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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: Soy Intake Modifies the Relation Between Urinary Bisphenol A Concentrations and Pregnancy Outcomes Among Women Undergoing Assisted Reproduction
Authors: Jorge E. Chavarro, Lidia Mínguez-Alarcón, Yu-Han Chiu, Audrey J. Gaskins, Irene Souter, Paige L. Williams, Antonia M. Calafat, and Russ Hauser, for the EARTH Study Team
Journal: J Clin Endocrinol Metabolism

CRITERIA	SCORE	COMMENTS
Biological relevance: exposure biomarker (level of quantitative relationship between biomarker and external exposure, internal dose, or target dose)		Urinary BPA concentrations were measured by spot analysis. No quantitative measurements of soy isoflavones or its metabolites were conducted. Study used a food questionnaire for dietary soy intake. A dietary questionnaire is not sufficient for quantitative measurement of a biomarker.
Biological relevance: effect biomarker (level of specificity of biomarker to reported effect)		Biological relevance unknown. This is the first study to report a possible protective effect of dietary soy on infertility treatment outcomes in women undergoing IVF.
Specificity (one parent compound with one biomarker or multiple parent chemicals with varying effects)		Study measured urinary BPA concentrations. Study did not measure any of the possible biomarkers for soy isoflavones in serum or urine (*e.g.* soy isoflavones (*e.g.* genistein, daidzein, and glycitein).
Method sensitivity/detection limits (accuracy and precision of methods used to quantify the biomarker)		In regards to BPA, the urinary concentrations of the sum of free and conjugated BPA species (total BPA) were measured using online solid-phase extraction coupled with isotope dilution–HPLC-tandem mass spectrometry. However, the intake questionnaire is not a precise measurement of soy exposure. On page 4, the authors cite a mean intake of 3.4 mg/d but this is just an estimate based on the questionnaire results.
Known or documented stability of biomarker		In regards to BPA, the limit of detection provided. In addition to study samples, low concentration and high concentration quality control materials prepared with spiked urine samples and reagent blanks were included. Urine

		samples were dived into aliquots to prevent loss due to freeze/ thawing.
Prevention of sample contamination		Study described methods to prevent BPA contamination.
Method requirements (appropriateness and description of measurement method)		Methods adequately described.
Matrix adjustments (appropriate reporting and weighting of differences in collection requirements and sample processes)		Study adjusted for urinary dilution using specific gravity. Free and conjugated BPA was measured.
Study design and execution: temporality (claim of causation supported by observation of the putative causal exposure preceding the outcome)		The study does not address temporality between exposure and outcome. The food intake survey considered dietary exposure to soy 3 months prior to study enrollment, and BPA was measured at some point during the IVF cycle. However, although the pregnancy outcomes were measured after study enrollment, there was no assessment of soy intake during the IVF cycle or during pregnancy.
Study design and execution: exposure variability and misclassification (sufficient number of samples)		There may be misclassification due to use of food questionnaire for soy intake. Misclassification of women in BPA exposed group due to a spot urine sample.
Study rationale (specific design to evaluate hypothesis)		The authors had previously reported that soy intake was positively associated with the probability of having a live birth *via* IVF while BPA had no effect on IVF outcomes. In addition, previous animal studies suggested that the adverse reproductive effects of BPA can be modulated by specific dietary factors (*e.g.* soy). Therefore, the authors examined whether this interaction occurred in women undergoing IVF.
Study participants (unbiased selection)		All women are IVF participants. It is difficult to extrapolate results in women undergoing IVF to the general population.
Data analysis (control of extraneous factors, distinction between causal and predictive)		Models were adjusted for age, BMI, race, and infertility diagnosis. Sensitivity analyses were conducted. However, important confounders known to influence IVF outcome were not discussed or evaluated in final models. Moreover, the results were no longer significant after adjusting for dietary folate and B12.
Reporting (Study clearly states its aims and allows the reader to evaluate the number of tested hypotheses)		Aims and study clearly stated and the authors indicate that the results need to be repeated in a larger study population.

Notes:

Overall, this paper is not adequate for assessing causation because it has 3 major flaws.

1) The exposure assessments for soy and BPA were inadequate and subject to misclassification. Spot urine samples are not the best method for assessing BPA exposure. However, the largest detraction of the manuscript is that soy isoflavones were not measured in the serum or urine of the women undergoing IVF. Pharmacokinetic studies of soy isoflavones in premenopausal women indicate that the bioavailability of isoflavones vary depending on type (Stechell *et al*., 2003). Moreover, urinary isoflavone concentrations correlate poorly with maximal serum concentrations, indicating the limitations of urine measurements as a predictor of systemic bioavailability (Stechell *et al*., 2003). Furthermore, the bioavailability of two isoflavones is nonlinear at higher intakes, suggesting that uptake is rate-limiting and saturable (Stechell *et al*., 2003). Taken together, the use of the dietary questionnaire is not an adequate indicator of soy isoflavone exposure and its results cannot be used to extrapolate dietary exposure in relation to health outcomes.

2) The study fails to discuss all confounding factors related to IVF outcome .Supplemental data (Table 1) indicated that when additional adjustments for dietary patterns were made or intakes for folic acid intake and vitamin B_{12} were made, *the associations between BPA and implantation were not statistically significant.* In addition, there are many other factors including alcohol use, caffeine consumption, and exercise levels, for example, that adversely affect IVF outcome that were not included in the final models (Gormack et al, 2015).

3) The timing of exposure and outcome are questionable and are difficult to interpret. For instance, soy intake was estimated for 3 months prior to study enrollment, whereas BPA exposure was measured during IVF cycle. However, although the pregnancy outcomes were measured after study enrollment, there was no assessment of soy intake during the IVF cycle or during pregnancy. It would have been better if soy exposure was measured at the same time as BPA.

It is also important to note, that in a previous manuscript the authors state that they found little evidence for an association between urinary BPA and adverse reproductive and pregnancy outcomes in women undergoing IVF. They did however report that soy was positively associated with a live birth outcome in women undergoing IVF. The population used in this study is the same as those in the two aforementioned studies by the same group, except the population was this time stratified by dietary soy. Taken together, the results from the initial study and the current study both suggest that BPA is not associated with IVF outcome.