

REVIEW ARTICLE

Weight of evidence evaluation of potential human cancer risks from exposure to polychlorinated biphenyls: An update based on studies published since 2003

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Abstract

Drawing on all data available in 2003, the WoE of the human epidemiological data for polychlorinated biphenyls (PCBs) demonstrates that exposure to a mixture of PCBs (i.e. Aroclors) did not pose a cancer risk to humans (Golden et al. (2003)). This evaluation was based on criteria established by the US Environmental Protection Agency (EPA) as well as on a different methodology used by the Agency for Toxic Substances and Disease Registry (ATSDR). Subsequently, at least 15 more studies on the potential cancer risks (both incidence and mortality) of PCBs have been published. All studies published since 2003 are critically reviewed using the criteria established by the EPA (2005) and ATSDR (2000). None of the studies published since 2003 change the conclusions drawn by Golden et al. (2003): "that the weight of evidence does not support a causal association for PCBs and human cancer". This conclusion pertains to all cancers combined, as well as to the various cancers that have been sporadically reported in the occupational cohort mortality studies. With respect to breast cancer risk, the WoE is compelling that environmental exposure to PCBs is not etiologically implicated in breast-cancer risk. This conclusion is supported by the consistently negative findings for increased breast-cancer mortality in occupational studies, which now involve almost 9,000 women occupationally exposed to PCBs. Similarly, the incidence studies in which PCB background levels are reported to be associated with increased risk of non-Hodgkin's lymphoma or prostate, testicular, and intestinal cancer are not corroborated by occupational cohort studies with PCB exposures far in excess of environmental exposures. The most likely explanation for these discordant findings is discussed in this review. Finally, the recent elucidation of the mode of action by which PCBs promote liver tumors in rats, combined with the demonstration that none of the key events in the mode of action occurred until substantial tissue accumulation of total PCBs had occurred, casts further doubt that PCB exposure at environmental or occupational levels poses a carcinogenic risk to humans. The dramatic differences between rodents and humans in sensitivity to PCB-mediated induction of *CYP1A1* suggests that even occupational exposures to PCBs have never resulted in PCB body burdens approaching the levels required to initiate the sequence of events involved in the promotion of liver tumors in rodents.

Keywords: Cancer; humans; polychlorinated biphenyls (PCBs); polymorphisms; weight of evidence

Introduction

Whether exposure to polychlorinated biphenyls (PCBs) might pose a cancer risk to humans remains controversial. In 1999, the Agency for Toxic Substances and Disease Registry (ATSDR) released the *Draft Toxicological Profile for Polychlorinated Biphenyls*. In reviewing the potential human carcinogenicity of PCBs, the ATSDR (1999) concluded that "the weight of evidence does not support a causal association for PCBs and human cancer at this

time". However, 1 year later, in an updated toxicological profile for PCBs, the ATSDR changed its mind, stating that "overall, the human studies provide some evidence that PCBs are carcinogenic" and that "some of these studies provide meaningful evidence that PCBs are carcinogenic in humans" (the ATSDR, 2000). The only study published after the ATSDR (1999) draft evaluation and before the ATSDR (2000) final evaluation is by Kimbrough et al. (1999). This study, the largest occupational study at the time of a

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population of workers heavily exposed to PCBs, found no significant associations between PCB exposure and deaths from any cancer or any other disease. Of all the studies that had investigated potential associations between PCB exposure and increased risk of cancer, this study had the longest latency. It also confirmed the results of four previous studies of this cohort of PCB-exposed workers. This study clearly added to the weight of evidence (WoE) against a causal association between PCB exposure and human cancer. Nevertheless, in the 2000 version of the *PCB Toxicological Profile*, the ATSDR did not cite Kimbrough et al. (1999) as further support for its previous conclusion that “the weight of evidence does not support a causal association for PCBs and human cancer at this time”. Instead, the ATSDR abandoned the WoE approach in favor of another methodology not endorsed or used by any regulatory agency. As detailed in the comprehensive review by Golden et al. (2003), this methodology was based on a book chapter by Nicholson and Landrigan (1994), in which the summed observed and expected cancer mortality rates (for men and women combined) from several capacitor-worker studies were tested for statistical significance. This 1994 analysis provided the basis for the ATSDR’s (2000) conclusion that there was “some” or “meaningful” evidence of an association between human PCB exposure and cancer, even though the ATSDR did not determine if that conclusion held when all relevant pre-1994 and post-1994 data were combined in this way. As shown in Golden et al. (2003), none of the cancers highlighted by the ATSDR (2000) was significantly elevated when standardized mortality ratios (SMRs) using all available data were tabulated as suggested by Nicholson and Landrigan (1994).

The ATSDR (2000) evaluation of PCBs is the latest government review of the potential human carcinogenicity of PCBs. However, the conclusions of this review were clearly not based on a WoE review using all data available at the time, or on the guidelines now recommended by EPA (2005). It should also be noted that while the ATSDR does not seem to have a document summarizing WoE guidelines, this concept is embraced on their website (www.atsdr.cdc.gov/HEC/CSEM/pediatric.appendixf.html). Thus, the conclusions of the ATSDR (1999) as confirmed in Golden et al. (2003) stand as the most recent evaluations regarding the human carcinogenicity of PCBs based on the WoE. It does not appear that any other government agency is planning to address this issue in the near future.¹

Given that it has been almost 8 years since the last government assessment of the human carcinogenicity of PCBs, and 5 years since the last private assessment of this issue, as well as the fact that additional relevant studies have been published in the interim, a re-evaluation of the issue seems warranted. A re-evaluation also seems appropriate since the EPA has finalized revised guidelines for carcinogen risk assessment (EPA, 2005). Some key highlights from these guidelines should be noted. In discussing the assessment of evidence of carcinogenicity

from human data, the EPA (2005) states: “All studies that are considered to be of acceptable quality, whether yielding positive or null results, or even suggesting protective carcinogenic effects, should be considered in assessing the totality of the human evidence. Conclusions about the overall evidence for carcinogenicity from available studies in humans should be summarized along with a discussion of uncertainties and gaps in knowledge”. Further, the guidelines suggest that conclusions regarding the strength of the evidence for positive or negative associations, as well as evidence supporting judgments of causality, should be clearly described. In assessing the human data within the overall WoE, the guidelines stress that determinations about the strength of the epidemiologic evidence should clearly identify the degree to which observed associations may be explained by other factors, including bias or confounding.

The EPA guidelines also address statistical considerations, stating that “the analysis should apply appropriate statistical methods to ascertain whether the observed association between exposure and effects would be expected by chance”. In particular, the issue of combining statistical evidence across studies is addressed as follows: “Meta-analysis is a means of integrating the results of multiple studies of similar health effects and risk factors. This technique is particularly useful when various studies yield varying degrees of risk or even conflicting associations (negative and positive). It is intended to introduce consistency and comprehensiveness into what otherwise might be a more subjective review of the literature. *The value of such an analysis is dependent upon a systematic review of the literature that uses transparent criteria of inclusion and exclusion*” (emphasis added).

In discussing evidence for causation, the EPA (2005) guidelines embrace the well-known criteria described by Sir Bradford Hill (1965), including strength of association, consistency of association, biological plausibility, temporality, and biological gradient (i.e. exposure-response relationship). The systematic application of these criteria is often referred to as a WoE evaluation. These ‘causation criteria’ were explicitly followed in the review by Golden et al. (2003). These guidelines are embraced not only by the EPA (2005), but also by the ATSDR and International Programme on Chemical Safety (IPCS, 1999). The Food and Drug Administration (FDA, 1998) also applies similar guidelines for assessing the efficacy of new drugs that embrace virtually all of these criteria. This is not surprising, since the role of FDA is to determine if a new drug ‘causes’ a beneficial health effect (i.e. whether it has efficacy).

The present review is intended to evaluate the WoE from 2003 onwards regarding the relationship, if any, between human exposure to PCBs and cancer. While the WoE evaluation process necessarily involves scientific judgment, the goal of the present review (as well as that of the previous review) is to be as transparent as possible. This includes considering all available studies, applying clear weighting procedures (e.g. follow-up studies vs. one-time-only

studies), evaluating confounding factors, and clearly describing study deficiencies. Studies were identified using PubMed searches both initially and throughout this evaluation, as a number were published while this paper was in preparation. Using the EPA (2005) guidelines as a foundation, this review will separately address five factors: (a) incidence studies reporting associations between environmental PCB exposure and four types of cancer; (b) updates of previously reported PCB occupational cohort mortality studies; (c) a new PCB occupational cohort mortality study; (d) an assessment of the WoE linking environmental and occupational PCB exposure to breast-cancer risk; and (e) the methodology using observed and expected mortality to compute a summary SMR, because of its endorsement by the ATSDR (2000).

General population exposure incidence studies on specific types of cancer

A number of incidence studies published after 2003 have reported the association of four types of cancer (i.e. prostate, testicular, colon, and non-Hodgkin's lymphoma [NHL]) with environmental exposure to PCBs. These studies are reviewed below. However, because it is difficult to directly compare incidence data with mortality data, and also because none of these cancers have been reported as significantly elevated in occupational mortality studies (see below for additional discussion of prostate cancer), the WoE is evaluated separately for each type of cancer.

Prostate cancer

Ritchie et al. (2003)

This small pilot study investigated the relationship between organochlorine pesticides, PCBs, and prostate cancer in 58 prostate cancer patients and 99 controls. On the basis of self-reported chemical exposures, it does not seem that any cases had been occupationally exposed to PCBs or any other organochlorine compounds. Gas chromatography was used to measure 30 PCB congeners and 18 organochlorine pesticides in serum. The magnitude of association was assessed by multiple logistic regression analysis. After adjustment for age, body mass index, and a history of prostatitis, oxychlordane and PCB 180 were associated with a significantly increased risk of prostate cancer. For PCB 180, the risk of prostate cancer was statistically significantly increased (Odds ratio [OR] = 3.13, 95%CI 1.33–7.34) at the intermediate serum level (0.009–0.041 µg/g), but not significantly increased (OR = 1.47, 95%CI 0.58–3.73) at the highest serum level (>0.041 µg/g). Consequently, the findings provided no evidence of a dose–response relationship. All stages of disease were represented in the 58 cases in this study (i.e. Gleason II, III, III–IV and IV—severity scores designed to measure disease progression). This fact suggests that increased levels of organochlorine compounds in cancer cases cannot be unequivocally associated with disease incidence, since it may represent redistribution from lipid stores due to disease-induced

weight loss or treatment-related effects, both of which are known to affect PCB serum levels (Gammon et al., 1996; Baris et al., 2000). The description of patient characteristics did not seem to account for this possibility. As noted by the authors, this study was small and designed to generate hypotheses. Furthermore, there was no significant association between total PCB (Σ PCB; all 12 congeners) and risk of prostate cancer. It is difficult, if not impossible, to determine the etiological role that might be played by a single PCB congener (e.g. PCB 180) and, indeed, no biologically plausible explanation is offered by the authors. Since no dose–response relationship was demonstrated and many comparisons were made, this finding may represent a chance observation.

Ritchie et al. (2005)

This study was an extension of the Ritchie et al. (2003) study, which explored associations between the same 58 cases of prostate cancer and different groupings of 30 PCB congeners. These groupings were based on known chemical and biological properties of PCBs, including degree of chlorination (i.e. low, moderate, or high), enzyme induction properties and biological action (i.e. estrogenic or neurotoxic, antiestrogenic [Ah-receptor agonists], and enzyme-inducing phenobarbital-type cytochrome P-450). Some of these groupings have been used to assess potential risk of breast cancer (e.g. weakly estrogenic PCBs); however, there is little, if any, biological basis for assuming that any of them might be etiologically associated with prostate cancer. Two PCB groupings, moderately chlorinated and phenobarbital-type inducers, were reported as having identical significantly increased ORs and trends for prostate cancer (OR = 2.44, 95%CI 1.01–5.90, $p = 0.043$). However, neither of these findings was significant when the serum values were lipid adjusted.

The associations reported by Ritchie et al. in 2005 and 2003 are inconsistent with the results of several large occupational cohort studies, in which exposure to PCBs was substantially greater than the environmental exposures of the 58 cases in this study (see comment below). There is no evidence of any increased mortality risk of prostate cancer in the overall results of any of these studies. None of these studies are mentioned by Ritchie et al. (2003, 2005).

Hardell et al. (2006a)

This was an incidence study involving 58 cases of prostate cancer and 20 controls. Adipose-tissue samples were collected from cases and controls and analyzed for 37 PCB congeners), polybrominated diphenyl ethers, chlordane, dichlorodiphenylethylene (DDE), hexachlorobenzene (HCB), and lipid content. Prostate specific antigen (PSA) level was also measured. All Gleason-score stages of disease were represented. As with previous incidence studies of this type, the authors investigated associations between a number of PCB-congener groupings (e.g. estrogenic, lower-chlorinated, moderately chlorinated, higher-chlorinated, enzyme-inducing, and toxicity equivalent [TEQ] groupings) and various PSA categories (<4, 4–10, >10, <16.5,

and > 16.5). There were no significant differences between cases (PSA < 16.5 or > 16.5) and controls in adipose-tissue concentrations of Σ PCB. However, there was a significant difference ($p=0.005$) between cases with PSA > 16.5 and controls in tissue concentrations of PCB 153. In addition, there were some seemingly random statistically significant findings in cases with PSA > 16.5 and congener groupings: enzyme-inducing PCBs (OR = 4.97, 95%CI 1.25–19.8), lower-chlorinated PCBs (OR = 3.75, 95%CI 1.01–13.9), known and predicted phenobarbital-type inducers (OR = 4.97, 95%CI 1.25–19.8). There were also seemingly random groupings in cases with PSA > 10: enzyme-inducing PCBs (OR = 3.52, 95%CI 1.06–11.7) and known and predicted phenobarbital-type inducers (OR = 3.52, 95%CI 1.06–11.7). Disease-induced weight loss was considered as a possible explanation for higher concentrations in cases than controls, but there were no significant differences in body mass index at the time of disease diagnosis or one year before diagnosis. Adjustments for age were also considered in the analysis. There was no significant difference in Σ PCB (ng/g lipid) between cases (mean 1,087, min–max 230–2,574) and controls (mean 1,121, min–max 447–4222). With respect to PCB 153, other than its ubiquitous presence and ease of detection, there was no biological basis offered by Hardell et al. (2006a) for why this congener, or any of the congener groupings used in this study, might play an etiological role in the development of prostate cancer. The fact that Σ PCB was not associated with increased risk at any PSA level, as well as the wide confidence intervals for the few significant findings, suggests that the data were unstable and that observed associations could have been chance observations.

Weight of evidence evaluation for prostate cancer

On the basis of the key causation criteria (i.e. strength of the association, consistency of the association, dose–response relationship, temporality, and specificity of the association), the WoE from occupational cohort mortality studies does not demonstrate that exposure to PCBs is a risk factor for prostate cancer. While not all of the studies reported prostate cancer as a separate cause of death, there were at least seven that do. In those studies (i.e. three single and four follow-up studies involving a total of more than 9,000 male workers) in which prostate cancer was listed as a specific cause of death, no SMRs in the cohort were significantly elevated for occupational exposure to PCBs (Gustavsson and Hogstedt, 1997; Kimbrough et al., 1999, 2003; Charles et al., 2003; Ruder et al., 2006; Prince et al., 2006a, 2006b). Given that these studies involved workers subject to high-dose occupational exposure to PCBs, it is biologically implausible that the background PCB-related prostate-cancer cases in the incidence studies by Ritchie et al. (2003, 2005) or Hardell et al. (2006) were etiologically associated with exposure to PCBs. The study by Charles et al. (2003; reviewed below with mortality studies), which found no significant association between occupational exposure to PCBs and increased risk of prostate cancer,

adds to the WoE that PCBs are not etiologically associated with prostate-cancer risk.

As reported by Ritchie et al. (2003) and Hardell et al. (2006), PCB 180, PCB 153, and various PCB congener groupings were significantly associated with increased incidence of prostate cancer. If any of these findings of an association between PCBs (single congener or congener grouping) and increased risk of prostate cancer were causal for prostate cancer, it is reasonable to expect an even greater effect would have been reported in occupational mortality studies, all of which involved substantially greater exposure to both PCB 153 and PCB 180, as well as to the PCB congeners in the various groupings used by Ritchie et al. (2003) and Hardell et al. (2006). Furthermore, the congeners associated with prostate cancer in the Ritchie et al. (2003) and the Hardell et al. (2006) studies differed, and the confidence intervals were wide, suggesting either an observation made by chance or a consequence of multiple comparisons. It should also be pointed out that these studies are similar in concept to the early breast-cancer studies. That is, both sets of studies measured serum PCB levels in active cancer cases where serum levels can be affected by weight loss or by chemotherapy, thereby resulting in spurious associations (Gammon et al., 1996; Baris et al., 2000). The results of the early breast-cancer studies were invalidated in large part by an abundance of prospective data (i.e. analysis of PCBs in serum collected well before disease diagnosis) that demonstrated no association between PCB body burdens and increased risk of breast cancer.

It is often difficult to determine whether the criterion of biological plausibility can be applied to a particular disease outcome because of a lack of relevant data. However, prostate-cancer data suggest that it is biologically implausible that exposure to PCBs is etiologically implicated in this disease. In what is generally recognized as the definitive PCB cancer bioassay, male and female Sprague–Dawley rats were exposed for 24 months to PCB Aroclors 1016, 1242, 1254, and 1260 (Mayes et al., 1998, 1999). While the results showed increases in hepatic tumors, there were striking decreases in extra-hepatic tumors, including a marked decrease in prostate tumors from all Aroclors tested. Consequently, the animal data suggest that it is not biologically plausible that PCBs are a risk factor for prostate cancer.

