein, 1984; Fein et al., 1984; Jacobson et al., 1984a) were reviewed in the context of page 17 of the ATSDR document, Section 2.2.1.2, Developmental Toxicity. Basically, we have serious doubts as to the true relevance of the above findings and their definition of small changes in the above-mentioned parameters as "toxic" effects of PCBs. These comments have been made previously and so will not be reiterated here. However, we will again note that even the ATSDR document states that the small changes observed in these studies cannot be attributed to PCBs, and as ATSDR states on p. 42, these effects are not

well validated.

In addition to the numerous shortcomings of these specific studies, the fact that a similar studies by Rogan et al. (1986; 1987) and a study of women working in a capacitor factory by Taylor et al. (1984) failed to confirm or observe these effects, demonstrates that the above studies cannot be relied upon. Therefore, ATSDR should minimize its discussions of these papers and should cite them in a manner that does not mislead the lay public as to the actual limited significance of these particular studies.

40. Page 63, Sec. 4.3.3.2, π1. "Contaminated fish consumption was also positively correlated with impaired autonomic maturity, increased numbers of abnormal reflexes, and decreased range of state (Jacobson et al. 1984b)..."

Response: This study was also commented upon earlier in this review, pointing out that:

- 1) It was not established whether these behavioral effects were lasting or transitory;
- 2) While contaminated fish consumption correlated with these behavioral deficits, cord serum PCB levels did not. Thus, an implied history of exposure rather than an actual dose was found to correlate with the observed changes.
- 3) Therefore, the association would appear to be due to something other than PCBs in the contaminated fish.

41. Page 63, Sec. 4.3.3.2, π3. "Jacobson et al. (1985)... There was a dose-related decrease in fixation to novelty: cord serum levels of 0.2 to 1.1 ng/ml were associated with mean scores of 61%, 1.2 to 2.2 ng/ml with mean scores of 60%, 2.3 to 3.5 ng/ml with scores of 57%, and 3.6 to 7.9 {ng/ml} with scores of 50%."

Response: The document cites the results of this study without mentioning the authors' suggestion that, while their study indicates that high cord PCB levels may be associated with developmental delay in the performance of a visual task, their results cannot be extrapolated to indicate that any permanent PCB-induced damage had occurred. Indeed, postnatal exposure to PCBs in breast milk did not correlate

with changes in visual recognition memory. Although the authors accounted for a number of confounding variables in their analysis, one obvious oversight was the failure to include an evaluation of serum or cord lead concentrations. Considerable evidence suggests that lead may induce subtle changes in learning behavior in children born to mothers with slightly elevated blood lead concentrations, and the study of Jacobson et al. (1985) should be considered flawed for failing to consider the potential effect of this important environmental contaminant.

42. Page 64, Sec. 4.3.3.2, π3. "Haake et al. (1987) reported that treatment of pregnant C57B/6 mice with Aroclor 1254 by gavage at 244 mg/kg on day 9 of gestation did not result in any fetuses with cleft palate."

Response: It would be far more complete to also state that PCB treatment antagonized TCDD-induced terata (birth defects). This important fact is omitted from the ATSDR document and illustrates bias in reporting the findings of specific studies.

43. Page 64, Sec.4.3.3.4, π2. "Reports of reduced birth weight and gestational age in infants of mothers with occupational and environmental exposure to Aroclors (Taylor et al. 1984, Fein 1984, Fein et al. 1984) are inconclusive but consistent with the animal developmental effects data."

Response: Even though Taylor et al. (1984) reported a trend toward reduced birth weight and gestational age in infants born to mothers with occupational exposure to PCBs, the effects were not statistically significant ($p < 0.05$). Failure to observe a significant effect in the Taylor study indicates that there would not be any reduction of birth weight or decrease in the length of gestation in children born to mothers who were exposed to the considerably lower PCBs exposures stemming from environmental contamination. Therefore, the Taylor study (and its larger but as yet unpublished update) provides a strong contradiction of the weak and "inconclusive" findings of Fein (1984) and Fein et al. (1984).

44. Page 65, Sec. 4.3.3.4, π2. "That intrauterine exposure may be more harmful than postnatal exposure is also suggested by the results of the Jacobson et al. (1985) study, which indicated that behavioral effects were correlated more with prenatal exposure (cord serum PCBs) than with exposure via breast milk."

Response: In addition to the fact that the results of the Jacobson et al. (1985) study have already been shown to be of limited value, the animal studies generally indicate that considerably greater PCB exposure and toxicity occur during lactation. Studies in rats, mice, monkeys and mink have failed to find evidence of terata at doses not producing considerable maternal toxicity. Further, these studies indicate that if the greater exposure to PCBs occurring during lactation is kept low enough so that acutely toxic levels are not achieved in the neonate, then few, if any, adverse effects are observed in the infant animal. Thus, the ATSDR comment which suggests that greater harm occurs via intrauterine PCB transfer is not supported by the literature. (See also comments on Section 4.2.2.1 of the ATSDR Document.) This is but another example that SRC has included unsupported statements in this draft of the PCB Profile.

45. Page 66, Sec 4.3.5.2. "The only positive responses were obtained by Wyndham et al. (1976), who observed increases in reversion frequency in *Salmonella typhimurium* strain TA1538 exposed to 4-chlorobiphenyl and, to a lesser extent, Aroclor 1221 only in the presence of metabolic activation."

Response: The relevance of the only positive *in vitro* mutagenicity investigation of PCB mixtures has been discounted by one of the authors of the paper. In an affidavit from Dr. Safe (one of the authors of the Wyndham et al. (1976) study; see appendix D), he indicated that based on his own inability to reproduce the findings of the Wyndham et al. study, 4-chlorobiphenyl should not be considered mutagenic. Considering the fact that this was the more active of the two positive compounds reported in the Wyndham et al. (1976) study, Aroclor 1221 should likewise not be considered a mutagenic substance.

46. Page 66, Sec. 4.3.5.2, π2. "Weakly positive results (chromosomal aberrations) were obtained in ring dove (*Streptopchia risoria*) embryos from doves fed Aroclor 1254 at 10 ppm in the diet."

Response: The Peakall et al. (1972) study is cited as weak positive evidence of the mutagenicity of Aroclor 1254. In conjunction with a study measuring the effects of PCBs on the breeding success of ring doves fed a 10-ppm diet of Aroclor 1254, Peakall et al. (1972) also reported on the observed incidence of chromosomal aberrations in the eggs of these birds. The average aberration rate changed from 0.8% in the control or untreated birds to 1.8% in the PCB-treated birds. A single embryo irradiated with X-rays and serving as the positive control had an aberration rate of 18%. However, the average rate of chromosomal aberrations measured in the eggs of PCB-treated birds was only higher than the highest control value of 2% in 4/17 eggs coming from birds treated with PCBs. The frequency of chromosomal aberrations in these eggs were 2.4%, 2.6%, 3.1% and 9.4 %, respectively. Thus, it is the consensus of this review, as it was the conclusion of the authors of this study, that these results are inconclusive.

47. Page 66, Sec. 4.3.6.1. "Bahn et al (1976, 1977) reported an increased incidence of malignant melanomas in employees of a northeastern US petrochemical plant where Aroclor 1254 was used for 9 years in the 1950s..."

Response: Reports of high cancer rates among Mobil Oil employees exposed to PCBs (Aroclor 1254) at Mobil's Paulsboro, New Jersey, refinery have been interpreted by ATSDR as an indication that PCB exposure was linked to skin (melanoma) or pancreatic cancer (Bahn et al., 1976; 1977). In this preliminary study, eight cancers were found to have developed between 1957 and 1975 among 92 employees. Of the 92 persons in this cohort, 51 were apparently employed in research and development, and only 31 of these employees were considered to be heavily exposed to PCBs. The remainder of the cohort consisted of 41 refinery workers. The level of exposure to Aroclor 1254 was not provided or discussed, and the maximum duration of exposure was only 9 years (Bahn et

al., 1976). Of the eight cancers ultimately reported, three were malignant melanomas and two were cancers of the pancreas. According to NIOSH (1977) "This is significantly more skin cancer (melanoma) and pancreatic cancer than would be expected in a population of this size, based on the Third National Cancer Survey."

However, there are several reasons why it is difficult to draw any conclusions from this study. For example, Lawrence (1977), of the New York State Department of Health, criticized the authors of this preliminary report for failing to identify other chemicals to which these refinery workers and research chemists might have been exposed. Lawrence (1977) points out that PCB fluids typically contained epoxides which were added as stabilizers. In fact, in the capacitor plant he was investigating at the time of his letter, epoxides comprised 0.5% of the capacitor fluids being used. Since the epoxides had vapor pressures 1,000 times that of the PCB fluids to which they were added, the risk of exposure to epoxides was greater than that for PCBs. Because several epoxides have been shown to be carcinogenic in animals, this potential confounder was an obvious oversight of the Bahn report. Additional confounders were also represented by the number of chemicals common to the air around petroleum refineries, e.g. benzene, that are known to be human or animal carcinogens.

In response to the criticism of Lawrence (1977), Bahn et al. (1977) did agree that further information was essential, and apparently withdrew this study for revision (Gaffey, 1981); but as yet no follow-up has ever been released. Therefore, we are compelled to ask ATSDR why this withdrawn, poor and unrepeatabe study is even included in this section as it clearly adds nothing relevant to the issue being discussed.

48. Page 69, Sec. 4.3.6.2, π 2. "Statistically significant excess risk of liver cancer has been reported in Yusho patients that were studied for a follow-up period of over 16 years (Amano et al. 1984, Kuratsune 1986)... Although the findings are suggestive..."

Response: If the ATSDR document did not intend to review the adverse effects observed in the Yusho and Yu Cheng incidents (as is stated in paragraph 5, page 42), why is PCB exposure in the Yusho incident linked to liver cancer in humans on page 69? The document invalidates its own opinion that there is a suggested link between PCBs and liver cancer, since it states, "effects from the incidents (Yusho and Yu Cheng) are not reviewed in this report because the exposure was to Kaneclors and because the effects cannot be attributed specifically to the Kaneclors" and "There appears to be general agreement that the PCDF contaminants, particularly the more potent isomers, contributed significantly to the health effects observed in the Yusho and Yu Cheng patients". For the above reasons, combined with those given elsewhere in this critique, it is strongly requested that the ATSDR document not consider any of the adverse effects observed in Yusho and Yu Cheng victims until such time that the observed and cited change can be shown to be based on something other than speculation.

The statements on page 69 about the Yusho data indicate ATSDR has once again changed its opinion as the document progresses. We should like to point out, however, that ATSDR statements made on page 42, as well as information supplied in this critique (see specific comment 22), completely invalidate the position ATSDR attempts to propose here on page 69.

49. Page 69, Sec. 4.3.6.2, π3. "Kimbrough et al. (1975) fed groups of 200 female weaning Sherman rats diets containing 0 or 100 ppm Aroclor 1260..."

Response: The ATSDR discussion of the Kimbrough et al. (1975) study omits important information which is necessary for a complete and objective review of these results. For example, only liver tumors are discussed, and the effect of Aroclor 1260 on extrahepatic tumor incidence is omitted. Kimbrough et al. (1975) published the first major positive study demonstrating that Aroclor 1260 can produce hepatocellular carcinoma in the rat. In this study 200

female Sherman strain rats were fed Aroclor 1260 at a dietary level of 100 ppm for approximately 21 months. The incidence of the histopathological findings from this study are summarized in the table that follows this comment. The most consistent histopathologic difference in the PCB treatment group was the finding of hyperplastic or neoplastic nodules in 144/184 (78%) of the livers and the finding of hepatocellular carcinoma in 26/184 (14%) of the PCB-treated animals. Tumors in areas other than the liver were not listed as significantly different. However, in some cases there was a substantial decrease in the tumor incidence of other tissues, e.g. as in the case of parafollicular cell tumors of the thyroid. Furthermore, the total incidence of tumors was not changed by PCB treatment. The total incidence of all tumors in the control population was 135/173 (78%) while the incidence in the PCB-treated animals was 135/184 (73%). In other words, the PCB-induced increase in liver tumors was offset by a decreased incidence of extra-hepatic tumors in Aroclor 1260-treated animals of 110/183 (60%) compared to an extrahepatic tumor incidence in control animals of 134/173 (77%). The Aroclor 1260 diet was also without adverse effect on the life-span of the animals. In fact, about twice as many control animals had died for various reasons before the experiment was terminated at 23 months than had PCB-treated animals (Kimbrough et al. 1975).

Results of Carcinogenesis Bioassay of Aroclor 1260

		<u>Tumor Incidence</u>	
Organ/Tissue	Lesion Type	Control Animals	Aroclor 1260 Animals
Incidence of Other Pathological Changes			
Liver	Neoplastic nodules	0/173	144/184
	Areas of cytoplasmic alteration	28/173	182/184
Tumor Incidence			
Liver	Hepatocellular carcinoma	1/173	26/184
Thyroid gland	Parafollicular cell tumor	37/160	18/166
Adrenals	Pheochromocytoma	1/173	1/167
Pituitary gland	Chromophobe adenoma	41/153	28/139
"	Carcinoma	0/153	1/139
Uterus	Endometria polyp	18/149	25/163
"	Adenocarcinoma	0/149	2/163
"	Sarcoma of endometrial stroma	3/149	7/163
Urinary bladder	Papilloma	1/167	0/169
Salivary gland	Fibrosarcoma	1/173	0/184
Lung	Adenoma	2/173	2/184
Adipose tissue	Lipoma	0/173	2/184
Brain	Glioma	0/173	2/184
Ovary	Granulosa theca cell tumor	5/149	0/163
"	Papillary adenoma	1/149	2/163
Mammary gland	Fibroadenoma	17/173	13/184
"	Adenocarcinoma	5/173	1/184
Blood	Granulocytic leukemia	1/173	0/184
"	Lymphoma	0/173	0/184
Kidney	Hemangioma	0/173	1/184
Thymus	Thymoma	1/173	0/184
Parathyroids	Adenoma	0/173	2/184
Skin	Fibroma	0/173	1/184
Total Tumor Load		135/173	135/184
(% = total tumors/N)		(78%)	(73%)
Extrahepatic Tumor Load		134/173	110/184
(% = extrahepatic/N)		(77%)	(60%)

Adapted from Kimbrough et al. (1975)

50. Page 70, Sec. 4.3.6.1, π4. "EPA (1987a) used the Norback and Weltman (1985) study ... Because this study demonstrated the progression of hepatocellular lesions through neoplastic nodules to carcinomas, it provides justification for using the combined incidence for quantitative risk assessment."

Response: As is well-known to the EPA, neoplasia and carcinoma are histologically distinct definitions which deserve separate consideration, particularly in terms of the interpretation of animal carcinogenicity studies using rodent models. There have been many studies showing the high incidence of neoplasia among control animals late in the course of chronic bioassays, and this fact underlies the reason why it is incorrect to treat neoplastic nodules as though they were carcinomas. Examples of the reasoning for this are cited in the study of Schaeffer et al. (1984) which showed that the highest incidence of neoplastic growths was among control rats (see the Table below). It can be argued that if neoplastic nodules were considered carcinomas, a number of studies which previously showed increased liver cancer may now be interpreted as not showing significantly increased cancer incidence due to the high incidence of liver neoplasia in the control groups. Neoplasia should thus remain a characteristic which is considered completely separate from carcinoma, and therefore should not be included in risk extrapolations.

