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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Epidemiology of PCB's: Concordance of Liver and Gallbladder Cancer Coding Between Hospital Diagnosis and Death Certificates With Respect to Brown (1988)

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This memorandum discusses several issues arising in my recent comparison of PCB cancer risks between animals and human studies for Vic Kimm, Acting Assistant Administrator for Pesticides and Toxic Substances. During this presentation, you raised a question regarding the accuracy of death certificate codings for liver, gallbladder, and biliary tract cancers. You suggested that death certificates for two of the five deaths observed with cancer at these sites had been coded for secondary rather than primary tumors. If these death certificates are miscoded (e.g., are really secondary rather than primary tumors), this would limit any comparison of animal- and human-risks since observed risks by Brown (1988) would overestimate the true underlying cancer risk.

The question of whether the two questioned death certificates are correctly or incorrectly coded cannot be directly addressed given the amount of information cited on the pathology report. One may, however, indirectly examine the validity of the observed risks in Brown (1988) by obtaining an understanding of death certificate codings for the population to which the deaths were compared, in this instance, the U.S. population. Another related issue concerning the use of Brown in

any comparison of animal- and human-risks regards basing human-observed risks on an aggregate of cancer sites, for Brown, this aggregate consists of cancers of the liver, gallbladder, and biliary tracts. One needs to identify what data exist to support the need to aggregate specific organ sites.

Constance Percy and coworkers (Percy et al., 1981) at the National Cancer Institute have examined the accuracy of death certificate codings by comparing to hospital diagnoses for a large sample (48,826) of deaths in the U.S. population. Cancers of specific sites, including liver, gallbladder, and biliary tract were examined. Observations from this study can be applied to address both of the above issues.

Death certificates are coded for underlying cause according to the International Classification of Diseases (ICD), a structure in which specific causes of deaths are based on etiology and are assigned a series of numbers according to a branching system. For neoplastic diseases, the scheme is broken into organ systems (e.g., gastrointestinal) and subdivided into specific sites (a series of 3-digit numbers; e.g., 155 indicates neoplasms from liver and biliary tract cancer). Organs that are anatomically close are assigned adjacent numbers (e.g., 155, liver and intrahepatic bile ducts; 156, gallbladder and extrahepatic bile ducts). These 3-digit numbers are further subdivided into 4-digit codings for specific locations within the organ (e.g., 155.0, liver; 155.1 intrahepatic bile ducts). Since knowledge of disease processes is never constant, the ICD incorporates changes by periodically issuing revisions. The examination by Percy et al. (1981) is based upon the same revision of the ICD (ICDA-8) as that which was used for the coding of deaths in Brown (1988). Thus, the results of Percy et al. have direct application to our consideration of the Brown results.

Percy et al. (1981) found that the death certificate coding of liver cancer does not correspond well to disease for "primary liver cancer" (ICD 155.0) and "liver cancer, not otherwise specified" (ICD 197.7). Approximately 52% of liver-malignancy-attributed deaths actually had hospital diagnoses of liver cancer; the remaining 48% had hospital diagnoses other than liver cancer and, thus, can be considered miscoded. In Brown (1988), two of the five deaths had codes for liver cancer: one of these is a death brought into question by you. The death certificate was coded as "liver cancer, not otherwise specified"; the hospital diagnosis noted metastatic disease, with the primary site unknown. The hospital diagnosis cited by Brown (1988) lacks information on the primary tumor site; this death could be a

primary liver cancer or it could be miscoded. If this death is due to a primary tumor other than liver cancer, the bias in Brown (1988) is no greater than that expected, based upon Percy et al. (1981), in the reference population. In fact, if the death in Brown (1988) is actually due to liver cancer (i.e., no miscoding of the death certificate), the risk in Brown (1988) may actually be higher than that observed since the reference rates are biased.

The second death in Brown which you brought into question was coded as "extrahepatic bile duct cancer", with the hospital report citing the likely origin as the bile ducts. The pathology report noted, however, a prior history of uterine cancer. Percy et al. (1981) did not find any hospital diagnosis of uterine cancer among 709 deaths coded as gallbladder and extrahepatic bile duct cancer, nor did these researchers find any death certificates coded as uterine cancer as having a hospital diagnosis of gallbladder and bile duct cancer. These findings are consistent with the hospital coding noted by Brown (1988) in which the bile duct was identified as probably being the primary tumor site. Additionally, I contacted Dr. Karl Baetcke of the Oncology Branch, Health and Environmental Review Division, OTS, (conversation 9 May 1989) regarding likely sites for uterine cancer metastases; Dr. Baetcke did not believe the extrahepatic bile ducts were a likely site for metastasis from cancer of the uterus. There seems reason to believe that the cause of death as coded on the death certificate is likely to be cancer of the bile duct. Whether miscoding occurred in ascribing the location of the tumor (i.e., intrahepatic or extrahepatic bile duct) however, cannot be determined based upon the hospital report.

How suitable is the grouping of sites chosen by Brown (1988)? There are several reasons to analyze mortality for the grouping of liver, gallbladder, and biliary tract neoplasms. First, classification of neoplastic diseases of the liver and of the gallbladder and bile ducts is complicated by the fact that liver cancer is difficult to detect, and once detected, typically it is in a late stage, increasing the potential for concurrent metastases and biliary tract involvement. This confounds the assignment of the cause of death on the death certificate. Percy et al. (1981) found the largest percentage of miscoding for a hospital diagnosis of liver cancer was accounted for by death certificate coding of gallbladder and bile duct cancer, whereas the largest percentage of miscoding for hospital diagnoses of neoplasms of the gallbladder and bile duct was by liver cancer on the death certificate. Thus, to reduce the potential for bias, Brown (1988) chose to analyze the data for a grouped site. Percy et al. (1981) notes that a more accurate total of liver malignancy deaths is obtained by combining the categories for primary liver disease (ICD 155.0) and for liver disease, not otherwise specified (ICD 197.7).

A second reason for aggregating various organ sites is the belief that several sites besides the liver may be susceptible to injury from PCBs. The toxic species, the compound likely engendering the cancer risk, is believed to result from metabolism of PCBs. Metabolism occurs in the liver with the metabolites excreted through the bile. The potential, therefore, exists for interaction between the toxic species of PCB and the liver, gallbladder, and biliary tract, giving biological plausibility for performing analyses on an aggregation of these sites.

Third, performing analyses on an aggregation of sites gives greater statistical power to the analysis. This is particularly important since the Brown cohort is relatively small in epidemiologic terms and is limited in detecting anything less than very large site-specific cancer risks. Thus, since biological reasons exist for grouping specific organs, performing analysis on the grouped sites increases the probability for detecting cancer risks, if such risks exist, giving greater weight to any observed result in a weight-of-evidence approach.

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