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James Cogliano, PhD
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Dear Jim:

This is written in response to your request to take a look at the recent Kimbrough et al paper on the PCB exposure cohort. After speaking with you I decided I should go back and look at the previous papers (i.e. Brown & Jones, Brown, Sinks et al, and Bertazzi et al) in order to get appropriate perspective.

As I indicated to you on the phone, I found the Kimbrough paper to be well designed, appropriately analyzed, and fairly interpreted. The follow-up was complete. The results are internally consistent, and show the expected social class effects. I am no expert in assessing the magnitude of exposure, but as far as I can see the magnitude of exposure implied by the various production tasks is similar to those previously studied. As in any environmental study, much less any occupational study, the individuals with the maximum exposure are probably few and unidentifiable. Nonetheless, the persons in this study probably have a higher average exposure than any population likely to come to our attention in terms of risk prediction.

When I looked at the previous studies, I was not very impressed with the positive findings, and not just because of the inconsistency. The Silk and Bertazzi papers in presenting the evidence for indications of risk for melanoma and lymphoma (actually mostly Hodgkin's disease) honestly described the compatibility with chance but did not assess the differences according to education, important in both of those outcomes. Unlike the Kimbrough study, neither investigator divided workers into salaried and hourly categories. The evidence for CNS tumors is statistically very flimsy, and that for liver from the Brown paper, ostensibly the most interesting because of the mouse data, actually represents an excess of biliary carcinomas and not liver at all. We know that the known determinants and risk factors are very different. The lung cancer excess in Bertazzi was not assessed with respect to smoking. What is described as gastrointestinal tract in the same paper are cancers of the stomach (2), pancreas (2), liver (1) and biliary (1). Again, these tumors have disparate epidemiology which, given the small numbers, greatly lessens the credibility of a common origin.

That really leaves cancers of the rectum, as a site that has appeared at least once and is worthy of suspicion a priori. The finding of a few extra rectal and "intestinal" (presumably colon, unlikely to be any small bowel) cancers here in low exposure hourly women is as strong as any previous

finding, that is to say not very strong at all. It is true that colorectal cancers are very complex etiologically, involving several heritable syndromes in interaction with several dietary (i.e. chemical) constituents, and it is impossible to rule out some small causal role for PCB's.

I have not seen the reported excess of cases in the Yusho cohort, but it is my understanding that colorectal cancers were involved. However, the material contaminating the cooking oil contained not just PCB's but also PCDF's, and therefore might not be completely pertinent. On the other hand, superheating of PCB's is said to produce PCDF's, so maybe it is not completely irrelevant.

I guess my bottom line is that the summary statements ("lack of any significant elevations adds important information" and "lack of consistent findings----would suggest a lack of an association") in the paper are appropriate. I think that it is appropriate to downgrade the priority given to PCB's. However, based on the animal studies (and recognizing a. the possibly limited relevance to man and b. the absence of any confirmation of liver cancer in humans) and on this very small amount of information pointing to colorectal tumors, I don't think that the potential carcinogenicity of PCB's can be *completely* dismissed. I recognize the flimsiness of the evidence, and that a less conservative person could persuasively argue the other way.

I'm sure this has not been particularly useful for you, but it's the best I can do. If I can help in any other way, don't hesitate to ask.

Sincerely,

A handwritten signature in black ink, appearing to read "Tom Mack", with a long, sweeping horizontal line above the name.

Thomas Mack, MD
Professor