Letters Re: “Cyclosiloxanes Produce Fatal Liver and Lung Damage in Mice”

It is EHP's stated editorial policy to serve as a forum for discussion of issues of environmental health, encouraging the expression of scientific opinion and fostering healthy scientific debate. Your editorial policy states that “all scientific articles are subject to rigorous peer review. The primary criteria are environmental significance and scientific quality.” Based on these criteria, it appears that the journal has failed to hold the paper of Lieberman et al. (1) to these standards. This paper is a blatant and deliberate misdirection of the reader, providing misinterpretation of a poorly designed study that is not up to the standards of modern toxicology or EHP.

Lieberman et al. (1) indicate that they distilled breast implant gel at 180°C at reduced pressure for 24 hr and imply that this material represents what would leak from implants. It is well known that silicone polymers can thermally depolymerize to form cyclic siloxanes under the authors' distillation conditions (2), but this does not represent “real life” conditions. Lieberman et al. (1) administered this distillate to mice by intraperitoneal (ip) injection at doses up to 35,000 mg/kg—surely an unacceptably high dose that would cause direct irritation. It is therefore no surprise that the identified ip median lethal dose (LD50) was 28,000 mg/kg and that lung and liver lesions were noted. Perhaps the animal care committee should have requested a revision of the testing protocol before the study was initiated. Lieberman et al. (1) reported that one of the individual components of the distillate, identified as CS-4 based on an ip LD50 of 6,000–7,000 mg/kg, is equivalent in toxicity to oral exposures to carbon tetrachloride; they characterized the distillate and individual distillate materials as highly toxic. For regulatory purposes, any material with an LD50 greater than 2,000 mg/kg (3) or 5,000 mg/kg (4–9) is considered to be the highest dose necessary to test. Materials with LD50 values greater than these dose levels are considered to be virtually nontoxic.

If this misinterpretation of toxicity data were to remain quiet in the annals of EHP, it would be merely a problem of editorial carelessness. However, this paper has been picked up by several of the news services (e.g., Reuters, BBC), with online and print media declaring “Silicones Kill Mice!” and no longer noting that the dose and dose route are responsible for the lethality, not the inherent toxicity of the material. Publishing this paper, EHP has become a source for junk science reporters. The fact that the NIEHS is a well-respected scientific body only adds more credence to this ill-conceived and misinterpreted study.

I implore you be more attentive to the content of the articles published in EHP. It weakens the reputation of the NIEHS, feeds the junk science machine, and diminishes the credibility of all toxicologists when articles such as this are given space in a peer-reviewed scientific journal.

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In the February issue of EHP, Lieberman et al. (1) reported that the intraperitoneal (ip) injection of either cyclosiloxanes (CSs) from silicone breast implant distillate or CS-D4, a component of breast implant distillate, was lethal and caused liver and lung damage and increased hydroxy radical formation. This paper is flawed and contains a number of scientific issues that need to be addressed.

Lieberman et al. (1) reported that a distillate from an explanted breast implant contains anywhere from 2 to 60% cyclosiloxanes, with CS-D4 being present at the highest concentration. It is well known that destructive distillation of a siloxane polymer or gel at high temperature under vacuum "cracks" the polymer causing, under these destructive conditions, the formation of large amounts of cyclosiloxanes (2). There is no doubt that the low molecular weight cyclosiloxanes collected by Lieberman et al. (1) were created during the distillation by a "cracking" process. The conditions required to crack a polymer do not exist in the human body. Our own analysis of an intact silicone breast implant shows that CS-D4 levels rarely, if ever, exceed approximately 700 ppm (i.e., 700 µg/g). Migration of CS-D4 from an implant occurs at a rate of about 0.58 µg/day (3) which, for a 60-kg women, equates to a 0.010 µg/kg/day exposure to CS-D4.

Lieberman et al. (1) reported that after a single subcutaneous injection in mice of 250 mg (or about 10 g/kg body weight) of breast implant distillate, the cyclosiloxanes are widely distributed to many organs and can be detected as much as 1 year following a single injection. In their original paper (4), many of the values reported for tissue concentrations of cyclosiloxanes at 9 weeks and later appeared to be at or below the limit of detection of their analytical methodology and were well below what would be considered the limit of quantitation, making some of their conclusions misleading. In our own studies (5–7) using 14C-CS-D4 administration to rats by various routes of exposure, we also showed that CS-D4 was uniformly distributed to tissues, but with an elimination half-life of 50–200 hr, depending on the tissue, and < 0.0078% of the radioactivity left in tissues at 6 weeks postexposure. These data indicate that it is unlikely that CS-D4 would be found in tissues 1 year after administration.

As for the acute toxicity effects reported by Lieberman et al. (1), many of the reported findings oppose the conventional wisdom of toxicology. Administration of up to 1 ml of a substance into the peritoneal cavity of a 25–30-g mouse (which is equivalent to 2.4 L injected into the abdominal cavity of a human) basically represents the maximum dose that can be administered to a mouse and far exceeds the dose of CSs that could be encountered by humans under any condition, including women with breast implants. The LD50 values of ~28 g/kg and ~6–7 g/kg reported by Lieberman et al. (1) for the distillate and CS-D4, respectively, were used to indicate extreme toxicity, which is absurd. Credible references in toxicology (8,9) would consider compounds with acute LD50 values of 5–15 g/kg to be practically nontoxic, whereas compounds with LD50 values of >15 g/kg are considered relatively harmless. Based on the data presented by Lieberman et al. (1) and using these widely accepted criteria, one should interpret that CS-D4 is practically nontoxic and the improperly prepared breast implant distillate is relatively harmless. Lieberman et al. (1) further suggest that by comparing ip LD50 values to the oral LD50 values of carbon tetrachloride and trichloroethylene, "the value for CS-D4"
indicates that this compound exhibits toxicity comparable to these other agents. Conventional toxicity tables (8,9) comparing LD50 values show that the ip LD50 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 LD50 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 size women to achieve a dose equivalent to the LD50 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.

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 silicon" (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.

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