It is also important to consider how one (or a few) congeners in a complex mixture would be etiologically responsible for causing a particular disease. With PCBs, it is now clear that some congeners induce mixed-function oxidases (MFOs), while other congeners suppress MFOs (Brown et al., 2007). Given the agonist–antagonist properties of PCB mixtures, the only biologically plausible metric is Σ PCB, since only this metric ‘integrates’ the mixture effects of induction and suppression. Although both Ritchie et al. (2003, 2005) and Hardell et al. (2006) implicated individual PCB congeners or groupings of PCB congeners in prostate-cancer risk, Σ PCB was not significantly associated

with prostate cancer in either study. In addition, there is no biological basis (and none is suggested by the authors) for assuming that the moderately chlorinated congeners, enzyme-inducing congeners, or phenobarbital-type congeners might have an etiological link with prostate cancer. Once again, it should be noted that no occupational cohort study reports an association between exposure to PCBs (i.e. all congeners) and increased risk of prostate cancer. In all of these studies, individuals were exposed to PCB 153 and 180, as well as to the PCB congeners that make up any of the various groupings reported as associated with prostate cancer. Finally, as reviewed in greater detail below for NHL and breast cancer, it is becoming increasingly clear that disease risk may be influenced by metabolic gene variants, some of which may coincidentally affect the metabolism, excretion, or retention patterns of PCBs, thereby leading to non-causal associations between slightly elevated PCB concentrations (all within the normal population background range) and increased risk. For prostate cancer, this includes genetic polymorphisms of a number of genes, many of which are involved in PCB metabolism (Yang et al., 2006; Daly, 2006; Fukatsu et al., 2004; Suzuki et al., 2003; Tanaka et al., 2002; Murata et al., 2001). In individuals with one or more of these polymorphic genes, background levels of PCBs (including individual congeners) might be minimally elevated (or decreased) leading to spurious associations with disease risk. Consequently, the WoE suggests that exposure to PCBs is not associated with increased risk of prostate cancer.

Testicular cancer

Hardell et al. (2003, 2004, 2006b)

While increased mortality from testicular cancer has never been associated with exposure to PCBs, Hardell et al. (2003, 2004, 2006b) report that prenatal exposure might be a risk factor for testicular cancer as a consequence of *in utero* exposure to PCBs. The hypothesis is that testicular cancer is initiated during the fetal period by exposure to weakly estrogenic chemicals. The Hardell et al. (2003, 2004, 2006b) studies all report on the same 58 cases of testicular cancer (seminoma representing ≈ 30 –40% of all cases and non-seminoma representing ≈ 60 % of all cases) and 61 age-matched controls, as well as 44 case and 45 control mothers. Blood was collected from all study participants between 1997 and 2000 and frozen for later analysis for 37 PCB congeners, DDE, HCB, and chlordanes. Since the mean age of case and control men at the time they provided blood samples was approximately the same (31 years), it seems that blood was collected from mothers about 30 years after they were pregnant with their sons. The means, medians, and ranges of Σ PCB in case and control mothers were 859, 792, and 236–2114 ng/g lipid and 592, 563, and 141–1193 ng/g lipid, respectively, and were significantly different ($p = .0006$). The reproductive histories of case and control mothers were assessed by questionnaire and, as indicated in Hardell et al. (2003), there were no significant differences between cases and controls in

duration of breast feeding or birth order. There were no significant differences between case and control men in total serum PCB levels or various congener groupings. However, case mothers had significantly increased serum concentrations of Σ PCB (OR = 3.8, 95%CI 1.4–10.0), as well as significantly increased concentrations of PCB congeners in two groups: enzyme-inducing PCBs (OR = 2.6, 95%CI 1.03–6.50) and TEQ congeners (OR = 3.3, 95%CI 1.3–8.4). Estrogenic PCBs were not significantly different in case and control mothers (OR = 2.4, 95%CI 0.95–6.00). Adjustments were made for age and body mass index in the analyses.

Weight of evidence evaluation for testicular cancer

The Hardell et al. (2003, 2004, 2006b) studies are based on the hypothesis that *in utero* exposure to maternal levels of PCBs, probably acting as weakly estrogenic substances, initiates the onset of testicular cancer as a result of this property. The authors cite a number of papers supporting the theory that *in utero* exposure to weakly estrogenic chemicals might be a contributing factor for testicular cancer (e.g. Sharpe and Skakkebaek, 1993; Skakkebaek et al., 2001), even though their results showed no association between estrogenic PCB congeners and testicular cancer. However, Hardell et al. failed to cite the key paper from the same authors that largely retracted this hypothesis. In 1993, Sharpe and Skakkebaek put forth the “estrogen hypothesis” as a biologically plausible explanation for an apparent increase in male reproductive-tract disorders, including testicular cancer. They speculated that *in utero* exposure to a number of weakly estrogenic compounds could explain this phenomenon. In revisiting this hypothesis, Sharpe (2003) noted that “... all of the identified environmental estrogens’ possess weak or very weak intrinsic estrogenic activity when measured by conventional *in vitro* and *in vivo* assays for estrogenicity... Based on estrogenic potency, human exposure to the most potent environmental estrogens would need to be at least 1000-fold higher than this level for adverse effects relevant to the human male to be induced, and such levels of exposure are remote”. Other reviews have also concluded that the “estrogen hypothesis” as it pertains to testicular cancer etiology (i.e. excess estrogen during gestation) is likely invalid (Hsieh et al., 2002; Dieckmann et al., 2001).

With respect to two other PCB congener groupings (enzyme inducing and TEQ) associated with testicular cancer, there is no biological basis for speculating that *in utero* exposure to either grouping plays an etiological role in the development of testicular cancer. Indeed, Hardell et al. did not provide any citations to studies that might support a hypothetical etiological role in testicular cancer for either enzyme-inducing PCBs or TEQ congeners. It is questionable that the testes are a site for the development of cancer due to PCB exposure, given that Mayes et al. (1998) reported no increase in testicular cancer even at the highest doses of Aroclors 1016, 1242, 1254, and 1260 in a chronic cancer bioassay (although this study only involved

postnatal exposure). The Aroclors used include all the congeners in the various groupings assessed by Hardell et al. (2003, 2004, 2006). In addition, there is little reason to believe that the testes are a target organ for *in utero* PCB exposure, with the exception of animal studies involving exposures that are orders of magnitude greater than any possible human environmental exposure (ATSDR, 2000). Finally, the hypothesis that *in utero* exposure to weakly estrogenic chemicals might be etiologically associated with increased risk of testicular cancer is also refuted by the extensive human data on diethylstilbestrol, which has thousands of times more estrogenic activity than PCBs. In the most recent follow-up of diethylstilbestrol-exposed cohorts, 3,613 men whose *in utero* exposure to diethylstilbestrol was known were assessed from 1978 to 1994. Testicular cancer incidence in diethylstilbestrol-exposed men was not significantly elevated when compared with non-diethylstilbestrol-exposed controls (Strohsnitter et al., 2001).

Because of the questionable biological plausibility of the Hardell et al. findings compared with the results of the effects of *in utero* exposure to diethylstilbestrol, no causal association between maternal PCB serum levels and testicular cancer in later life can be assumed. PCB serum levels in mothers whose sons later develop testicular cancer may be hypothetically relevant if they were determined during the pregnancy of the child who later developed testicular cancer. However, PCB levels determined 30 years later are clearly of questionable relevance.

It is also difficult to explain or account for how or why serum PCB levels in case mothers remained elevated (albeit still in the normal range) 30 years after giving birth to sons who later developed testicular cancer, or even to determine whether their serum levels were elevated during their pregnancies. The inference that the minimal difference in serum PCB levels between case and control mothers was causal for testicular cancer is not biologically plausible, particularly as a consequence of the weakly estrogenic properties of some PCB congeners. Not addressed by Hardell et al. (2003, 2004, 2006b) is the fact that, while some PCB congeners are weakly estrogenic, other congeners are weakly anti-estrogenic, thereby further reducing the net estrogenic effects of the mixture. Hardell et al. (2006b) speculate that a biological peculiarity (e.g. polymorphism of *CYP* enzymes) might have altered the metabolism of PCBs in case mothers, thereby slightly raising background serum levels above levels in controls. If this were the case, the minimally elevated PCB levels in mothers whose sons developed testicular cancer would not necessarily be etiologically linked to the disease. This would be similar to the *CYP1A1* polymorphism that has been reported to be associated with increased risk of breast cancer in conjunction with similarly elevated PCB serum levels. However, as described below, this finding is not causal, but rather the result of other factors that produce this seemingly enigmatic finding. Consequently, until the findings of Hardell et al. (2003, 2004, 2006b) are

confirmed in a more rigorous prospective study, the results of a single questionable study are insufficient to conclude that *in utero* exposure to PCBs is a risk factor for testicular cancer.

Since the Hardell et al. (2003, 2004, 2006b) studies report on a single cohort, the data are insufficient in themselves to establish a potential causal association between PCB exposure and testicular cancer because they cannot fulfill the WoE consistency criterion. Moreover, given the lack of any plausible etiological role for PCBs in the development of testicular cancer, the results of these studies can only be considered as hypothesis generating pending completion of a long-term prospective study. This is the only way to determine if *in utero* exposure is etiologically linked with the development of testicular cancer. However, given the present, very low environmental PCB exposures of the general population, such a study may not be feasible. While none of the occupational cohort studies have reported an increase in testicular-cancer mortality, this is not surprising given that the incidence of testicular cancer peaks between the ages of 30 and 35 years and would probably not be picked up in a mortality study of older workers.

Finally, the key premise of this study—that *in utero* exposure to weakly estrogenic substances is a risk factor for testicular cancer—is refuted by the most recent data from studies of diethylstilbestrol-exposed cohorts, which demonstrate that testicular cancer is not significantly increased following *in utero* exposure to this potent estrogen. In fact, Hardell et al. specifically looked at possible associations between weakly estrogenic PCB congeners and testicular cancer risk and found none. While there is no known plausible explanation for the findings reported by Hardell et al. (2004), the available evidence suggests that PCBs are not a risk factor for increased incidence of testicular cancer.

Intestinal cancer

Howsam et al. (2004)

In an incidence study, Howsam et al. (2004) reported an association between colorectal-cancer risk in both men and women and serum levels of several individual PCB congeners, particularly as a function of mutations at the K-ras and p53 genes. In this study, lipid-corrected serum levels of seven PCB congeners (28, 118, 52, 101, 138, 153 and 180) were determined along with those of other organochlorine compounds (HCH, HCB, DDT and DDE). All measurements were conducted in active cases of colorectal cancer (57 men and 43 women) and compared with those from a control population similar to the cases in all respects, except that the controls consumed significantly less ethanol. The authors do not address this issue.

Howsam et al. (2004) reported significant associations between colorectal cancers and exposure to PCB 28 (less than the limit of detection) and between both K-ras wild-type and mutated-form colorectal cancers and exposure to PCB 28 (less than the limit of detection): OR = 2.78, 95%CI 1.24–6.25 and OR = 2.83, 95%CI 1.13–7.06, respectively).

The authors also reported a significant association between exposure to PCB 118 (highest tertile) and K-ras wild-type colorectal cancer (OR=2.27, 95%CI 1.04–4.96). In addition, PCB 118 (highest tertile) was significantly associated in cases with mutated p53 (OR=2.79, 95%CI 1.22–6.37)

In discussing how these results might be biologically plausible, Howsam et al. (2004) describe CYP1A and CYP2B enzyme induction by PCB 118 and PCB 28, even though their respective toxicity equivalency factors are 0.0001 and 0.0000 (van den Berg et al., 2006). It should also be noted that there is no evidence that CYP1A1 or CYP2B1 is induced by PCB exposure, even in heavily exposed workers (Brown and Lawton, 2001). Howsam et al. (2004) also imply that exposure to these congeners might be responsible for K-ras or p53 mutations, but provide no evidence that either congener can produce this effect. Not considered or discussed was the possible effect of chemotherapy, which is known to affect serum PCB levels in cancer patients (Gammon et al., 1996; Baris et al., 2000). In addition, from the way the cases are described, it is not possible to determine if they were all colon cancer cases or if some were rectal cancer. This makes it difficult to compare these results with those from studies that reported separate data for colon and rectal cancer.

Weight of evidence evaluation for intestinal cancer

A significant association between occupational exposure to PCBs and rectal-cancer mortality was reported by Brown and Jones (1981), although this finding had disappeared by the first follow-up of this cohort (Brown, 1987). The workers assessed in the Brown and Jones (1981) and Brown (1987) studies were included in the Kimbrough et al. (1999, 2003) studies and the Prince et al. (2006a, 2006b) studies. In none of these studies was an association found between PCB exposure and mortality from rectal cancer. These studies involved prolonged occupational exposure to all PCB congeners, including the seven individual PCB congeners selected for investigation by Howsam et al. (2004).

In the numerous occupational cohort mortality studies, a statistically significant increase in intestinal cancer in women has been reported once in the total cohort by Prince et al. (2006a, 2006b), and a similar, although non-significant increase was reported by Kimbrough et al. (1999, 2003). The workers in the Kimbrough et al. (1999, 2003) studies were included in the Prince et al. (2006a, 2006b) studies, as were the workers studied by Brown and Jones (1981) and Brown (1987). The authors of these reports emphasized the lack of evidence of an exposure-response trend for intestinal cancer even in the most highly exposed workers. No increased mortality from intestinal cancer has been seen in any of the other PCB occupational mortality studies. Howsam et al. (2004) considers virtually none of these studies, which involved exposure to the same PCB congeners—at substantially higher levels—and all the other PCB congeners in the Aroclors to which the workers were exposed.

Other than their persistence and ease of detection, Howsam et al. (2004) do not explain why only seven PCB congeners were considered in their study and why no results based on total PCBs were presented. It is now known that a mixture of PCB congeners (i.e. Aroclors) has both tumor-promoting and tumor-inhibiting properties, so an analysis limited to individual congeners cannot account for these interactive effects (Brown et al., 2007). The failure by Howsam et al. (2004) to provide analyses based on Σ PCB makes it impossible to account for such effects. Finally, the authors' hypothesis that mono-ortho PCBs, as a consequence of their dioxin-like properties, might cause intestinal cancer is not borne out by the dioxin epidemiological data. Considering the little information provided by Howsam et al. (2004) and the extensive occupational cohort studies, which include greater exposure to all PCBs, including mono-ortho PCBs, the WoE suggests that PCBs are not causally associated with an increased risk of intestinal cancer.

Non-Hodgkin's lymphoma

De Roos et al. (2005)

On the basis of previous reports suggesting an association between environmental exposure to PCBs and increased incidence of NHL, De Roos et al. (2005) investigated a subset of participants from a case-control study of NHL conducted by the National Cancer Institute. Cases included 1,321 patients newly diagnosed with NHL and 1,057 controls. Cases and controls were selected from four different SEER (Surveillance Epidemiology and End Results) reporting regions. Plasma from 100 cases and 100 controls was analyzed for 36 non-coplaner PCB congeners, coplaner PCB congeners, dioxins, furans, and 13 organochlorine pesticides. Care was taken to collect blood samples only from patients who had not undergone chemotherapy, since this is known to affect PCB serum levels (Baris et al., 2000).

Primary emphasis was placed on investigating associations between individual PCB congeners and NHL. Of the non-coplaner PCB congeners, two were significantly associated with NHL at the highest plasma concentration quartile: PCB 180 (OR=3.5, 95%CI 1.34–9.15) and PCB 194 (OR=2.68, 95%CI 1.04–6.90). PCB 156 was not significantly associated with NHL at the highest plasma concentration quartile (OR=2.7, 95%CI 0.97–7.50). However, all three congeners showed significant trends with exposure, albeit with wide confidence intervals. When data were analyzed by total non-coplaner PCBs, the association with NHL was not significant (OR=1.85, 95%CI 0.67–5.14) nor was the trend with exposure ($p=0.24$).

None of the coplaner PCBs were significantly associated with NHL. When stratified by degree of chlorination, the highest quartile of highly chlorinated PCBs was significantly associated with the presence of NHL (OR=2.68, 95%CI 1.04–6.90) with a significant trend ($p=0.04$). However, it seems that this group only contained a single detectable congener (PCB 194). The data were not analyzed on the

basis of Σ PCB. Finally, there was no significant association or trend between PCB TEQ and NHL, even in the highest quartile of exposure.

Engel et al. (2007a)

In this prospective study involving three cohorts of individuals with NHL, specific PCB congeners were evaluated for associations with disease incidence (Engel et al., 2007a). The Janus cohort consisted of \approx 87,600 Norwegian men and women. This group comprised 190 individuals who had developed NHL before 1999. The entire cohort had provided blood samples during a routine health examination between 1972 and 1978. Serum from these samples was frozen and later analyzed for DDE and 36 PCB congeners. The CLUE I cohort consisted of 23,938 residents of Washington County, MD, USA who had participated in the Campaign Against Cancer and Stroke in 1974. At this time, a blood sample was collected and the serum was separated and stored for later analysis. The serum samples from NHL cases were ultimately analyzed for DDE and 28 PCB congeners. The cases from this group were 74 individuals who had developed NHL between January 1975 and May 1994. The Nurses Health Study began in 1976 and involved 121,700 registered nurses who completed health-related questionnaires every 2 years. Between 1989 and 1990, 32,826 participants provided a blood sample from which serum was separated and stored. The samples from NHL cases were ultimately analyzed for DDE and 21 PCB congeners. In total, 33 women were diagnosed with NHL between the date they provided a blood sample and May 1994. Because the three cohorts differed in the timing of blood-sample collection, types of samples analyzed, and analytical methods, exposure-disease associations were assessed separately. All measurements were lipid corrected.

The basic finding from the Engel et al. (2007a) study was evidence of statistically significant correlations between increased risk of NHL and high serum concentrations of PCB congeners 118, 138, and 153, with a concentration-response trend most apparent in the CLUE I cohort. There was a significant concentration-risk trend in the CLUE I cohort, but not in the Janus cohort, suggesting an association between Σ PCB and increased risk of NHL. In all three cohorts, concentration-risk correlations were strongest in the periods closest to the time that blood samples were collected, with weaker and non-significant correlations in later periods. Table 1 illustrates the ORs and trends based on quartiles (or tertiles for the Nurses Health Study) of concentrations of PCB 118, 138, and 153, Σ PCB, and DDE during

the earlier follow-up periods. As shown in Table 1, while there are a number of significant findings regarding concentration quartiles, the confidence intervals for most are very wide, which substantially undermines the precision of the estimates. Concentration of PCB congener 180 was related to significantly increased risk of NHL in the Janus cohort, but not in the other two cohorts. It should be noted that the median levels (ng/g lipid) for either PCB congeners or Σ PCB in the various concentration quartiles were approximately doubled from the lowest to the highest quartiles in all cohorts. In addition, the median PCB levels in NHL cases were only a few percent higher than in controls.

