with $^1$H nuclear magnetic resonance (NMR) technique using an internal control (5). Blood samples from animals given feed without siloxanes showed no signals originating from the siloxanes tested. In all blood samples from animals given feed with siloxanes, they were detected. In samples from animals given feed with PDMS, the mean concentration (± standard deviation) of siloxanes of 26 ± 14 μg/cm$^3$ was noted; in samples from animals given feed with cPDMS, the mean concentration of siloxanes of 70 ± 97 μg/cm$^3$ was noted. The difference was not significant. These results conform well to those obtained previously in Rhesus monkeys by Calandra et al. (6). In our opinion, the absorption and toxicity of siloxane-based drugs should be more intensively studied.

Our study was supported by the Polish State Committee for Scientific Research (KBN) (grant 4P05D06612).

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In their recent publication, Lieberman et al. (1) described the acute toxicity in mice after intraperitoneal injection of distillates containing either a mixture of cyclosiloxanes or a component of the mixture’s distillate (octamethylcyclotetrasiloxane). The dose levels in the series of studies ranged from 3.5 to 35 g/kg. The median lethal dose of the distillate was 28 g/kg, or 1.68 kg for a 60-kg human.

The authors drew sweeping conclusions regarding this class of chemicals based on a minimalist investigation of toxicity. The acute doses administered by the intraperitoneal route were clearly excessive and were much greater than the limit doses recommended by the U.S. Environmental Protection Agency (EPA) and the Organisation for Economic Co-operation and Development (OECD) as maximum dose levels in studies of this type. Few compounds are tested at dose levels this high because of concerns regarding unnecessary pain and suffering of animals. A basic tenet of toxicology is that all chemicals have the potential to be toxic at sufficiently high dose levels. The toxicity observed after administering extremely high dose levels is not useful for comparative purposes (because few compounds are tested at such high levels) or for risk assessment (because the dose levels are so much greater than potential human exposures to the agents of concern). Acute lethal studies conducted by the intraperitoneal route deliver a bolus dose with the equivalent of 100% absorption. Lethality is not a surprising finding under these conditions and would be observed with table salt and other substances generally considered to be innocuous.

Furthermore, the conclusion that cyclic siloxanes are similar in toxicity to carbon tetrachloride and trichloroethylene is unfounded. The no-observed-adverse-effect level (a standard benchmark of toxicity) for carbon tetrachloride that has been used to set a drinking water standard is 1.0 mg/kg/day in a 12-week gavage study in rats. This was 3,500 times less than the lowest level used by Lieberman and colleagues (1). They did not present any evidence that carbon tetrachloride and trichloroethylene share a common mechanism of toxicity with the siloxanes.

In summary, the publication of Lieberman et al. (1) does not advance our understanding of the toxicity of this class of compounds. The paper is likely to be cited by plaintiffs in tort cases, but the study results are of limited use to those of us who are concerned with the safety evaluation and risk assessment of these substances.

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I recently read the paper “Cyclosiloxanes Produce Fatal Liver and Lung Damage in Mice” (1). Although siloxanes are not a particular interest of mine, I was curious. Lieberman et al. (1) administered the distilled mix at a rate of 35-35 g/kg body weight. As a toxicologist, I was intrigued because 35 g/kg is 3.5% of body weight, injected intraperitoneally yet! Toxicologically, such a dose is akin to hitting the mouse with a stick. Lieberman et al. reported that “some or all of the components of the distillate are lethal, with an LD$_{50}$ for the distillate of about 28 g/kg.” Do we ever find a substance that is not lethal at some dose?

Lieberman et al. (1) then make the following statement:

Our data demonstrate that a mixture of low-molecular-weight CSs contained in breast implants is highly toxic and that at least one specific compound, CS-D4, is toxic as well.

Highly toxic indeed!

Five grams per kilogram is usually considered virtually nontoxic in the world of pesticides, and here we are told that 28 g/kg is highly toxic. CS-D4 comes a bit closer at 6--7 g/kg. There appears to be a three-order-of-magnitude nomenclature problem here.

The finding of hydroxyl radical formation as a result of treatment with CS-D4 sparked a moment of interest, which died when I saw that the animals were given a lethal dose, and no dose--response information was obtained. [Lieberman et al.’s Figure 4 (1) does not disclose the dose, but it was found in text, fortunately nearby.]

It also occurred to me that there was some missing context. Lieberman et al. (1) did not explain what fraction of an implant actually can be extracted in such a distillate, even though they quoted an earlier paper with that information (2). Approximately 1% of the implant can be considered mobile, if distillation describes mobility. Mobilization in vivo is obviously slow, unlike the intraperitoneal assault on the mice.

I am curious about the point of this paper. I do not follow the implant problem, but I know that it is highly charged politically and emotionally. As the newspapers tell us, implants are litogenic and produce much exercise for the courts. The only conclusion I can draw is that the terminology here is political. It is the kind of rhetoric that comes from activists who ignore science.

It is important to learn what happens to this foreign material placed in the body and to try to track the biological interactions. Lieberman et al. (1) make a small contribution, but I predict that this paper...
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 (0.1–1 mL intraperitoneally) 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 trichloroethyene (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 ethyl alcohol ingestion. 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 octamethylcyclotetrasiloxane (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.