Incidence of Neoplasia Animals Necropsied up to Day 800

Lesion	Controls	Clophen A30	Clophen A60
Number of animals not dying	131	138	129
Number necropsied	78	51	44
(% necropsied)	60%	37%	33%
Other neoplasias	52	28*	18*

Adapted from Schaeffer et al., 1984

* denotes significance (p<0.05)

51. Page 71, Sec. 4.3.6.2, π1. "Although their incidence was not statistically significant, the low historical incidence of these lesions suggest that they might have been treatment related. NCI (1978) concluded that the high incidence of hepatocellular

proliferative lesions in male and female rats was related to treatment, but that Aroclor 1254 was not carcinogenic in this bioassay."

Response: This statement provides further support for the separate consideration of the risks due to PCB exposure by Aroclor mixture. Here and at several other points in the ATSDR document, differences in toxic effects and potencies between different PCB mixtures are mentioned, yet ATSDR states on page 49, Section 4.3 that it considers all Aroclors to be equally toxic. This conclusion is contradicted by the negative findings of the NCI (1978) study and the negative data that Schaeffer et al. (1984) reported for chronically administered Clophen A-30.

52. Page 71, Sec. 4.3.6.2, ¶4. "Kimura and Baba (1973) fed diets containing 38.5 to 616 ppm Kanechlor 400 to groups of 10 rats..."

Response: The PCB Profile has previously stated on page 42 that it considers the Kaneclors to be toxicologically distinct from the Aroclors. We agree that there is sufficient evidence to toxicologically separate the different commercial PCB mixtures. In this and the next paragraph, studies by Kimura and Baba (1973) and Ito et al. (1974) are discounted as being inadequate for use in assessing the carcinogenic potential of PCB mixtures. Although these investigators fed rats high doses of various Kaneclors over a period of time less than that required for a chronic study, prevailing theories in chemical carcinogenesis would suggest that the increased doses used in these studies would decrease tumor latency while increasing tumor incidence. This runs counter to the idea that these studies were not chronic bioassays and that they provide little evidence concerning the carcinogenicity of the PCB mixtures.

53. Page 72, Sec. 4.3.6.3, ¶2 "Berry et al. (1978) reported that Aroclor 1254 was not a skin tumor promoter in female CD-1 mice that had been initiated with DMBA, nor did it produce tumors when tested without DMBA initiation at a level of 1 mg administered twice weekly."

Response: For completeness, the findings by Berry et al. (1979) showing PCBs afford protection against the development of papillomas should also be included in this section.

54. Page 72, Sec. 4.3.6.4, General discussion

Response: ATSDR should remove the discussion of the NCI bioassay because this portion of the text is speculative rather than descriptive. ATSDR should also recognize that decidedly different results would have been obtained if the experiments of Schaeffer et al. (1984) or those of Norback and Weltman (1985) had been performed for the traditional two year period rather than the 27-29 month duration used in these two studies. For example, by day 800 the liver cancer incidence was only 20% on the Schaeffer et al. (1984) study, a much smaller incidence than the 61% obtained by the end of the study; and the data provided in the Norback and Weltman (1985) study indicates that only 9% of the tumors identified were found in animals sacrificed during the first 24 months. The fact that the tumors develop late in life and do not share the characteristics of malignant tumors (Norback and Weltman, 1985), combined with the fact that chronic PCB exposure tended to increase the longevity of the animal and decrease the incidence of extra-hepatic tumors (Kimbrough et al., 1975; Schaeffer et al, 1984), and the fact that this effect appears limited to PCB mixtures of 60% when the dose is 100 ppm or higher are all findings that greatly limit concern for the potential of PCBs of 60% chlorine content to induce human cancer. This is especially true when one remembers that human PCB exposures via environmental contamination are considerably lower than that of capacitor workers, who in turn had exposures that were considerably lower than those used in animal studies.

For a more in-depth and analytical review of the animal carcinogenicity studies, see Appendix A of this critique. It is clear from the data presented in Appendix A that ATSDR

has failed to evaluate critically all of the evidence presented in the papers ATSDR cited and relied upon in section 4.3.6.4 of the PCB Profile. It is also clear that there is considerable scientific evidence that is counter to the conclusions and statements rendered in this subsection of the PCB Profile.

55. Page 73, Sec. 4.4, "INTERACTIONS WITH OTHER CHEMICALS"

Response: The document has omitted several references which indicate that PCBs have either anti-tumorigenic effects or no effect on tumorigenesis. The multiple studies listed in the Table that follows this comment indicate that PCBs are certainly not initiators, and have in fact been noted to decrease tumor incidence on several occasions. It is quite clear from these findings that the low levels of PCBs which the US population is exposed to from prenatal life onward will most probably either protect against tumorigenesis or have no effect whatsoever on the progression of tumors induced by other chemical exposures.

In addition, although ATSDR cites Haake et al. (1987) and is therefore aware of this paper, ATSDR fails to inform the reader that Aroclor 1254 has a positive interaction with dioxin (TCDD) that antagonizes the teratogenicity of this compound and should lower the risk of birth defects that might be associated with environmental exposure to TCDD.

Summary of Studies Reporting PCB Antagonism or Negative Interaction with Chemical Carcinogenesis

Study	Carcinogen	Results
<u>A. PCBs Administered After the Carcinogen :</u>		
Hendricks et al., (1980)	aflatoxin B1	no effect
Gans & Pitauro, (1986)	diethylnitrosamine	liver scarring no effect (liver nodules)

B. PCBs Administered Before or With the Carcinogen :

Makiura et al., (1974)	Me-DAB N-2-fluorenylacetamide diethylnitrosamine	fewer liver tumors fewer liver tumors fewer liver tumors
Kimura et al., (1976)	Me-DAB	fewer liver tumors
Hendricks et al., (1977)	aflatoxin B-1	fewer liver tumors
Nishizumi (1980)	diethylnitrosamine	fewer liver tumors
Anderson et al., (1983)	diethylnitrosamine	fewer liver & lung tumors
Shelton et al., (1984b)	aflatoxin B-1	fewer liver tumors
Kerklivet & Kimeldorf (1977)	tumor cell injection	lower tumor incidence
Berry et al., (1979)	dimethylbenzanthracene, TPA (phorbol acetate)	fewer skin tumors
Hayes et al., (1985)	2-acetylaminofluorine, carbon tetrachloride	no initiation of liver lesions
Nesnow, et al., (1981)	benzo-a-pyrene	little or no effect in fibroblast culture
Nishizumi (1985)	dimethylhydrazine	no effect on G.I. tumors
Stott & Sinnhuber (1978)	aflatoxin B-1	reduced mutagenicity in the Ames Assay

Me-DAB = 3'-methyl-4-dimethylaminoazobenzene

56. Page 75, Section 5.2 , π 1.

Response : The basis for the PCB Profile's estimate of the sale of 1 billion pounds of PCBs in North America since 1970 is unclear. The document estimates that approximately 280,000,000 pounds were produced by Monsanto in the United States; that other production sources may have contributed up to an additional 280,000,000 pounds of PCBs, and that the import of PCB's to the United States was likely less than 1,000,000 pounds per year. Accordingly, the basis for this estimate of the sale of a billion pounds of PCBs in North America should be verified.

57. Page 76, Section 5.4.

Response : The PCB Profile is misleading in describing

the typical size of capacitors utilizing PCBs. No discussion is provided as to the average size of a capacitor or to the amount of PCBs typically contained in "small" or "medium" sized capacitors.

58. Page 76, Section 5.5

Response : The statement that the TSCA regulations promulgated on April 18, 1978 required PCB disposal by incineration is incorrect. Many PCB-contaminated materials were disposed of in accordance with these regulations by land disposal or dechlorination. At the time the TSCA regulations were promulgated, little incineration capacity for PCBs existed in the United States; only two incinerators were permitted for PCB incineration after TSCA promulgation. Accordingly, most PCB waste was not disposed of through incineration following promulgation of these regulations. The significance of ATSDR's error is two-fold: It illustrates SRC's lack of care and depth of knowledge in preparing the PCB Profile; and, more specifically, it leads to an underestimate of the amount of PCBs in the environment, and therefore to an underestimate of the prevalence of exposure, because it implies that all PCB disposal from 1978 to at least 1983 was by incineration.

59. Page 77, Section 6.1.

Response : The statement that Aroclors with a high degree of chlorination are resistant to biodegradation appears to be somewhat inconsistent with statements made later on in Section 6.3.2 of this document. While there is evidence that the more highly chlorinated PCB congeners are resistant to aerobic degradation, recent work conducted by several researchers (Brown, Tiedje, and New York State Department of Health) show anaerobic biodegradation to be suitable for the dechlorination of PCBs. Anaerobic biodegradation of PCBs has been demonstrated in Hudson River sediments, and in Silver Lake, Massachusetts, sediments by

one researcher. Accordingly, additional consideration should be given to biodegradation as an ultimate degradative process for PCBs contained in soils and sediments.

60. Page 79, Section 6.3.2. Excessively high PCB bioconcentration factors have been reported in the PCB Profile. For example in the last paragraph of page 79 the PCB Profile states, "A Summary of Experimentally Determined Bioconcentration Factors of Various Aroclors (1016, 1248, 1254 & 1260) in Aquatic Species (Fish, Shrimp, Oyster) has found Aroclor bioconcentration factors ranging from 26,000 to 260,000 (Leifer et al. 1983)"

Response: While Leifer may have found bioconcentration factors in some species as high as those he mentions i.e., 26,000 to 260,000 ppm, his selection of these numbers shows a lack of objectivity for he did not comprehensively discuss the significant factors that may affect bioconcentration or biomagnification.

Bioconcentration in aquatic species depends on a number of factors, some relating to the characteristics of the species being measured, others relating to the physicochemical characteristics of the polychlorinated biphenyl. In regard to the characteristics of the species being measured bioconcentration factors can depend upon the species habitat, whether more demereal or nektonic, the phyletic group, and the role the species occupies in the food chain. In regard to the physicochemical properties of the polychlorinated biphenyls, bioconcentration is dependent upon such things as degree of chlorination, water solubility and partition coefficients, and stereo chemistry.

Bioconcentration factors in aquatic species range from very low or less than 1 ppm to factors as high as those mentioned by Leifer. For instance Tatem (1986), in a study of fresh water prawns, found bioconcentration factors ranging from .11 to .90 ppm for Aroclor 1242 and .20 and 2.40 ppm for Aroclor 1254. In clams he found bioconcentration factors ranging from 0.54 to 12.52 ppm.

The relationship of bioconcentration factors to properties of the polychlorinated biphenyls have also been discussed in a paper by Sanborn, et al. (1975). Bioconcentration factors in the green sunfish (Lepomis cyanellus) ranges from 54 to 1,510 depending upon whether trichlorobiphenyls or pentachlorobiphenyls were being measured. Sanborn also noted the effect water solubility and partition coefficients as well as stereochemistry could have on bioconcentration in certain species. In general he found the more highly chlorinated isomers were bioconcentrated to a greater extent.

Notwithstanding the fact that the relationship of various environmental and physical chemical factors to the bioconcentration of polychlorinated biphenyls is an extremely complex one, the effect of the bioconcentration of PCBs is highly variable. Depending upon the tissue in which the polychlorinated biphenyls are concentrated and the susceptibility or sensitivity of the species to any biochemical interactions, the toxicological effects may be highly variable.

61. Page 82, Sec. 7.2.2 "WATER..."; and Page 93, Sec. 9.2.2.2 "Water..."

Response: Consideration of PCB water concentrations at various locations in the U.S. together with the risk estimates prepared for water would lead the reader to believe that a considerable portion of the population is at risk from PCB-induced cancer. For example, persons served by Waterford Water Co., where PCB levels were found to range from 0.12-0.8 ppb, may have a lifetime cancer risk higher than 10^{-4} (based on the risk estimate listed in EPA's new draft of its drinking water criterion document). It is also interesting to note that ambient levels of PCBs approach the 10^{-4} risk level for conditions in the North Sea.

However, the PCB Profile fails to put these potential exposures into context and fails to mention the fact that a 10^{-4} risk is similar to that risk posed by the chloroform

standard promulgated by the EPA for drinking water, and is considerably lower than the risk posed by the EPA's arsenic drinking water standard (a risk of about 10^{-2}). As stated earlier in this critique, the fact that the epidemiologic evidence can be used to invalidate the EPA's cancer risk estimate (which is derived from animal studies) should be noted and mentioned in the PCB Profile. To do so would provide the reader with a more accurate perspective of the actual risks posed by environmental exposures to PCBs. This information would also be helpful for the uninformed reader as it would demonstrate the limited confidence that one can actually place on the numbers generated by current risk assessment methodologies when they are derived from chronic, high dose animal data.

62. Page 94, Sec. 9.2.3, ¶2 "...EPA (1987a) recommended that all commercial PCB mixtures be considered to have a similar carcinogenic potential and classified all PCB mixtures in category B2."

Response: The EPA position that all PCB mixtures should be considered to have equal carcinogenicity must be doubted in light of the current evidence to the contrary and the fact that even EPA (on p.73) states that only the carcinogenicity of PCB mixtures of 60% chlorine "appears to have been demonstrated." This decision is also contrary to other areas in the ATSDR document which allude to the fact that each of the commercial PCB mixtures has a characteristic and distinct toxicity (see comment #27).

Introduction to Appendices

These Appendices are included in order to describe and analyze in detail the studies discussed in the Specific and General Comments. The material in the Appendices therefore does not directly critique the PCB Profile, but rather provides a full explanation of the bases of the opinions and conclusions, concerning the studies that are stated in the Specific and General Comments.

Carcinogenicity Studies of PCBs in Rats

Kimura and Baba (1973) exposed 10 male and 10 female Donryu rats to a variable dietary level of Kanechlor 400 for 400 days. The diet initially contained 38.5 ppm and was fed to the animals for 4 weeks; the dietary level was then doubled and provided for the following 8 weeks; the initial dietary level was then increased 4-fold and provided for 3 weeks; it was then increased 8-fold and fed to the animals for another 3 weeks; finally it was increased to 16 times the initial level and fed to the animals for 3 more weeks. This last increase in the dietary levels of PCBs (a level that was approximately 616 ppm) was found to be too toxic and caused a considerable weight loss in the animals. In response to the toxicity observed at this dose, the dietary level was reduced to 462 ppm for the remaining 32 weeks of the study. Further complicating interpretations of this study is the fact that animals died or were sacrificed at various times throughout the experiment; therefore the total PCB dose each animal received may differ. In general, the total amount ingested was thought to be 1300-1800 mg for the group of male animals and 1100-1500 mg for the female animals. Microscopically the livers of all of the treated animals contained fatty degenerative changes, and while 6/10 of the livers from female animals had adenomatous nodules, none of the livers of the male animals contained such nodules. However, the liver nodules observed in the female animals do not appear to be related to the PCB treatment as 2/5 (40%) of the livers from the control female animals also contained adenomatous nodules.

In a second study Kimura et al. (1976) fed 12 female Donryu rats diets containing 400 ppm Kanechlor 400 for 6 months. The estimated dose corresponded to a total of 531 mg of PCBs during this period. Eight of the 12 animals were then sacrificed 590 days after the feeding began. None of these animals developed hepatocellular carcinoma, and 9/12 of the livers were normal in appearance, suggesting that the degenerative changes observed in the previous study are reversible.