Thus, the increased risks of NHL associated with being in the highest quartile (or tertile) of PCB concentrations, reported as ORs in the range 2.5–14.2 (Table 1), were associated with lipid-based Σ PCB concentration increases of only about 1 ppm on a lipid basis and less for individual congeners. The observation of a statistical association between two parameters does not indicate which parameter (or its covariant) is the cause and which is the consequence. In this case the observed correlations indicate that either (a) the adipose PCB concentrations were increasing the risk of NHL or else (b) NHL, or its underlying biochemical or physiological preconditions, were coincidentally also causing small decreases in PCB clearance rates, thereby resulting in slightly increased serum concentrations.

Arguing for the first alternative, Engel et al. (2007a) and others have suggested mediation of NHL by PCB-induced immunosuppressive effects. The biggest problem of this interpretation, however, is that there were very small differences between PCB serum concentrations in cases and controls. To overcome this finding would require the potency of PCBs as inducers of NHL to be enormous, with 1 ppm in serum lipids causing several-fold increases in NHL incidence. This is at odds with data for occupationally exposed workers with PCB serum concentrations up to hundreds of times larger. There were no significant increases in NHL in these cohorts (Table 2).

The second alternative, however, is fully compatible with the data in Tables 1 and 2. Variations in chronic PCB concentrations within populations sharing a common background exposure are heavily influenced by variations in PCB clearance rates. Human PCB clearance is known to be largely metabolic (Brown, 1994) and mediated by P450 cytochromes that are constitutive rather than PCB-induced (Brown and Lawton, 2001). For example, in healthy humans, the mean clearance half-times for PCB congeners 118, 138,

Table 1. Odds ratios (ORs) for risk of non-Hodgkin's lymphoma in relation to quartiles and tertiles of individual PCB congeners, total PCBs (Σ PCBs) and dichlorodiphenylethylene (DDE).

Exposure	Janus study OR (95% CI)	CLUE I study OR (95% CI)	Nurses Health Study OR (95% CI)
PCB 118	5.3 (1.5–18.8) ^a	13.0 (1.6–106.8) ^a	3.3 (0.9–12.4) ^a
PCB 138	2.5 (0.9–7.1) ^b	7.8 (1.8–34.6) ^b	3.8 (1.1–13.6) ^a
PCB 153	3.6 (1.3–9.9) ^b	2.7 (0.7–9.8) ^a	3.2 (0.9–11.8)
Σ PCBs	2.9 (1.0–8.2) ^a	14.2 (2.2–91.0) ^b	4.7 (1.2–18.9) ^a
DDE	4.3 (1.2–15.0) ^a	2.1 (0.7–6.3)	2.0 (0.7–6.1)

^a $P_{\text{trend}} < 0.05$; ^b $P_{\text{trend}} < 0.005$. Adapted from Engel et al. (2007a)

Table 2. Observed and expected cancer mortality from lymphatic, hematopoietic cancer and non-Hodgkin's lymphoma in male and female workers occupationally exposed to PCBs.

Study (<i>n</i>)	Lymphatic and hematopoietic cancer			Non-Hodgkin's lymphoma ^b			Sex of participants	ICD codes used	D-R trend analysis
	Observed	Expected ^a	SMR (95% CI)	Observed	Expected ^a	SMR (95% CI)			
Tironi et al., 1996 (1,556)	4	2.3	1.77 (0.48–1.53)	NR	NR	NR	Female	ICD 200-202	NR
Loomis et al., 1997 (138,905)	439	532	0.82 (0.75–0.91)	69	90	0.77 (0.6–0.97)	Male	ICD 200-208; 200;	NR
				176	170	1.04 (0.89–1.2)		202–203	
Kimbrough et al., 2003 (7,075)	25	25	1.0	NR	NR	NR	Male and female	ICD 200, 202, 203	NR
Ruder et al., 2006 (3,569)	20	19	1.08 (0.7–1.7)	9	7.3	1.23 (0.6–2.3)	Male and female;	ICD 200–208; 200, 202	NR
Prince et al., 2006a (2,588)	22	20	1.09 (0.68–1.65)	10	7.6	1.31 (0.63–2.41)	Male and female	ICD 200–208; 200, 202	No significant trend
Prince et al., 2006b (14,458)	99	94	1.05 (0.85–1.28)	35	36	0.98 (0.68–1.36)	Male and female	ICD 200–208; 200, 202	No significant trend

Note: ICD, International Classification of Diseases; NR, not reported; SMR, standardized mortality ratio.

^aWhen only observed reported expected approximated by O/SMR.

^bWhen non-Hodgkin's lymphoma (ICD 200 and 202) is reported separately or if ICD coding permits an approximation of likely cases.

and 153 are 5.9, 7.9, and 12.8 years, respectively (Brown, 1994); congener-specific and intra-individual variations in clearance rates over the decades of exposure involved can have sizeable effects on residual PCB concentrations. In the data shown in Table 1, the differences in congener and Σ PCB concentrations in the individuals who subsequently developed NHL were modest—generally under 20%. However, the methodology used in the calculations seems to have transformed small differences between the mean PCB levels in the patients and non-patients into large values for the apparent OR. This occurred because the overall distributions of PCB levels in the entire populations were quite narrow, meaning that those for PCB levels in the patient and non-patient sub-populations would have been narrower still. As a result, even a modest shift between the mean values for the PCB distributions in the patient versus non-patient sub-populations means that the upper quartile of the entire distribution can contain mostly patients and the lower quartile mostly non-patients. This means that the ratio of patient counts in the two quartiles (i.e. OR) can be quite high, and the apparent potency of the PCBs (ORs divided by the very small difference between upper and lower quartile PCB levels) can be enormous.

Thus, the surprising values for the ORs and the implied potency as indicated by the data in Table 1 are fully consistent with the second alternative—that the minor increase in PCB levels in the NHL population is simply a biochemical marker for a rather small decrease in the activity of the constitutive PCB-metabolizing P450 cytochromes, which in turn leads to a slight increase in PCB concentration, although still in the normal range.

The control of constitutive P450 expression in humans does not seem to have attracted much study; however, from rat and mouse studies it is now well established that

both the constitutive P450s and the insulin-like growth factors (IGFs; IGF 1 and IGF 2) are regulated in parallel by neuroendocrine factors, including the level and timing of growth-hormone release from the pituitary, and that such factors can increase the expression of some P450s while decreasing that of others (Waxman and O'Connor, 2006). Such findings suggest that increased risk of NHL may be related to some type of neuroendocrine signaling that leads to increased production of growth factors such as growth hormone and the IGFs, along with a net suppression of P450 activity (Keller et al., 2005; Mauras et al., 1988). This interpretation is consistent with several reports indicating that polymorphic variants of certain *CYP* genes, including those involved in PCB metabolism, can have the effect of slightly altering background PCB serum levels, (see below in the discussion of breast cancer) resulting in non-causal associations between minimally elevated PCB levels and disease. In this regard, it has been reported that NHL risk may be associated with a number of metabolic gene variants in *CYP1B1* (De Roos et al., 2006), *CYP17A1* (Skibola et al., 2005), *GST* (Kerridge et al., 2002), and *CYP2E1* (Soucek et al., 2002). Consequently, the first alternative interpretation described above for the data in Table 1—that trivial PCB concentrations increase NHL risk—can be unequivocally rejected on the basis of the data summarized in Table 2.

In attempting to explain the data in Table 1, which are consistent with previously reported case-control incidence studies of NHL (Hardell et al., 2001; De Roos et al., 2005), and also why the concentration-risk correlations were strongest in the period closest to the time that blood samples were collected, Engel et al., (2007a) suggested an etiological role for immunosuppression. In support of this role, they cited the immunosuppressive effects of anti-rejection drugs used

in organ transplants (a median time from transplant to NHL of 1–5 years) and AIDS-related lymphoma (a median time from HIV infection to NHL diagnosis of 6–8 years). Engel and colleagues then noted that many of the PCB congeners associated with increased risk of NHL in this study have been proposed to be immunotoxic (citing Wolff et al., 1997), to alter immune function (citing Tryphonas, 1994), and that the Epstein–Barr virus may potentiate the effects of PCBs (citing Rothman et al., 1997 and Hardell et al., 2001), so that any role of PCBs in the etiology of NHL may be mediated through immunotoxic mechanisms (citing Vineis et al., 1992). However, there is no evidence to support PCB-induced immunotoxicity, particularly clinical immunosuppression in humans, as an explanation for the reported findings. Wolff et al. (1997), in a non-peer reviewed letter, propose that PCB congeners be grouped into categories according to their biological function. While PCB 118 and 138 are proposed for Group 2 (potentially antiestrogenic and immunotoxic), PCB 153 is in Group 3 (phenobarbital-like, CYP1A/B inducers, persistent) and is not suggested to be immunotoxic. No data are cited in support of the possibility that PCBs have the ability to clinically suppress the immune system in humans, particularly at background exposure levels.

The Tryphonas (1994) review of the immunotoxicity of PCBs summarizes information available up to the date of that study, including the hypothesis that the immunotoxic effects of some dioxin-like PCBs are likely mediated via the AhR and that other PCBs would be antagonistic to the effects of individual congeners. No data reviewed by Tryphonas (1994) suggest that PCBs have been associated with clinical immunosuppression in humans. While the immunosuppressive effects of anti-rejection drugs used in organ transplants and HIV or AIDS are well established as risk factors for NHL, the suggestion that background PCB levels in blood would have similar effects is unwarranted and unsupported by any data. If this were the case, it is reasonable to expect that workers occupationally exposed to PCBs would have demonstrated not only increased mortality from NHL, but would also have exhibited clinical findings consistent with immunosuppression. No such findings have been reported. Finally, the review by Vineis et al. (1992) does not mention PCBs as possible etiological factors in the development of NHL.

Cocco et al. (2008)

Finally, in a recent case-control study involving cohorts from Spain, France, and Germany with a total of 174 cases of NHL, plasma samples were collected and analyzed for 17 organochlorine pesticides, HCB, chlordane, aldrin, dieldrin, endrin, mirex, DDT, and 9 PCB congeners (28, 52, 101, 118, 138, 153, 1709, 180, and 194; Cocco et al., 2008). Results were presented according to the major NHL subtypes (diffuse large B-cell lymphoma and chronic lymphatic leukemia), and the various PCB congener groupings typically used (pseudo-estrogens 28, 52, and 153, highly chlorinated anti-estrogens 170, 180, and 194, phenobarbital-inducing

101, 153, and 180, mixed PC/MC-inducing 118, 138, and 170, and immunotoxic PCBs 138, 153, 180). Risk of NHL (or any subtype) was not significantly increased with exposure to any individual PCB congener, congener grouping, or Σ PCB, nor were there any significant trends based on PCB plasma levels.

Weight of evidence evaluation for NHL

The study by De Roos et al. (2005) begins by saying that “Several studies have suggested a role of the polychlorinated biphenyls (PCB) in development of non-Hodgkin’s lymphoma”. Cited in support of this statement are three studies: Hardell et al. (1996), Rothman et al. (1997), and Laden et al. (2000). The studies by Hardell et al. (1996) and Rothman et al. (1997), each of which reported a significant association between PCBs and incidence of NHL as a consequence of environmental exposure, have methodological limitations, as reviewed by Golden et al. (2003). Subsequently, Engel et al. (2007a) also reported significant associations between selected PCB congeners and increased risk of NHL. The study by Laden et al. (2000) is an abstract and, without any details, cannot be afforded any weight. Moreover, a similar incidence study by several of the same authors (Quintana et al., 2004) found no association between NHL and total adipose-tissue PCB concentration (SMR = 1.05, 95%CI 0.63–1.76 and SMR = 1.08, 95%CI 0.40–2.92 for 1–3 ppm and >3 ppm, respectively). Since none of the large occupational cohort studies, with much greater PCB exposures than any of these studies, have reported a significant association between PCB exposure and NHL incidence (Table 2), it is unwarranted to conclude that environmental exposure to PCBs is causally related to NHL. In addition, it is biologically implausible that PCBs would play a role in NHL etiology, since no lymphohematopoietic malignancies of any kind have been reported in any of the high dose PCB bioassays conducted in rodents (e.g. Mayes et al., 1998).

Neither De Roos et al. (2005) nor Engel et al. (2007a) offer a biologically plausible explanation for why certain PCB congeners (i.e. those with higher degrees of chlorination such as 118, 138, or 153) would be etiologically implicated in increased risk of NHL when higher exposure to the same congeners in occupational studies does not result in significantly increased risk of NHL. The suggestion by Engel et al. (2007a) that environmental exposure to PCB congeners 118, 138, or 153 produces immunosuppression similar to that produced by known risk factors for NHL (i.e. immunosuppressant drugs or HIV/AIDS) is not biologically plausible, nor are any data cited suggesting this capability. All the occupational studies (many of which involve extensive follow-up of the same cohorts) involved prolonged occupational exposure to all PCB congeners, including the same individual PCB congeners selected for analysis by De Roos et al. (2005) and Engel et al. (2007a). While De Roos et al. (2005) acknowledge the possibility of chance associations due to multiple comparisons, they do not discuss their findings in the context of the lack of similar findings

in occupational studies. Engel et al. (2007a), however, acknowledge the discrepancy between the lack of findings in occupationally exposed cohorts and the associations reported as a consequence of environmental exposures in the general population, suggesting that this needs further exploration before conclusions can be drawn. Finally, the suggestion that PCB exposure closer to disease onset may be more etiologically important than exposure more distant from disease onset, is not supported by the occupational cohort data. If this hypothesis were correct, the initial studies reported by Brown (1981) and Bertazzi et al. (1981) should have detected this 'early onset' effect, but neither study reported such an effect. This hypothesis is also inconsistent with the fact that there is a latency period between the onset of exposure and cancer induction. Therefore, cancer latency should be longer at lower exposure and certainly greater than 1–2 years.

All studies suggesting an association between environmental blood levels of PCBs and an increased risk of NHL were reviewed by Engel et al. (2007b). This review noted the contrast between these studies and the occupational cohort mortality studies that have shown no association between exposure to PCBs and increased risk of NHL. The authors also noted that risk of NHL (in the environmental exposure studies) is elevated primarily in the time period closest to sample collection and disease diagnosis suggesting consistency with other established risk factors for NHL (i.e. intentional clinical immunosuppression following organ transplants and HIV/AIDS). However, there is no evidence, and indeed none is offered by Engel et al. (2007b), that exposure to PCBs (particularly at background levels) induces clinical immunosuppression comparable to that produced by immunosuppressive drugs or HIV/AIDS. Furthermore, comprehensive reviews of PCB immunotoxicity do not document the type of immunosuppression known to be associated with increased risk of NHL (ATSDR 2000). If PCBs were capable of producing this degree of immunosuppression, it should have been observed in the numerous studies on PCB-exposed workers.

Engel et al. (2007b) also acknowledge the possibility that PCB levels measured in the blood of individuals diagnosed with NHL may reflect not only cumulative environmental exposure, but also endogenous processes that might affect storage, dilution, or elimination. However, on this key point Engel et al. (2007b) acknowledge neither the growing body of evidence on gene variants of the types likely to minimally affect PCB metabolism and thereby background serum concentrations nor the association between additional gene variants and risk of NHL, some of which could also affect PCB metabolism and serum concentrations, as described above.

Finally, as previously noted, there is no evidence that occupational exposure to PCBs is associated with increased risk of NHL. Table 2 summarizes the available occupational studies of PCB-exposed workers. While it is difficult to directly compare all studies because of the manner in which data on various lymphohematopoietic malignancies

are reported (i.e. ICD codes), it is clear that occupational exposure to PCBs is not associated with increased mortality from NHL or with lymphohematopoietic malignancy in general. If the results reported by Engel et al. (2007a) are attributable to immunosuppression from background PCB levels in blood leading to the development of NHL, one might logically expect to see much larger effects from PCB blood levels—effects approximately 100 times greater. The conspicuous lack of such effects at substantially greater exposure levels suggests that PCBs are not etiologically linked to NHL.

The hypothesis that either Σ PCB or certain PCB congeners may contribute to increased NHL risk cannot be reconciled with the fact that much greater occupational exposures to Σ PCB or the same individual congeners have not been demonstrated to lead to an increased risk of NHL. In addition, the large study by Cocco et al. (2000), demonstrating no association between increased risk of NHL and Σ PCB, individual congeners, or groupings of congeners, adds to the WoE suggesting that PCBs have no role in NHL etiology. There also seems to be an unexplained inconsistency in the associations with individual PCB congeners, with De Roos et al. (2005) reporting significant associations between and trends with NHL and PCB 156, 180, and 194, Engel et al. (2007a) reporting significant associations and trends for PCB 118, 138, and 153, and Cocco et al. (2000) reporting no associations with any of these congeners. This would suggest that factors other than a causal association (e.g. metabolic differences between different study populations leading to non-causal differential serum concentrations of PCB congeners) are a more likely explanation for the reported findings. In other words, the findings in all of the studies reporting significant associations between background levels of different PCB congeners and increased risk of disease are most plausibly explained as resulting from NHL rather than causing it. Consequently, at present, the WoE suggests that PCBs are not a risk factor for NHL. Finally, since the effects of different congeners vary among the studies, the association between NHL and specific congeners may have occurred by chance.

New occupational-exposure cohort mortality studies since 2003

The studies reviewed below were all published in or after 2003, most of them occupational mortality studies. Following a presentation of the results of each study, a comment is presented if issues exist pertaining to interpretation of the data in the context of a WoE evaluation. It should be noted that these workers had much higher PCB exposures than the general population, as they produced capacitors and transformers that were filled with PCBs from about 1938, 1946, and 1951 to 1977 in the different plants studied. No exposure information is available for the workers from these plants in the early years, since analytical methods for PCB measurements were not available until the late 1960s. For example, in several plants, PCB area and personal air levels

in 1975 ranged 227–1,500 $\mu\text{g}/\text{m}^3$, while in 1977, when PCBs were being phased out, levels had dropped to 170–576 $\mu\text{g}/\text{m}^3$, with air levels of 3–50 $\mu\text{g}/\text{m}^3$ in areas where PCBs were not used. Reductions in air concentrations resulted after the filling operation of capacitor canisters had been automated and ventilation systems had been improved (Kimbrough et al., 2003). Similar air levels were also found in other plants studied (Brown and Jones, 1981). Wolfe et al. (1982) reported in 290 self-selected employees PCBs serum levels on a wet-weight basis that ranged from 6 ng/mL to 2,530 ng/mL (ppb) for the lower chlorinated congeners and from 1 ng/mL to 546 ng/mL for the higher chlorinated PCB congeners, whereas the general population had average PCB serum levels of 5–7 ng/mL. Lawton et al. (1985a, 1985b) found similar high levels of serum PCBs in a cohort of 190 workers. Since these studies were performed when PCBs were being phased out, it is reasonable to assume that earlier PCB levels were even higher.

