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C-Reactive Protein Levels in Pregnancy

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van den Hooven et al. (2012) found a non-significant association between high levels of maternal and fetal C-reactive protein (CRP) and exposure to air pollution when they examined the correlation of CRP levels with inflammation and obstetric morbidity. The authors reported that elevated fetal CRP levels at delivery were associated with higher long-term average maternal exposure to PM₁₀ (particulate matter ≤ 10 μm in aerodynamic diameter) and NO₂ (nitrogen dioxide). Other studies have reported that neither preeclampsia (Kristensen et al. 2009) nor pregnancy loss (Boggess et al. 2005) is associated with a systemic inflammation as reflected by CRP levels. However, van den Hooven et al. (2012) insisted that exposure to air pollution may lead to systemic inflammation in pregnancy. Although this statement is defensible, the confounding results regarding CRP levels should be clarified.

CRP is accepted as a good marker of acute inflammation, particularly within infection, but its value in chronic inflammation depends on the inflammation pathway involved and the underlying process. In an examination of autoimmune inflammatory responses triggered by the indoor environment in sick buildings, CRP was < 0.1 mg/dL (normal range, 0.1–0.5 mg/dL) in 27% of patients (Blasco 2011). Interestingly, 13% of patients had suffered miscarriages. CRP may be low or typically very low during a flare-up of some connective tissue disorders, such as systemic lupus erythematosus (SLE) or undifferentiated connective tissue disease. The erythrocyte sedimentation rate more accurately reflects SLE disease activity in patients without associated infection. Therefore, the presence of normal or low CRP levels does not guarantee the absence of inflammation or a positive pregnancy outcome. It would be interesting to assess possible individual immune susceptibility markers and other markers, such as autoantibodies or tumor necrosis factor α, in future studies of systemic inflammation induced by air pollutants during pregnancy.

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Editor's note: In accordance with journal policy, van den Hooven et al. were asked whether they wanted to respond to this letter, but they chose not to do so.

Use of Meta-analyses by IARC Working Groups

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In their letter, Kogevinas and Pearce (2012) suggested that meta-analyses should be more routinely prepared for the evaluations of the International Agency for Research on Cancer (IARC) Monographs program. We concur that meta-analyses are useful in many cases, but there are also counter examples where they have not been useful. For example, when Kogevinas et al. (1998) reviewed the carcinogenicity of cancer hazards in the rubber-manufacturing industry, they argued against using meta-analytic techniques because of the heterogeneity of exposure circumstances within and between manufacturing plants and differences of exposure classifications used in the studies. They concluded that a single summary risk estimate would be uninformative. Based on their systematic narrative review, the authors concluded that there is an increased risk of neoplasms of the urinary bladder, lung, and larynx and an increased risk of leukemia (Kogevinas et al. 1998). In contrast, Alder et al. (2006) performed a meta-analysis of cancer occurrence among workers in the rubber-manufacturing industry. Based on summary estimates for the entire rubber industry and two major sectors of this industry, these authors concluded that excesses other than for leukemia were not substantiated by their synthetic meta-analysis (Alder et al. 2006). After reviewing all the pertinent studies, a later IARC Working Group concluded that there is sufficient evidence for an increased

risk of several types of cancer in rubber manufacturing (Baan et al. 2009).

In contrast, when the IARC Working Group for Volume 98 reviewed the evidence on shift work and cancer, a published meta-analysis had reported a statistically significantly increased risk for breast cancer among women who regularly worked the night shift (Megdal et al. 2005). Nevertheless, the IARC Working Group concluded that there was only limited evidence for carcinogenicity in humans (IARC 2010).

In the context of the Volume 98 Monographs meeting, the Working Group performed a meta-analysis and concluded that there was sufficient evidence for the carcinogenicity of exposures as a painter (IARC 2010). In preparation for the Volume 100 series of the *IARC Monographs*, this meta-analysis was further developed, taking into account studies published after the Volume 98 meeting (Guha et al. 2010). This meta-analysis and another one (Bachand et al. 2010) were available to the Working Group for Volume 100F. Bachand et al. (2010) did not provide results by duration of employment or for nonsmokers, but they argued that the increased risks could be due to residual confounding. After reviewing all published evidence, the IARC Working Group reconfirmed the carcinogenicity of exposures as a painter.

In general, during the last two decades meta-analyses have become more widely used in epidemiology, and the 2006 amendment of the IARC Preamble now specifically mentions the possibility of premeeting and ad hoc meta-analyses during the course of a Monograph meeting (IARC 2006). In practice, this has been done even earlier, for example, when the Working Group for Volume 83 updated a published meta-analysis on involuntary smoking and lung cancer (IARC 2004). Anticipating scenarios as described above, the Preamble (IARC 2006) stresses the need “that the same criteria for data quality be applied as those that would be applied to individual studies.”

