indicates that this compound exhibits toxicity comparable to these other agents. Conventional toxicity tables (8,9) comparing LD$_{50}$ values show that the ip LD$_{50}$ for sodium chloride is 4 g/kg. Thus, ordinary table salt is more toxic than either CS-D4 or breast implant distillate! To further put this into perspective relative to silicone breast implants, it would take about two 660-pound breast implants in an average size woman to achieve a dose equivalent to the LD$_{50}$ reported for CS-D4 by Lieberman et al. (1). This is based on the unrealistic assumption that all of the CS-D4 in an implant would be released at one time.

The histopathologic findings reported by Lieberman et al. (1) are an enigma. Tables 2 and 3 in their paper show the reported histopathologic changes and average grade of the reported lesions for implant distillate and CS-D4, respectively. The findings reported in these tables are clearly not dose related. For example, in Table 2 (1), the highest incidence (3 of 6 animals) of extensive necrosis was produced by the lowest dose (3.5 g/kg), which had the lowest incidence (1 of 6 animals) of individual cell necrosis. Conversely, a dose of 35 g/kg had a 1-of-6 incidence of extensive necrosis and a 5-of-6 incidence of individual cell necrosis. Further, the increases reported by Lieberman et al. (1) for the three liver enzymes (Figure 3A and B) are minimal, relative to the high doses administered, and do not appear to be dose related. There is no indication in the figures that the observed values are statistically significantly different from control. Statistical significance is difficult to determine from examination of the figures because of the tremendous variability and the fairly consistent or uniform response across all the doses. The observation in this study that death of the animals occurred 5–8 days after the ip injections of either distillate or CS-D4 indicates that death was not due to a direct toxic effect of the test materials. The delayed deaths are consistent with an infectious process probably related to the quality of the test material or to a highly inflammatory process related to the route and volume of test material administered with a resultant peritonitis. It is perplexing that Lieberman et al. (1) apparently did not perform a microbiologic assessment on the test material or the animals at necropsy to rule out an infectious process. Certainly the apparent increase in free radical formation can be associated with an inflammatory response. It is also noteworthy that, in the study to assess free radical formation, the dose of CS-D4 administered was greater than the reported LD$_{50}$ for this compound by this route.

Lieberman et al. (1) state in their discussion section that

We have no evidence that these compounds are metabolized, but it is clear they evoke strong biological responses.

This is in marked contrast to all of the available literature. Studies by McKim et al. (10) clearly show that CS-D4 induces cytochrome P450 2B1/2B in rats in a time, dose-dependent, and "phenobarbital-like" manner. In other words, it is an adaptive effect. Studies conducted by Plotzek et al. (5–7) and Varapath et al. (11) provide compelling evidence that CS-D4 (and probably other cyclosiloxanes) are extensively metabolized by rats and that metabolism and subsequent elimination of hydrophilic metabolites in urine and feces is an important clearance mechanism from mammalian species. In particular, the rates of metabolism and clearance of CS-D4 and its metabolites (5,6) suggest that these compounds will not be unusually persistent in mammalian organisms and are inconsistent with the suggestion by Lieberman et al. (1) that these compounds will persist in mice for "at least a year..." in a number of organs and fat.

In summary, this paper [Lieberman et al. (1)] is deficient in several areas including data interpretation, review of existing and relevant research, and application of basic toxicology principles. The authors have ignored the central paradigm of toxicology as put forth by Paracelsus (12), which, as paraphrased, states "the dose makes the poison."

Judge Sam C. Pointer, Jr., the federal judge overseeing the multidistrict breast implant litigation, appointed an expert scientific panel to review the available data on breast implants. Their toxicology review "reaffirmed the low systemic toxicity of silicone" (13). The data of Lieberman et al. (1) (contrary to the authors' interpretations) also reaffirm this conclusion of low systemic toxicity. Although the authors acknowledge funding from Consumer Advocates for Product Safety (CAPS), they fail to note that funding for CAPS is obtained through attorneys for plaintiffs in the breast implant litigation.

Robert G. Meeks
Toxicology and Risk Assessment
 Dow Corning Corporation
 Midland, Michigan
E-mail: robert.meeks@dowcorning.com

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In the February issue of EHP, Lieberman et al. (1) published an interesting study on the toxicity of cyclosiloxanes. Briefly, they intrauterinely injected mice with a breast implant distillate consisting of a mixture of cyclosiloxanes. After 4–14 days, they performed histopathologic studies and measured the formation of hydroxyl radical and levels of serum enzymes. The experiments are well done and the observations that were made are certainly believable. However, I am somewhat puzzled by the way the findings are interpreted. In several places Lieberman et al. stated that these compounds [i.e., hexamethylyclotrilsiloxane (D3), octamethylcyclo-trisiloxane (D4), decamethylcyclopentasiloxane (D5), and dodecamethylcyclohexasiloxane (D6)] are highly toxic. In further research, they make a previsous study which apparently showed that following a single subcutaneous injection, cyclosiloxanes are "widely distributed" throughout the body. (2)
According to Lieberman et al. (1), the LD_{50} for the distillate was 28 g/kg body weight; for D4, a component of the mixture, the LD_{50} was 6-7 g/kg. According to the first edition of the now classical Casarett's and Doull's *Toxicology* (3), such values are not characteristic for highly toxic compounds. As a matter of fact, agents having an LD_{50} of 5-15 g/kg are usually classified as slightly toxic, and those having an LD_{50} of ≥ 15 g/kg are labeled practically nontoxic. The latest edition of *Casarett and Doull's Toxicology* (4) no longer carries this classification, but provides the following on the spectrum of toxic doses:

Some chemicals produce death in microgram doses and are commonly thought of as being extremely poisonous. Other chemicals may be relatively harmless after doses in excess of several grams.