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Ito et al. (1974) fed male Wistar rats Kanechlor 300, Kanechlor 400 or Kanechlor 500 at dietary levels of 100, 500 or 1,000 ppm for up to 52 weeks. No hepatocellular carcinomas were found in the livers of any of the PCB treated rats (see Table A-1). The highest dose of all three Kanechlors did produce a cholangiofibrosis of the liver, but this effect was not observed at lower doses in any of the Kanechlors. Nodular hyperplasia was observed in 30-40% of the rats exposed to the two highest doses of Kanechlor 500 (i.e. doses of 500 ppm and 1,000 ppm) and in animals receiving a diet containing 1,000 ppm of Kanechlor 400. Oval cell proliferation and proliferation of the bile duct cells were observed in all treatment groups. Hypertrophy of the centrilobular cells was also evident in animals receiving the highest dose of the two most heavily-chlorinated PCB mixtures. Fatty changes and fibrosis were also observed in the livers of animals of several of the treatment groups. The fatty changes, hypertrophy and fibrosis of the liver all tended to be present and correlate with the observation of nodular hyperplasia, suggesting that these changes may have been contributory factors.

Table A-1

Histopathological Findings in the Livers of Wistar Rats
Fed Various Levels of Kanechlors 300, 400 and 500.

PCBs in diet (ppm)	Oval cell/ Bile duct proliferation	Fatty changes	Hepato- cellular hypertrophy	Fibrosis	Cholangio- fibrosis	Nodular hyperplasia
Kanechlor-500						
1000 ppm	+	+	++	±	4/13 (30%)	5/13 (39%)
500 ppm	+	+	+	-	0/16 (0%)	5/16 (31%)
100 ppm	±	±	±	-	0/25 (0%)	3/25 (12%)
Kanechlor-400						
1000 ppm	+	±	++	++	2/10 (20%)	3/10 (30%)
500 ppm	±	-	+	-	0/8 (0%)	0/8 (0%)
100 ppm	±	-	+	-	0/16 (0%)	2/16 (13%)
Kanechlor-300						
1000 ppm	+	+	+	-	2/15 (13%)	0/15 (7%)
500 ppm	±	±	+	-	0/19 (0%)	0/19 (0%)
100 ppm	±	±	±	-	0/22 (0%)	1/22 (5%)
Controls	-	-	-	-	0/18 (0%)	0/18 (0%)

Adapted from Ito et al. (1974)

Kimbrough et al. (1975) published the first major positive study demonstrating that Aroclor 1260 can produce hepatocellular carcinoma in the rat. In this study 200 female Sherman strain rats were fed Aroclor 1260 at a dietary level of 100 ppm for approximately 21 months. There was a statistically significant 6-7% decline in the weight gain of the animals exposed to PCBs in this study suggesting that the dose used approximated the maximally-tolerated dose. The incidence of the histopathological findings from this study are summarized in Table A-2. The most consistent histopathologic difference in the PCB treatment group was the finding of hyperplastic or neoplastic nodules in 144/184 or (78%) of the livers. More important, however, was the finding of hepatocellular carcinoma in 26/184 (14%) of the PCB-treated animals. Tumors in areas other than the liver were not listed as significantly different. However, in some cases there was a substantial decrease in the tumor incidence of other tissues, e.g. as in the case of parafollicular cell tumors of the thyroid. Furthermore, the total incidence of tumors was not changed by PCB treatment. The total incidence of all tumors in the control population was 135/173 (78%) while the incidence in the PCB-treated animals was 135/184 (73%). In other words, the PCB-induced increase in liver tumors was offset by a decreased incidence of extra-hepatic tumors in Aroclor 1260-treated animals (e.g., 110/183 or 60%) compared to the extra-hepatic tumor incidence in control animals (i.e., 134/173 or 77%). The Aroclor 1260 diet was also without adverse effect on the life-span of the animals. In fact, about twice as many control animals had died for various reasons before the experiment was terminated at 23 months than had died in the PCB-treatment group (Kimbrough et al. 1975).

TABLE A-2

Results of Carcinogenesis Bioassay of Aroclor 1260

Organ/Tissue	Lesion Type	Tumor Incidence	
		Control Animals	Aroclor 1260 Animals
Incidence of Other Pathological Changes			
Liver	Neoplastic nodules	0/173	144/184
	Areas of cytoplasmic alteration	28/173	182/184
Tumor Incidence			
Liver	Hepatocellular carcinoma	1/173	26/184
Thyroid gland	Parafollicular cell tumor	37/160	18/166
Adrenals	Pheochromocytoma	1/173	1/167
Pituitary gland	Chromophobe adenoma	41/153	28/139
"	Carcinoma	0/153	1/139
Uterus	Endometria polyp	18/149	25/163
"	Adenocarcinoma	0/149	2/163
"	Sarcoma of endometrial stroma	3/149	7/163
Urinary bladder	Papilloma	1/167	0/169
Salivary gland	Fibrosarcoma	1/173	0/184
Lung	Adenoma	2/173	2/184
Adipose tissue	Lipoma	0/173	2/184
Brain	Glioma	0/173	2/184
Ovary	Granulosa theca cell tumor	5/149	0/163
"	Papillary adenoma	1/149	2/163
Mammary gland	Fibroadenoma	17/173	13/184
"	Adenocarcinoma	5/173	1/184
Blood	Granulocytic leukemia	1/173	0/184
"	Lymphoma	0/173	0/184
Kidney	Hemangioma	0/173	1/184
Thymus	Thymoma	1/173	0/184
Parathyroids	Adenoma	0/173	2/184
Skin	Fibroma	0/173	1/184
Total Tumor Load		135/173	135/184
(% = total tumors/N)		(78%)	(73%)
Extrahepatic Tumor Load		134/173	110/184
(% = extrahepatic/N)		(77%)	(60%)

Adapted from Kimbrough et al. (1975)

In 1978 the National Cancer Institute examined the carcinogenic potential of Aroclor 1254 (NCI, 1978). Groups of 24 male and 24 female Wistar rats were fed Aroclor 1254 at dietary levels of 25, 50 or 100 ppm for 105 weeks. Clinical signs of toxicity including hair loss, facial edema and cyanosis occurred by week 72 in the high dose animals and the mean body weights were roughly only 2/3-3/4 that of their respective controls. This decrease in body weight exceeds the no more than 10% weight loss guideline for the estimated maximally-tolerated dose that is part of the NCI guideline for cancer bioassays (NCI, 1979). The clinical signs noted in the high-dose group by week 72 and in the mid-dose group by week 104 were alopecia, amber-colored urine, facial edema, exophthalmos, and cyanosis. In addition to the clinical evidence of toxicity in these animals, a decrease in the survival of the male animals showed a significant dose-related trend. Several histopathologic changes occurred in the livers of animals receiving PCBs that appeared to be related to the PCB treatment, particularly the incidence of hyperplastic nodules and adenomas (see Table A-3). Male animals had two hepatocellular carcinomas in the 100 ppm group, 1 in the 50 ppm group, and none in the group fed 25 ppm. No such tumors were observed in the female animals at any dietary level of Aroclor 1254. Although the incidence of these tumors was not significant, the observed incidence of non-neoplastic hyperplastic nodules did appear to be dose-related. These proliferative lesions were similar in appearance to what was termed at this time "focal areas of cellular alteration" if classified using the scheme proposed by Squire and Levitt (1975). The foci of these hyperplastic nodules generally involved two or more hepatic lobules, occasionally contained severely vacuolated hepatocytes, and in some instances small foci of basophilic hepatocytes. The adenomas were characterized as involving several swollen lobules of severely vacuolated hepatocytes, but these cells still maintained the general sinusoidal structures of normal hepatic lobules.

Table A-3

**Summary of the Hepatic Lesions in Fischer 344 Rats
Following the Chronic Administration of Aroclor 1254**

Lesion	Male Animals			Female Animals		
	25 ppm	50 ppm	100 ppm	25 ppm	50 ppm	100 ppm
Number of Animals Necropsied	24	24	24	24	24	24
Nodular Hyperplasia	5	8	12	6	9	17
Adenomas	0	0	1	0	1	2
Hepatocellular carcinoma	0	1	2	0	0	0

Adapted from NCI, 1978

The summary of this report noted that although there was no statistically significant increase in the incidence of cancer in any tissue, the incidence of nonneoplastic heperplastic nodules appeared to be dose-related. These data were also reviewed by the Data Evaluation/ Risk Assessment subgroup of the Clearinghouse on Environmental Carcinogens, a group responsible for providing peer review of NCI studies. The primary reviewer noted that with regard to the liver pathology caused by PCBs in the rat, once the proliferative stimulus was removed the hyperplastic nodules regress and disappear. This reviewer felt that the animal data indicated Aroclor 1254 may act like a tumor promotor and not a complete carcinogen, and the following conclusion was adopted by the subgroup :

"It is concluded that, under the conditions of the bioassay, Aroclor 1254 was not carcinogenic in Fischer 344 rats; however, a high incidence of hepatocellular proliferative lesions in both male and female rats were related to treatment. In addition, the carcinomas of the gastrointestinal tract may be associated with treatment in both males and females. Based on the liver

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proliferative lesions in the treated rats and published reports, it is suggested that Aroclor 1254 may be a tumor promoter." (emphasis added)

Morgan et al. (1981) have taken the same tissue sections that originated in the NCI bioassay (NCI, 1978), stained the stomach sections for alkaline phosphatase, and then re-sectioned these tissues for further histological evaluation. The overlap between pathologic evidence of a lesion and alkaline phosphatase (AP) activity was incomplete. For example, in the 100 ppm group 63% of the lesions were at sites of focal AP activity while 25% were located in regions of diffuse AP activity and 13% were in areas which had no detectable level of AP activity. The final incidence of intestinal metaplasia was 6.4% in controls, 8.3% in animals fed 25 ppm Aroclor 1254, 10.4% in the 50 ppm group, and 31.3% in the 100 ppm animals (see Table A-4). Intestinal metaplasia was not found in any of the eight animals that died before the 73rd week of

Table A-4

**Incidence of Stomach Lesions In Rats Chronically Fed
Aroclor 1254 : A Re-evaluation of the NCI Study**

Dose level	Animals per group	Intestinal metaplasia	(%)	Adenocarcinoma	(%)
0 ppm	47	3	(6.4%)	0	(0%)
25 ppm	48	4	(8.3%)	1	(2.1%)
50 ppm	48	5	(10.4%)	3	(6.3%)
100 ppm	48	15	(31.3%)	2	(4.2%)

Adapted from Morgan et al., 1981

the experiment. This suggests that this type of lesion occurs late in the life of the animal, and no correlation was found between early deaths and the incidence of stomach lesions. Additionally, no correlation was found between the incidence of stomach lesions and liver lesions in the animals. The stomach lesions were most often noted in the pyloric region of the stomach and duodenum (88% of all lesions were found in these areas), suggesting a toxicity

specific to the cells of these areas. Gastric adenocarcinomas comprised six of the 33 total lesions identified in these slices. Three were found in tissues from the 50 ppm treatment group and two in the animal group fed 100 ppm. Thus, the incidence of this lesion did not appear to be a dose-related change. The authors concluded that the actual number of stomach lesions they believed should have been observed in the G.I. tract tissue sections of the NCI study was twice the number of lesions reported in the original NCI study. On the basis of their findings, the authors of this paper further concluded that chronic oral Aroclor 1254 exposure leads to the induction of intestinal metaplasia in the Fischer 344 rat, and probably leads to induction of adenocarcinoma of the glandular stomach (Morgan et al., 1981).

Ward (1985) has also published a review of the slides originating from the NCI bioassay. In addition to the aforementioned dose-related depression of body weight, Ward (1985) also discusses, in some detail, the substantial decrease in animal survival that occurred in this study. While the survival rate in control animals and in the treatment group receiving 25 ppm was 92% and 83%, respectively, only 58% of the animals receiving the 50 ppm diet and 46% of the animals fed diets containing 100 ppm survived to the end of the bioassay. Focal hyperplasia was of the eosinophilic type and was only observed in PCB-treated animals. According to his own classification scheme, if compression was found on two sides of the foci, Ward diagnosed the lesion as hepatocellular adenoma. Based on his diagnosis of the NCI bioassay slides, Ward identified a total of 13 eosinophilic, basophilic or vacuolated adenomas of the liver (see Table A-5). All of these occurred, with one exception, in those animals fed the two highest dietary levels of Aroclor 1254 and the occurrence of adenomas was slightly greater in the male animals (8/13). In contrast to the findings of the NCI (1978) report, Ward reported finding only two liver carcinomas, and both occurred in male animals receiving the 100 ppm diet. Ward (1985) also reported that Aroclor 1254 increased the incidence of intestinal metaplasia and gastric

Table A-5

**Summary of the Hepatic Lesions Reported by
Ward Following His Review of the NCI Bioassay***

Lesion	Male Animals			Female Animals		
	25 ppm	50 ppm	100 ppm	25 ppm	50 ppm	100 ppm
Number of Animals Necropsied	24	24	24	24	24	24
Adenomas	1(0)	2(0)	5(1)	0(0)	3(1)	2(2)
Hepatocellular carcinoma	0	0(1)	2(2)	0(0)	0(0)	0(0)

* Numbers in parentheses indicate the findings of the NCI study

Adapted from NCI, 1978

adenocarcinoma. As in his earlier paper with Morgan and Hartman (Morgan et al., 1981), the change in adenocarcinoma was neither significant nor dose-related. A significant increase in intestinal metaplasia was only observed in the 100 ppm dose group. Thus, the Ward (1985) study is relatively consistent with the previous NCI (1979) bioassay. No statistically significant increase in liver cancer or cancer of other tissues was observed, but the 100 ppm dose did result in significant intestinal metaplasia. Ward mentions the fact that the liver lesions he observed were predominantly of the eosinophilic type rather than the basophilic type generally observed in the control animals. Based on these changes Ward proposes the idea that these data may suggest that PCBs are capable of initiating liver tumors rather than promoting the background tumor incidence. Yet, in contradiction of his suggestion, Ward also makes note of the fact that inducing agents like PCBs and phenobarbital cause a proliferation of the smooth endoplasmic reticulum (SER) of the liver. As a proliferation of the SER gives rise to an eosinophilic appearance of the cytoplasm, the liver hypertrophy and induction of microsomal enzymes associated with PCB exposure provides an obvious explanation for the basophilic to eosinophilic change Ward noted in the cellular

appearance of the liver tumors of PCB-treated animals.

Schaeffer et al. (1984) used a total of 432 weanling Wistar rats to examine the effects produced by chronically feeding rats Clophen A60 (equivalent to Aroclor 1260) or Clophen A30 (similar in composition to Aroclor 1242; Brinkman and DeKok, 1980). The study consisted of three groups. Group 1, a control group of 139 animals receiving the normal diet, Group 2 with 152 animals receiving a diet containing 100 ppm of Clophen A30, and Group 3 which consisted of 141 animals fed a diet containing 100 ppm of Clophen A60. After day 801 animals were randomly selected and killed, and the experiment was terminated on day 832. The Clophens used in this study were reported to be free of any chlorinated dibenzofuran contamination, but the level of detection for this analysis was not specified. In those animals necropsied prior to day 800, hepatocellular carcinomas were only identified in the PCB treatment groups and were first observed after 700 days. One was found in Group 2 and a total of 9 were identified in Group 3. This latter number was statistically significant for the Clophen A60 treatment, but represented a liver cancer incidence of only 7% for the entire group. In contrast, the incidence of thymoma was significantly reduced by PCB treatment declining from 12% in the control group to 3-4% in the treatment groups. Likewise the total number of the remaining types of neoplasms was significantly reduced by the PCB treatment, with Clophen A60 causing the greatest reduction (from 52 in controls down to 18 in the Clophen A60 group). The results up to day 800 of this experiment are provided in Table A-6.

