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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-toluenediamine (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 ^{14}C 2,4-TDA as Kulig claimed in his comments. The ^{14}C 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 (*1*). 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 First, it is important to understand that the polyurethane foam breast implant has been voluntarily withdrawn from the commercial market since 17 April 1991. 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 intravenouly 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.

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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 night-time exposure level (ENEL), are the adjusted day–evening–night equivalent sound level ($L_{Aeq,den}$) and the adjusted night-time equivalent sound level ($L_{Aeq,23-07h}$), 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: 700–1900 hr; evening: 1900–2300 hr; night: 2300–700 hr), 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

35,000 respondents in more than 350 socioacoustic surveys that have been compiled by TNO Prevention and Health (*6*).

The two Health Council reports (*3,5*) and the Leicester report (*4*) present data and tools for policy makers to reduce noise exposure in effective and efficient ways. If such policies are carried out, this will improve the health and well-being of the affected populations.

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Corrections and Clarifications

Two errors of omission were made in the September 1998 Focus article, "Natural Born Killers." 1) On p. A434, middle of the first column, the quote by John Kough should read: "Food allergies don't lend themselves to classical models of toxicity testing," he says. "There is no animal model that can be used to address them." 2) On p. A434, middle of second column, the text should read: "These plants may contain varying levels of glycoalkaloids, which can be toxic if eaten in sufficient quantities. Plant breeders now recognize that these substances could pose a problem for some consumers, and routinely screen for levels of glycoalkaloids when working with these particular varieties." *EHP* regrets the error.

Notification to Our Readers

An *Environmental Health Perspectives* reader noted that nearly identical abstracts were used in a 1998 *EHP* article (Calabrese EJ, Baldwin LA. Hormesis as a biological hypothesis. Environ Health Perspect 106[suppl 1]:357–362 [1998]) and a 1997 article in the *International Journal of Toxicology* (Calabrese EJ, Baldwin LA. The dose determines the stimulation (and poison): development of a chemical hormesis database. Int J Toxicol 16:545–559 [1997]).

On inspection, the papers were found to be very similar, including several tables and figures. No attribution was given in the *EHP* paper to the previously published *International Journal of Toxicology* article.

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