Lifetime Risk from Polyurethane Covered Breast Implants

The recent article by Luu et al. (1) predicting an excess lifetime risk from polyurethane covered breast implants of 1 in 400,000 is based upon numerous questionable assumptions and cannot go unchallenged. I have listed below several of the more obvious problems with this study and its conclusions.

The estimated dose of polyurethane was too high. The authors use a weight of foam in their dosage estimates of 4.87 grams, but they do not reference the source for that figure. Presumably they meant two implants, and not one as stated. From the best available data, the Food and Drug Administration (FDA) has previously used the figure of 1.35 g of foam per implant, or 2.7 g for two implants (2). Even with two implants, the polyurethane exposure is almost half of that estimated by the authors.

Polyurethane oligomers were incorrectly assumed to be 2,4-toluenediamine (2,4-TDA). In one part of the study, 14C-labeled foam was implanted subcutaneously in rats (no information about where or how was provided) at a dose of 80 mg/kg body weight (bw), and counts were measured in urine and feces for up to 56 days. The authors appeared to assume that any radioactive breakdown products of polyurethane were 2,4-TDA and not oligomers or metabolites. Because there is no evidence that polyurethane oligomers are mutagenic or carcinogenic, this difference is of critical importance.

Implanted polyurethane in doses up to 267 mg/kg bw did not form DNA adducts in a model where adducts could be demonstrated from 2,4-TDA (3). It has clearly been shown that 2,4-TDA is artificially created from oligomers in urine during the extraction process (4,5). Luu et al. (1) were unable to measure any quantity of 2,4-TDA in blood or urine after polyurethane implantation, yet they graphically plotted and described data (see Tables 3 and 4 in their paper) and calculated a risk assessment as if they had. There was no mention of any evidence (or lack thereof) of polyurethane-induced neoplasia in this study, either grossly or histologically. There were apparently no controls in this or any other part of the study.

An inappropriate scaling factor was used. The authors used a scaling factor of 45 in their extrapolation of rat doses to humans, based on an article by Ramsay and Anderson (6), which reported styrene exposure by inhalation in a rat model. Inhalation studies must take into account many factors, such as alveolar surface area, that are not relevant to this discussion. Using the scaling factor created for an inhalational model is not acceptable for an injection or implantation model. If one uses the estimated weight ratio of 58 kg for a human female (as used by Luu) and 0.25 kg for the rat, the conversion factor is 232 and not 45. The authors by this error alone have overestimated the dose by a factor of five.

Previous risk assessments, polyurethane studies in both animals and humans, and relevant epidemiology were not considered in the risk analysis. It was surprising that the authors referenced as allegedly showing "a potential health risk" the prior risk assessment performed by the FDA, which estimated a lifetime cancer risk from two implants of 5 in 10 million (2). This FDA risk assessment used the same potency factor [0.21 (mg/kg/day)1 and degradation rate (88 ng/g foam/day)] as that of Luu et al. It assigned variables that would overestimate the risk, as compared to Luu who included a 35-year exposure time (vs. 10 years) and a patient weight of 50 kg (vs. 58 kg). The amount of foam estimated was less in the FDA study, as noted above. A separate calculation was performed to determine the risk if all of the 2,4-TDA that could possibly be released from two implants actually was. The FDA concluded that "the study showed that the risk of cancer from TDA released by polyurethane breast implants is negligible. FDA estimates it is unlikely that exposure to TDA will cause cancer in even one of the women with these implants. The health risk connected with surgical removal of the implants is far greater than the risk of developing cancer." (7).

Another recently published risk assessment (5) and the report of a Canadian Medical Association Expert Panel (8) are both in agreement with the FDA. While it is acknowledged that Luu et al. (1) used a physiologically based pharmacokinetic (PBPK) model that is different from the others, it creates the appearance of a crucial bias when the major works of others are not recognized in the discussion, and assumptions are made that clearly overestimate a possible dose. This negates whatever advantage the PBPK model might provide.

Luu et al. (1) did not mention any polyurethane implantation studies in animals showing no chemical carcinogenesis (9-11), clinical studies in humans demonstrating no cancers (12-14), or epidemiologic studies showing no increased risk of cancer from exposure to 2,4-TDA-containing hair dyes (15-17) or in polyurethane foam manufacturing plant workers (18-20). In attempting to determine if 2,4-TDA is a human carcinogen, and if so, at what dose, it would seem important to consider these published studies. Only a few of the many articles on these subjects are referenced in this letter.

The author's calculated theoretical risk is not reliable. The primary conclusion remains, as Luu et al. (1) so stated, that "there is no data available at this time to show a cause and effect relationship between the use of this PU foam and production of cancer in humans." Their calculated risk of 1 in 400,000 would not reliably predict a single neoplasm among the 100,000-200,000 women with polyurethane covered breast implants. The fact remains that polyurethane and 2,4-TDA are toxicologically distinct and cannot scientifically be considered equivalent. To avoid the groundless fear that this paper might produce, patients with polyurethane covered breast implants and their doctors need to know that the risk assessment of Luu et al. (1) is a theoretical maximum risk based on assumptions that greatly overestimate the dose, and that the actual risk is far more likely to be null.