The results for the animals still alive after 800 days, i.e. those animals randomly selected, killed and necropsied on days 801-832, are provided in Table A-7. The liver cancer incidence was significantly elevated, but only in those animals receiving the Clophen A60. Therefore, the results of this study were consistent with previous rat studies in that a commercial PCB mixture containing 60% chlorine was reported to have induced hepatocellular carcinoma, but the lesser-chlorinated PCB mixture was clearly not carcinogenic.

Table A-6

**Most Frequently Occurring Lesions in
Animals Necropsied up to Day 800**

Lesion	Controls	Clophen A30	Clophen A60
Number of animals not dying	131	138	129
Number necropsied	78	51	44
(% necropsied)	60%	37%	33%
Hepatocellular carcinoma	0	1	9*
Thymoma	16	4*	2*
Other neoplasias	52	28*	18*

Adapted from Schaeffer et al., 1984

* denotes significance ($p < 0.05$)

Table A-7

**Most Frequently Occurring Lesions in
Animals Necropsied on Days 801-832**

Lesion	Controls	Clophen A30	Clophen A60
Hepatocellular carcinoma (%)	1/53 (2%)	3/87 (3%)	52/85* (61%)
Thymoma (%)	9/53 (17%)	12/87 (14%)	0/85* (0%)
Other neoplasias (%)	19/53 (36%)	33/87 (38%)	13/85 (15%)
Nephritis (%)	21/53 (40%)	7/87* (8%)	0/85* (0%)

Adapted from Schaeffer et al., 1984

* denotes significance ($p < 0.05$)

The Schaeffer et al. (1984) study also confirmed another finding of the Kimbrough et al. (1975) study, i.e. chronic PCB treatment was associated with a significant decrease in the incidence of extra-hepatic tumors.

Of additional interest was the temporal progression of the liver lesions listed as preneoplastic lesions (foci of hepatocellular alterations), neoplastic nodules and hepatocellular carcinoma. As can be seen in Table A-8, all of these lesions

Table A-8
Frequency of Hepatocellular Alterations Induced by Chronic Feeding Studies with Clophen A30 and Clophen A60

Time Interval	<u># of Foci</u>	<u>Neoplastic Nodules</u>	<u>Hepatocellular carcinoma</u>
Control Animals			
301-400	0%	0%	0%
401-500	11%	0%	0%
501-600	8%	8%	0%
601-700	6%	12%	0%
701-800	5%	0%	0%
801-832	32%	4%	2%
Clophen A30			
301-400	0%	0%	0%
401-500	0%	0%	0%
501-600	55%	0%	0%
601-700	33%	17%	0%
701-800	50%	5%	5%
801-832	49%	40%	3%
Clophen A60			
301-400	0%	100%	0%
401-500	0%	0%	0%
501-600	40%	60%	0%
601-700	0%	100%	0%
701-800	3%	67%	30%
801-832	0%	40%	61%

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

Adapted from Young (1985)

occurred to some extent in control animals and were primarily a feature of older animals (i.e. > 500 days old). Clophen A30 did increase the incidence of foci and neoplastic nodules, but this effect tended to occur very late in the life of the animal and did not progress to hepatocellular carcinoma. In contrast, after 500 days of exposure there was a rapid progression from foci to neoplastic nodule and finally hepatocellular carcinoma in those animals fed Clophen A60. This complete loss of foci in these animals after day 600, and the progressive shift from foci to nodule and then carcinoma might be interpreted as a promotional effect induced by Clophen A60.

In a letter to the editor, Young (1985) comments on several interesting and important aspects of the Schaeffer et al. (1984) study that received little attention by the authors of this paper. Young's analysis of the Schaeffer et al. (1984) data focused on the effects of PCB exposure on tumor incidence in liver, on tumor incidence in extra-hepatic tissues, and on mortality. The tables generated by Young (1985) are provided on the next page in Table A-9. Young points out that the Schaeffer et al. (1984) study actually demonstrated three things. These are : 1) that a significant increase in hepatocellular carcinoma occurred only in the animals receiving Clophen A60, 2) that PCB treatment resulted in a significant decrease in other neoplastic lesions, and 3) that PCB treatment significantly increased the chances of survival of the animals.

Given these findings, Young states that after careful consideration it is difficult to conclude, given the balance of the data, whether or not PCB treatment was in fact detrimental to the rats. That is, typically we would not consider a treatment detrimental if it significantly enhanced the rate of survival and significantly decreased the total tumor load of the exposed rats. In essence then, he questions the human relevance of tumors which occur only very late in the life of the animal, are not life-shortening and do not metastasize to other organs of the body.

Table A-9

**The Incidence of Hepatocellular Carcinoma, Other
Neoplastic Lesions, and Mortality by Time Period**

Time Interval (days)	Treatment Group		
	Control	Clophen A30	Clophen A60
A. Hepatocellular Carcinoma			
301-400	0/137	0/150	0/135
401-700	0/111	0/122	0/115
701-800	0/92	1/107	9/85*
B. Other Neoplasms			
301-400	0/137	1/150	2/150
401-700	32/111	11/122*	9/115*
701-800	30/92	15/107*	7/85*
C. Incidence and Percentage (%) of Mortality			
101-400	2/139 (1.4%)	2/152 (1.3%)	3/141 (2.1%)
401-700	45/137 (32.8%)	43/150 (28.7%)	23/138 (16.7%)
701-800	39/92 (42.4%)	20/107 (18.7%)	30/85 (35.3%)
1-800	86/139 (61.9%)	65/152 (42.8%)*	56/141 (39.7%)*

* Different from control value ($P < 0.05$), χ^2
Adapted from Young (1985)

Thus, to quote Young :

"Usually, carcinogenic studies are terminated at some arbitrary point, such as two years. Some have argued that the dire consequences of tumors would occur if the animals were allowed to live. Here the animals were allowed to live out their life-span and, on balance, the animals in the treated groups benefited as measured by total tumor load and longevity.

If the purpose of long-term studies is to extrapolate to humans, then one finds it difficult to

infer dire consequences to humans when the treatment is beneficial in the model system. Is the model only useful for inferring bad events? The model should be equally valid for detrimental and beneficial effects."

Lastly, the analysis of Young also calls to question a suggestion made by Schaeffer et al. (1984), which was that the decrease in the incidence of thymoma might be caused by immunosuppressive effects of PCBs. While PCBs cause thymic atrophy at certain doses, any proposed immunosuppressive effect cannot be considered to have a significant clinical impact when the treated animals did not ultimately suffer a greater incidence of morbidity or mortality from either infectious diseases or the hepatocarcinoma induced by this treatment.

The most recent rat study reported is that of Norback and Weltman (1985). These investigators fed 70 male and 70 female Sprague-Dawley rats a diet containing 100 ppm Aroclor 1260 for 16 months followed by a reduction to 50 ppm for the next 8 months. The animals were then fed a control diet for the remaining 5 months of their lives. All results were compared to a control group which initially consisted of 126 animals, 63 of either sex. At various time points throughout this study two control animals of each sex and three PCB-treated animals of each sex (10 animals in total) were anesthetized with ether and the medial left lobe of the liver of each animal was surgically removed. These tissue samples were taken at 1, 3, 6, 9, 12, 15, and 18 months. At 24 months a similar group was killed and at the end of 29 months all remaining animals were sacrificed. The induction of liver hypertrophy in the centrilobular area of the lobule was evident at the first observation period made one month after the PCB diet was initiated. By the 18th month the liver:body weight ratio had increased from 4% to 12% in the female animals. Macroscopically these investigators noted evidence characteristic of neoplastic nodules near the capsular surface, hepatocellular carcinomas and adenofibrosis. In the PCB-exposed group, the observed lesions appeared in the

following sequence: centrilobular hypertrophy at 1 month, foci of cells appeared at 3 months, foci of altered cells in the centrilobular and midzonal regions at 6-9 months, neoplastic nodules appeared at 12 months, trabecular carcinoma was observed after 15 months and adenocarcinoma at 24 months. Simple cystic cholangioma and adenofibrosis appeared in animals 18-23 months after the exposure began. There was no evidence of metastases to the lungs. All trabecular carcinomas had cell arrangements with a glandular, ductal or cystic pattern and all adenocarcinomas had some elements of the trabecular pattern of growth. The lumens of the adenocarcinomas were the apparent result of cellular necrosis. The incidence of tumors in animals 18 months or older are presented in Table A-10. It should be remembered that 7-8 animals sacrificed after 18 months, i.e., at least 15% of the group of animals in which late developing tumors were observed, had undergone a partial hepatectomy during the first 18 months. The effect of this cannot be determined from this experiment, but partial hepatectomy has been used as a promotional stimulus to increase the incidence of liver tumors induced by other carcinogens. Therefore, it is unfortunate that the authors did not note or describe the possible influence that this might have had on the final tumor incidence measured.

Another important factor to consider which is not readily apparent from Table A-10 is that almost all of the tumors reported in this study were very late-developing tumors. In Table 1 of this paper, only four trabecular carcinomas and only two adenocarcinomas had developed between the 18- and 24-month sacrifices (see Table A-11). Thus, 35/41 or some 87% (39/45) of the liver tumors observed in this study developed in the last 25-29 month period of the study. Furthermore, there is a notable sex-related difference in the response to Aroclor 1260. Only two male animals developed liver tumors, a number (4%) which most probably is not significantly different from the control group. In contrast, 96% of the tumors observed in these animals occurred in the females, and 91% were not identified until the 29-month sacrifice. These tumors had not metastasized to other organs, and

Table A-10
Incidence of Hepatocellular Neoplasms

	Incidence or % Tumors Observed (The actual number of animals with tumors)		
	Male	Female	Total
A. Control Animals	(N=32)	(N=49)	(N=81)
Trabecular carcinoma	0% (0/32)	0% (0/49)	0% (0/81)
Adenocarcinoma	0% (0/32)	0% (0/49)	0% (0/81)
Number negative	100% (32/32)	98% (48/49)	99% (80/81)
B. Aroclor 1260 Animals	(N=46)†	(N=47)††	(N=93)
Trabecular carcinoma	4% (2/46)	40% (19/47)	23% (21/93)
Adenocarcinoma*	0% (0/46)	51% (24/47)	26% (24/93)
Neoplastic nodule only	11% (5/46)	4% (2/47)	8% (7/93)
Number negative	85% (39/46)	4% (2/47)	44% (41/93)

† The total number includes 8 animals that had received a partial hepatectomy during the first 18 months.

†† The total number includes 7 animals that had received a partial hepatectomy during the first 18 months.

* Animals with both trabecular carcinoma and adenocarcinoma were placed only in the adenocarcinoma group.

Adapted from Norback and Weltman (1985)

Table A-11

**Temporal Development of the Hepatocellular Neoplasms
Identified in the Norback and Weltman Study**

Time Interval	Neoplastic Nodule	Trabecular Carcinoma	Adenocarcinoma
Male Animals			
1 month	0	0	0
3 months	0	0	0
6 months	0	0	0
9 months	0	0	0
12 months	0	0	0
15 months	0	0	0
18 months	0	0	0
24 months	1	0	0
29 months	5	2	0
Female Animals			
1 month	0	0	0
3 months	0	0	0
6 months	0	0	0
9 months	0	0	0
12 months	1	0	0
15 months	3	1	0
18 months	3	2	0
24 months	3	2	2
29 months	2	19	24

Adapted from Norback and Weltman, (1985)

none appear to have been life-shortening. Concerning this last aspect, unfortunately no information is given describing the cause of death for any animals dying early, or revealing 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 hepatocellular carcinoma."

The authors further 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.

Summary of Carcinogenicity Studies in Rats

PCB commercial mixtures varying from 42% to 60% chlorine content have been examined for carcinogenicity in chronic rodent bioassays. Just as most other effects of PCBs are dependent upon chlorine content, the carcinogenicity also appears to be a function of the extent of chlorination, with positive results consistently demonstrated only for mixtures of the containing 60% chlorine by weight (Kimbrough et al., 1975; Schaeffer et al., 1984; Norback and Weltman, 1985). The results are negative for the 54% chlorine PCB mixtures (i.e., Aroclor 1254 [NCI, 1978]; Kanechlor-500 [Ito et al., 1974]) and for mixtures of 42% chlorine content (e.g., Clophen A-30, Schaeffer et al., 1984).

It is interesting to note that while 60% chlorine PCB mixtures produce an increase in liver carcinomas, the overall tumor load for animals subjected to lifetime exposure to PCBs is unchanged or diminished. The liver tumors appear late in the life of the animal, and the animal seems to suffer no ill effect from them -- the rats in these studies lived as long or longer than the control rats. Therefore while 60% chlorine PCB mixtures may be classified as carcinogenic, the nature of the neoplastic response somewhat attenuates the concern for the impact of this potential effect on human health.

It might also be noted that in keeping with their lack of genotoxicity, the hepatocellular changes produced by chronic PCB treatment appear to regress if the exposure is terminated (Kimura et al., 1976). This observation and the slow progressive changes noted by Schaeffer et al. (1984) and Norback and Weltman (1985) are consistent with the conclusion that the carcinogenic PCB mixtures (those of 60% chlorine) induce liver tumors by an epigenetic mechanism. This and the steep dose-response curve for hepatocellular changes noted by Ito et al. (1974) suggests there are clear thresholds for these responses in the rat.

Reproductive Effects of PCBs
in Environmentally Exposed Persons

It appears from a number of studies that PCBs can cross the placenta resulting in prenatal exposure. Evidence for this has come from studies in which cord blood was sampled at birth for quantitation of PCBs. Cord blood PCB concentrations are typically significantly lower than the corresponding maternal serum PCB levels. For example, Jacobsen et al. (1984a) found a mean cord blood PCB level of 2.0 ppb (N = 198) while the mean maternal blood PCB concentration was 4.7 ppb (N = 196). Kodama and Ota (1980) reported mean maternal and cord blood PCB levels for women in each of three years. The results were:

	1974	1975	1976	Total
maternal blood (ppb)	5.1 ± 3.0	5.1 ± 3.3	3.6 ± 2.1	4.5 ± 2.9
cord blood (ppb)	1.5 ± 1.3	1.1 ± 0.8	0.8 ± 0.6	1.1 ± 1.0

Similar differences were reported by Ando et al. (1985). Somewhat higher absolute PCB values were found in the study by Rogan et al. (1986a), but the relationship between cord and maternal serum PCB concentrations was the same (mean cord serum, <4.27 ppb, N = 744; mean maternal serum 9.06 ppb, N = 872). These results indicate that the placenta may serve as a partial barrier to PCBs.

