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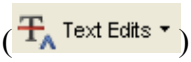
Use the **Text Edits** tool (

) to insert, replace, or delete text.

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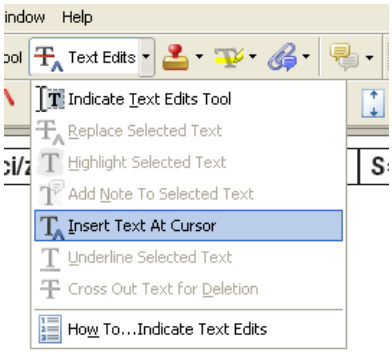

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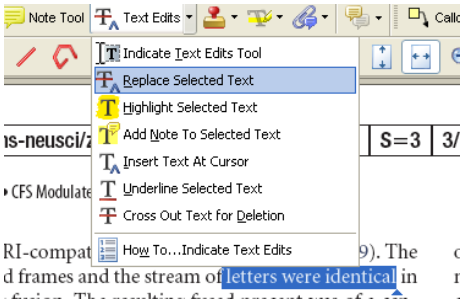

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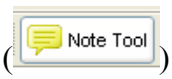
Use the Sticky Note tool (

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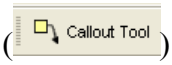
Use the **Callout tool** (

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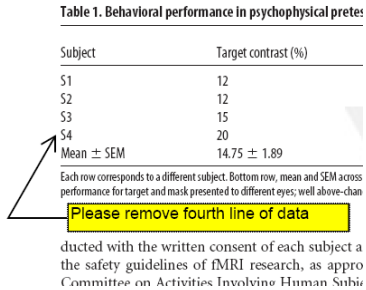

- Use the **Highlight tool** () to indicate font problems, bad breaks, and other textual inconsistencies. You can describe the problem with the Callout tool (above), a sticky note, or by double clicking highlighted text (a pop-up window will appear where you can add your comment).

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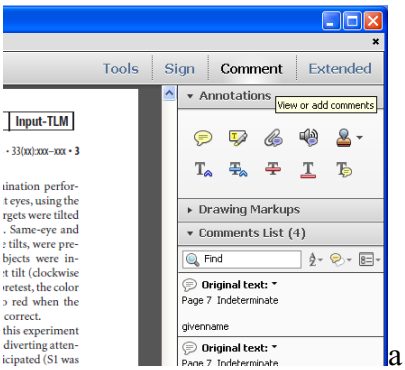

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<u>Note:</u> To use the comments/notes features on this PDF you will need Adobe Reader version 10.1.2 or higher. This program is freely available and can be downloaded from http://get.adobe.com/reader/.

Response to the Letter by G. M. H. Swaen and R. Otter

This industry-funded commentary misrepresents the rigorous methodology used to evaluate human literature associating phthalate exposure with endometriosis. It ignores consistency in findings from human and animal studies and substantial laboratory data strongly supporting causative effects carefully documented in our manuscript (1).

Given previous emphasis that Swaen has placed on documenting protocols for evaluating evidence (2), it is surprising that Swaen and Otter omitted key details of their own approach. In contrast, our expert panel deliberations are openly and transparently delineated (1). Indeed, studies included by Swaen and Otter suffer from crucial methodological flaws (3–6), effectively biasing their meta-analysis results to the null. In contrast, we excluded as methodologically flawed studies that relied on self-reported endometriosis rather than the "gold standard" of surgically visualized disease, that used inappropriate comparison groups, or assessed phthalate exposure after diagnosis. Sample size was a secondary consideration. In contrast, the Buck Louis et al (7) study used modern exposure assessment, age and residence matching in recruitment, and direct surgical visualization of outcome in the operative cohort.

Although it has a short half-life, monoethylhexylphthalate (MEHP) is the most biologically active metabolite of di-2-ethylhexylphthalate (DEHP) (8). However, Swaen and Otter do not acknowledge the statistical significance for associations between endometriosis and four other DEHP metabolites in the population-based cohort of the Buck-Louis et al (7) study. Furthermore, multiple sensitivity analyses confirmed robust statistical associations between DEHP exposure and postoperatively confirmed diagnoses compared with women found to have a normal pelvis (7). Inter- and intra-rater reliability in the diagnosis and staging of endometriosis was a particular strength of the operative cohort (9).

Although confirmation is needed, especially with longitudinal measurements of exposure, these findings in women together with laboratory and animal studies provide solid evidence supporting a conclusion of likely causation. Uncertainty was carefully considered in assessing probabilities of causation for this exposure-response relationship, following rigorous criteria established by the Intergovernmental Panel on Climate Change (10). Swaen and Otter do not appear to recognize the substantial, >99%, probability that at least one endocrine-disrupting chemical (EDC) effect across the 15 exposure-response relationships we studied is causal (11). Our median estimate of €163 billion in costs represents a substantial underestimate of actual EDC-attributable disease, given its focus on < 5% of EDCs, examination of a subset of health effects, and exclusion of human suffering and other societal costs of EDC-attributable diseases (12).

The comments presented by Swaen and Otter do not diminish the impact of our conservatively formulated findings for policymakers considering methods to reduce exposure to the EDCs of greatest concern. The economic rewards of doing so are likely to be in the billions of Euros and accrue annually insofar as alternatives free of health effects are used.

Disclosure Summary: The authors have nothing to declare.

Patricia A. Hunt, Sheela Sathyanarayana, Paul A. Fowler, and Leonardo Trasande

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Abbreviations: DEHP, di-2-ethylhexylphthalate; EDC, endocrine-disrupting chemical.
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