Charles et al. (2003)

Charles et al. (2003) conducted a mortality study to investigate an association between occupational exposure to electromagnetic fields or PCBs and prostate cancer among US electric-utility workers. As part of the rationale for this study, the authors note that PCBs are among the environmental factors that have been suggested as possible causes of prostate cancer, although no relevant citations to any literature are provided. While the hypothetical etiological role of melatonin is mentioned, no relevant data (e.g. either from occupational mortality studies or animal studies) are provided suggesting that PCBs might play a plausible etiological role in the development of prostate cancer.

Participants were current and former employees of five large US electricity companies. Data on participants had been collected during 1987–1994, with mortality of the cohort followed up to 1988. This nested case-control study consisted of 387 cases of prostate cancer and 5 controls for each case. PCB exposure was estimated based on an analysis of job/exposure potential by a panel of industrial hygienists and others familiar with the use of PCBs in the electric utility industry—actual PCB measurements were not taken. While workers categorized in the highest 10% of electromagnetic-field exposure were twice as likely to die from prostate cancer as those exposed to electromagnetic fields at lower levels, the OR for PCB exposure and prostate-cancer mortality was not significant (OR = 1.47, 95%CI 0.97–2.24) after adjustment for suspected confounding factors. When exposure to PCBs was stratified according to cumulative exposure, there was no significant association with prostate cancer mortality even at the highest exposure level (i.e. >2800 h, OR = 1.16, 95%CI 0.78–1.74). There was also no significant increase in prostate cancer after a 5-year lag period at the highest total PCB exposure (OR = 1.14, 95%CI 0.76–1.71). Finally, as noted by the authors, “several studies have investigated or reviewed the incidence of other cancers in workers exposed to PCBs, and our literature review

found no consistent evidence that occupational exposure to PCBs was related to an increase in mortality from one or more cancers”.

Mallin et al. (2004)

This was a mortality study of 2,885 white workers employed between 1944 and 1977 at an electrical capacitor manufacturing plant where PCBs and chlorinated naphthalenes were used as dielectric fluids and various other chemicals were also used. Because PCBs were not used at this plant between 1944 and 1952, there was substantial exposure to chlorinated naphthalenes alone for 8 years and somewhat lesser exposure to these chemicals through to 1977. Since there were no measurement of PCB or chlorinated-naphthalene levels in the plant, it is not possible to associate findings exclusively with either group of chemicals. It is important to note that 20% of the cohort worked only 3 months or less at this facility between 1944 and 1977; an additional 30% of the cohort worked at the facility for only 60–90 days during this period. Consequently, fully 50% of the entire cohort worked at this facility for significantly less than 1 year. Additionally, 32% of the entire cohort (19% of men and 40% of women) worked at this facility before PCBs were introduced. Moreover, as noted by the authors “males were more likely to have been exposed to PCBs than females, and females were more likely to have been exposed to chlorinated naphthalenes than males”.

After adjustment for age and gender, SMRs for total mortality and all-cancer mortality were similar to expected rates for both men and women. For women, the only significant finding in the total cohort was for liver and biliary cancer (SMR = 2.27, 95%CI 1.04–4.31). In women employed 10 or more years, there was a significant increase in liver and biliary cancer (based on four cases; SMR = 6.2, 95%CI 1.70–15.92). Intestinal cancer was significantly elevated in women employed for 5–9 years (SMR = 3.69, 95%CI 1.19–8.62), but not 10 or more years. In men, stomach cancer (SMR = 2.2, 95%CI 1.03–4.27) and thyroid cancer (SMR = 15.2, 95%CI 3.14–44.50) were significantly elevated in the total cohort, although there were no significant effects on stomach-cancer when analyzed by duration of exposure. When analyzed by duration of employment, liver and biliary cancer in men (based on three cases) was significantly increased for 1–4 years’ employment (SMR = 6.02, 95%CI 1.24–17.59) but not for 5–9 years’ or >10 years’ employment. Consequently, there was no evidence for a significant exposure–response mortality trend for stomach, liver and biliary, or intestinal cancer in either women or men in the cohort.

A separate analysis was conducted on a subset of workers who worked anytime during 1952–1977 or 5 or more years during 1952–1977, which is the time period that PCBs were used in this facility (even though many of these workers began work at this facility well before 1952). There was a significant increase in stomach cancer (SMR = 2.82, 95%CI 1.13–5.80) in women who worked any time within 1952–1977 and intestinal cancer (SMR = 2.25,

95%CI 1.03–4.27) and liver and biliary cancer (SMR = 5.57, 95%CI 1.52–14.25) in women who worked 5 or more years in 1952–1977. However, it is important to note that most of the workers in this sub-analysis were also exposed to chlorinated naphthalenes, with women far more likely to have been exposed than men. For example, since at least four of the five cases of liver/biliary cancer in this sub-cohort were exposed to chlorinated naphthalenes prior to the introduction of PCBs, the meaning of this association is uncertain.

Comment

While data were analyzed and presented on the basis of 5 or more years' employment during 1952–1977, it seems that many of, or perhaps all, the cancer cases in this study were individuals employed prior to 1952—that is, during the time when chlorinated naphthalenes were the only dielectric fluid used. Consequently, it is not possible to ascertain whether findings reported from 1952 to 1977 could have been attributable to exposures prior to 1952. For example, with respect to liver and biliary cancer in women, of the nine cases, four worked at this facility for 60 days or less, thus undermining an association with a chronic occupational exposure at this facility. Additionally, of the nine cases, all but one worked at the facility during the time when chlorinated naphthalenes were in use. Chlorinated naphthalenes have been associated with substantial hepatic toxicity, including cirrhosis of the liver (a recognized precursor for liver cancer) in both men and women (World Health Organisation [WHO], 2001), and cirrhosis was significantly more common in men in the total cohort. Therefore, it is not possible to conclude that any of the effects reported were due to PCBs alone, chlorinated naphthalenes alone, or a combination of these or other chemicals. Given the documented hepatotoxicity of chlorinated naphthalenes, it is not possible to rule out a possible etiologic role in the increased liver and biliary cancer in women. It should also be noted that exposure to chlorinated naphthalenes has been associated with increased mortality from cancers of the stomach, rectum, trachea, esophagus, bronchus, and lung after relatively short exposure to these compounds for most of the cohort (Ward et al., 1994). Because of the mixed nature of the exposures in the Mallin et al. (2004) study (particularly to chlorinated naphthalenes during 1944–1952), it is impossible to attribute the findings exclusively to PCBs. Consequently, the strength of the associations reported in this study is undermined by probable confounding from exposure to other chemicals with recognized hepatotoxicity. However, even with the confounding due to the presence and probable previous exposure to chlorinated naphthalenes, the lack of a significant exposure–response trend for any of the reported cancers (i.e. stomach, liver and biliary, or intestinal) in either women or men in the cohort undermines an association with any exposure.

Finally, the probable confounding by substantial exposures to chlorinated naphthalenes in Mallin et al. (2004) makes it impossible to determine the extent to which PCBs

might have played an etiologic role in the reported results. While the authors describe the results of a small 1994 study on PCB serum levels in 60 former workers, there is no discussion of or any attempt to characterize potential exposure to or effects from chlorinated naphthalenes. Since 32% of the cohort (i.e. 918 employees) worked at this facility in 1944–1951, with exposure exclusively to chlorinated naphthalenes, the mortality experience of these workers would have permitted a determination of potential effects without confounding by simultaneous exposure to PCBs. The authors missed the opportunity to evaluate this confounder and it is not known why this was not done, as there are many cohort studies with far less than 918 individuals, particularly since the average latency in these workers was on the order of 40–50 years.

Prince et al. (2006a, 2006b)

Two overlapping studies by Prince et al. (2006a, 2006b) are follow-ups of cohorts from two electrical capacitor plants in New York (Plant 1) and one in Massachusetts (Plant 2) in the US. Workers from these plants were studied by Brown and Jones (1981) and Brown (1987). Plant 1 workers were also studied by Kimbrough et al. (1999, 2003) in separate follow-ups. The Prince et al. studies are reviewed separately below, followed by a comment on their reported findings.

As reported by Brown and Jones (1981), excess mortality (in men and women combined) was observed for rectal cancer (SMR = 336, 95%CI 92–860) and liver and biliary cancer (SMR = 280, 95%CI 58–820), although neither finding was statistically significant. The only statistically significant finding occurred in women (based on three cases) from Plant 2 for rectal cancer (SMR = 336, $p < 0.05$). In the follow-up study (Brown, 1987), the total-cohort SMR for rectal cancers decreased from 336 to 211, and although the SMR for rectal cancer in women at Plant 2 remained higher than at Plant 1, the difference from normal values was no longer statistically significant. However, there was a significant excess when liver, biliary, and gall-bladder cancers were grouped together, although one case was metastatic disease and should not have been counted as a primary liver cancer. These studies are reviewed in detail in Golden et al. (2003).

In the study by Prince et al. (2006a), mortality was updated through to 1998 for 2,572 workers. These workers were employed for at least 90 days in electrical-capacitor manufacturing at Plant 1 and 2 and were selected because they held jobs identified as having the highest and most direct exposure to PCBs. These workers had been studied earlier by Brown and Jones (1981) and Brown (1987). There was a significant excess in the total cohort (Plants 1 and 2 combined) when liver, biliary, and gall-bladder cancers were grouped together (SMR = 2.11, 95%CI 1.05–3.77), but rectal cancer was not significantly increased (SMR = 1.47; 95%CI 0.54–3.21). One of the liver cancers of a female worker in Plant 2 was metastatic disease rather than a primary liver cancer (Brown, 1987). The only other significant

finding was in women from both plants combined, where mortality from intestinal cancer was significantly higher than normal (SMR=1.89, 95%CI 1.21–2.82). Also of interest was the finding of a statistically significant decrease in breast-cancer mortality in the total cohort (SMR=0.59, 95%CI 0.33–0.98). Three duration-of-employment groupings were used as a proxy for exposure to permit comparisons with results from previous studies of this cohort (i.e. employment for <5, 5–9, and >10 years). Cancer mortality was not associated with duration of employment for any of the reported increases noted above or for breast or prostate cancer, myeloma, or NHL.

Prince et al. (2006b) is a much larger cohort mortality study of 14,458 workers who had worked ≥ 90 days at Plants 1 or 2. Estimated cumulative PCB exposure was assessed using a semi-quantitative job–exposure matrix. Plant-specific PCB air-concentration data were used to assign values to the combined qualitative inhalation and dermal exposure ratings (high, medium, low, background). In the total cohort, no cancers of *a priori* interest (i.e. all cancers, cancer of the liver, intestine, stomach, breast, prostate, brain, melanoma or NHL) were significantly elevated. However, there was a statistically significant increase in intestinal cancer mortality in women (SMR=1.31, 95%CI 1.02–1.66), and a statistically significant decrease in mortality from cancers of the trachea, bronchus, and lung in men (SMR=0.78, 95%CI –0.65 to 0.93). There was also a significant increase in myeloma mortality in all workers (SMR=1.85, 95%CI 1.23–2.67), in men (SMR=2.31, 95%CI 1.32–3.76), and in all Plant 1 workers (SMR=2.02, 95%CI 1.13–3.34).

When the data were analyzed by internal cumulative exposures (i.e. exposure–response for no lagging, 10-year lagging, and 20-year lagging) the trends for no lag and 10 year lag were statistically significant for total cancers and stomach cancer in men. There was also a significant trend with no lag for “other/unspecified parts of the uterus” and significant trends for no lag, 10-year lag, and 20-year lag for prostate cancer. For cancer of the liver and biliary passages or gall-bladder there was a significant exposure–response trend with a 20-year lag, but not with no lag or a 10-year lag. There were no significant exposure–response trends for cancer of the intestine, rectum, breast, brain, melanoma, myeloma, or NHL.

Comment

In the introductions of both of the Prince et al. studies, which are clearly focused on occupational exposure and mortality risks, the authors describe the goals of the studies by citing previously reported mortality excesses for a variety of cancers, either in these cohorts or in cohorts from other studies. In particular they note “other *a priori* outcomes of interest”, citing examples that either were not confirmed in follow-up studies (none of which were cited) or had never been reported in an occupational-exposure study. For example, they noted increased all-cancer mortality by citing Bertazzi et al. (1987), but omitted Tironi et al. (1996), who did not confirm this in a follow-up study of

the same cohort. They noted NHL, citing two non-occupational incidence studies by Rothman et al. (1997) and Hardell et al. (2001), even though NHL has never been significantly elevated in an occupational mortality study, and breast cancer, citing a single, largely irrelevant incidence study (Falck et al., 1992), while ignoring the fact that breast-cancer mortality has never been significantly elevated in any occupational cohort study and in fact was found to be significantly decreased in Prince et al. (2006a).

On the basis of 11 cases (some of which may have been metastases), mortality from liver, biliary, and gall-bladder cancers (as a group) was found to be significantly elevated in the total cohort in Prince et al. (2006a), but there was no exposure–response trend. In Prince et al. (2006b), on the basis of 21 cases (some of which may have been metastases), there was no significant elevation in mortality in the total cohort, although a significant trend with a 20-year lag was found. As detailed in Golden et al. (2003), there is no biological basis for grouping cancers of the liver, biliary passages, and gall bladder together, given that each has different etiologies and risk factors (DeVita et al., 1993). In agreement with this interpretation, it is noteworthy that in the International Agency for Research on Cancer (IARC, 2000) publication on the pathology of digestive system tumors, tumors of the liver and intrahepatic bile ducts are addressed in one chapter, while tumors of the gall-bladder and extrahepatic bile ducts are considered in a different chapter. It should also be noted that Brown (1987; Table 8) provided details of the liver or gall-bladder and biliary-tract cancer deaths on the basis of an analysis of death certificates and pathology reports, revealing that some of the cancers had metastasized from other sites. Given the uncertainty surrounding this issue, it is not unreasonable to expect that Prince et al. (2006a, 2006b) would have discussed this or conducted a sensitivity analysis similar to what was done by many of the same authors for brain cancer (e.g. Ruder et al., 2006). This could be important if the same proportion of the cases reported by Brown (1987) were questionable as to their origin in the liver, as in the present studies. As noted by the ATSDR (2000), if the metastatic liver cancer from Brown (1987) is not included in the analysis, the SMR for the combined liver–biliary–gall-bladder cancers in the whole cohort is no longer statistically significant. Finally, as acknowledged by Prince et al. (2006b), ethnic differences in Plant 2 as a consequence of a large population of workers of Cape Verdean and Portuguese descent (who have a recognized increased risk of liver cancer) may further confound any potential association with PCBs.

There also seems to be a disparity between the two studies by Prince et al. (2006a, 2006b). In the smaller study of the most highly exposed workers, when the SMRs for selected causes of death were stratified by duration of employment (i.e. a proxy for exposure), none of the trends for any cancer were statistically significant, including all cancers (as a group), cancer of the intestines, liver, biliary passages, or gall-bladder, breast, prostate, NHL, and myeloma. However, in the larger cohort study, there was a significant

mortality trend for all cancers and stomach cancer in men with no lag and 10-year lag, for liver, biliary-tract, and gall-bladder cancer with 20-year lag, and for prostate cancer with no lag, 10-year lag, and 20-year lag. Since the subset of workers in the smaller study (Prince et al., 2006a) was the most highly exposed, it is difficult to reconcile these differences even after recognizing the greater statistical power of the larger study. Since mortality from all cancers and liver, biliary, and gall-bladder, prostate, or stomach cancer were not elevated in the cohort, it is puzzling as to how these findings should be interpreted. One possible explanation is the conundrum of multiple comparisons. For example, in Table 3, there are three lagged analyses for 15 cancer outcomes with three exposure categories compared with the reference group for each relative risk (RR) estimate. Excluding the trend tests, this means that there are $3 \times 15 \times 3$ comparisons in this table (a total of 135 RR estimates), which, on the basis of a 95%CI approach, means that approximately seven estimates should be significant. Setting aside the two significant trends for all cancers combined (since there is no biologically plausible basis for assuming that exposure to PCBs would be a cause of every kind of cancer), there are seven significant trends. In addition, while the RR estimates based on the internal analysis in Prince et al. (2006b) show a trend for increased cancer mortality with exposure, the external analysis shows no increase in prostate-cancer mortality. Since both of these findings can't be correct, and given the fact that no other studies (including Prince et al., 2006a) have corroborated this finding, it seems reasonable to conclude that prostate cancer is not a consequence of exposure to PCBs.

In their conclusion, Prince et al. (2006a) note that "Our results are consistent with previous studies of this cohort which also reported significantly elevated mortality from liver cancers which was not found to be associated with length of employment." However, while liver, biliary, and gall-bladder cancer was questionably elevated (see above) in the Plant 2 cohort, as reported by Brown (1987), it has never been elevated in the Plant 1 cohort, despite several follow-up studies (e.g. Kimbrough et al., 1999, 2003). With respect to the significant finding of increased levels of intestinal cancer in women in the total cohort, as noted by Prince et al. (2006a), this finding was probably due to intestinal-cancer deaths among women at Plant 2 in the updated time period, and may have been influenced by the known increased incidence for intestinal cancer in the Northeastern portion of the US, which is also greatly influenced by ethnicity (Howe et al., 2001; Schottenfeld et al., 1996). In addition, neither of the Prince et al. studies (2006a or 2006b) reported a significant exposure-response trend for intestinal cancer. As this is the only report of significantly increased mortality from intestinal cancer in the total cohort in any of the numerous studies of occupationally exposed workers, and was not significant when stratified by either duration of employment or cumulative exposure, it is not plausible that this isolated finding was a consequence of exposure to PCBs.