As a result of this potential intrauterine exposure to PCBs, numerous studies have examined the effects of PCBs on human reproduction. Wassermann and coworkers (1982) published a study in which serum concentrations of several organochlorine compounds, including PCBs, were determined in 17 women who had premature deliveries. Ten women with normal third trimester pregnancies served as controls. The average blood concentration of PCBs was higher in the premature delivery group than in the control group (71.55 ± 67.28 ppb vs. 19.25 ± 10.32 ppb, mean ± SD), but only 8 of the 17 cases of premature delivery were women with PCB blood levels

that were relatively higher than those of the control group. Other than observing that women in the premature delivery groups also had higher serum levels of several organochlorine compounds including DDT, BHC, dieldrin, and heptachlor epoxide, Wasserman et al. (1982) did not control for life-style related confounders. For example, heavy smoking is associated with a higher incidence of premature delivery, but smoking was not controlled for in this study. The authors also failed to report the comparative age distribution for the women in the groups compared, a factor which has important bearing on the incidence of both premature delivery and higher PCB blood concentrations. Thus, the authors concede in their discussion that a cause-and-effect relationship cannot be established based on their data.

These authors also determined PCB concentrations in women with spontaneous or missed abortions and compared these concentrations to control subjects with normal pregnancy. Missed abortion is defined as the retention in the uterus of the products of conception six weeks or more after the death of the fetus. Death of the fetus in missed abortion occurs before the twentieth completed week of gestation. There was no statistically significant difference in serum PCB concentrations between women with spontaneous abortion and the normal pregnancy group (Wassermann et al., 1985).

In the study of women with missed abortions, there were 17 subjects with recent missed abortions (RMA), 7 subjects with a history of one or several missed abortions (former missed abortions, FMA), and 7 women with normal, second trimester pregnancy (Bercovici et al., 1983). The mean serum PCB concentration was significantly higher in the RMA group than in the control, although approximately half of the women with RMAs had concentrations similar to the controls. The authors divided the RMA group into two subgroups based upon their PCB concentrations -- those with low PCB levels (not different from controls) and those with high levels (Table B-1). There were no differences in the numbers of missed abortions between these groups. Therefore, there

Appendix B

were two groups of women with the same PCB concentrations (controls and low PCB concentration RMA group), yet no significant differences in RMAs. There were also two groups of women with the same incidence of RMAs but significantly different PCB levels (low and high PCB concentration RMA groups). These data would not seem to support a role for PCBs in the RMAs.

The authors reported in this study that the women with FMA had significantly higher PCB levels than the control women with normal pregnancy. It was not described in the methods how the history of missed abortion was established. Unless medical records were used to verify the history of these subjects, the validity of this group may be questioned. Rogan et al. (1985) have pointed out that women's recall of previous abortions is incomplete, and recall bias may occur if women are alarmed that they may have been exposed to a potential toxin. There are other problems with the study which apply equally to the RMA and FMA comparisons. As with the previous Wassermann et al. (1982) study, the variables such as age, etc. which might influence observed associations were poorly controlled. Further, women in the RMA and FMA groups also had significantly higher levels of a number of other organochlorine compounds. It is therefore impossible to interpret these results as indicating an effect of PCBs to cause missed abortion.

Table B-1
Polychlorinated Biphenyl Serum Levels in Women with
Recent and Former Missed Abortions

Peak ¹	Control	Recent Missed Abortions		Former missed abortions
		Low PCB Levels	High PCB Levels	
1 + 2 + 3	1.51 + 1.01	2.09 + 3.06	2.79 + 2.69	1.11 + 1.80
4 + 5 + 6	14.39 + 6.69	17.4 + 6.42	46.47 + 10.6*	51.3 + 11.7*
7			1.22	0.14
8 + 9 + 10	4.79 + 5.01	6.79 + 6.25	51.4 + 20.7*	28.8 + 11.7*
13 + 14			1.20	0.67 + 1.18
Total	20.69 + 10.55	26.29 + 11.60	103.04 + 37.58*	82.00 + 21.40*

¹ Peaks correspond to individual PCB congeners. The identity of these congeners is not specified.

Values expressed as mean \pm SD

* $P \leq 0.001$ (Controls versus high PCB level missed abortion and former missed abortion groups).

Smith (1984) studied the effects of PCB exposure on infant birth weight and health of children born to women from Sheboygan, Wisconsin who consumed game fish. Birth weight and gestational age were positively correlated with maternal PCB blood levels, i.e. women with higher PCB levels had a longer gestation time and delivered heavier babies. A positive correlation was also observed for maternal blood PCB concentration and the frequency of illness in the infants during the first four months. Little can be concluded from this study, however, because maternal PCB blood concentrations were apparently independent of the level of exposure (the amount of PCB-containing game fish consumed), and the PCB concentrations in the "exposed" women were in fact lower than those observed for the general population.

Fein et al. (1984) compared 242 infants born to mothers who consumed moderate amounts of Lake Michigan fish and mothers who did not consume Lake Michigan fish at all. PCB exposure was based on reported consumption of fish and on PCB levels in cord serum. Some differences in results were obtained depending on which of these two criteria was used to compare the exposed and non-exposed groups. There was agreement between both exposure criteria that birth weight and head circumference were lower in the PCB-exposed group. While the differences were statistically significant, they were small (e.g. 160-190 g for birth weight, 0.56-0.65 cm for head circumference) and of questionable clinical significance (see Table B-2). There was a small but significant change in neuromuscular maturity reported for babies born to fish-eating women, but neuromuscular maturity and physical maturity were not significantly different when PCB blood levels were the basis for comparison. Possibly one factor contributing to the observed birth weight difference was the fact that the gestational age of the babies in the exposed group was 5 days shorter than the non-fish eating group. One criticism of this study is that the exposed and unexposed groups were not well-matched with respect to other variables which might affect birth weight (see Table B-3). For example, the exposed group had three times the percentage of women who consumed alcohol during pregnancy. This group also had higher percentages of other concurrent exposures during pregnancy, such as caffeine consumption and the use of cold medications. A second criticism is the fact that the average maternal PCB serum levels for this group was 5.5 ± 3.7 ppb and serum cord PCB levels were only 2.5 ± 1.9 ppb. Thus, the entire study population had serum PCB levels that were in the low end of the range of values reported for unexposed populations. A third problem is that fish from Lake Michigan are contaminated with a number of organochlorine compounds, particularly DDT. Thus, the potential that the reported associations might also be shown to exist for the serum levels of other chemicals common to these women was not addressed. Last, in a second report by Jacobsen et al. (1985) which examined 123 infants (92/123 were in the fish-eating category), the reported

Table B-2
Adjusted Birth Size and Gestational Age Measures By
Overall Contaminated Fish Consumption
and Cord Serum PCB Level

	Overall Contaminated Fish Consumption		P
	Non-Fish Eaters (n = 71)	Fish Eaters (n = 242)	
Birth weight (kg)	3.66 ± 0.54	3.47 ± 0.53	<0.05
Head circumference (cm)	35.48 ± 1.36	34.92 ± 1.31	<0.01
Gestational age (based upon last menstrual period) (wk)	40.82 ± 3.07	40.31 ± 2.97	
Gestational age (Ballard examination) (wk)	39.85 ± 1.42	39.15 ± 1.40	<0.01
Neuromuscular maturity	19.96 ± 2.48	18.52 ± 2.44	<0.001
Physical maturity	17.13 ± 2.25	16.67 ± 2.19	

	Cord Serum PCB level		P
	< 3 ng/ml (n = 166)	≥ 3 ng/ml (n = 75)	
Birth weight (kg)	3.57 ± 0.54	3.41 ± 0.54	<0.05
Head circumference (cm)	35.28 ± 1.18	34.63 ± 1.19	<0.001
Gestational age (based upon last menstrual period) (wk)	41.03 ± 3.01	39.77 ± 3.06	<0.05
Gestational age (Ballard examination) (wk)	39.41 ± 1.40	39.47 ± 1.41	
Neuromuscular maturity	19.95 ± 2.42	19.00 ± 2.40	
Physical maturity	16.96 ± 2.14	16.94 ± 2.15	

Adapted from Fein et al. (1984)

significant differences in birth weight and head circumference of infants born to fish eaters or non-fish eaters are considerably smaller (i.e. 89 g and 0.1 cm, respectively), and are apparently not significantly different for the two groups.

Table B-3

**Control Variables Yielding Differences for Exposed vs.
Non-exposed Infants**

Exposed	Non-Exposed	P	
Overall contaminated fish consumption ¹			
Maternal prepregnancy weight (kg)	62.0 ± 11.6	66.1 ± 14.7	<0.10
Type of deliver (% spontaneous)	67.4	77.5	<0.05
Alcohol prior to pregnancy (%)	54.2	28.2	<0.001
Alcohol during pregnancy (%)	22.7	7.0	<0.01
Caffeine ² prior to pregnancy (%)	40.1	28.2	<0.10
Caffeine ² during pregnancy (%)	22.7	12.7	<0.10
Cold medications during pregnancy (%)	<0.01	28.6	13.2
Cord serum PCB level ³			
Maternal age (yr)	27.1 ± 5.3	26.0 ± 4.2	<0.10
Weight gain during pregnancy (kg)	12.7 ± 4.6	13.8 ± 4.6	<0.10
Type of delivery (% spontaneous)	63.2	73.5	<0.10

¹ Fish consumption: exposed defined as ≥ 11.8 kg over 6 years, n=242; nonexposed n = 71.

² Equivalent of > 2 cups of coffee per day.

³ Exposed defined as ≥ 3.0 ng/ml, n=75; nonexposed n=166.

Adapted from Fein et al. (1984)

Jacobsen et al. (1984b) have also published a report evaluating neonatal behavioral deficits in children born of women who had eaten contaminated Lake Michigan fish in comparison with those who had not eaten contaminated fish. Though not explicitly stated in the report, these would appear to be the same neonates examined in the Fein et al. (1984) paper. Behavioral status was evaluated by the Brazelton Neonatal Behavioral Assessment Scale (NBAS). In all but three (out of 287) of the newborns, testing was performed on day three after birth. For purposes of statistical analysis, the 44 items of this scale were reduced to seven summary

clusters. Attempts were made to control variables other than exposure which might influence results. A total of 36 variables were examined, including demographic background; maternal prepregnancy weight and height; sex of infant; parity and gravidity; stress during pregnancy; prenatal care and diet; weight gain during pregnancy; alcohol, caffeine, and nicotine consumption before and during pregnancy; delivery complications; obstetrical medication; age (in hours) at NBAS examination; and cord serum levels of polybrominated biphenyls (PBBs). The strongest statistical relationships for contaminated fish consumption were with cluster classified as relating to autonomic maturity, number of abnormal reflexes, and range of state (Table B-4). Maternal consumption of contaminated fish was highest for neonates classified as "worrisome" in these three clusters. It was not established whether these behavioral effects were lasting or transitory. While contaminated fish consumption correlated with these behavioral deficits, cord serum PCB levels did not. Thus, the association would appear to be due to something other than PCBs in the contaminated fish.

Jacobson et al. (1985) examined children born to mothers in Grand Rapids, Michigan to study the possible association of umbilical cord PCB levels with the occurrence of subtle neurological changes. The test population consisted of 123 white, predominantly middle-class infants. Approximately 75% (92/123) of the mothers of these infants were considered to be moderate to heavy consumers of PCB-contaminated Lake Michigan fish. The other mothers did not eat these fish. The seven-month old infants were tested for their ability to recognize visual stimuli. In this test, the children were exposed to a visual target, and later during the procedure were simultaneously re-exposed to the same target and a novel target. Visual recognition was defined as the percent of visual fixation on the novel target. The authors stated that there was a statistically significant dose-effect relationship between cord PCB levels and fixation of the novel target. Children born to mothers with cord serum PCB levels of 0.2-1.1 ng/ml fixed their gaze on the novel target approximately 61% of the time.

Infants born to mothers with cord serum PCB levels of 1.2-2.2, 2.3-3.5, and 3.6-7.9 ng/ml had visual fixation percentages of approximately 60%, 57% and 50%, respectively. The difference between the fixation times of infants in the high cord serum PCB group and the two low cord serum PCB groups was statistically significant ($p < 0.05$). The possible effect of confounders such as demographic background, pregnancy and delivery complications, stress, diet, smoking, alcohol, and caffeine exposure were factored into the analysis. The authors suggested that while their study indicates that high cord PCB levels may be associated with developmental delay in the performance of a visual task, the results of this study cannot be extrapolated to indicate that any permanent PCB-induced damage had occurred. Indeed, postnatal exposure to PCBs in breast milk did not correlate with changes in visual recognition memory. Although the authors accounted for a number of confounding variables in their analysis, one obvious oversight was the failure to include an evaluation serum or cord lead concentrations. Considerable evidence suggests that lead may induce subtle changes in learning and behavior in children born to mothers with slightly elevated blood lead concentrations, and the study of Jacobson et al. (1985) should be considered flawed for failing to consider the potential effect of this important environmental contaminant.

Taylor et al. (1984) looked at 388 pregnancies in 354 women who worked at capacitor manufacturing plants. Information for this study was obtained from birth certificates and hospital records. The women were divided into two groups, high-exposure and low-exposure, depending on the location of their job in the plant. Measurements of PCB concentrations were not made for any of the women. The birth weights for offspring of the women in the high-exposure group were on average 153 g lower than those for the low-exposure group but this difference was not significant at the $P < 0.05$ level. When birthweights were adjusted for gestational age, there was no difference between exposure groups. Mean gestational age was an average of 6.6 days shorter in the high-exposure group. While maternal age, parity, ethnic, and educational status were

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included in the analysis, other factors known to influence birthweight and gestational age (e.g. tobacco use, underlying medical conditions, maternal height, and previous history of low birth weight) could not be included because of the manner in which the study was conducted. A serious flaw in the design of this study is that neither PCB-exposure group was compared to an age-matched control population. The authors suggest that PCBs might cause a shortening of gestation, but add:

"The small number of observations, lack of information on important influencing factors, binary exposure measurement, and uncertainty in assigning biological significance to birthweight and gestational age differences of this magnitude mandate that such a conclusion be considered tentative."

Table B-4

Worrisome Performance on Three NBAS Clusters by Contaminated Fish Consumption

Cluster	Non-exposed controls	High exposure (>6.5 kg/yr)	χ^2
Autonomic maturity			
Normal	64	67	
Worrisome	1	6	3.18*
Reflexes			
Optimal or normal	55	48	
Worrisome	10	24	4.97**
Range of State			
Optimal, normal, or excessively labile	64	65	
Worrisome (flat, depressed)	1	7	4.16**

NBAS = Neonatal Behavioral Assessment Scale

* p < 0.10, ** p < 0.05

Adapted from Jacobsen et al. (1984b)

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As part of the North Carolina Breast Milk and Formula Project, Rogan et al. (1986b) have looked for potential effects of prenatal exposure to PCBs and dichlorodiphenyl dichloroethane (DDE). This exposure was estimated by determining the concentration of PCBs or DDE in maternal milk fat at birth. Birth weight and head circumference at birth were taken from the infant's chart or measured directly. Neonates were administered the NBAS in the first (59%), second (20%), or third (16%) week of life. To facilitate comparison with the results of Jacobsen et al. (1984b), individual scales were divided into the same seven clusters. Decreased birth weight was associated with sex of the infant and maternal weight and smoking, but not with PCB or DDE levels. Head circumference was also unaffected by PCB or DDE levels, as was hyperbilirubinemia. Of the various NBAS cluster scores, only the tonicity and reflex scores were affected by PCB and DDE levels. PCB levels were associated with less muscle tone and activity, but only at the higher concentrations (Table B-5). Similarly, hyporeflexia was associated with PCB levels, but only for the highest concentrations (Table B-6). If analysis is restricted to neonates administered the NBAS within three days of birth, as has been recommended for this examination, the trends remain the same but only hyporeflexia was statistically significant. Two important precautions must be considered in interpreting the results of this study. Hyporeflexia was associated with both PCBs and DDE. It is therefore impossible to determine if hyporeflexia is the result of exposure to PCBs, DDE, or some other substance for which these compounds serve as a marker. Also, as noted by the authors, the NBAS is an evaluation of the infant when newborn and is generally not strongly predictive of later findings. Therefore, the NBAS cannot distinguish between lasting and transient behavioral abnormalities.

