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2200 Pennsylvania Avenue NW, Suite 100W • Washington, DC 20037-1701 • 866-522-0950 • www.metal-pack.org

BPA Study Report Card

The criteria identified in this Report Card were established in the *Environment International* article, "A proposal for assessing study quality: Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C) instrument." The BEES-C instrument is designed to evaluate the quality of research studies that incorporate biomonitoring data on short-lived chemicals. More detailed explanation on the various criteria and the ranking system are included in the publication, which is available online.

Study Meets Criteria	Study Criteria Unknown or not applicable	Study fails criteria

Study: High bisphenol A (BPA) concentration in the maternal, but not fetal, compartment increases the risk of spontaneous preterm delivery
Authors: Faranak Behnia, Morgan Peltier, Darios Getahun, Cheryl Watson, George Saade, and Ramkumar Menon
Journal: Journal of Maternal-Fetal & Neonatal Medicine

CRITERIA	SCORE	COMMENTS
Biological relevance: exposure biomarker (level of quantitative relationship between biomarker and external exposure, internal dose, or target dose)		No information was collected on possible BPA exposures (diet, medical devices). Single spot serum and amniotic fluid analysis has low precision and accuracy.
Biological relevance: effect biomarker (level of specificity of biomarker to reported effect)		Preterm births occurred. Unknown relevance of BPA to preterm birth.
Specificity (one parent compound with one biomarker or multiple parent chemicals with varying effects)		Assay kit has 85% cross reactivity with BPA-glucuronide and possibly other non-BPA glucuronides.
Method sensitivity/detection limits (accuracy and precision of methods used to quantify the biomarker)		Frequency of detection is high, high likelihood that compounds other than BPA are identified. Bisphenol A Assay Kit- IBL with detection limit of 0.3 ng/mL. Not as sensitive as liquid chromatography and mass spectrometry techniques. Assay kit has 85% cross reactivity with BPA-glucuronide, indicating possible measuring of other compounds like isoflavones, that are components of the human diet and are excreted as glucuronides.
Known or documented stability of biomarker		Single BPA measurements in serum or amniotic fluid are not representative of concentrations throughout pregnancy.
Prevention of sample contamination		No methods described to prevent BPA contamination. Complex sample preparation procedures for analytical method may introduce contamination due to release of BPA from reagents and materials used. Did not test plastic containers for presence of BPA. Authors acknowledge high false-positive rate of analytical method. 100% of serum and amniotic fluid contained BPA.

Method requirements (appropriateness and description of measurement method)		Methods for collection of serum and amniotic fluid not fully described. Medical devices used to collect these fluids and devices used to care for pregnant women (polycarbonate IV setups, polycarbonate speculum for vaginal examination) are possible sources of BPA and are not identified in article.
Matrix adjustments (appropriate reporting and weighting of differences in collection requirements and sample processes)		Only quantified total BPA, no measurement of free (biologically active) BPA or conjugated BPA.
Study design and execution: temporality (claim of causation supported by observation of the putative causal exposure preceding the outcome)		This study does not establish a time order between exposure and outcome. In fact, exposure is measured after assessment of outcome. Serum and amniotic fluid were collected after admission for term birth (B), preterm birth (PB), or preterm premature rupture of membranes (pPROM). Serum and fluid collection occurred after examination with medical devices potentially containing BPA and after determination of B, PB, or pPROM. It is difficult to know if BPA concentrations represent those present during pregnancy.
Study design and execution: exposure variability and misclassification (sufficient number of samples)		Exposure is measured based on a single sample. The potential for exposure misclassification based on known high rate of false positive measurements in BPA analytical method used in this study.
Study rationale (specific design to evaluate hypothesis)		Mechanisms underlying preterm birth are not fully understood. Authors hypothesize that aberrant inflammation resulting in preterm birth may be caused by BPA which is structurally similar to the pro-inflammatory compound B-estradiol.
Study participants (unbiased selection)		No follow-up needed. Unbiased selection.
Data analysis (control of extraneous factors, distinction between causal and predictive)		Several known risk factors for preterm birth including maternal weight, tobacco and drug use, lack of prenatal care, and time since last pregnancy were not evaluated or controlled for in this study.
Reporting (Study clearly states its aims and allows the reader to evaluate the number of tested hypotheses)		Conclusions are overstated. Lack of correlation between BPA in serum and amniotic fluid (correlations not presented). Results indicate no significant associations between amniotic

		fluid BPA and preterm or pPROM births. Authors also failed to present ranges of BPA concentrations for the various groups. Figure 1A is likely mislabeled as "Log"BPA concentrations (ng/mL) when the concentrations are non-log scale. This Log-scale for the concentrations reported in A would result in study serum BPA concentrations ranging from 40 to over 6,000 ng/mL when concentrations of total BPA in serum for highly exposed adults are 0.4-1.3 ng/mL (Teeguarden et al., 2011). Interestingly, the scale for fetal samples in Figure 1B appear to be using a log scale, as negative values are reported.

Note:

Overall, this paper is not adequate for assessing causation due to several methodological and analytical issues:

1) Temporality between exposure and outcome was not established in this study. Blood serum measurements and amniotic fluid collection occurred after women were admitted for preterm labor. Thus, the biological processes leading to preterm birth outcome occurred prior to exposure assessment. It is therefore difficult to assess whether the BPA levels measured at a single point in time in blood serum or amniotic fluid were relevant during the pregnancy.

2) The study failed to adjust for several known risk factors of preterm birth, including maternal weight, weight gain during pregnancy, tobacco and drug use, lack of prenatal care, and reduced time since last pregnancy (Mayo-Clinic, 2015). The simple adjustment for socioeconomic factors is insufficient to address these known risk factors.

3) Analytical methods lack specificity and sensitivity in that they assessed exposure for not only BPA, but also other isoflavones, which have a molecular weight similar to that of BPA and are also excreted as glucuronides (Volkel *et al*., 2005). The ELISA assay used to measure BPA is also unable to distinguish between free (biologically active) and conjugated forms of BPA. The lack of controlling for sample contamination further decreases the accuracy of the exposure assessment.