Kogevinas and Pearce (2012) referred to a recently published meta-analysis for asbestos and ovarian cancer that we coauthored (Camargo et al. 2011). Interestingly, another meta-analysis of this same question was published by Reid et al. (2011). Whereas our meta-analysis focused on occupational cohorts with well-documented exposure to asbestos and identified almost twice as many cases from occupational cohorts, Reid et al. also included environmental and household exposures as well as linkage and case-control studies. Nevertheless, both meta-analyses reported increased risks overall and in most stratified analyses. However, while Reid et al. (2011) believed that increased risks may be

due to disease misclassification, we (Camargo et al. 2011) concluded that our meta-analysis supports the IARC classification. This illustrates again that meta-analyses are not free from subjective decisions and interpretations.

In conclusion, meta-analyses are a quantitative statistical tool that, in some instances may inform causal inference, but they never alleviate the need for critical review of all available data; narrative reviews by an interdisciplinary IARC Working Group may be, in some cases, more informative than a synthetic meta-analysis. Therefore, although a comprehensive review of all original data is required, a comprehensive review of all meta-analysis may not be warranted, particularly when the meta-analyses are outdated or cover only a subset of the original studies. The current “Preamble to the *IARC Monographs*” (IARC 2006) provides the Working Group with all options to perform quantitative meta-analysis where appropriate and helpful for causal inference. Different approaches have been applied in the history of the *IARC Monographs*. The Volume 100 series of the *IARC Monographs* confirmed all Group 1 carcinogens identified during the 40-year history of the monographs, which in turn confirmed that the procedures of the *IARC Monographs* are robust. With more epidemiological studies becoming available for each agent, additional cancer sites being investigated, and relatively small effect estimates becoming center of the discussion, the need for meta-analyses is likely to increase.

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Presentation of Study Results: The Authors' Responsibility

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We read with interest the article by Kalkbrenner et al. (2012) in which they explored maternal smoking during pregnancy as a risk factor for autism spectrum disorders (ASD). We believe that the following shortcomings of the study did not allow an evaluation of the results and therefore that the paper provides little evidence to judge whether data suggest a “link.”

The findings of Kalkbrenner et al. (2012) regarding “higher-functioning” ASD include three null associations and one association in the smallest subgroup of 375 cases (ASD-not otherwise specified; ASD-NOS) that was “statistically significant” only in sensitivity analysis. Therefore, we question their interpretation of the data when an effect was suggested in only one of the four tests of the same hypothesis. Furthermore, ASD-NOS is a difficult diagnostic subtype to understand because it includes, as the authors noted, a heterogeneous mixture of diagnoses.

Although socioeconomic status (SES) is a well-known correlate of both smoking and ASD, the authors used only maternal education to control for SES; thus, residual confounding from other aspects of SES is likely (King and Bearman 2011; Rai et al. 2012).

Kalkbrenner et al. (2012) did not appropriately control for confounders, and this affected sensitivity analysis central to their conclusions. In their sensitivity analysis for outcome misclassification, they did not correct for covariates, thus basing all of their interpretations on results that were contaminated by confounding. They could have used Monte Carlo methods (Bodnar et al. 2010) to adjust for confounding while accounting for outcome misclassification, obtaining confidence intervals that account for random simulation error, but they did not do this. Thus, the reported confidence intervals for the sensitivity analyses are likely to be too narrow.

Kalkbrenner et al. (2012) did not quantitatively assess the impact of exposure misclassification. The quoted 0.8 concordance of smoking data on birth certificates with the medical record means that smoking exposures of > 125,000 persons in the sample were expected to be incorrectly classified. Sensitivity of maternal smoking on U.S. birth certificates is likely to be only 0.5 (Kharrazi et al. 1999). Epidemiologists ignore measurement error at great peril (Jurek et al. 2006) while correction procedures exist (MacLhose and Gustafson 2012).

Finally, we would like to point out the difficulties of this article in communicating scientific results to the general public. Because, as Kalkbrenner stated, “the study doesn’t say for certain that smoking is a risk factor for autism” (UWM News 2012), then it is the author’s responsibility to more carefully report to the media what the study actually does say. It is easy to blame journalists for the sensational findings that have been reported about this study (e.g., Goodwin 2012). However, given the historic legacy of blaming parents, particularly mothers, for their child’s diagnosis, we would better serve the communities for whom we do this research if we developed standard practices for reporting preliminary findings in ASD risk factor research. One suggestion would be to report these findings without discussion in media (e.g., Palmer 2011) and scholarly publications, as was done by Adam et al. (2011), who produced experimental data demonstrating that the speed of light was exceeded:

Despite the large significance of the measurement reported here and the robustness of the analysis [$p < 0.00006\%$], the potentially great impact of the result motivates the continuation of our studies in order to investigate possible still unknown systematic effects that could explain the observed anomaly. We deliberately do not attempt any theoretical or phenomenological interpretation of the results.

We encourage caution when promoting findings of “potentially great impact” on