Table B-5

Association of PCBs With Tonicity Cluster Score and Its Components

PCB Level	No. of babies	Tonicity cluster score (%<5)	Activity scale (%<4)	General tone scale (%<5)
0.0 - 0.99	49	10.2	10.2	6.1
1.0 - 1.49	241	7.1	6.6	2.5
1.5 - 1.99	276	10.9	8.3	3.3
2.0 - 2.49	151	13.9	6.6	6.0
2.5 - 2.99	66	12.1	6.1	7.6
3.0 - 3.49	34	8.8	5.9	0.0
3.5 - 3.99	20	20.0	10.0	10.0
4.0 +	29	20.7	17.2	10.3

PCBs given as ppm in milk fat at birth
Adapted from Rogan et al. (1986b)

Table B-6

Association of PCBs With Abnormal Reflexes

PCB Level	No. of babies	Abnormal reflexes (%4+)	Low reflexes (%4+)
0.0 - 0.99	49	12.2	8.2
1.0 - 1.49	241	10.4	6.2
1.5 - 1.99	276	14.1	8.3
2.0 - 2.49	151	14.6	9.3
2.5 - 2.99	66	13.6	9.1
3.0 - 3.49	34	14.7	8.8
3.5 - 3.99	20	25.0	25.0
4.0 +	29	27.6	17.2

PCBs given as ppm in milk fat at birth
Adapted from Rogan et al. (1986b)

Many of the infants in the Rogan et al. report of 1986 were followed for one year to determine if PCB (or DDE) exposure via breast milk was associated with adverse health consequences. Health effects were evaluated by infant weight and frequency of physician visits for various illnesses. PCB exposure for breast-fed babies was calculated using measured PCB milk levels, information regarding the length of breast-feeding, and assumptions as to milk fat content and amount of breast milk consumed per day. PCBs appeared to have no effect on growth as determined by body weight gains. The most common ailments resulting in a physician visit were upper respiratory tract infections (colds, flu, sore throat, etc.), otitis media, and gastroenteritis (diarrhea, vomiting, etc.). As stated by the authors, "None of these diseases showed any evidence of harmful effects of PCBs or DDE; in fact, the trends usually were in the opposite direction". Data from this study relating to method of feeding, PCB exposures, and incidence of illness appear in Table B-7.

Table B-7

**Per Cent of Children Ever Having Upper Respiratory
Infection (URI), Otitis Media (Ear), or Gastroenteritis
(GI) in Various Age Intervals by Feeding Method and
Contaminant Amounts**

0 - 3 Months

mg	No. of Children	% Ever Having		
		URI	Ear	GI
Bottle-feeders	80	16	18	24
Ex-Breast-feeders	--	--	--	--
Breast-feeders	689	21	11	11
PCBs				
0 - 1	74	36	22	27
1 - 2	194	20	14	11
2 - 3	238	22	9	8
3 - 5	145	13	8	6
5 +	38	11	5	16

3 - 6 Months

mg	No. of Children	% Ever Having		
		URI	Ear	GI
Bottle-feeders	80	28	33	13
Ex-Breast-feeders	172	35	39	14
Breast-feeders	503	24	22	6
PCBs				
0 - 1	71	37	25	10
1 - 2	180	24	29	5
2 - 3	164	23	14	6
3 - 5	51	12	14	4
5 +	37	16	22	3

Table B-7 (continued)

6 - 12 Months

	mg	No. of Children	URI	% Ever Having	
				Ear	GI
Bottle-feeders		80	48	58	25
Ex-Breast-feeders		321	54	63	29
Breast-feeders		353	49	52	17
PCBs					
	0 - 1	54	33	50	17
	1 - 2	84	62	65	21
	2 - 3	95	48	48	15
	3 - 5	69	54	47	16
	5 +	51	41	47	18

For each time period, children are divided into bottle-feeders, ex-breast-feeders, and current breast-feeders. Current breast-feeders are further divided by the estimated amount (mg) of PCBs consumed during the time period. Entries are the percent of children ever having the disease during the time period. Diseases are upper respiratory infections (URI), otitis media (ear), and gastroenteritis (GI).

Adapted from Rogan et al. (1987)

Summary of Environmental Exposure to PCBs

A number of studies have attempted to determine the effects of PCBs from environmental exposure on reproduction and the health of the offspring. Using a variety of approaches, associations between maternal PCB levels and premature deliveries, spontaneous abortions, missed abortions, birth size and weight of neonate, behavioral deficits in the neonate, and susceptibility to illness in early life of the offspring have been sought. While some positive associations have been noted, study designs have generally precluded any cause-and-effect conclusions related to PCBs. In many studies, "exposed" groups were poorly matched with controls with respect to important variables such as maternal age, smoking, alcohol consumption, etc. Some studies, such as those of women who ate contaminated Lake Michigan gamefish, were unable to demonstrate

that their exposed populations in fact had significantly higher PCB body burdens than the controls. Further, studies which also measured other organochlorines typically found that elevated PCB levels were correlated with elevated levels of other compounds such as DDE. It is therefore impossible to know if an effect associated with a particular PCB level is in fact due to the PCBs or to another, similarly-accumulated environmental contaminant. In view of these study limitations, it cannot be concluded at this time that environmental exposure to PCBs results in any adverse effect on human reproduction or fetal and neonatal health.

Mortality Studies Of Human PCB Exposures

Reports of high cancer rates among Mobil Oil employees exposed to PCBs (Aroclor 1254) at Mobil's Paulsboro, New Jersey, refinery were interpreted as an indication that PCB exposure was linked to skin (melanoma) or pancreatic cancer (Bahn et al., 1976; 1977). This preliminary study included eight cancers which developed between 1957 and 1975 among 92 employees. Of the 92 persons in this cohort, 51 were apparently employed in research and development, and only 31 of these employees were considered to be heavily exposed to PCBs. The remainder of the cohort consisted of 41 refinery workers.

The level of exposure to Aroclor 1254 was not provided or discussed, and the maximal duration of exposure was only 9 years (Bahn et al., 1976). Of the eight cancers ultimately reported, three were malignant melanomas and two were cancers of the pancreas. According to NIOSH (1977) "This is significantly more skin cancer (melanoma) and pancreatic cancer than would be expected in a population of this size, based on the Third National Cancer Survey." However, it is difficult to draw any conclusions from this study. For example, Lawrence (1977), of the New York state Department of Health, criticized the authors of this preliminary report for failing to identify other chemicals these refinery workers and research chemists might have been exposed to. Lawrence (1977) points out that PCB fluids typically contained epoxides which were added as stabilizers. In fact, in the capacitor plant he was investigating at the time of his letter, epoxides comprised 0.5% of the capacitor fluids being used. As these epoxides had vapor pressures 1,000 times that of the PCB fluids to which they were added, the risk of exposure to epoxides was greater than that for PCBs. Because several epoxides have been shown to be carcinogenic in animals, this potential confounder was an obvious oversight of the Bahn report. Additional confounders were also represented by the number of chemicals common to the air around petroleum refineries, e.g. benzene, that are known to be human or animal carcinogens. In response to the criticism of Lawrence

(1977), Bahn et al. (1977) did agree that further information was essential, and apparently withdrew this study for revision (Gaffey, 1981); but as yet no follow-up has ever been released.

Zack and Musch (1979) have reported a small historical prospective mortality and morbidity study using male workers exposed to PCBs at one of the Monsanto manufacturing plants located in Sauget, Illinois. This report remains unpublished but is of interest because the number of deaths examined approximates that examined in more recent studies by Bertazzi et al. (1987) and Gustavsson et al. (1986). PCBs were manufactured at this plant from 1936 to 1977. All employees who had worked in the PCB department for at least six months, between January 1, 1945 to December 31, 1965, were selected for this study. During this period of time the process by which PCBs were manufactured remained relatively constant. It basically consisted of batch chlorination of biphenyl in the presence of iron and iron chloride catalysts. Through interviews of plant personnel, the authors determined that PCB exposure levels did not vary much within the PCB department. Other chemical exposures in this department included hydrochloric acid, tri- and tetrachlorobenzene, biphenyl and chlorine gas. The exposed worker cohort was identified from the plant's computerized work history system, and 89 employees met the criteria for inclusion in this study. Of the eighty-nine members of the cohort 30 were verified as deceased by death certificate and 58 were verified to be living. Thus, the vital status was ascertained for 99% of the cohort. The underlying cause of death was coded to the 8th revision of the International Classification of Disease, Adapted for Use in the United States by an experienced nosologist. The mortality comparisons were made to the general U.S. population.

A total 1,800 person-years were calculated for this population. Most of these were contributed by middle-aged employees with 1,333 person-years, or 74% of the total, resulting from persons 35-60 years of age. The average length of exposure for the living members of the cohort was 3.2 years while that of the deceased group was 3.7 years. Of the total number of deaths

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there was an almost two-fold excess of malignant neoplasms and a greater than two-fold excess in deaths from cardiovascular disease (see Table C-1). The only statistically significant increase in mortality was for diseases of the circulatory system (see Tables C-1 and C-2). As can be seen in Table C-2, the excess of malignant neoplasms was caused solely by an increase in lung cancer which was almost exclusively a phenomenon of the white population.

A similar trend was not observed in non-white males, and no significant associations were found in this subgroup of the cohort. In contrast to the initial report by Bahn et al. (1976), no deaths were observed for malignant melanoma or pancreatic cancer (Table C-1). In contrast to animal data, there was no evidence of liver cancer. The identities of the 8 specific cancers observed in this cohort are as follows : 1 carcinoma of the colon, 2 carcinomatosis (one of the kidney), 4 carcinomas of the lung, and 1 multiple myeloma. Given the fact that the increase in lung tumors and cardiovascular disease was race specific, and as the smoking histories of the members of this cohort were not examined, the significance of these two findings can not be determined.

Table C-1
Mortality by Category for the Zack and Musch Study

I.C.D..	Cause of Death	Observed/Expected	SMR
	All causes	30/22.88	131
140-209	All malignant neoplasms	8/4.46	179
140-149	Buccal cavity/pharynx	0/0.16	0
150-159	GI tract/peritoneum	1/1.33	75
155,156	Liver	0/0.10	0
162,163	Lung	4/1.44	278
185-189	Urinary tract	1/0.51	196
200-209	Lymphatic/hematopoietic	1/0.40	250
390-458	Diseases- circulatory system	16/11.17	143
410-413	Atherosclerotic	7/7.19	97
----	All others	9/3.98	226*
460-519	Diseases of the respiratory system	1/1.27	79
520-577	Diseases of the digestive system	2/1.20	167
----	All other diseases	2/2.40	83

* P < 0.05; number of persons observed 89
Adapted from Zack and Musch (1979)

Table C-2

A. Mortality by Category for White Males

I.C.D.	Cause of Death	Observed/Expected	SMR
	All causes	18/13.53	133
140-209	All malignant neoplasms	4/2.70	148
150-159	GI tract/peritoneum	0/0.75	0
155,156	Liver	0/0.05	0
162,163	Lung	3/0.89	337
185-189	Urinary tract	0/0.28	0
200-209	Lymphatic/hematopoietic	0/0.28	0
390-458	Diseases- circulatory system	11/6.82	161
410-413	Atherosclerotic	4/4.99	80
----	All others	7/1.83	526*
460-519	Diseases of the respiratory system	0/0.73	0
520-577	Diseases of the digestive system	1/0.75	133
----	All other diseases	2/1.10	182

* P < 0.05; number of persons observed 60

B. Mortality by Category for Nonwhite Males

I.C.D.	Cause of Death	Observed/Expected	SMR
	All causes	12/9.35	128
140-209	All malignant neoplasms	4/1.76	227
150-159	GI tract/peritoneum	1/0.58	172
155,156	Liver	0/0.05	0
162,163	Lung	1/0.55	182
185-189	Urinary tract	1/0.23	435
200-209	Lymphatic/hematopoietic	1/0.12	833
390-458	Diseases- circulatory system	5/4.35	115
410-413	Atherosclerotic	3/2.20	136
----	All others	2/2.15	93
460-519	Diseases of the respiratory system	1/0.54	185
520-577	Diseases of the digestive system	1/0.45	222
----	All other diseases	0/1.30	0

* P < 0.05; number of persons observed 29

Adapted from Zack and Musch (1979)

Bertazzi et al. (1981) reported the results of a retrospective mortality study of workers employed at a capacitor manufacturing facility located just north of Milan, Italy. This facility had been manufacturing large power capacitors impregnated with PCB dielectric fluids since 1946. From 1946-1964 the PCB fluids used at this plant were commercial mixtures containing 54% chlorine, i.e. Aroclor 1254 and Pyralene 1476. Starting in 1965 these fluids were progressively replaced by mixtures of 42% chlorine content, primarily Pyralene 3010 and 3011, and by 1970 these latter products were the only ones in use. Although no reliable data were available detailing the magnitude of past exposures, three cases of chloracne had been reported in 1954. These cases had developed in three young autoclave workers some 4-7 months after their work in this area had begun. Air samples collected in their area of the plant were reported to contain PCB concentrations of 5.2, 6.4 and 6.9 mg/m³, levels which exceed an air standard of 1.0 mg/m³ for PCB mixtures of 42% chlorine. The results of an industrial hygiene survey performed at this plant in 1977 also provide some insight as to the level of PCB exposure experienced by the workers of this plant, and the values cited appear to be those reported by Maroni et al. (1981a). That is, 9 TWA area air samples ranged from 48-275 µg/m³, 18 surface samples ranged from 0.2-159 µg/cm², and the skin wipes of 9 workers ranged from 0.3-9.2 µg/cm².

The cohort studied consisted of all male and female workers who had accumulated at least 6 months of employment during the period of 1946 through December 31, 1970, excluding the clerical workers in administrative departments. Some 1,310 persons met this criterion, 1,020 women and 290 men. The mortality study of these workers covered a 25-year period (from 1954-1978), and the vital status of each individual was ascertained as of December 31, 1978. The vital status of the study population was reported to be 98% complete, and an estimated 20,565 person-years were accumulated by the 1,310 individuals of this cohort.

As of 1978 only 27 deaths had occurred in this population. When mortality was broken down by cause of death, 14/27 (52%) were

related to cancer while only 5.65 were expected. This greater than two-fold excess in the cancer mortality resulted primarily from an unusually high incidence of cancer in the male population, where 8 out of 12 reported deaths (67%) were cancer-related. In the female population this ratio was only 6 out of 15, or 40%. As can be seen in Table C-3, Bertazzi et al. (1981) reported finding higher-than-expected incidences of cancer of the digestive organs and cancer of the lymphatic or hematopoietic systems. However, these changes were not significant for either sex. In fact, the data provided is not particularly descriptive as most cancers have been lumped into one of two major categories for the male population and only one category is described for the female population. It is notable, however, that no liver or skin cancers were reported for this cohort (even though the digestive sites did include the biliary tract), and it does not appear that lung cancer was elevated as previously reported in the study of Zack and Musch (1979).

