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Response to Invited Commentary

Kadhel et al. Respond to "Interpreting Exposure Biomarkers in Pregnancy"

Philippe Kadhel*, Christine Monfort, Nathalie Costet, Florence Rouget, Jean-Pierre Thomé, Luc Multigner, and Sylvaine Cordier

* Correspondence to Dr. Philippe Kadhel, Centre Hospitalier et Universitaire de Pointe-à-Pitre/Abymes, Pôle Parent/Enfant, Service de Gynécologie et Obstétrique, Pointe-à-Pitre, Route de Chauvel, 97159 Pointe à Pitre, Guadeloupe, France (e-mail: philippe.kadhel@orange.fr).

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We certainly agree with Dr. Savitz (1) that the use and interpretation of exposure biomarkers require caution, and we appreciate the fact that he took the opportunity of our publication (2) to formalize his arguments. We would like, in response, to consider the example of chlordecone exposure and its biological measurement within the framework proposed.

First, there is the issue of confounding due to "differences in spatial patterns of exposure in the community" (1, p. 000). Environmental exposure to chlordecone in Guadeloupe is through polluted soil and water, a consequence of treatment of land dedicated to banana crops. We are not aware of any evidence that populations living near these areas have socioeconomic characteristics that differ from those of the rest of the island's population.

Next, there is possible confounding due to "variation in behaviors that result in exposure" (1, p. 000). Chlordecone is now banned and has been for some years, but it persists in the environment. As a result, exposure to chlordecone is currently exclusively from dietary sources, and the major contaminated food groups have been identified: root vegetables, cucurbitaceae, and seafood. We took various socioeconomic determinants of diet (maternal place of birth, level of education, and marital status) into account. Nevertheless, the population of Guadeloupe includes several communities with different dietary habits and different vulnerabilities, so we cannot exclude the possibility that this leads to some differences in exposure.

There are also "interindividual differences in metabolism" (1, p. 000). The metabolism of chlordecone in humans has been well documented (3). Unlike many currently topical agents with suspected reproductive toxicity, chlordecone has several properties that make the use of exposure biomarkers more robust than for other compounds. Its half-life in blood is approximately 6 months, which provides reasonable confidence that even a single measurement during pregnancy will be representative of chronic exposure. There is indeed interindividual variability in metabolism and elimination, but the magnitude of the diversity is modest (4). Unlike other nonpolar organochlorine compounds, most chlordecone in blood is bound to albumin (nearly 50%) and high-density lipoproteins (5), and its main storage site is the liver (3, 4). This makes the complex issue of storage and potential association between measurement and medical conditions related to lipid metabolism (6) less crucial.

We agree that the physiological or pathological events likely to occur during pregnancy may influence biomarker measurements and have the potential to confound the association between an exposure biomarker and pregnancy course. Maternal plasma volume expansion is common during pregnancy, with vast individual variation (7). We therefore took into account several factors that can influence plasma volume expansion, in particular maternal prepregnancy body mass index, parity, maternal place of birth, and pregnancy-induced hypertension disorders including preeclampsia.

The influence of preeclampsia, which leads to induced preterm birth, is less clear. It is clinically defined by hypertension and proteinuria and may significantly impair renal function. As a consequence, the clearance of chlordecone may increase, resulting in a lower plasma concentration. On the other hand, preeclampsia has been reported to be associated with lower plasma volume expansion; this lower hemodilution would be expected to lead to a higher measured plasma chlordecone concentration. In view of these considerations, our analysis took into account the existence of complications of pregnancy, including preeclampsia.

In conclusion, we cannot exclude the possibility that medical conditions or unknown socioeconomic determinants not considered in our analysis contribute to the association observed. A better knowledge of the pharmacokinetics and pharmacodynamics of chlordecone during pregnancy would certainly be valuable. It may not be feasible to replicate this study in settings other than Guadeloupe, as recommended by Dr. Savitz (1), because chlordecone contamination seems only to be found in the French West Indies.

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Author affiliations: Centre Hospitalier et Universitaire de Pointe-à-Pitre/Abymes, Pôle Parent/Enfant, Service de Gynécologie et Obstétrique, Pointe-à-Pitre, France (Philippe Kadhel); Institut National de la Recherche Médicale (INSERM) U1085, Institut de Recherche sur la Santé, l'Environnement et Travail, Rennes and Pointe-à-Pitre, France (Philippe Kadhel, Christine Monfort, Nathalie Costet, Florence Rouget, Luc Multigner, Sylvaine Cordier); Université de Rennes 1, Rennes, France (Philippe Kadhel, Christine Monfort, Nathalie Costet, Florence Rouget, Luc Multigner, Sylvaine Cordier); and Université de Liège, Center for Analytical Research and Technology, Liège, Belgium (Jean-Pierre Thomé).

Conflict of interest: none declared.

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