According to Lieberman et al. (1), the LD$_{50}$ for the distillate was 28 g/kg body weight; for D$_4$, 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 de rigueur requirement in distribution studies. Nevertheless, from Figure 2B [Kala et al. (2)] it can be estimated 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 polymer, 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.

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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 silicones, 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 silicones (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 silicones in rats (4). We examined the blood of Wistar rats fed 12 days with a granulated feed diet without silicones (LSM; Wytówna Pasz w Motycz, Poland) with added 5% PDMS (n = 5 animals), 5% cPDMS oil (n = 5), or without silicones (n = 5). Viscosity and molecular mass of silicones 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 Gdańsk institutional guidelines. The silicones were extracted from the rats’ blood and quantitatively measured.

**A 442**  
Volume 107, Number 9, September 1999 • Environmental Health Perspectives
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 ($\pm$ standard deviation) of siloxanes at 26 $\pm$ 14 µg/cm$^3$ was noted; in samples from animals given feed with cPDMS, the mean concentration of siloxanes at 70 $\pm$ 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.

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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 (2). 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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