Ruder et al. (2006)

The study by Ruder et al. (2006) is an update of Sinks et al. (1992), which reported significantly increased mortality from melanoma and non-significant increases in brain cancer. The present study added 14 years of latency to the cohort of 3,643 capacitor workers (833 women and 2,706 men). In the overall cohort, the only significant finding was increased mortality from melanoma (SMR=2.43, 95%CI 1.1-4.6). However, there was no evidence of a dose-response relationship for melanoma, with the highest mortality in the lowest tertile of exposure (SMR=3.72, 95%CI 1.2-8.7) and no significant excess in the middle and highest tertiles. Similarly, when analyzed by estimated cumulative exposure to PCBs, only in the lowest cumulative-exposure group (<11,000unit/days) was there a significant increase (SMR=3.72, 95%CI 1.2-8.7). Cumulative exposure in the middle (11,000-89,999unit/days) and highest (>90,000unit/days) groups was not significantly associated with increased mortality from melanoma.

It should also be noted that one of the cases of melanoma was diagnosed two months prior to employment at this facility and one case originated in the gall-bladder and should not have been coded as a skin tumor. Exclusion of these cases could have changed the mortality figures (Sinks et al., 1989). In addition, there was no information on exposure to sunlight, the major risk factor for this disease.

On the basis of 12 cases, brain-cancer mortality was not found to be significantly elevated in the cohort (SMR= 1.91, 95%CI 1.0-3.3). A sensitivity analysis of brain-cancer deaths indicated that two cases were likely to be metastases, and that, after omitting these two deaths, the already non-significant risk was further decreased (SMR=1.59, 95%CI 0.8-2.9). No other cancers, including lymphatic and hematopoietic (including NHL), rectal, pancreatic, prostate, breast, and liver, biliary-tract, or gall-bladder, were significantly elevated in this cohort. As noted by the authors, "...melanoma mortality was not associated with estimated cumulative PCB exposure, and for brain cancer, the association between mortality and estimated PCB cumulative exposure did not demonstrate a clear dose-response relationship".

Yassi et al. (2003)

This study by Yassi et al. (2003), while not mentioning PCBs, is interesting nevertheless, as it is a follow-up of a previous study (Yassi et al., 1994) of the same cohort, which did consider PCB exposure. Yassi et al. (2003) is an extension of the same authors' analysis of cancer incidence and mortality in a cohort of 2,222 men who worked at a transformer-manufacturing plant with extensive use of mineral-oil transformer fluid and minimal exposure to PCBs. In the first study, despite the fact that exposure was predominantly to mineral oils, it was concluded that PCBs played some etiological role in the significantly increased mortality from pancreatic cancer observed in the study. This study had numerous limitations, which are described in detail in

Golden et al. (2003). As in the previous study, there was a statistically significant increased risk of pancreatic cancer. However, unlike in the previous study, Yassi et al. (2003) makes no mention of PCBs as playing any etiological role in the development of pancreatic cancer or any other cancers. Instead, as noted by the authors, "This study contributes further evidence to the growing body of literature indicating the carcinogenic properties of mineral oils used in occupational settings, in particular those used prior to 1970s." As Yassi et al. (1994) was the only study that implied an association between PCB exposure and increased risk of pancreatic cancer, the determination by Yassi et al. (2003) that PCBs played no role in disease etiology is further confirmation that pancreatic cancer is not causally linked with exposure to PCBs.

Pavuk et al. (2004)

In this population-based, cross-sectional (i.e. ecological) study, Pavuk et al. (2004) measured serum levels of 15 PCB congeners and three organochlorine pesticides (DDT, DDE, and HCB) in residents of two districts in eastern Slovakia. The population considered 'exposed' lived in an area with extensive environmental contamination from a former PCB production plant. This population was compared with a population matched on the basis of geography, but with low serum levels of the compounds studied. The age-adjusted geometric means for the sum of 15 measured PCB congeners (as well as DDT and DDE) were statistically significantly higher in subjects from the exposed area versus the background area.

The study compared cancer incidence in these two areas from 1985 to 1994. Standardized incidence ratios and 95% CIs for each area and cancer type were calculated. In exposed (but not background-area) men, there was a significant increase in the incidence of cancer of the tongue, pharynx, and lung. In exposed (but not background-area) women, there was a significant increase in the incidence of cancer of the lip and stomach. In background (but not exposed) women, there was a significant increase in the incidence of cancer of the kidney and thyroid.

The authors speculate that their results "...raise the possibility that high environmental exposure to organochlorines in the [exposed] district may be associated with higher rates of certain cancers, particularly stomach and lung cancer". However, it is well established that ecologic studies, by their very nature, are incapable of establishing causal associations (Gordis, 2000; Rothman and Greenland, 1998). Given the large number of carefully conducted cohort studies (particularly follow-up studies) on occupationally exposed populations, it would be inappropriate to use the results of Pavuk et al. (2003) in a WoE evaluation. At best, ecologic studies are hypothesis-generating studies. The fact that none of the cancers reported by Pavuk et al. (2003; i.e. tongue, pharynx, and lung in men and lip and stomach in women) have ever been reported in the occupational cohort studies suggests that they are most likely not etiologically associated with exposure to PCBs. Finally,

it may be noteworthy that most of the cancers reported by Pavuk et al. (2003) have been associated with smoking and alcohol consumption. While a superficial analysis suggests that both populations were similar in this regard, ecologic studies cannot account for these potential confounding factors.

Bosetti et al. (2003; review)

As noted in Golden et al. (2003), as well as in the ATSDR (1999), numerous independent reviews of the PCB occupational cohort studies have concluded that the WoE does not support a causal association between exposure to PCBs and cancer. Bosetti et al. (2003) is another such review that reaches a similar conclusion. This review was conducted with support from the Italian Association for Cancer Research and the Italian League Against Cancer. The review considers many of the studies summarized in Golden et al. (2003) and relies on a methodology similar to that endorsed by the ATSDR (2000): summing the observed and expected mortality figures from studies which report effects on liver, gall-bladder, and biliary-tract, lymphatic and hematopoietic, and breast cancers, and all cancers combined. The authors came to the following conclusions: "Overall, no excess for all cancer mortality was observed in the six studies providing information (573 cancer deaths versus 630.4 expected, corresponding to a standardized mortality ratio (SMR) of 91). Among neoplasms potentially related to PCB exposure, there were 12 deaths from liver cancer compared with 9.5 expected (SMR = 126). No excess was found for cancers of the breast (40 observed versus 47.4 expected, SMR = 84) and of the lymphatic and haematopoietic system (51 observed versus 53.2 expected, SMR = 96). Therefore, studies on occupational exposure to PCBs do not show any excess in all cancer mortality, or in mortality for specific cancer sites of interest."

Although Bosetti et al. (2003) obviously could not consider the relevant post-2003 studies, it nevertheless adds to the list of independent analyses of the available data by suggesting that occupational exposure to PCBs is not etiologically associated with increased risk of cancer. While relying on essentially the same methodology as used by the ATSDR (2000), Bosetti et al. (2003) considered all available data in support of their conclusions, while the ATSDR (2000) did not.

Weight of evidence evaluation for occupational cohort mortality studies published after 2003 (Excluding breast-cancer related studies)

As detailed by Golden et al. (2003), the WoE, considering the mortality studies published at that time, did not support a causal association between exposure to PCBs and increased risk of cancer. This conclusion was based on a detailed analysis of the extent to which each of the causation criteria were satisfied by all the available data on PCBs at that time (see Table 2 in Golden et al., 2003).

As described above, the six occupational mortality studies published since that time are by Charles et al. (2003), Prince et al. (2006a, 2006b), Ruder et al. (2006), Yassi et al. (2003), and Mallin et al. (2004). Only Mallin et al. (2004) studied a cohort not previously investigated. In addition, there are several incidence studies that have reported associations between PCBs and several types of cancer. As discussed above, the incidence studies do not change the WoE conclusion reached in 2003: that PCBs are not causally associated with increased risk of cancer (prostate, testicular, intestine, or NHL). The lack of causality in these studies is underscored by the fact that none of the cancers reported in these incidence studies have been found to be significantly elevated in the occupational cohort mortality studies. The following narrative considers whether the six most recent mortality studies are consistent with the conclusion reached in 2003, or if that conclusion should be modified.

As discussed above, the findings in the study by Mallin et al. (2003) are substantially confounded by both prior exposure to chlorinated naphthalenes and simultaneous exposure to chlorinated naphthalenes and PCBs. Thus, the increase in cancer mortality reported is difficult, if not impossible, to associate with PCB exposure. The principal findings of this study—that liver and biliary cancer and digestive-organ cancer in women and stomach cancer in men are increased, with no evidence of an exposure–response relationship—are difficult to compare with those of other studies. Particularly with respect to liver and biliary cancer, the probable heavy exposure to chlorinated naphthalenes cannot be ruled out as either a contributory or sole causal factor, given that chlorinated naphthalenes have been associated with substantial hepatic toxicity, including cirrhosis of the liver (a recognized precursor for liver cancer; WHO, 2001). Indeed, it seems that many, or perhaps all, of the cancer cases in this study occurred in individuals employed prior to 1952 (i.e. during the time when chlorinated naphthalenes were the only dielectric fluid used). In addition, of the nine cases of liver or biliary cancer in women, four were employed for two quarters or less, making it unlikely that exposure to chlorinated naphthalenes or PCBs was etiologically involved. As a result of this confounding, the results from the study by Mallin et al. (2003) cannot contribute meaningfully to the overall WoE and, therefore, are not used for this purpose.

The study by Ruder et al. (2006) demonstrated no statistically significant increases in mortality from liver, biliary, or gall-bladder, intestine, stomach, prostate, or brain cancer in the capacitor-worker cohort. While there was a significant increase in melanoma mortality in the lowest tertile of exposure, there was no evidence of an exposure–response trend. This finding, together with the fact that one melanoma was diagnosed pre-employment and one originated in the gall bladder, and also because there was no information on potential exposure to sunlight, suggests that there is no causal association between exposure to PCBs and increased risk of melanoma or any other cancer.

The two studies by Prince et al. (2006a, 2006b) are perhaps the most difficult to reconcile with the findings from previous studies particularly with respect to liver, biliary, and gall-bladder cancer mortality. While this grouping of cancers was significantly elevated in Prince et al.'s (2006a) total cohort, consisting of 2,572 of the most heavily exposed workers, there was no exposure–response trend, thereby undermining the likelihood of a dose–response relationship. By contrast, in the expanded cohort of 14,458 workers, there was no significant increase in the total cohort, but a significant exposure–response trend with 20-year lag. However, the liver, biliary, and gall-bladder findings are based on only 21 cases in the expanded cohort, and there was no consideration by Prince et al. (2006b) of the likelihood that some of these cases may have been metastatic from other sites. Consequently, this finding is questionable as to an association with exposure to PCBs. It is noteworthy that, when the ATSDR (2000) eliminated the metastatic liver, biliary, and gall-bladder cases from the SMR analysis, the findings were no longer significant. Because Prince et al. (2006a, 2006b) was an update of Brown (1987), which provided a detailed description of the liver, gall-bladder and biliary-tract cancer deaths (i.e. dates and length of employment, cause of death notation on death certificate and hospital or pathology report) in the cohort, it is not unreasonable to expect that similar care would have been taken to address this key issue in the updated study. While intestinal cancer was significantly increased in the Prince et al. (2006a) study in the most highly exposed female workers, there was no indication of an exposure–response relationship, thus undermining a possible causal association. Similarly, this cancer was significantly increased in women in the larger study (Prince et al., 2006b), but also with no evidence of an exposure–response trend, thereby also undermining a causal association. Because intestinal-cancer was not statistically significantly increased in Ruder et al.'s (2006) study or any previous studies of PCB-exposed workers, the WoE suggests that intestinal cancer is not associated with exposure to PCBs. Neither was prostate cancer significantly elevated in the most heavily exposed workers (Prince et al., 2006a) or in the expanded cohort (Prince et al., 2006b). The finding of a significant exposure–response trend in the later cohort is unexplained, particularly since no other study of PCB-exposed workers has reported increased mortality from prostate cancer. While the trend analysis, according to the authors, was corrected for age, information on how this was done was not provided. Consequently, despite this isolated finding, the WoE suggests that prostate cancer is not etiologically associated with exposure to PCBs.

The conclusion in 2003 was that the WoE did not support a causal association between exposure to PCBs and increased risk of cancer, and the findings from the six studies conducted subsequently do not change that conclusion. While liver, biliary, and gall-bladder cancer continues to be sporadically reported, there is uncertainty regarding

this grouping, as liver, biliary and gall-bladder cancer each has its own etiology and risk factors (DeVita et al., 1993), and as some proportion of these cases may be metastases rather than primary tumors. Of the six studies published in or after 2003, one (Mallin et al., 2004) is so confounded that the results are not useful for causal inference, another (Yassi et al., 2003) does not mention PCBs, and yet another (Ruder et al., 2006), while reporting an equivocal (i.e. no exposure-response relationship) mortality finding for melanoma, reported no significant increases in mortality from any other cancer. The results of the two studies by Prince et al. (2006a, 2006b) are inconsistent. In applying the causation criteria to the findings from all studies conducted to date, several conclusions, outlined below, can be reached.

Extent to which the causation criteria are fulfilled by the available data on PCBs

Consistency of the observed association

As noted by the EPA (2005), "An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality." On the whole, the cohort mortality data on PCB-exposed workers demonstrate a striking lack of consistency with respect to key findings, with seemingly random associations appearing and disappearing in different studies. With the large number of studies conducted to date on highly exposed worker cohorts, including many follow-up studies of the same cohorts, it is reasonable to expect that some consistency in the reported associations would have emerged if PCBs were causally related to increased cancer risk.

Strength of the observed association

As described by the EPA (2005), "The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. A modest risk, however, does not preclude a causal association and may reflect a lower level of exposure, an agent of lower potency, or a common disease with a high background level." For liver, biliary, and gall-bladder cancer mortality, the findings from the studies by Ruder et al. (2006) and Prince et al. (2006b) do not approach statistical significance (cohort SMRs of 0.51 and 0.89, respectively), whereas the mortality finding in the first study by Prince et al. (2006a) barely does (cohort SMR = 2.11, 95%CI 1.05–3.77). The likelihood that this association was influenced by the possible inclusion of metastatic cases also weakens this finding. Mortality from intestinal cancer in the total cohort was not significantly increased in the study by Ruder et al. (2006; SMR = 1.43), was clearly increased in women in the first study by Prince et al. (2006a; SMR = 1.89), and only just significantly increased in the second study Prince et al. (2006b; SMR = 1.31, 95%CI 1.02–1.66). No other mortality studies in PCB-exposed cohorts have reported this finding. For increases in stomach-cancer incidence, which was a weakly significant finding in the study by

Mallin et al. (2004; SMR = 2.25, 95%CI 1.03–4.27), which as noted above has been reported as associated with exposure to chlorinated naphthalenes, mortality from this cancer has not been reported as significantly increased in any other studies. For melanoma, other than the equivocal finding reported by Ruder et al. (2006; SMR = 3.72), no studies have reported a statistically significant finding. Prostate-cancer mortality was not significantly elevated in the total cohorts in either study by Prince et al. (2006a, 2006b; SMR = 1.14 and 1.04, respectively) or in any other studies. While multiple myeloma was significantly elevated in one of the studies by Prince et al. (2006b; SMR = 1.85) it did not approach significance in the other (Prince et al., 2006a; SMR = 2.11, 95%CI 0.84–4.34) and has not been reported in any other studies. It should also be noted that no specific chemical exposure (including PCBs) has been etiologically implicated as a risk factor for multiple myeloma. Overall, the elevated SMRs for specific cancers show a doubling at most, with most not achieving statistical significance, suggesting that occupational exposure to PCBs is not a risk factor for increased cancer mortality.

Specificity of the observed association

This criterion was originally intended to judge if one cause was associated with a single effect or disease; that is, that a finding from one study could be used to predict the outcome of other studies. As noted by the EPA (2005), "Based on our current understanding that many agents cause cancer at multiple sites, and many cancers have multiple causes, this is now considered one of the weaker guidelines for causality." However, because PCB exposure produces essentially only liver tumors in chronic bioassays (Mayes et al., 1998) with notable decreases in tumors at other sites, there is no biological basis for inferring that PCB exposure causes cancer at multiple sites in humans. Overall, the data do not support the notion that PCB exposure increases all-cancer mortality. Consequently, though a weaker guideline for causality, the seemingly random reports of different cancers in different cohorts, which typically disappear on follow-up, suggests that this criterion is not fulfilled by the available data.

Temporal relationship of the observed association

Clearly, substantial exposure to PCBs is known to have preceded the findings reported in the numerous occupational cohort studies. Indeed, the extensive follow-up of some cohorts (e.g. Bertazzi et al., 1981 and Tironi et al., 1996; Brown and Jones, 1981 and Kimbrough et al., 2003; Prince et al., 2006a and 2006b) attests to the study of temporal relationships over time. While this is "among the strongest criteria for an inference of causality", the failure to satisfy the other criteria undermines the weight that can be placed on the fulfillment of this criterion.

Biological gradient (Exposure-response relationship)

As noted by the EPA (2005), "A clear exposure-response relationship (e.g., increasing effects associated with greater

exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure (e.g., increasing effects observed following longer exposure times).” As described by Golden et al. (2003), there was no exposure–response relationship for any of the randomly occurring cancers in any of the occupational cohorts reported to that time. Subsequently, as described in this review, the results of six additional mortality studies have been published. The study by Mallin et al. (2004) is not considered, as exposure was confounded by previous exposure to chlorinated naphthalenes. Ruder et al. (2006) did not find a significant exposure–response relationship for all cancers, melanoma, or brain cancer (the only cancers assessed). Prince et al. (2006a), in >2,500 of the most heavily exposed workers, did not find a significant exposure–response relationship for all cancers, liver, biliary or gall-bladder cancer, or any other type of cancer including intestine, rectum, breast, and prostate cancer. By contrast, Prince et al. (2006b) reported a significant exposure–response trend for liver, biliary or gall-bladder cancer for no lag and 10-year lag, but not for 20-year lag. With respect to the reported exposure–response trend for liver and biliary cancer, this is not supported by the most recent follow-up of the Yucheng cohort. This poisoning incident involved simultaneous ingestion-based exposure to high levels of PCBs and PCDFs (polychlorinated dibenzofurans) from contaminated cooking oil. The spectrum of toxic effects that resulted from this exposure (as well as the Yusho poisoning incident) is generally acknowledged to be predominantly due to the PCDF components of this mixture, and not to PCBs. For example, when reviewing the data for an earlier PCB toxicological profile, the ATSDR (1997) stated that “The effects from these incidents are not reviewed in this profile because CDFs appear to be the main causal agent.” Additionally, the Japanese government has concluded that PCDFs, and not PCBs, as had been previously believed, were the causative agent responsible for the symptoms of the rice-oil poisoning incident, noting that “The Health, Labor and Welfare Ministry determined today that the cause of mass poisoning from cooking oil in the Kyushu region during the late 1960s to early 1970s was a type of dioxin contained in the products” (Japanese Health, Labor and Welfare Ministry, 2002). The 24-year follow-up study reported by Tsai et al. (2007) involved 1,823 Yucheng subjects. Liver and bile-duct cancer was not significantly increased (SMR = 0.7, 95%CI 0.3–1.4) and there was no indication of a mortality trend based on years since first exposure (i.e. latency). These data suggest that this exposure was not a risk factor for liver cancer.