Bertazzi et al. (1987) have recently published an update of their study of PCB-exposed capacitor workers. In this second report the cohort has been modified to include non-production workers at the plant, the minimum period of employment was reduced from six months to one week, and mortality was followed through 1982. The vital status of employees was determined in greater than 99% of the population. These changes increased the size of the cohort to 2,100 total employees (544 males and 1,556 females), the number of person-years to 41,010, and the number of deaths to 64. The results for male and female workers, which were analyzed separately, are summarized below in Table C-4. For males, the mortality from cancer was significantly greater than expected (14 versus 5.5 expected). Among specific tissues, the observed incidence of neoplasms of the GI tract was significantly higher than expected. The incidences of lung and hematologic neoplasms were also greater than expected, but neither increase was statistically significant. In spite of these elevations, the total mortality for all causes was no greater than expected. Among

Table C-3
Mortality in Italian Capacitor Workers

Cause of Death	Observed	Expected	SMR
<u>Males</u>			
All causes	12	12.72	94
All neoplasms	8	3.32	241*
digestive organs and peritoneum	3	0.88	340
lymphatic and hematopoietic	2	0.46	435
Accidents, etc.	3	2.56	117
<u>Females</u>			
All causes	15	7.72	194*
All neoplasms	6	2.23	253
lymphatic and hematopoietic	2	0.45	444
Accidents, etc.	5	2.23	224

* reported as significantly different, $P < 0.05$

Adapted from Bertazzi et al. (1981)

Table C-4

**A. Mortality From Selected Causes of
Male Workers Exposed to PCB**

Cause of death	Observed	Reference Cohort			
		National		Local	
		Expected	SMR	Expected	SMR
All causes	30	27.8	108	29.8	101
Malignant tumors	14	5.5	253 ^a	7.6	183 ^b
Cancer of G.I. tract	6	1.7	346 ^c	2.2	274 ^d
Lung cancer	3	1.2	250	1.6	187
Hematologic neoplasms	3	0.8	375	1.1	263
Cardiovascular disease	8	7.9	101	9.4	95
Accidents	6	6.8	88	5.8	103
Confidence limits (95%)	^a = 144-415 ^b = 104-300	^c = 141-721 ^d = 112-572			

**B. Mortality From Selected Causes of
Female Workers Exposed to PCB**

Cause of death	Observed	Reference Cohort			
		National		Local	
		Expected	SMR	Expected	SMR
All causes	34	25.8	132	16.5	206 ^a
Malignant tumors	12	7.7	156	5.3	226 ^b
Hematologic neoplasms	4	1.5	266	1.1	377 ^c
Cardiovascular disease	2	4.7	42	3.0	66
Accidents	9	4.0	225	4.0	225
Confidence limits (95%)	^a = 145-285 ^b = 123-385	^c = 115-877			

Adapted from Bertazzi et al. (1987)

females, higher-than-expected incidences were observed in total mortality for all causes, mortality from cancer, and in the incidence of hematologic neoplasms. While these differences were of statistical significance when the cohort was compared to local mortality rates, none were significant when compared to national mortality rates. Although the neoplasms were again grouped by organ-system for statistical analysis, some specific tumor sites were also reported. Among both male and female members of the cohort, there was only one case of liver cancer, occurring in a person with limited PCB exposure, and no cases of rectal cancer.

Although the authors state that any interpretation of their results is limited by the small number of deaths that have occurred thus far in their cohort, the authors proceed to suggest that their study supports the possibility that PCBs pose a carcinogenic risk to humans. However, this study suffers from more limitations than merely a small number of deaths.

First, there was no apparent association between duration of exposure, latency, or year of first exposure for any of the causes of mortality. This is in direct contrast to what one would expect to find if a chemical were actually carcinogenic.

Second, the fact that when the cohort was enlarged to include administrative personnel, and others only minimally or not exposed to PCBs, the same trends for excess cancer were observed suggests PCB exposure was not the causal factor in these cancers. For example, Bertazzi et al. (1987) admit the following in one paragraph of this article :

"However, interpretation of such a result is limited by an examination of individual cancer cases; of the two workers dying from stomach cancer, one had been hired at an advanced age and had experienced a very short exposure, and the other one was a plant guard not involved in production processes; both workers who died from cancer of the liver and biliary tract had been

employed in the production area, albeit for rather short periods. The cases of pancreatic cancer occurred in another plant guard (no direct exposure reported) and in a worker who had been exposed directly in the process area for over 20 years. Given this information, no clear cut and definite conclusion regarding the association between cancer of the GI tract and exposure to PCBs can be drawn from the results of the study." (emphasis added)

If one subtracts those persons not exposed (two guards) or minimally-exposed (i.e. ≤ 4 months) as shown in Table C-5 (i.e. Table 6 of Bertazzi et al., 1987), the ratio for the number of observed cancer deaths of the GI tract versus the expected number of deaths drops to 2/2.2 for an SMR of 91 (when compared to the local mortality rates). If the definition of minimally-exposed were a year or less, the ratio of observed to expected becomes 1/2.2 for a SMR of only 45. Similarly, the reported significant increase in hematologic cancers in women disappears if one removes the two persons only minimally exposed, i.e. only 0.2 and 0.7 years of exposure. This change seems particularly justified as the two women with minimal exposure also represent the two persons for whom the latency period was only 0.2-2 years. This criteria reduces the SMR from 377 to either 182 or 133 (2/1.1 or 2/1.5) depending upon which reference mortality is used, and neither comparison would be significant. In addition to those cancers which were reported to be significantly elevated in either sex, it is apparent that of the three lung cancers observed, one occurred in a person first employed at an advanced age (hired at the age of 60), and the other two represent persons with exposures of very short duration (only 1-6 months). If the above information is taken into consideration, and those cancers not likely to be related to the men's work history are subtracted, the total number of cancers observed in men is reduced to seven. The SMR then becomes 92 or 127, depending upon which reference values the data are compared to. Thus, it does not appear that any of the "significant" associations reported by Bertazzi et al. (1981) are in fact a result of PCB exposure.

TABLE C-5

**A. Characteristics of Selected Cases of
Cancer Deaths Among Male Workers Exposed to PCBs.**

Cancer type/site (ICD 8th revision)	Age at hire(y)	Year of hire	Length of exposure(y)	Latency (y)	Age at death(y)
Stomach (151)	59	1948	.4	7	66
Stomach (151)	49	1951	17.2	23	72
Liver (155)	33	1957	.3	17	50
Biliary tract (156)	41	1959	1.0	14	55
Pancreas (157)	53	1969	5.8	5	58
Pancreas (157)	35	1960	21.7	22	57
Lung (162)	60	1951	6.7	26	86
Lung (162)	28	1954	.1	7	35
Lung (162)	38	1962	.5	19	57
Reticulum cell sarcoma (200)	27	1952	7.0	15	42
Acute myelocytic leukemia (205)	21	1961	19.0	19	40
Acute hemocytoblastic (205)	32	1967	2.2	2	34

**B. Characteristics of Selected Cases of
Cancer Deaths Among Female Workers Exposed to PCBs**

Cancer type/site (ICD 8th revision)	Age at hire(y)	Year of hire	Length of exposure(y)	Latency (y)	Age at death(y)
Hodgkins disease (201)	20	1960	21.8	22	42
Hodgkins disease (201)	19	1949	12.2	15	34
Hodgkins disease (201)	17	1960	0.2	0.2	18
Lymphosarcoma (200)	24	1968	0.7	2	26

Adapted from Bertazzi et al. (1987)

A third flaw in this study is the fact that the proposed significant associations are sex specific. In males, only cancers of the GI tract are significantly elevated. Although several limitations of these data have already been discussed, another factor undermining this association is the fact this cancer was not elevated in women. In fact, this category of cancer was not even listed by Bertazzi et al. in their analysis of the female employees (see Table C-4). In women, hematological cancers were significantly elevated, but this association was not significant in men. Furthermore, the specific types of cancers observed in women

were not observed in the male population (see Table C-5).

A fourth limitation in this study is the fact that other confounding contributors to mortality have not been identified and controlled for in this study. For example, in the female population both "all causes of death" and "death by accidents" are significantly elevated, yet neither can be attributed to PCBs. To quote the authors, :

"The elevated cancer mortality (in women) might be interpreted, in our view, in the light of some peculiar occupational factor in addition to the the already named social factors".

Another confounder is the fact that an excess of leukemia is common to jobs with exposure to electromagnetic fields. Thus, as the authors note, this may have contributed to the excess hematologic neoplasms observed in women.

Given the above limitations of the Bertazzi et al. (1981, 1987) studies, the conclusion of this review is that the associations put forth in these studies are tenuous at best, and the substantial number of problems inherent to these numbers do not provide a causal association between PCBs and cancer of any kind. (The authors themselves stated in the conclusion of this article : "The limitations discussed did not permit a causal association to be either proved or dismissed.")

Brown and Jones (1981) conducted a retrospective cohort mortality study of 2,567 employees from two plants where PCBs were used to manufacture electrical capacitors. These particular plants were selected for study because : a) each had a large work force, b) PCBs had been used for more than 30 years, c) there was considerable exposure to PCBs with little potential for exposure to other chemicals that might confound the interpretation of these results, and d) the workers' records were readily available. At the time of the study both plants were still using PCBs. Plant #1,

located in New York, was actually two facilities, one which had made small industrial capacitors since 1946 and a second facility that had made large power capacitors since 1951. Plant #2 was located in Massachusetts, and had manufactured PCB-containing capacitors since 1938. Both plants used similar manufacturing procedures, including a trichloroethylene wash, and both had used several different PCB fluids, progressing from Aroclor 1254 to Aroclor 1242 and finally Aroclor 1016.

All workers included in the study were employed for at least three months in areas of PCB exposure, but if the work history indicated an employee had potential exposure to trichloroethylene, that employee was excluded from the cohort. The vital status of 98% of the population was determined and 39,018 person-years were accumulated (see Table C-6). The remaining 2% (55 persons) of the cohort for which the vital status was unknown were assumed to be alive as of January 1, 1976 for the purposes of analysis. The study period was from 1940 until the first day of 1976.

An industrial hygiene survey was performed at both plants in the Spring of 1977, or approximately one year after the end of the study period. In Plant #1, the TWA for personal air samples ranged from 24-393 $\mu\text{g}/\text{m}^3$ and for area samples from 3-476 $\mu\text{g}/\text{m}^3$. In Plant #2, these measurements ranged from 170-1260 mg/m^3 for personal air samples and from 50-810 $\mu\text{g}/\text{m}^3$ for area samples. Although these data suggest exposure was greater in Plant #2 at the time of the survey, the historic exposures may have been more equivalent. Furthermore, Plant #1 had used several different stabilizers (< 1%) since the 1960s, including two potentially carcinogenic epoxides.

Table C-6

**Vital Status and Duration of Employment
of the Brown and Jones Cohort**

	<u>Plant #1</u>			<u>Plant #2</u>			Grand Total
	Males	Females	Total	Males	Females	Total	
<u>A. Vital Status of Cohort</u>							
Known to be alive	520	360	880	633	836	1,469	2,439
Known to be deceased	55	18	73	28	62	90	163
Unknown vital status	8	7	15	14	26	40	55
Total	583	385	968	675	924	1,599	2,567
Person-years	7,825	5,185	13,010	9,229	16,779	26,008	39,018
<u>B. Duration of Employment of Cohort</u>							
3-6 months	137	79	216	211	207	418	634
0.5-1 year	88	59	147	127	161	288	435
1-2 years	93	92	185	118	175	293	478
2-3 years	53	41	94	64	82	146	240
3-10 years	165	82	247	123	188	311	558
10 years	47	32	79	32	111	143	222
Total	583	385	968	675	924	1599	2,567

Adapted from Brown and Jones (1981)

The major causes of death for the 163 persons who had died during the interval studied are listed in Table C-7. There were no statistically significant differences observed for cancer of any kind, but the rectal cancer rate in the female population of Plant #2 was much higher than expected (Table C-8). It should be noted however, that the capacitor plants in this study are located in an area where mortality from rectal cancer is greater than the U.S.

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average to which these mortality figures were compared (Gaffey, 1981), and that a similar higher-than-expected rectal cancer rate was not found in females at Plant #1 or in the male population of either plant. The other mortality rates which were higher than expected but not statistically significant were liver cancer and cirrhosis of the liver. However, as can be seen in Table C-9 and Table C-10, there was no relationship between latency or length of exposure and the incidence of liver cancer as would be expected if PCBs were the causal agent. In addition, alcohol consumption, an obvious potentially confounding factor related to the development of cirrhosis, was not considered in this study. The authors' analysis of the relationship between latency and mortality in this cohort was as follows :

"For 'all cancer' there is no apparent pattern in either cohort. For cancer of the rectum, there is a slight increase with an increase in the latency periods. All of the deaths due to liver cancer occur before 20 yr of latency and there is no trend of increasing risk with an increase in the latency period. The risk of mortality due to cirrhosis of the liver does not show a consistent increase with an increase in the latency periods; there is, however, a greater risk after the 20-yr period."

