will be dreadfully misused. I also have other concerns about the work. If I had been a reviewer, I would have considered this paper publishable only if the language and implications were modified.

Perhaps of greatest importance, this paper does not create confidence in EHP; there seems to have been a lack of diligence in the review of this manuscript. EHP should be a flagship among journals, but poor reviewing will set it adrift.

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Response from Lieberman and Colleagues

Several of the scientists who responded to our paper (1) raised similar questions, mostly showing a concern about the high doses used in our study. However, we would like to point out that, to the best of our knowledge, our paper is the first to examine the LD₅₀ of cyclosiloxanes (CSs). While there may be a difference of opinion about the interpretation of these data, for the first time there are data to discuss. Of equal importance is that we provide data on doses lower than the LD₅₀. These data demonstrate elevated serum enzyme values and histopathologic changes following administration of CSs and CS-D₄ at nonlethal doses (0.1 mL/mouse; 3.5 g/kg). All of these considerations underscore the value of our work. Other studies have used similar doses and the same route of administration to examine the toxicity of organic compounds including siloxanes (2–4). In our studies, no effects were noted when 1 mL soy oil was administered as a control. Our studies were intended to examine the acute toxicity of these agents rather than to evaluate their chronic toxicity or to determine the minimal level at which they produced a toxic effect.

Another concern raised by readers was the comparison of cyclosiloxanes with carbon tetrachloride (CCl₄) and trichloroethylene. We included this discussion to clarify the fact that even though the LD₅₀ for CS-D₄ is high (6–7 g/kg), it falls in the range of known toxic organic solvents such as CCl₄ and trichloroethylene (2). Both CCl₄ and trichloroethylene have been used at gram levels to study their acute toxicity by intraperitoneal injection (2, 5, 6). Witschi states that CCl₄ is moderately toxic and trichloroethylene is relatively nontoxic. However, the Agency for Toxic Substances and Disease Registry (ATSDR) has published profiles on the toxicity of these compounds and the potential human exposure and health hazards of these solvents (5, 6). In these documents they note that the maximum contaminant level (MCL) for each of these compounds in drinking water is 5 μg/L. Because CSs and these organic solvents have similar LD₅₀ values in the gram per kilogram range, it is possible that after thorough study of the toxicity of the CSs, similar MCLs may be set. In addition, trichloroethylene has been identified among the top 20 hazardous materials on the 1997 ATSDR priority list (ranked 15) (7). This fact emphasizes that compounds with LD₅₀ values in this range are important public health concerns. Clearly there is considerable variation in the verbal descriptors of the toxicity of these compounds.

The point is raised that CSs show about the same acute toxicity as alcohol and sodium chloride and that these chemicals are freely available in most homes. The presumption is that, for this reason, we should have minimal concern about the toxicity of CSs. Yet we know that analysis of ethyl alcohol and sodium chloride has led to the opposite conclusion. Ethyl alcohol is an important liver toxicant, and many people worldwide suffer from liver disease as a result of chronic ethanol intake. Fetal alcohol syndrome is also well documented. As for sodium chloride, the relationship between ingestion of high amounts of salt and high blood pressure and stroke is well known. We emphasized the need for additional studies of CSs in the concluding two sentences of our paper:

Further, our studies have not evaluated possible long-term effects of CSs such as chronic inflammation, chronic pulmonary and liver disease, or neoplasia. Nevertheless, our results underscore the importance of a complete analysis of the toxicity of CSs.

Witschi also suggests that the phrase "cyclosiloxanes are widely distributed" is a misinterpretation of our data because only 0.1–0.5% is found in different organs (8). The term "widely distributed" is used not as an index of the abundance of CSs in different organs but as a statement of their presence. We would also like to point out that we only measured unmetabolized CSs in these studies. If these compounds were modified by biotransformation and existed as new, low-molecular species or bound to macromolecules, we would not have detected them by our analysis. Further, most studies of siloxanes until recently were carried out without any quantitative assessment, that is, tissue level of siloxanes versus tissue injury (9). In recognition of this problem, our group has developed methods for the detection and quantitation of cyclosiloxanes in biological tissues (10).

Carlton and Meeks raise the issue of the preparation of the distillate and the fact that the "cracking" process at 180°C has no relationship to breakdown in the intact implant in vivo. In our paper we made no inferences about the relationship of distillate preparation to breakdown. Rather, we used the distillation process as a convenient way to produce a mixture of siloxanes, which we found migrated out of intact implants (11). We could have just as easily purchased the components from a chemical company, and in fact, that is what we did with the octamethylocyclooctasiloxane (CS-D₄). This purchased CS-D₄ produced effects that were indistinguishable from those of the distillate.

Meeks also suggests that these mice died of infection. First, if they had died of infection, this would be an important finding because only mice exposed to the distillate or CS-D₄ died or developed evidence of tissue injury. However, the histopathologic picture is not one of infection. The histopathology of the liver showed a classic pattern of chemically induced cell death, and the lung lesions were not typical of bronchopneumonia or lobar pneumonia.

Meeks raises the question of metabolism and clearance. He is accurate that we do not cite any of the references he has provided in our discussion. We were in error in not including the contribution of McKim et al. (12). The paper was published in 1998 and we simply missed it. All of the other references on CS-D₄ metabolism that he cites are abstracts and not full-length, peer-reviewed articles. Meeks raises an important point. He interprets his data to mean that CS-D₄ is metabolized and is rapidly cleared from the body. While this may be true, nevertheless, many compounds are metabolized via more than one metabolic pathway; some of the pathways lead to detoxification/inactivation and others lead to active chemical species that cause tissue injury, cell death, or neoplasia. The abundant literature on compounds such as aflatoxin, benzo(a)pyrene, acetylaminofluorene, and related compounds provide examples of this principle. We would also like to point out that the study Meeks refers to was an inhalation study, which may not be directly relevant to our findings.
We believe that much more work on the low molecular weight cyclosiloxanes is necessary. Inhalation studies like the one referred to by Meeks, ingestion studies like the one summarized by Lukasik et al., and injection studies are all necessary to develop an understanding of the biologic importance of these agents.

We are confident that our paper represents an important contribution to the study of silicone toxicology and hope that it will encourage many additional studies in this area.

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