For prostate cancer mortality, while not significant in the total cohort, there was a significant trend whether lagging for 0, 10 or 20 years, although this is the only study which has reported this finding. In addition, while age was corrected for according to the authors, it is uncertain if this procedure was adequately conducted. On the basis of the experience of one of the authors of this review article (RK), the mean age at death for all workers (other than those who died from prostate cancer) in Kimbrough et al. (2003)

was approximately 64 years, while the mean age of workers who died from prostate cancer was 74 years. There were no exposure–response trends across lag categories for stomach, intestine, rectum, breast, or brain cancers, melanoma, or myeloma. Taking into account all the reported findings (some of which are contradictory) on exposure–response relationships, the WoE suggests that this criterion has not been satisfied.

Biological plausibility and analogy

As noted by the EPA (2005), “An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms,” and “Similarly, information on mode of action for a chemical... can inform decisions regarding likely causality.” As stated in most of the occupational cohort mortality studies on PCB-exposed workers in which the grouping of liver, biliary, and gall-bladder cancers was reported as significantly elevated, the biological plausibility of the finding is hypothetically supported for liver cancer (but not gall-bladder cancer or cancers at any other sites) by the numerous animal studies showing increased liver tumors in PCB Aroclor-dosed rats (e.g. Mayes et al., 1998). This is a correct interpretation based on the clear qualitative similarities between animals and humans—for example, both accumulate PCBs, have the same xenobiotic receptors, such as arylhydrocarbon hydroxylase receptor, constitutive androstane receptor, and pregnane X receptor, and many similar MFO enzymes. However, the analogy breaks down when quantitative differences between animals and humans are considered. The recent determination of the probable mode of action (MOA) by which PCB Aroclors 1016, 1242, 1254, and 1260 promote increased liver tumors in male and female Sprague–Dawley rats now suggests that it is biologically implausible that occupational exposure to PCBs would produce even liver cancer in humans, much less cancer at any other site (Brown et al., 2007), because of the fact that liver tumors (predominantly in female rats) were only observed after tissue accumulation of Σ PCB far greater than any known human exposure had been achieved in the Aroclor-dosed animals. Furthermore, as reviewed below in regard to breast cancer, induction of the various MFOs, such as *CYP1A1*, ultimately responsible for PCB-promoted tumors in rats simply does not occur in humans, even at occupational-exposure levels. Moreover, *in vitro* data demonstrate that human liver cells are many orders of magnitude less responsive to Aroclor 1254-induced *CYP1A1* induction than rat liver cells (Silkworth et al. 2005). The fact that *CYP1A1* induction is the first key event in the MOA for PCB-promoted tumors in rats suggests that humans would not be susceptible to PCB-induced liver tumors. In addition, as documented in Brown et al. (2007) Aroclor-dosed animals showed significant decreases in several types of extrahepatic tumors including those of the pituitary, mammary gland, adrenals, prostate, and pancreas. On the basis of knowledge of PCB levels in occupationally exposed workers, there is no evidence that body

burdens sufficient to approach the PCB levels required to produce tumors in animals have ever been achieved in humans. For example, rats fed a diet containing 100 ppm PCB would receive a daily dose of PCBs of 4–5 mg/kg body weight, which would be equivalent to a daily dose of approximately 280–350 mg for a 70 kg human. The yearly equivalent human exposure would be between 102,000 and 127,000 mg/person. However, even during occupational exposure, humans receive daily PCB doses only in μ gram/kg. This further illustrates the biological implausibility that occupationally exposed humans would accumulate body burdens even remotely close to the PCB body burdens in rats that develop liver tumors. Consequently, on the basis of the recently elucidated mode of action of PCB-promoted tumors in rodents, it is quantitatively biologically implausible that PCBs would be carcinogenic in the human liver, or any other site in the human body.

There is also another important consideration pertaining to biological plausibility. Target-organ specificity is a key concept that must be addressed when assessing PCB mortality studies. Studies have shown time and again that human responses to exposures to carcinogens are consistent (i.e. of the same type or nature), although the magnitude of effect might vary among individuals or populations. There are no data suggesting that people with different levels of exposure to the same chemical will develop different types of cancers. It is well known that virtually all chemical carcinogens display striking target-organ specificity (e.g. cancer chemotherapy, aflatoxin, vinyl chloride, benzene, asbestos). This specificity is attributable to the fact that different tissues and organs have different metabolizing, detoxification, and DNA repair processes. Consequently, these organ-specific factors respond to carcinogen exposure in different ways. Carcinogen target-organ specificity, therefore, renders the striking lack of consistency for tumor types among PCB studies much more likely to be the result of random findings than of causal associations. Simply stated, there is no biologically plausible explanation for how PCBs could cause increases in the incidence of different kinds of cancer in different cohorts, or for why these chemicals would behave differently to other chemicals that have been causally associated with increases in the incidence of specific kinds of cancer. In corroboration of the above, even high-dose cancer bioassays have not shown that PCB Aroclors are capable of causing tumors in multiple target organs. In fact, as noted above, in the Mayes et al. (1998) study, PCBs were associated with increased incidence of liver tumors only, and with decreased incidence of tumors in other organs.

Breast cancer and environmental exposure to PCBs

While breast cancer was not the focus of the Golden et al. (2003) review, the findings of numerous breast-cancer studies were briefly summarized. These studies fall into several different categories. The early (generally pre-1994) studies

involved few cases of breast cancer, their results were subject to considerable chance variation, and often known risk factors for breast cancer were not taken into account. In addition, the data in these studies were derived from active cases of breast cancer, in which disease-induced weight loss may have contributed to spurious elevations of PCB levels in breast tissue and serum. Moreover, PCBs and other chlorinated compounds tend to have a longer half-life in persons with greater body mass (Brown and Lawton, 2001), so that studies in which body mass was not accounted for could have produced skewed results. Critical reviews of the literature available up until about 1994 have concluded that there is no association between environmental exposure to PCBs and increased risk of breast cancer (Key and Reeves, 1994; Adami et al., 1995).

Virtually none of the numerous large studies conducted subsequently detected a statistically significant increased risk of breast cancer associated with PCB exposure. Many of these studies were prospective in design, thereby eliminating the possible confounding effects of disease-related alterations in PCB serum levels. While a few studies did report a significant association between PCBs (or individual PCB congeners, see below) and breast cancer in some population subgroup (e.g. postmenopausal women who had never lactated), the results of these studies have largely not been replicated. In a comprehensive review of environmental risk factors and breast cancer, Laden and Hunter (1998) concluded that “In summary, most of the recent large studies have not found evidence of increased breast cancer risk associated with blood levels of DDE or total PCBs. The possibility that a positive association might be limited to women with particular reproductive characteristics [e.g., women who have never breast fed, as observed by Moysich] should be examined carefully in the large ongoing studies. Nevertheless, it appears that these environmental exposures are unlikely to be responsible for rising breast cancer rates”.

One of the largest studies, by Zheng et al. (2000), concluded that “...the results do not support the hypothesis that DDE and PCBs increase the risk of breast cancer as encountered through environmental exposure”. Likewise, Demers et al. (2000) concluded that “... taken together, results from six large epidemiological studies reported during the last 2 years, including our own, provide little indication that organochlorine exposure is a risk factor for [breast cancer]”. In another review, Laden et al. (2001) summarized the results of five of the largest studies, noting: “Combined evidence does not support an association of breast cancer risk with plasma/serum concentrations of PCBs or DDE. Exposure to these compounds, as measured in adult women, is unlikely to explain the high rates of breast cancer experienced in the northeastern United States”.

In addition, the IPCS published the comprehensive *Global Assessment of the State-of-the-Science of Endocrine Disruptors* (2002). This assessment considered the issue of endocrine-active compounds and the strength of the evidence that exposure to weakly estrogenic substances

might be etiologically associated with breast cancer in women. The emphasis was on weakly estrogenic organochlorine compounds such as PCBs and DDT. In assessing the likelihood that breast cancer might be associated with exposure to endocrine-active compounds, the IPCS (2002) concluded that “Although numerous human epidemiological studies have been conducted to determine whether environmental EDCs may contribute to an increased risk of breast cancer, the results remain inconclusive. Overall, the current scientific evidence (from human and animal studies) does not support a direct association between exposure to environmental EDCs and increased risk of breast cancer.”

Subsequent to the above-described studies, a number of additional studies have been published that address whether PCB exposure may be a potential risk factor for breast cancer. None of these studies demonstrated a significant association between serum Σ PCB levels and increased risk of breast cancer. However, several studies have reported significant associations between individual PCB congeners or specific genetic polymorphisms (e.g. *CYP1A1*) and increased risk of breast cancer. These studies are reviewed below.

Some of the more recent studies involved active cases of breast cancer. As noted above, these studies have been shown to be of questionable value compared with prospective studies. However, most of the more recent studies have been prospective in nature. These studies are briefly reviewed below. However, it is appropriate to address one key issue before turning to the studies. Most of the earlier studies sought associations between risk of breast cancer and body concentrations of total PCBs (i.e. Σ PCB). In some of the more recent studies, mainly case-control studies, the authors have sought associations between various outcomes (e.g. breast-cancer risk, estrogen-receptor status, survival) and concentrations of individual PCB congeners. Rubin et al. (2006) suggested that future research should consider the effects of individual PCB congeners, even while correctly noting that congener-specific effects can vary from estrogenic to anti-estrogenic effects. Seeking associations between breast cancer risk and individual PCB congener concentrations, rather than Σ PCB, is likely to generate results that are misleading and, frankly, useless. Suggesting that researchers use PCB congeners rather than Σ PCB as exposure metrics ignores a large body of data on receptor-mediated effects that demonstrates that competitive binding to the estrogen receptor by estrogenic (agonist) and anti-estrogenic (antagonist) substances determines the net effect. Because some PCB congeners exhibit estrogenic effects, while others exhibit anti-estrogenic effects, using Σ PCB as the exposure metric is the only way of ensuring that net effects are properly integrated and are representative of what humans are exposed to.

For example, several studies single out PCB 180 as a risk factor for breast (or other types of) cancer. However, PCB 180 has no known distinctive toxicological activity (and none is cited in studies in which this congener is suggested as having

a putative role in breast-cancer etiology), other than being highly resistant to MFO-mediated metabolism. Among the more persistent PCB congeners, the activity of PCB 180 toward the Ah receptor is less than that of PCB 126 or 156, and it does not have a toxicity-equivalency-factor value. If PCB 180 happens to correlate with some response, but PCB 156 or PCB 187 (both of which are almost as persistent as PCB 180) do not, it is likely that the correlation occurred either by chance or as a consequence of differential metabolism as described below in the section on PCBs as a risk factor for breast cancer through *CYP1A1* genetic polymorphisms. It should also be noted that numerous studies (e.g. Mayes et al., 1998) demonstrate that chronic exposure to PCB Aroclors produces a decreased incidence of mammary tumors in rats, which also suggests that the effect of the mixture (i.e. Σ PCB) is the proper metric.

Pavuk et al. (2003)

Pavuk et al. (2003) conducted a case-control study involving 24 active cases of breast cancer (diagnosed between 1997 and 1999) and 88 controls. This study was designed to investigate possible associations between PCBs, DDT, DDE, and HCB exposure and risk of breast cancer in an area of high environmental exposure in eastern Slovakia. Levels of 15 individual PCB congeners, DDE, DDT, and HCB were measured in the serum of the breast-cancer patients and population controls. Known risk factors for breast cancer were considered in the analysis. The median serum levels of Σ PCB were similar in cases and controls. When PCB congeners were divided into groupings of estrogenic, anti-estrogenic, and enzyme-inducer PCB congeners, median serum concentrations of all groupings were lower in cases than in controls. However, the risk of breast cancer decreased with increasing serum levels of all congeners and groupings. This study provides no support for an association between PCBs and increase risk of breast cancer.

Hoyer et al. (2000a)

In a study designed to investigate whether organochlorine exposure (i.e. PCBs, dieldrin, DDT, DDE, and HCB) had an effect on breast cancer survival, Hoyer et al. (2000a) examined 195 breast-cancer cases in which serum concentrations of these substances had been determined in 1976–1978 and 1981–1983. Known risk factors for breast cancer were considered in the analysis. There were no differences between the first and second measurements of serum organochlorine compounds and no effect of Σ PCB on tumor characteristics or survival was observed.

Hoyer et al. (2000b)

Hoyer et al. (2000b) conducted a study on the same cohort (Hoyer et al., 2000a), which involved 155 breast cancer cases and 274 matched controls with the goal of evaluating if repeated measurements of organochlorine exposure would provide a more precise measure of breast cancer risk. Blood donated in 1976–1978 and 1981–1983 was

analyzed for Σ PCB (118, 138, 153, and 180), DDT, dieldrin, and β -HCH. Known risk factors for breast cancer were considered in the analysis. Breast-cancer risk was not significantly associated with Σ PCB or any individual congener taken over the course of two measurement periods. However, using data from the second sampling period, the concentration of one congener (PCB 118) in the second exposure quartile was significantly associated with breast cancer (OR=1.9, 95%CI 1.1–3.1). There was no attempt to explain how this congener might have played a role in breast-cancer etiology.

Woolcott et al. (2001)

In a similar case-control study, Woolcott et al. (2001) measured levels of 14 PCB congeners, DDT, DDE, HCB, chlordan, and β -HCH in breast adipose tissue from 217 cases of active breast cancer and 213 biopsy controls to investigate possible associations between organochlorine concentrations and cancer risk by estrogen-receptor and progesterone-receptor status, tumor size, and tumor grade. There were no significant associations between Σ PCB and estrogen-receptor or progesterone-receptor status, tumor size, or tumor grade. There were, however, two significant associations between the middle tertiles of exposure: PCB 156 was associated with estrogen-receptor-negative tumors and PCB 180 was associated with progesterone-receptor-negative tumors. Given the high number of comparisons made in this study, as well as the biologic implausibility of these middle tertile associations, these findings are likely to have occurred by chance given that multiple comparisons were made. Moreover, although the study accounted for known risk factors for breast cancer, it suffers from the same problem as most of the earlier studies on PCBs as potential risk factors for breast cancer—tissue samples were collected from active cases of breast cancer, resulting in uncertainty regarding whether observed associations were a cause or a result of the disease.

Rusiecki et al. (2004)

A more recent case-control study with 266 breast-cancer cases and 347 benign-breast-disease controls was conducted in India to investigate possible associations between breast cancer risk and combined estrogen-receptor/progesterone-receptor status (Rusiecki et al., 2004). Serum and breast-adipose-tissue levels of 9 PCB congeners were determined in cases and controls. There were no significant associations between joint estrogen-receptor/progesterone-receptor status and Σ PCB (i.e. 9 congeners) or any specific congeners or congener groupings (i.e. estrogenic, anti-estrogenic/dioxin-like, or phenobarbital-like). The authors concluded that “these results confirm previous findings in the literature of no positive association between environmental exposure to PCBs and risk of breast cancer”.

Laden et al. (2001)

In an expanded follow-up of a previously reported study (Hunter et al., 1997), Laden et al. (2001) added an

additional 143 cases of invasive postmenopausal breast cancer (a total of 381 cases). Plasma concentrations were determined for four PCB congeners (118, 138, 153, and 180) and DDE from 1 month to 4 years prior to disease diagnosis. There was no significant association between breast-cancer incidence and lipid-adjusted plasma levels of DDE, Σ PCB, or any of the individual congeners. The authors concluded that “overall, our results do not support the hypothesis that exposure to DDT and PCBs increases the risk of breast cancer”.

Rubin et al. (2006)

Rubin et al. (2006) conducted a retrospective case-control study involving 63 women who developed breast cancer and 63 age-matched controls. Banked serum collected between 1981 and 1987 was available for analysis of PCBs (28 congeners), DDT, DDE, and 13 other organochlorine compounds. Most risk factors for breast cancer were accounted for in the analysis. Mean and median Σ PCB concentrations, as well as mean and median serum concentrations of individual congeners, were significantly lower in cases than in controls. The study found a significantly decreased risk for breast cancer across tertiles of Σ PCB in a univariate analysis, although the trend was no longer significant in a multivariate analysis. Overall, there was no indication that PCBs were associated with increased risk of breast cancer.

Gammon et al. (2002)

In a study of breast-cancer risk in relation to serum organochlorine levels (DDE, dieldrin, and 24 PCB congeners), Gammon et al. (2002) used blood samples from 646 cases of *in situ* or invasive breast cancer and 429 controls from a population-based case-control study on Long Island. Known risk factors for breast cancer were considered in the analysis. Potential breast-cancer associations were restricted to the sum of the concentrations of the four most prevalent congeners or “peak-4 PCBs” (i.e. 118, 138, 153, and 180), which represented approximately 50% of the 24 congeners measured. Risk of breast cancer was not significantly associated with peak 4-PCBs or any other congener groupings. There were also no significant associations between peak 4-PCBs and parity, breastfeeding, menopausal status, body mass index, tumor stage, or estrogen-receptor/progesterone-receptor status. The authors concluded that “these findings, based on the largest number of samples analyzed to date among primarily white women, do not support the hypothesis that organochlorines increase breast cancer risk...”