TABLE C-7

**Major Causes of Death for Plant Workers Exposed to PCBs:
Aroclor 1016, 1242, and 1254**

Causes of Death	Observed/Expected	Standard Mortality Rate
	<u>All Causes</u>	
All malignant neoplasms	39/43.79	(89)
Diseases of nervous system	11/12.55	(88)
Diseases of circulatory system	60/62.93	(95)
Accidents	13/18.29	(71)
All other causes	40/44.79	(80)
All causes	163/182.35	(89)
	<u>Malignant Neoplasms</u>	
Cancer of stomach	1/1.66	(60)
Intestine	4/4.03	(99)
Rectum	4/1.19	(336)
Liver	3/1.07	(280)
Pancreas	1/1.90	(53)
Respiratory	7/7.98	(88)
Breast	7/6.84	(102)
Lymphatic	2/4.34	(46)
Other	10/14.78	(68)

Source: Brown and Jones (1981)

TABLE C-8

Observed Versus Expected Deaths for Plants #1 & #2 by
Specific Cancer Types and Cirrhosis of the Liver

Causes of Death	Plant #1		Plant #2	
	Males	Females	Males	Females
All malignant neoplasms	9/9.70	4/7.26	3/6.83	23/20.00
Cancer of stomach	0/0.51	0/0.22	1/0.31	0/0.62
Intestine except rectum	1/0.82	0/0.70	0/0.54	3/1.97
Rectum	1/0.31	0/0.18	0/0.20	3/0.50*
Biliary/Liver (not specified)	1/0.23	0/0.18	0/0.15	2/0.51
Pancreas	0/0.53	1/0.27	0/0.35	0/0.75
Respiratory	5/3.22	1/0.71	0/2.22	1/1.83
Breast	-----	1/1.86	-----	6/4.98
Lymphatic	0/1.10	0/0.59	0.94	2/1.70
Other	1/2.98	1/2.55	2/2.12	6/7.13
Cirrhosis of the liver	1/1.69	0/0.73	2/1.26	3/1.92

* P < 0.05

Source: Brown and Jones (1981)

TABLE C-9

Observed Versus Expected Deaths According to Latency†

Latency	Plant #1		Plant #2		Both Plants	
	Obs./Exp.	SMR	Obs./Exp.	SMR	Obs./Exp.	SMR
<u>All Cancers</u>						
< 10 yr	6/5.27	114	6/7.76	77	12/13.03	93
10-20 yr	3/6.61	45	16/10.91	147	19/17.52	108
> 20 yr	4/5.07	79	4/8.17	49	8/13.24	60
<u>Cancer of Rectum</u>						
< 10 yr	0/0.15	0	0/0.21	0	0/0.36	0
10-20 yr	0/0.19	0	2/0.29	690	2/0.48	417
> 20 yr	1/0.15	667	1/.021	476	2/0.36	556
<u>Liver Cancer</u>						
< 10 yr	1/0.12	833	1/0.18	556	2/0.30	667
10-20 yr	0/0.16	0	1/0.27	370	1/0.43	223
> 20 yr	0/0.12	0	0/0.21	0	0/0.33	0
<u>Cirrhosis of the Liver</u>						
< 10 yr	1/0.80	125	1/0.95	105	2/1.75	114
10-20 yr	0/1.01	0	1/1.35	74	1/2.36	42
> 20 yr	0/0.61	0	3/0.88	341	3/1.49	201

† latency = number of years from date first employed in exposed job

Source: Brown and Jones (1981)

TABLE C-10

**Observed Versus Expected Deaths
According to Length of Exposure**

Latency	Plant #1		Plant #2		Both Plants	
	Obs./Exp.	SMR	Obs./Exp.	SMR	Obs./Exp.	SMR
<u>All Cancers</u>						
3 mo.-5 yr	11/12.21	90	20/18.78	106	31/30.99	100
5-9 yr	1/2.95	34	2/4.10	49	3/7.05	43
10-14 yr	0/1.00	0	3/2.28	132	3/3.28	91
15-19 yr	1/0.69	145	1/1.04	96	2/1.73	116
≥ 20 yr	0/0.11	0	0/0.63	0	0/0.74	0
<u>Cancer of Rectum</u>						
3 mo.-5 yr	1/0.35	286	1/0.48	208	2/0.83	241
5-9 yr	0/0.09	0	0/0.11	0	0/0.20	0
10-14 yr	0/0.03	0	2/0.06	3,333	2/0.09	2,222
15-19 yr	0/0.02	0	0/0.03	0	0/0.02	0
≥ 20 yr	0/0.001	0	0/0.02	0	0/0.02	0
<u>Liver Cancer</u>						
3 mo.-5 yr	1/0.29	345	2/0.45	444	3/0.74	405
5-9 yr	0/0.08	0	0/0.11	0	0/0.19	0
10-14 yr	0/0.02	0	0/0.06	0	0/0.08	0
15-19 yr	0/0.02	0	0/0.02	0	0/0.04	0
≥ 20 yr	0/0.002	0	0/0.02	0	0/0.02	0
<u>Cirrhosis of the Liver</u>						
3 mo.-5 yr	1/1.79	56	2/2.26	88	3/4.05	74
5-9 yr	0/0.39	0	1/0.48	208	1/0.87	115
10-14 yr	0/0.12	0	1/0.24	416	1/0.36	278
15-19 yr	0/0.10	0	1/0.13	769	1/0.23	435
≥ 20 yr	0/0.02	0	0/0.08	0	0/0.10	0

† latency = number of years from date first employed in exposed job

Source: Brown and Jones (1981)

When the total exposure population was considered, there was no statistically significant relationship for any cause of death (Brown and Jones, 1981); or to quote the authors, the findings of this study can be summarized as :

"The only categories of cancer in which the number of observed deaths are greater than expected are for cancer of the rectum and cancer of the liver and only a slight increase for breast cancer. When both cohorts are combined none of the excesses are statistically significant.

There is no relationship between increasing durations of employment in jobs involving PCB exposure and the risk of mortality due to cancer or cirrhosis of the liver.

When cancer mortality is examined by plant, it is evident that most of the excesses occur in plant 2 - especially among the female group. This finding may be related to more exposures to PCBs at plant 2, as indicated by the industrial hygiene results. In addition, there was an opportunity for earlier exposures at plant 2, potentially allowing for a longer latency period. However, this difference in mortality may be a function of the size of the cohorts (plant 1 only has half the number of person-years as plant 2), and thus, simply be a statistical quirk.

A potential confounding variable or interaction variable in this study is the possible effect of alcohol ingestion on the observed increase in (plant 2) in mortality from cirrhosis of the liver. However, this cannot be properly assessed in the present study, since not enough is known about the ingestion of alcohol among the entire study cohort.

All-cause mortality is lower than expected, and there

was no increase in mortality for the major causes of death. "

Brown (1986) has recently updated his earlier study of workers employed at two plants involved in the manufacture of electrical capacitors. Unlike the Bertazzi study, the criteria for selecting the cohort was not changed in the update, and the number of deaths in the cohort has now increased from 163 to 295. Two findings were of particular interest. The first was the fact that no additional deaths from cancer of the rectum had occurred even though the total mortality had almost doubled. This brought the observed incidence of this form of cancer much closer to the expected value and suggests PCB exposure does not produce this form of cancer in humans.

The second finding of interest was the addition of two deaths attributed to cancer of the liver or biliary passages in females from Plant #2. If taken alone, the observed five cancers of the liver or biliary tract at first appear to represent a significant increase over the expected 1.9 cancer deaths for these tissues. However, caution must be exercised when interpreting these observations with respect to the risk of liver cancer from PCB exposure. First, the cohort used by Brown is the only one to date for which an increased incidence of liver neoplasms has been reported or even suggested. Second, close examination of the liver/biliary passage deaths in the 1986 report indicates that only one of these deaths was attributable to primary hepatic carcinoma (Table C-11). The other two carcinomas of the liver were the apparent result of metastases. When this fact is taken into consideration, the reduced SMR is no longer a significant value. Third, Brown (1986) notes in this paper that the distribution of specific types of liver and biliary system cancer is similar to that expected based on mortality figures for the United States. Thus, it does not appear that the incidence of any specific type of carcinoma has been enhanced by PCB exposure. Fourth, there was no apparent association between duration of exposure or latency and liver cancer mortality. For example, serious concern can be raised

concerning the actual etiologic agent of one of the liver cancers listed in Table C-11, as it occurred after only 0.3 years of exposure. In fact, 4/5 of the reported liver cancers occurred in persons with less than two years of significant PCB exposure (i.e. 0.3, 0.8, 1.0 and 1.5 yrs) compared to only one liver cancer in a person with more than 1.5 years of high PCB exposure (and this tumor is listed as a metastasized from another tissue). Thus, there is a clear disparity between the length of exposure and tumor incidence for the observed liver tumors. Lastly, as previously mentioned in the Brown and Jones (1981) study, alcohol consumption is one confounding variable that has not been addressed in this study.

TABLE C-11

Description of Liver/Biliary Passage Deaths

length of PCB exposure	Sex	Cause of Death	Hospital/Pathology Report
1 yr	male	Primary carcinoma of liver	Confirmed as intrahepatic bile duct cancer with metastasis
1.5 yr	female	Carcinoma of the biliary system	No reports available
9.8 yr	female	Carcinoma of the gallbladder	Adenocarcinoma of liver and gallbladder. Origin probably gallbladder, metastatic to liver
0.8 yr	female	Bile duct cancer	Cancer of the bile ducts. Origin probably from bile ducts. A history of cancer of the uterus.
0.3	female	Carcinoma of the liver	Hepatic coma due to hepatoma, due to metastatic disease, primary site unknown.

Note: When those liver tumors that represent metastases from other organs are deleted, the Observed/Expected ratio drops to 3/1.9 which is not a significant SMR. In fact, the SMR drops from the 280 reported in the initial study of Brown and Jones (1981) to only 157.

Adapted from Brown (1986)

Appendix C

Other than the cancer deaths in the liver/biliary category, no other striking differences were noted (see Table C-12). As in the previous study by Brown and Jones (1981), mortality from all causes was lower than expected as was mortality from all cancers (Brown, 1986).

The most recent published mortality study is that of Gustavsson et al. (1986). This study's cohort consists of 142 male Swedish workers engaged in the manufacture of electrical capacitors. In this plant PCBs were used from 1960 to 1978, and the dielectric fluid was one of 42% chlorine. The selection criteria for the cohort consisted of those persons employed for at least six months between years of 1965 and 1978. The vital status was determined for all 142 persons included in this study, and of these, 92 (65%) had a latency of at least 10 years. The expected number of deaths were calculated from national statistics and were standardized for sex, age, class and calendar year. The mean exposure duration was 6.5 years, and air sampling performed in 1973 showed a level of 0.1 mg/m³, although exposures in the 1960's may have been higher.

There were 21 deaths for this cohort, while 22.12 were expected. Of these, seven were caused by cancer, a small elevation that was not significant (see Table C-13). A subgroup of 19 individuals with higher exposures than the rest of the cohort, e.g. capacitor fillers and capacitor repairmen, were also analyzed separately. But there was no tendency toward an increase in mortality or an increase of cancer incidence in this high-exposure subgroup. While the authors note that the results of their study must be tempered by its small size, the confidence interval for the relative risk indicates that observing an excess in mortality over 1.5 is improbable, and that for total cancer incidence a relative risk in excess of 1.9 is likewise improbable.

TABLE C-12

**Major Causes of Death for Plant Workers Exposed to PCBs:
Aroclor 1016, 1242, and 1254**

Causes of Death	Observed/Expected	Standard Mortality Rate
	<u>All Causes</u>	
All malignant neoplasms	62/79.7	(78)
Diseases of nervous system	20/22.6	(88)
Diseases of circulatory system	120/115.6	(104)
Accidents	21/25.8	(81)
All other causes	72/73.9	(97)
All causes	295/317.6	(93)
	<u>Malignant Neoplasms</u>	
Cancer of stomach	1/2.8	(36)
Intestine	8/7.7	(104)
Rectum	4/1.9	(211)
Liver	5/1.9	(263)
minus metastases	3/1.9	(158)
Pancreas	2/3.7	(53)
Respiratory	10/16.9	(88)
Urinary	4/2.8	(143)
Hematopoietic	5/7.4	(68)
Breast	9/11.7	(102)

Adapted from Brown (1986)

Table C-13

**Mortality and Cancer Incidence in Swedish
Capacitor Manufacturing Workers**

Mortality	Observed/ Expected	Relative Risk	95% Confidence Interval
Total Mortality	21/22.12	0.95	0.58-1.45
Cancer	7/5.39	1.30	0.52-2.67
Circulatory disease	8/11.40	0.70	0.30-1.38
Ischemic heart disease	6/8.38	0.72	0.26-1.55
Respiratory diseases	2/0.96	2.08	0.25-7.50
Other causes	4/4.37	0.91	0.24-2.34
Total Cancer Incidence	7/7.58	0.92	0.37-1.90

Adapted from Gustavsson et al. (1986)

Summary of Mortality Studies

Several studies have examined causes of mortality among workers occupationally exposed to PCBs. The cause of mortality of particular interest is cancer. In order for there to be evidence of human carcinogenicity for PCBs, it should be minimally expected that the mortality studies show an increase in death from cancer in the exposed cohort. This increase should show a positive correlation with exposure and evidence of latency. The evidence for carcinogenicity would be strengthened if specific types or sites of neoplasms were consistently implicated. In reviewing the data from the mortality studies to date, none of these criteria has been met.

The largest cohort examined, that studied by Brown (Brown and Jones, 1981; Brown, 1986), was negative. There was no significant increase in overall mortality from cancer, and when neoplasms of questionable origin are removed from the analysis, there was no significant increase in cancer of the liver or any other specific type. The study of Bertazzi et al. (1986) reports finding significantly increased incidence of cancer in their cohort when different types of neoplasms are grouped under a single, less specific category. However, the study was small, and when individuals are removed whose possible PCB exposure is so small or

the latency period so short as to make any association with PCBs dubious, this study is also negative. The dubious findings of Bertazzi et al. (1986) are also contradicted by Gustavsson et al. (1986), also in a smaller study, which found no increase in cancer mortality among Swedish capacitor workers. While Zack and Musch (1979) observed an increase in lung cancer among workers in a PCB manufacturing plant, this increase was inexplicably found only in white male workers. Additionally, the obvious confounding variable of smoking status was not considered; thus it is not surprising that an increase in this type of cancer was not duplicated in any of the other mortality studies. The increase in melanoma and pancreatic cancer reported in the initial and very limited group studied by Bahn et al. (1976) was also not found in any of the other mortality studies. Further, Bahn et al. neglected to consider the likely exposure to other compounds, including known carcinogens, among their group of petroleum refinery workers.

When the mortality studies are considered collectively, the epidemiological evidence for human carcinogenicity is mostly negative. While higher than expected rates have been reported in two of the smaller studies, the findings were either sex-specific or race-specific and were not supported by any of the other studies. These problems are a strong indication that the etiologic factor responsible for each increase is not the same, and such contradictory evidence is inconsistent with most of the current theories on chemical-induced carcinogenesis. However, no final conclusions can be rendered at this time because each of these studies have been based on a relatively small number of deaths. Until larger epidemiological studies can be completed, that is, until a larger number of the persons included in these cohorts have passed away, the data must be considered inadequate to fully characterize the human carcinogenic potential of PCBs. Nevertheless, the failure of epidemiologic investigations reported to date to uncover any adverse human health effect that can be causally linked to relatively high, chronic PCB exposure suggests that the relatively low level PCB exposures that occur in our daily environment carry few, if any, risks to the human population.



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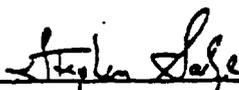
DEPARTMENT OF CHEMISTRY
COLLEGE OF PHYSICAL SCIENCE

AFFIDAVIT

1. My name is Stephen H. Safe. I am Professor of Biochemistry at the University of Guelph, Ontario, Canada. I was senior co-author of Wyndham, Devanish and Safe, The In Vitro Metabolism, Macromolecular Binding and Bacterial Mutagenicity of 4-Chlorobiphenyl, a Model PCB Substrate, Research Communication in Chemical Pathology and Pharmacology, Vol. 15, No. 3 (1976). I supervised the research reported in that paper. This paper reported the mutagenicity of 4-chlorobiphenyl.
2. This paper reported strong mutagenic activity, and there was a dose-response relationship. Accordingly, I would have expected that subsequent attempts at replication would have obtained comparable results using the same experimental protocol.
3. In 1978 a student, working under my supervision, attempted to repeat the experiment reported in my prior paper. He utilized the same experimental protocol, with new samples of the same bacterial strains acquired from the Ames laboratory. No mutagenic activity was observed, despite presence of mutagenic activity in a positive control (benzo(a)pyrene). The experiment was run several times, in order to confirm a lack of mutagenic activity. These results are reported in the student's thesis: Michael Robert Shilling, Halogenated Aromatic Hydrocarbons: Mutagenicity and Microsomal Enzyme Studies (Masters Thesis, University of Guelph, 1979).
4. Accordingly, 4-chlorobiphenyl must be considered non-mutagenic in the Ames test at the present time.
5. I have furnished this affidavit to Dow Chemical Company, with the understanding that it might be used in the Company's controversy with the U.S. Environmental Protection Agency concerning the regulation of monochlorobiphenyls.

23 April 1980

Dated



Stephen H. Safe
Professor of Chemistry

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