Kenneth Kulig
University of Colorado Health Sciences Center
Toxicology Associates
Denver, Colorado

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Response

In his comments on our paper, Kulig states that “the estimated dose of polyurethane was too high.” The polyurethane foam mass (4.87 g) used in this study corresponds to the mass of foam covering two implants of 500 g each. The 2.7 g referred by Kulig corresponds to the mass of foam covering two implants of 250 g each.

Another criticism was that “polyurethane oligomers were incorrectly assumed to be 2,4-toluidenediamine (2,4-TDA).” We did not assume that all the degradation products were oligomers. We also did not use an implant study to calibrate the model. The text and data in Figure 2 of our paper was clearly identified as an intravenous (iv) bolus of 0.52 mg/kg of 2,4-TDA. Obviously, this would result in serum concentrations above the detection limits, so that the model could be calibrated. We never claimed that the data in our Figure 2 was from an implant or that the implant degradation product, 2,4-TDA, could be detected in serum. This iv bolus data of pure 2,4-TDA was used initially to calibrate the PBPK model. Subsequently, the PBPK model was used to simulate routes of administration in the rat and in rat (0.021 g) and human (4.872 g) implants in our Table 2. Table 3 in our paper shows a list of metabolism and excretion parameters, and not plasma or urinary levels of 2,4-TDA as indicated in Kulig’s comments. In Figure 3, we plotted 2,4-TDA serum concentrations of the simulated low-dose rat iv bolus, feeding, and implant cases, and not, urinary 14C-2,4-TDA as Kulig claimed in his comments. The 14C data were used only to validate the excretion of 2,4-TDA in rats.

We did not use an inappropriate scaling factor. Metabolism has been clearly shown to scale with the 0.7 power of the body weight (L). Thus, the scaling factor is (58/0.25)^0.7 = (232)^0.7 = 45. This has nothing to do with the use of an inhalation route. This factor applies to the forward rate constant for metabolism in the liver.

Kulig stated that “previous risk assessments, polyurethane studies in animals and humans, and relevant epidemiology were not considered in the risk analysis.” First, it is important to understand that the polyurethane foam breast implant has been voluntarily withdrawn from the commercial market since 1974. It is beyond the scope of our paper to provide all the clinical evidence to inform physicians or calm patients fears with these implants. The purpose of this paper was to use a novel approach, the PBPK model, to predict the kinetics of chemicals and extrapolate between different routes of administration from animals to humans. Kulig states that we used variables to inflate the risk estimate. This is not correct. The variables used in the risk estimate in this study were chosen carefully to reflect available data from clinical reports. For example, the lifetime of an implant was consistently reported to be less than 10 years. This conclusion is based on “histological analysis of retrieved explants and clinical observations” as provided by the device manufacturer (2).

The predicted excess lifetime cancer risk of 1 in 400,000 in this study represents the upper limit on risk, based on the results of the kinetics of intravenously administered 2,4-TDA in the rat extrapolated to humans using PBPK modeling. Like many risk estimates, the estimate in this paper is only as good as the extrapolation of sometimes imperfect data from animals to humans. It is, however, consistent with the manufacturer’s risk estimates (2) and others previously conducted by the FDA (3,4). In any case, the risk estimate does not predict a significant increase in cancer incidence for those women implanted with the polyurethane foam-coated breast prostheses.

Hoaan-My Do Luu
Center for Devices and Radiological Health Food and Drug Administration Rockville, Maryland

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Environmental Noise Exposure

The article “Loud—but Not Yet Clear” in the May issue of Environmental Health Perspectives (1) discusses the subject of effects of noise on health. This is the second article in a short time that refers to this subject (2), which we think is commendable. Environmental noise exposure is an environmental factor that seriously affects health and well-being. This is also demonstrated by the table presented in your article. This table originated in the 1994 “Noise and Health” report of the Health Council of the Netherlands (3), as was duly mentioned in the report of the Leicester Institute for Environment and Health (4) to which your article refers.

We would like to bring a related matter to the attention of your readers. For an efficient policy to reduce noise-induced health effects outside the workplace, simple exposure metrics are urgently required. This led the Netherlands Minister of the Environment to request the Health Council to recommend such metrics to be used in national and in European noise abatement policies. In October 1997, the Health Council published its report, titled “Assessing Noise Exposure for Public Health Purposes,” (5) which was compiled by an international committee with European and North-American membership. This report recommended a method of aggregating noise exposure levels from different sources with different qualities, taking into account the exposure time of the day. The resulting two metrics are thought to have unambiguous relationships with noise annoyance and with waking during the night. The proposed metrics, the environmental exposure level (EEL) and environmental nighttime exposure level (ENEL), are the adjusted day—nighting—equivalent sound level (L eq,d) and the adjusted night-time equivalent sound level (L eq,n) respectively. As already indicated, the adjustments pertain to the source of the noise (mainly road traffic, rail traffic, air traffic, industrial sources), the nature of the noise (tonal, impulsive, industrial components) and the exposure time of the day (day: 7:00–19:00 h; evening: 19:00–23:00 h; night: 23:00–7:00 h), as these factors are known to modify the relationship between the equivalent sound level and the extent of noise-induced annoyance and sleep disturbance. Most adjustment factors were based on an evaluation by the committee of a comprehensive analysis of original data of