Negri et al. (2003)

Finally, in a recent quantitative review of the WoE concerning possible associations between environmental exposure to PCBs and risk of breast cancer, Negri et al. (2003) assessed the epidemiologic evidence on environmental exposure to PCBs and breast-cancer risk. This review was conducted with support from the Italian Association for Cancer Research and the Italian League Against Cancer. In

this review, ecological studies and studies with less than 50 cases of breast cancer were not considered. The majority (i.e. WoE) of both prospective and retrospective studies did not find any association between total PCB serum or plasma concentrations and breast-cancer risk. Furthermore, no association was found for congeners in Group I (potentially estrogenic) and Group III (biologically persistent phenobarbital-type cytochrome P450 inducers), according to the PCB-congener classification proposed by Wolff et al. (2000). Less consistent results were reported for Group II (potentially anti-estrogenic, immunotoxic, and dioxin-like) congeners. The authors concluded that “the epidemiological evidence does not support the hypothesis of an association of environmental exposure to PCBs in adulthood in the general population and risk of breast cancer”. While the authors noted some uncertainties for selected subgroups of women (e.g. women who had never lactated) or individual PCB congeners, these findings were based on a very small number of cases. Importantly, Negri et al. (2003) also cited the lack of increased risk of breast cancer in female workers occupationally exposed to PCBs as strengthening a conclusion that there is no association between PCBs and increased risk of breast cancer.

Breast cancer and occupational exposure to PCBs

In virtually all the studies in which breast-cancer risk has been investigated in conjunction with environmental exposure to PCBs, there is no mention of the findings from the occupational mortality studies. These data demonstrate unequivocally that PCBs are not etiologically associated

with increased risk of breast cancer. As described in Golden et al. (2003) and augmented by the additional occupational studies described in the present review, there is no evidence that occupational exposure to PCBs is associated with increased risk of breast-cancer mortality. In general, the occupational studies (now involving >8,600 women exposed to elevated levels of PCBs) have reported a deficit in breast-cancer mortality, with the study by Prince et al. (2006a) demonstrating a statistically significant decrease in breast-cancer mortality. The results of all occupational mortality studies that reported breast-cancer mortality are summarized in Table 3. This table illustrates that occupational exposure to PCBs is not associated with increased risk of breast cancer with an overall summary SMR of ≈ 0.84 . It should be noted that Table 3 is simply a compilation of results from individual studies, many of which are follow-ups of the same cohort, and is intended only to illustrate the consistent lack of increased mortality from breast cancer in the numerous occupational cohort mortality studies.

Finally, in a recent incidence study of breast cancer in 5752 occupationally exposed women employed at least one year in one of three capacitor manufacturing facilities, the overall breast cancer standardized incidence ratio (SIR) was 0.81 (95% CI 0.72–0.92, $n = 257$), and regression modeling showed little effect of employment duration or cumulative exposure (Silver et al. 2008). When broken down by race, in white women the SIR = 0.80 (95% CI 0.70–0.90, $n = 244$) while in women identified as non-white the SIR = 1.94 (95% CI 0.77–3.99, $n = 7$) was non-significantly elevated. However, in these cases there were positive, statistically significant associations with employment duration and cumulative exposure with only smoking, birth cohort, and self or proxy

Table 3. Occupational exposure levels to PCBs and breast-cancer mortality ratios.

Study	Description	Standardized mortality ratio	95% CI
Brown (1987)	Retrospective cohort mortality study of 1,318 women employed in capacitor manufacturing plants in New York (NY) and Massachusetts (MA).	0.77	0.35–1.46
Nicholson et al. (1987)	Retrospective cohort mortality study of 521 women employed in capacitor manufacturing plants in NY.	1.33	0.43–3.10
Taylor et al. (1988)	Retrospective cohort mortality study of 2,691 women employed in capacitor manufacturing plants in NY.	0.84	0.45–1.44
Sinks et al. (1992) ^a	Retrospective cohort mortality study of 846 women employed in capacitor manufacturing plants in Indiana.	0.51	0.06–1.85
Kimbrough et al. (1999)	Retrospective cohort mortality study of 2,544 women hourly workers and 469 salaried workers employed in capacitor manufacturing plants in NY.	0.82 (hourly) 1.04 (salaried)	0.53–1.21 0.34–2.44
Kimbrough et al. (2003)	Retrospective cohort mortality study of 2,544 women hourly workers and 469 salaried workers employed in capacitor manufacturing plants in NY.	0.88 (hourly) 0.87 (salaried)	0.60–1.24 0.31–1.89
Ruder et al. (2006)	Retrospective cohort mortality study of 852 women employed in capacitor manufacturing plants in Indiana.	0.83	0.4–1.6
Prince et al. (2006a)	Retrospective cohort mortality study of 1,325 highly exposed women workers employed in capacitor manufacturing plants in NY and MA.	0.59	0.33–0.98
Prince et al. (2006b)	Retrospective cohort mortality study of 7,772 women workers employed in capacitor manufacturing plants in NY and MA.	0.95	0.78–1.15
Summary standardized mortality ratio			0.84

^aBreast-cancer mortality rate not reported in original study, obtained from Adami et al. (1995).

questionnaire completion having statistically significant explanatory power in conjunction with exposure metrics. While interesting, the exposure-related risk elevations observed among non-white workers are difficult to interpret given the small number of cases.

PCBs as a risk factor for breast cancer through *CYP1A1* genetic polymorphisms

The WoE supports the conclusion that neither environmental nor occupational exposure (both reviewed above) to PCBs is a risk factor for breast cancer. However, several recent studies have reported potential interactions between PCBs and *CYP1A1* polymorphisms that seem to be associated with increased risk. The underlying biological basis for associating PCB exposure, *CYP1A1* polymorphisms, and breast-cancer risk involves estrogen as a primary risk factor for breast cancer. Indeed, most of the known endogenous risk factors for breast cancer are in essence surrogates for internal lifetime estrogen exposure (e.g. age at menarche, parity, lactation, age at menopause). However, estrogen *per se* is not believed to be the active molecular form that causes breast cancer. Rather, estrogen metabolites produced by a number of estrogen-metabolizing P-450 CYP enzymes have been implicated. Phase 2 enzymes (e.g. glutathione S-transferase, GST, UDP-glucuronosyltransferases, UGTs, and catechol-O-methyltransferase, COMT) also play key roles in the metabolism and excretion of estrogen metabolites. Oxidative metabolism of estrogens, mainly by hydroxylation, is mediated primarily by *CYP1A1* (producing primarily 2OH-estradiol). The catechol estrogens that are formed are intermediates for the generation of reactive quinones and semiquinones, which have both been hypothesized to have the ability to damage DNA through redox cycling and generation of reactive oxygen species (Bolton, 2002; Jefcoate et al., 2000; Liehr 1997; 1999, 2001; Yao et al., 2003).

At least four genetic polymorphisms of *CYP1A1* have been studied for potential relationships with breast-cancer risk. Many of these are prevalent with different frequencies in Caucasian, African-American, and Asian women. The four allelic changes are termed *m1*, *m2*, *m3* and *m4* (also referred to as *CYP1A1*2A*, *CYP1A1*2B*, *CYP1A1*3*, and *CYP1A1*4*, respectively) with the 'wild-type' designated as *CYP1A1*1*. (Wormhoudt et al., 1999). The *m2* variant encodes an isoleucine (Ile) → valine (Val) substitution at exon 7 (i.e. heterozygous Ile:Val; homozygous Val:Val). While it has been reported that the allelic variants can affect the inducibility of the P-450 isoform, the evidence is mixed on this phenomenon (Landi et al., 2005; Wormhoudt et al., 1999). This is particularly true since all of the data are from *in vitro* studies and it is unknown whether there is a functional change *in vivo*. Some studies have reported that the Ile→Val substitution affected the catalytic properties of the enzyme (Kiyohara et al., 1996), while others have reported a significant effect on EROD metabolism, but no effect on the hydroxylation of benzo[a]pyrene (Zhang et al., 1996). In a

study of metabolic activity toward B[a]P, *CYP1A1*1* showed the highest total metabolism, with *CYP1A1*2* at ≈50% and *CYP1A1*4* at ≈70% (Schwartz et al., 2001). Other studies have reported increased inducible enzyme activity of the *CYP1A1*2B* variant in human lymphocytes, as measured by EROD assay, when compared with *CYP1A1**. However, this has been seen only in 3-methylcholanthrene-induced lymphocytes and not in basal values of *CYP1A1* activity (Cosma et al., 1993; Crofts et al., 1994). Other studies have failed to confirm a clear association between polymorphisms of *CYP1A1* and increased enzyme induction as measured by EROD metabolism (Kiyohara et al., 1996; Jacquet et al., 1996; Smith et al., 2001).

On the basis of *in vitro* data suggesting that polymorphic forms of *CYP1A1* are more inducible, it has been hypothesized that there could be an interactive effect between PCB body burdens and certain *P4501A1* polymorphisms to increase breast-cancer risk. Moysich et al.'s (1999) was the first study to report that, in women with serum PCB levels above the median of the distribution in the control group and with at least one variant *CYP1A1m2* allele (Ile:Val or Val:Val), there was a significantly increased risk of postmenopausal breast cancer (OR=2.93, 95%CI 1.17–7.36, 19 cases). In this study, blood was collected for PCB analysis (73 congeners) from 154 women with postmenopausal breast cancer after disease diagnosis, but prior to chemotherapy treatment and the presence of the *CYP1A1 m2* polymorphism was determined. Known risk factors for breast cancer were considered in the analysis, although it is not clear whether post-menopausal use of hormone-replacement therapy (HRT) was considered. There was no association between the *CYP1A1 m2* genotype and breast-cancer risk in women with PCB levels below the median of controls. The low and high PCB groups were 0.75–3.72 ng/g and 3.73–19.04 ng/g, respectively. Breast-cancer risk was significantly increased in women with elevated PCB body burden and a *CYP1A1* polymorphism with a history of smoking (OR=7.74, 95%CI 1.12–53.90), but not in women who had never smoked (OR=1.43, 95% CI 0.53–3.87). As in other studies, there was no increase in breast-cancer risk based on ΣPCB body burdens alone, with the suggestion that this may have been attributable to the fact that only a small fraction of the populations studied were susceptible to the effects of PCB exposure (i.e. those with a *CYP1A1* polymorphism).

Layden et al. (2002) also studied breast-cancer risk with respect to potential interactions between *CYP1A1* polymorphisms and PCBs. In this study, plasma PCB concentrations (21 congeners) and the *CYP1A1 m1* and *m2* polymorphisms were determined in 367 breast-cancer case-control pairs (293 postmenopausal pairs) from the Nurses Health Study. Blood was collected for PCB analysis well before disease diagnosis, thereby avoiding possible disease-related or chemotherapy-related effects on serum levels. Known risk factors for breast cancer were considered in the analysis, although it is not clear whether post-menopausal HRT was considered. There was no independent

association of either of the *CYP1A1* variants or lipid-adjusted Σ PCB with breast-cancer risk. However, based on 19 cases, there was a borderline significant interactive relative risk of post-menopausal breast cancer (RR=2.78, 95%CI 0.99–7.82) associated with plasma Σ PCB levels in the highest tertile of the distribution (0.67–1.99 ug/g) and at least one *m2* variant allele compared with women with the wild-type allele and Σ PCB levels in the lowest tertile of exposure. There were no significant associations between post-menopausal or all breast cancer and a *CYP1A1 m1* polymorphism and plasma Σ PCB levels. As noted by the authors, because of the small number of cases (and the consequent wide CI), the finding of an increased risk of post-menopausal breast cancer in women with the *CYP1A1 m2* polymorphism and the highest PCB exposure warrants further study.

In a similar study, Zhang et al. (2004) investigated associations between serum PCB levels and *CYP1A1* polymorphisms in 374 cases of breast cancer and 406 non-cancer controls. Measurements of serum PCBs (9 congeners) and genotypes of *CYP1A1 m1*, *m2*, and *m4* were determined. Blood for PCB analysis was collected following a diagnosis of breast cancer and, therefore, measured levels are subject to possible disease-related effects. In addition, the extent to which chemotherapy-treatment-related effects on PCB serum levels might have influenced the results is unknown, since this potentially confounding issue was not addressed. Because variant alleles in the *CYP1A1* gene vary widely in frequency by race, the analysis was restricted to white participants, since there were few non-white participants in the total cohort. Known risk factors for breast cancer were considered in the analysis, although it is not clear whether post-menopausal HRT was considered. Lipid-adjusted serum Σ PCB levels were characterized as low (310–610 ng/g) and high (611–2600 ng/g). There were no significant independent effects on breast-cancer risk when assessed using Σ PCB. However, on the basis of analysis of the 40 cases in the total cohort, there was a significantly increased risk of breast cancer (OR=2.1, 95%CI 1.1–3.9) in women with the *CYP1A1 m2* variant (one variant allele or homozygous alleles), which increased in post menopausal women (OR=2.4, 95%CI 1.1–5.0). A significant interactive effect (OR=4.3, 95%CI 1.6–12.0) in post-menopausal women (21 cases) was also observed between high serum PCB levels and the *CYP1A1 m2* variant. As noted by the authors, because of the relatively low prevalence of the variant genotypes (i.e. 6% of the *m2* genotype in the control population), it was not possible to stratify the data by potentially major confounders such as lactation and menopausal status, despite the size of this study.

In the latest study of this type, Li et al. (2004) conducted a case-control study involving 612 breast cancer cases (242 African-American and 370 white) and 599 controls to investigate possible interactions between *CYP1A1* polymorphisms and Σ PCB. In all cases and controls, plasma concentrations of PCBs were determined in addition to

genotyping for *CYP1A1 m1*, *m2*, *m3*, and *m4* alleles. Blood for PCB analysis was collected following a diagnosis of breast cancer and, therefore, the measured levels are subject to possible disease-related effects. In addition, the extent to which chemotherapy treatment might have influenced PCB serum levels, and therefore study results, is unknown, since this potentially confounding factor was not considered. Because plasma Σ PCB levels were higher in African-American women than in white women, the analysis was conducted based on Σ PCB concentrations of <0.430 ng/ml and \geq 0.430 ng/ml (lipid adjusted) for the former and Σ PCB concentrations of 0.349 ng/ml and \geq 0.349 ng/ml for the latter groups of breast-cancer cases. Known risk factors for breast cancer were considered in the analysis, including the use of HRT or oral contraceptives.

Li et al. (2004) found no evidence of joint effects between *m1* genotypes and Σ PCB in either African-American or white women. There were also no significant interactive effects between Σ PCB and any *m2* variant in African-American or white women, any *m4* variant in white women, or any *m3* variant in African-American women. Greater than additive joint effects were reported between the *m2* genotype and Σ PCB in the total cohort with an interaction contrast ratio >0 with $p=0.03$. Although this statistic was not used in previous studies, which reported greater effects in post-menopausal women, the joint effects were stronger in pre-menopausal ($n=14$) than in post-menopausal ($n=12$) women. However, with respect to calculating additive interactions, it should be noted that, because the calculations were based on ORs, substituting ORs for risk ratios may result in misleading conclusions (Kalilani and Atashili, 2006).

In the first three of the above-described studies, the proposed mode of action for the effects reported was suggested on the basis of the hypothesis that polymorphic forms of *CYP1A1* were more inducible by PCBs (albeit with no direct *in vivo* evidence of this effect) with the increased induction leading to enhanced metabolism of estrogen to potentially toxic metabolites (which is biological plausible). However, the study by Li et al. (2004) proposes a different mode of action, suggesting instead that PCBs are metabolized by *CYP1A1* to produce free-radical-induced oxidative DNA damage in breast tissue. As support for this hypothesis, Li et al. (2004) cite a single *in vitro* study that reported that PCB dihydroxy metabolites are activated by enzymatic and non-enzymatic mechanisms (not involving *CYP1A1*) to reactive intermediates that produce oxidative DNA damage (Oakley et al., 1996). The authors did not consider the fact that while PCB-derived quinones formed DNA adducts *in vitro*, no DNA-adduct formation has been detected in PCB-dosed animals (Schilderman et al., 2000; Whysner et al., 1998). Furthermore, in an extensive analysis of the probable mode of action for PCB-induced promotion of hepatic tumors, the extent of PCB metabolism was not correlated with the development of tumors, implying that PCB metabolites did not contribute to tumor development (Brown et al., 2007).

Comment

Three of the studies summarized above suggest that there might be an interactive effect between the *CYP1A1 m2* variant and both Σ PCB serum levels and increased breast-cancer risk, predominantly in post-menopausal women. The fourth study suggested that the risk was greater for pre-menopausal women. Although all four studies, at least superficially, seem to satisfy the causation criterion of consistency and, perhaps, strength of association, there is uncertainty with respect to the dose-response criterion and, most importantly, the criterion of biological plausibility. However, because the results of these studies are based on small sample numbers and rather wide confidence intervals, the strength of association is weakened. It also should be noted that several comprehensive reviews have concluded that there is no independent association between breast-cancer risk and the *CYP1A1 m2* variant (Agundez, 2004; Masson et al., 2005; Li et al., 2005). While this does not eliminate the possibility of interactive effects with PCBs, it does illustrate the burden placed on the hypothetical role of PCBs, as these compounds are far from unique in the specific property (i.e. induction of *CYP1A1*) proposed as the key event in explaining the results of the four studies. This issue is reviewed in detail below.

Several other methodological issues also call into question the reported findings. One of the studies (Laden et al., 2002) was conducted in a cohort where blood specimens were collected prior to disease diagnosis, while three of the studies (Li et al., 2004; Moysich et al., 1999; Zhang et al., 2004) involved active cases of breast cancer with PCB levels measured in serum collected after breast cancer was diagnosed. Therefore, these three studies may very well suffer from the same problem as the early studies that used the same methodology—possible disease-induced redistribution of PCBs from breast tissue into the blood, particularly in the event that weight loss occurred. While the authors correctly note that current levels may not represent levels present when disease developed, they still fail to acknowledge the possibility of disease-related effects on current PCB levels. Related to this problem is the known effect of chemotherapy on PCB serum levels. Gammon et al. (1996) demonstrated that PCBs can be mobilized by treatment, and concluded that “the use of blood samples collected after treatment, rather than before treatment, for characterizing PCB levels may lead to misclassification of exposure”. The studies by Zhang et al. (2004) and Li et al. (2004) did not address this possibility. Moysich et al. (1999) collected blood samples prior to initiation of chemotherapy, but still after disease diagnosis. The extent to which the disease and chemotherapy treatment of the disease might have altered PCB serum or plasma concentrations, thereby leading to spurious interactive relationship with *CYP1A1* polymorphisms, is unknown.