An accompanying table (4) lists the LD_{50} values for ethyl alcohol and sodium chloride as 10 g/kg and 4 g/kg, respectively. These values are similar to those found for the cyclosiloxanes. Alcohol and salt are freely available in many homes, supermarkets, and restaurants and are usually not perceived as being highly toxic. Lieberman et al. (1) also compared the toxicity of the cyclosiloxanes to the toxicity of carbon tetrachloride and trichloroethylene. Carbon tetrachloride has been identified as moderately toxic to laboratory animals (5), and trichloroethylene called relatively nontoxic (6). Clearly, there is a considerable discrepancy between the usual toxicity classification and the descriptors used by Lieberman et al. (1).

It is also not justified to ascertain that cyclosiloxanes are widely distributed following subcutaneous injection. In their previous paper (2), Lieberman and colleagues deposited 250 mg of breast implant distillate subcutaneously in the suprascapular area of mice. They then measured total and individual cyclosiloxanes in 10 organs and tissues up to 1 year after treatment. Again, the data are credible. Unfortunately, however, the paper (2) fails to provide data on mass balance, which is considered to be a de rigueur requirement in distribution studies. Nevertheless, from Figure 2B [Kala et al. (2)] it can be calculated that the average concentration of total cyclosiloxanes 6 weeks after the injection, when maximum values were obtained, is approximately 6 μg/g wet tissue. Assuming that there is a uniform concentration of cyclosiloxanes in all tissues (an assumption which overlooks the fact that the highest cyclosiloxane concentrations were found in tissues which contribute little to overall body mass such as lymph nodes, uterus, and ovaries, whereas liver had < 1 μg/g and skeletal muscle approximately 6 μg/g), it then can be calculated that the total body burden away from the site of injection in a 25-g mouse would have been 150 μg cyclosiloxanes. This represents < 0.1% of all the material deposited in the suprascapular region. Where is the rest of the material? In the absence of a mass balance sheet that would provide complete data on distribution (and possible excretion) of the cyclosiloxanes, we must assume that > 99.9% of the injected material never left the site of deposition. Given these facts, it simply cannot be stated that "they are distributed widely." They are not.

The available evidence on the toxicity of silicones was recently reviewed by two independent bodies (7,8). The National Science Panel (7) concluded that

The results of this review indicate that the silicones used in silicone breast implants are of very low toxicity to animals. Although there is documented evidence of local inflammatory reactions to silicone breast implant material in animals, there is no convincing evidence for a significant systemic inflammatory response.

The Independent Review Group (8) stated

The information supplied about the local and systemic toxicity, genetic toxicity, reproduction toxicity and carcinogenicity testing showed that they were all relatively bland substances in a range of animal and in vitro tests... Tests looking with reliable, validated analytical techniques for the dissemination of silicones from implants in the body, including break down products of the polydimethylsiloxanes, have shown either no dissemination, or the presence of only very small amounts at distant sites following rupture of gel-filled implants, or after deliberate injection of the gel.

Clearly, the findings by Lieberman et al. (1,2)—and there is no reason not to believe their data—would much better support the conclusions drawn by two recent review groups rather than their own interpretation of their data. Thus, terms used such as highly toxic and widely distributed are of concern. Given the actual data, these descriptors are not in line with current valid and thoroughly validated concepts of toxicology. They may be misused because, taken out of context without the accompanying hard data, they will lead to serious misrepresentations of the hazards associated with silicone breast implants.

**Hanspeter Witschi**

Institute of Toxicology and Environmental Health University of California Davis, California E-mail: hrwitschi@ucdavis.edu

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We read with great interest the paper by Lieberman et al. (1) on the toxicity of cyclosiloxanes. In addition to their important observations, it should be noted that siloxanes, as dimethicone [British Pharmacopeia (2)] or simethicone [U.S. Pharmacopeia (3)], are used, for example, to treat intestinal gas in humans. They are mixtures of both linear (polymethylsiloxanes; PDMS), as the main component, and cyclic siloxanes (polycyclosiloxanes; cPDMS) of different molecular masses. For drugs registered in Poland, the current producers' information on simethicone- or dimethicone-based drugs stated that the drugs are not completely absorbed in the intestine and some of them permit a daily intake as high as 400–640 mg/day.

To verify the statements, we recently performed a placebo-controlled study on intestinal absorption of siloxanes in rats (4). We examined the blood of Wistar rats fed 12 days with a granulated feed diet without siloxanes (LSM; Wytówna Pasz w Motyczu, Poland) with added 5% PDMS (n = 5 animals), 5% cPDMS oil (n = 5), or without siloxanes (n = 5). Viscometry and molecular mass of siloxanes tested were equal to those most frequently used in oral drugs [viscosity of 300 centistokes (cST), which reflects molecular mass of about 15,000 Da; 1 cST = 10^{-6} m^2/sec]. All animals used in the research were treated humanely according to Medical University of Gdansk institutional guidelines. The siloxanes were extracted from the rats' blood and quantitatively measured.