Biological plausibility

The principal explanation for the findings in the above studies is that the *CYP1A1 m2* allele is more inducible by PCBs based on data derived from a variety of *in vitro* test systems. By contrast, human data on the differential metabolism

of PCB congeners in Aroclors 1242 and 1254 indicate that *CYP1A1* is not induced in humans at PCB serum levels resulting from occupational, much less environmental exposures. While a PCB metabolism pattern consistent with induction of *CYP1A1* is readily induced in rats (Mayes et al., 1998; Brown et al., 2007), a similar pattern is not induced in humans (Brown and Lawton, 2001). This was confirmed in a study of 48 occupationally exposed capacitor workers with mean lipid PCB levels of 195 ppm (range 37–1035 ppm), in which there was no indication of a decrease in serum levels of the specific PCB congeners that are known to be metabolized by *CYP1A1* (Brown and Lawton, 2001). That is, PCB congeners 28, 74, and 118 were not reduced in concentration due to increased metabolism resulting from *CYP1A1* induction. As noted by Brown and Lawton (2001), “the absence of P450 1A induction by Aroclors in the workers (or mice) could reflect either a lower responsiveness of the human (or mouse) Ah-receptor to PCBs, or the known tendency of non-coplanar PCBs to inhibit P450 1A1 induction (van der Plas et al., 1998), or both”. While occupational exposure to PCBs was not sufficient to induce *CYP1A1*, placentas from women poisoned from the accidental ingestion of PCBs and polychlorinated dibenzofurans as a result of the Yu-Cheng incident demonstrated *CYP1A1* catalytic activity increased approximately 100-fold, compared with control placenta (Lucier et al., 1987). These placentas contained 50–892 times more dioxin-equivalent chemicals than are present in background levels. By contrast, placentas from Inuit women from southern Quebec with mean blood TEQ levels approximately five times greater than those of controls showed no evidence of increased *CYP1A1* activity (Pereg et al., 2002). Collectively, these data demonstrate that PCB serum levels achievable by environmental exposures are not sufficient to induce *CYP1A1*.

The above discussion illustrates that, while it is unlikely that *CYP1A1* is induced in humans by exposure to PCBs alone, particularly from environmental exposures, sufficient exposure to TEQ can have this effect. This poses an interesting biological conundrum pertaining to the four breast cancer studies reviewed above: how could the *CYP1A1 m2* polymorphic form be induced by PCBs at environmental levels while *CYP1A1* is not induced by PCBs even at occupational-exposure levels? It is biologically implausible that the *m2* variant (i.e. either heterozygous or homozygous) would essentially change the functionality of the *CYP1A1* gene from non-inducible at occupational PCB levels to inducible by environmental PCB exposure levels. While the results of these studies seem to be in agreement, there remains considerable uncertainty whether the explanation for the reported findings is as simple as an interactive effect between the presence of a *CYP1A1 m2* variant and minimally elevated serum PCB levels, all of which are in the normal background range.

Finally, with respect to biological plausibility, the female occupational-exposure data are perhaps the most compelling. As reviewed above, these data demonstrate unequivocally that PCBs are not etiologically associated

with increased risk of breast cancer. These data, from >8,600 women exposed to elevated levels of PCBs, take on additional importance with the publication of the studies reviewed above, suggesting an increased risk of breast cancer in women with a *CYP1A1 m2* polymorphism and environmental exposure to PCBs. While none of the occupational studies considered *CYP1A1* polymorphisms, it can only be concluded that if the mode of action by which the findings in the above four studies is hypothesized to occur (i.e. greater induction of the *CYP1A1 m2* allele leading to increased production of potentially DNA-damaging estrogen metabolites as a consequence of background exposure to PCBs), then this would have occurred to an even greater extent in occupationally exposed women. For example, approximately 12% of women carry the *m2* allele (Zhang et al., 2004) which means that ≈ 1000 of the women exposed in the occupational cohort studies would have been far more susceptible to PCB-induced breast cancer if the findings in the above four studies were actually due to the hypothesized events. This would have resulted in greatly increased breast-cancer mortality in this subset of women, with an overall SMR in excess of 100 instead of the observed SMR of 94, as shown in Table 4.

Given the unequivocal evidence that occupational exposure to PCBs is not associated with increased risk of breast cancer, the seemingly enigmatic covariance of slightly elevated background PCB serum levels with cancer risk in a *CYP1A1 m2*-bearing subpopulation suggests an interesting biological paradox caused by two seemingly contradictory facts. The first is that the *CYP1A1 m2* variant is very similar in enzymatic activity to other *CYP1A1* types (Zhang et al., 1996; Schwartz et al., 2001), but is approximately three times more easily induced by the classical AhR agonist, 3-methylcholanthrene (Cosma et al., 1993; Crofts et al., 1994). The second is that, as described above, increased induction of *CYP1A1* (or any other PCB-metabolizing CYP) could not be detected even in occupationally exposed capacitor workers with 100-fold higher levels of PCBs than those in the background-exposed

study populations (Brown and Lawton, 2001). In an *in vitro* study, induction of *CYP1A1* in human hepatocytes by Aroclor 1254 also required far greater PCB concentrations compared with induction in rat or monkey hepatocytes (Silkworth et al., 2005). Therefore, even allowing for a threefold greater responsiveness of the *m2* variant, there is simply no conceivable way that PCBs at serum levels in the normal background range (i.e. ng/ml) could cause any induction of *CYP1A1 m2*. Consequently, it is necessary to explore an alternative explanation for the enigmatic correlation between increased breast-cancer risk in individuals with the *CYP1A1 m2* variant and slightly elevated background serum PCB levels.

It is well known that correlation does not necessarily equal causation. In the case at hand, it seems more likely that minimal *CYP1A1* induction (not due to PCBs) is causing slightly increased PCB serum levels rather than the opposite. This is likely due to the following three inter-related factors:

Although background PCB serum levels are clearly not sufficient for *CYP1A1* induction, other *CYP1A1* inducers are likely to be present in the study population (e.g. smoke from cigarettes and other combustibles, cruciferous vegetables, tryptophan metabolites, certain dietary flavonoids). Thus, some induction of *CYP1A1* isozymes is occurring in the study population, particularly in individuals with the *m2* allele.

A general peculiarity of CYP induction is that agents that induce one type of CYP are often inhibitors of another (Waxman and O'Conner, 2006). For example, it has been found that *CYP1A1* inducers can decrease expression of *CYP2C* and *CYP3A* isozymes in rodents (Shaban et al., 2005; Lee et al., 2006), and that similar effects occur in humans (Brown, 1989). Thus, cigarette smoke, which increases expression of CYPs *1A1* and *1A2*, decreases expression of those in the *CYP3A* family, CYPs *3A4*, *3A5*, *3A7*, *3A43* (Raunio et al., 2005). Yu-Cheng patients, who ingested PCBs contaminated with the strongly *CYP1A1*-inducing PCDFs, exhibited not only increased clearance of mono-*ortho* PCB congeners, known to be associated with *CYP1A1/2* induction (Brown et al., 2007), but also reduced clearance of the

Table 4. Observed and expected cancer mortality and standardized mortality ratios from studies of 19,825 capacitor manufacturing workers occupationally exposed to PCBs.

Type of cancer	Observed mortality	Expected mortality	Standardized mortality ratio ^b	<i>p</i> value ^a	Standardized mortality ratio ^c
All cancer	1241	1252	100	0.83	88
Liver, biliary, or gall-bladder	24	28	86	0.58	76
Intestine	121	107	113	0.35	97
Stomach	36	32	113	0.63	72
Rectum	22	21	105	0.88	81
Skin	28	19	147	0.19	110
Breast	119	127	94	0.77	-
Prostate	39	42	93	0.74	90
Lymphatic and hematopoietic	138	126	110	0.46	88
Non-Hodgkin's lymphoma	44	43	102	0.91	102

^a*p* values are two-sided for capacitor-worker summary standardized mortality ratios

^bStandardized mortality ratios based on Gustavsson and Hogstedt (1997), Tironi et al. (1996), Ruder et al. (2006), and Prince et al. (2006b)

^cStandardized mortality ratios include studies in footnote b, plus observed and expected mortality data from Loomis et al. (1997).

di-*ortho* PCB congeners (Brown et al., 1989). This indicates suppression of the constitutive oxidase activity (e.g. *CYP3A4/5*) normally involved in their metabolism.

Most of the PCBs present in human tissue residues consists of di-*ortho*-substituted and tri-*ortho*-substituted species (e.g. congeners 99, 138, 153, 170, 180, 187) that are slowly metabolized by the *CYP3A*, but are not metabolized by the *CYP1A* oxidases (Brown, 1994).

On the basis of simple pharmacokinetic considerations (Brown, 1994), individuals in a population with chronic exposure to PCBs at background levels will attain steady-state PCB levels that are inversely proportional to PCB clearance rates, which, in turn, are primarily determined by CYP-mediated metabolism. Thus, in individuals where *CYP1A1* activity has been somehow induced, which would be slightly more common in the 10–15% of the population with the *CYP1A1 m2* allele, there will be a concomitant suppression of *CYP3A* activity and consequent increase in steady state blood levels of di-*ortho* and tri-*ortho* PCB congeners. As a result, there will be an observable correlation between PCB levels (albeit in the background range) and cancer risk in the *m2* subpopulation. This occurs because low-level PCB exposure can serve as a biomarker for *CYP* induction and inhibition by other agents, even though it cannot produce observable *CYP* induction in humans.

Association between occupational exposure to PCBs and increased risk of cancer based on ATSDR methodology

As described in the introduction, the ATSDR (2000) did not rely on a WoE approach when evaluating the occupational cohort PCB mortality data, but rather used the meta-analysis-type methodology used by Nicholson and Landrigan (1994). Using this methodology, the summed observed and expected cancer mortality rates (for men and women combined) from five studies were tested for statistical significance. Importantly, this analysis only included data available up to 1994, even though the ATSDR acknowledged that additional data were available. Table 4 uses the same methodology as described by Nicholson and Landrigan (1994) and combines the data from all of the capacitor-worker occupational cohort mortality studies published to date. For the purposes of this analysis, mortality statistics for men and women are combined and, when more than one study has been conducted on the same cohort, only the most recent study is included to avoid double counting (i.e. Ruder et al., 2006 rather than Sinks et al., 1992, Prince et al., 2006b rather than Brown et al., 1987 or Kimbrough et al., 1999 or 2003, and Tironi et al., 1996 rather than Bertazzi et al., 1987). Consequently, the data from the following four studies are summarized in Table 4: Gustavsson and Hogstedt (1997), Tironi et al. (1996), Ruder et al. (2006), and Prince et al. (2006b). Data from Mallin et al (2004) are not included in Table 4, since, as discussed above, the reported effects were predominantly from exposure to chlorinated naphthalenes and

not PCBs. When only observed mortality is reported, the expected mortality is calculated by dividing the observed mortality by the SMR.

In contrast to the data relied on in the ATSDR (2000) analysis, involving approximately 5386 workers, Table 4 includes mortality data on almost 20,000 PCB-exposed workers. The summary SMRs for each cancer were tested for statistical significance from a Poisson distribution as described by Nicholson and Landrigan (1994). As shown in Table 4, based on the insignificant p-values, none of the SMRs for all cancers or any specific cancer is significantly elevated. In addition, the right column of Table 4 has been added to incorporate the data from Loomis et al. (1997) into the SMR analysis. While the almost 139,000 individuals in this study were male electrical-utility workers, with probably lower exposure to PCBs than capacitor workers, there were approximately 20,000 workers with between 1,000 and 10,000 cumulative hours of exposure to PCBs. As shown in the right column of Table 4, the summary SMRs are further decreased and none are statistically significantly elevated. The above discussion demonstrates that the methodology relied upon by the ATSDR (2000), while not following any recognized guidelines, reaches the same conclusions about cancer risk in PCB-exposed cohorts as the WoE approach used in this review—that there is no evidence of a causal association between exposure to PCBs and increased risk of any type of cancer.

Overall conclusions

None of the studies published since the previous review (i.e. Golden et al., 2003) change the conclusions of that review (i.e. “The weight of evidence does not support a causal association for PCBs and human cancer”). This pertains to all cancer combined, as well as to the specific cancers that have been sporadically reported as elevated in incidence in the occupational cohort mortality studies. Special emphasis should be placed on the issue of PCBs as a risk factor for breast cancer. While the WoE supporting the conclusion that environmental exposure to PCBs is not etiologically implicated in breast-cancer risk is compelling, it is nonetheless surprising that virtually none of the breast-cancer studies mention the consistently negative findings for increased breast-cancer mortality in the occupational studies. These data, now including almost 9,000 women occupationally exposed to PCBs, show no evidence whatsoever of increased breast-cancer mortality. Similarly, virtually none of the incidence studies reviewed above, in which PCB background levels are reported to be associated with increased risk of NHL and prostate, testicular, and intestinal cancer, cite the conflicting results from the occupational cohort studies. Because the occupational studies involve PCB exposure far in excess of environmental exposures, this discrepancy should be acknowledged in future incidence studies. In addition, the possibility that serum PCB levels (all of which are in the normal population range) in such studies can be influenced by disease or

its treatment also needs to be considered. Finally, lacking any relevant or persuasive supporting evidence, there does not seem to be any biologically plausible basis for concluding that either a particular PCB congener or grouping of congeners is etiologically implicated with a particular cancer.

While the ATSDR (2000) did not follow the principles endorsed by the EPA (2005) for evaluating a body of epidemiological data, the conclusions of that document—that there is either “some evidence” or “meaningful evidence” that PCBs are carcinogenic in humans—are not supported even when the methodology employed by the ATSDR (2000) is applied to all relevant data. Notwithstanding, because of the substantial limitations of this methodology, it is suggested that this kind of procedure not be relied upon for critically evaluating epidemiological data.

All relevant data published since 2003 were evaluated in the present review with careful reliance upon and consideration of the WoE criteria established by the EPA (2005) for evaluating epidemiological data. When these criteria are followed, it can only be concluded that exposure to PCBs, whether environmental or occupational, does not increase cancer risk in humans. In another recent critical evaluation of most of the same studies considered in the present review or in previous reviews, Shields (2006) concluded as follows:

“The epidemiologic evidence fails to establish PCBs as human carcinogens. This has been an extensively studied topic in the occupational setting, and more recently in the general population. There are reported positive associations in some studies, but the literature fails to identify a consistent target organ and the animal studies do not indicate that PCBs are multiorgan carcinogens. Some cancer relationships from environmental studies are not consistent with studies of highly exposed workers.”

The above conclusions are now also supported by the recent elucidation of the mode of action by which PCBs cause liver tumors in rats (Brown et al., 2007). This study, based on the Mayes et al. (1998) chronic bioassay of Aroclors 1016, 1242, 1254, and 1260, described the key events underlying the mode of action for PCB-promoted liver tumors in Sprague-Dawley rats. Most important, from the standpoint of the present review, is the fact that none of the key events in the mode of action occurred until substantial amounts of Σ PCB or TEQ had accumulated in hepatic tissues. The relevance of these findings to the human epidemiological data is that even prolonged occupational exposure to PCBs has never resulted in PCB burdens even approaching the levels required to initiate the sequence of events required for the development of tumors in rodents.

Finally, it should be noted that the few positive findings sporadically reported in the numerous studies of PCB-exposed workers (i.e. the conspicuous lack of consistency of association) can be more logically explained based on the principle embodied by Occam’s razor. This is often paraphrased as ‘all things being equal, the simplest solution

tends to be correct’; that is, that the explanation that introduces the fewest assumptions and is dependent upon the fewest hypothetical entities is most likely to be correct. This is particularly the case now that the mode of action for PCB-promoted liver tumors in rats has been elucidated, with the strong likelihood that, because of substantial species differences, humans are unlikely to be susceptible to PCB-caused cancers. Consequently, for liver, biliary, and gall-bladder cancer, rather than assuming that this was due to PCB exposure, a less complex (and more biologically plausible) explanation for the isolated reported findings would involve the following: (a) the inappropriate grouping of these cancers to achieve statistical significance; (b) metastasis from other sites; (c) undocumented alcohol consumption; or (d) ethnic factors. For melanoma, this would include exposure to sunlight or misclassification. Other findings, such as prostate cancer, are even less likely to be due to PCB exposure.

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End note

- 1 Although PCBs are on the list of substances the EPA intends to reevaluate as part of the Integrated Risk Information System, there is no indication that this will be done anytime soon. The most recent Integrated Risk Information System evaluation of PCB carcinogenicity is current to 1996, reviews only three studies (Bertazzi et al., 1987; Brown, 1987; Sinks, 1992) and also cites (with no review) NIOSH (1977), Gustavsson et al. (1986), and Shalat et al. (1989). Clearly, this does not qualify as a WoE assessment. Similarly, PCBs are not on the National Toxicology Program candidate list of chemicals for consideration in the 12th Annual Report on Carcinogens. With respect to international bodies, the International Agency for Research on Cancer (IARC) updated its PCB evaluation in 1987, citing a total of five studies (Brown and Jones, 1981; Brown, 1987; Bertazzi et al., 1981, 1987; Gustafsson et al., 1986). This also cannot be considered a WoE assessment and, indeed, the IARC typically does not conduct these types of assessments. The evaluation by the WHO through the International Programme on Chemical Safety (IPCS) is current as of 1993 and cites the same studies as the IARC (1987). Finally, the IPCS, in its Concise International Chemical Assessment Document series (2003), also reviewed the potential human carcinogenicity of PCBs, concluding that “Epidemiological studies suggest exposure-related increases in cancers of the digestive system, especially liver cancer, and malignant melanoma. However, the limitations of exposure information, the inconsistency of the results, and, in some cases, the presence of confounding exposures preclude a clear identification of an exposure–response relationship.” While some 50 studies were considered in the IPCS evaluation, and although the conclusions seem correct, they were not based on a formal WoE process. This is true despite the existence of explicit IPCS guidelines for evaluating bodies of epidemiological data using a WoE processes (IPCS, 1999).

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