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Measurement of 2,4-Toluenediamine in Urine and Serum Samples from Women with Même or Replicon Breast Implants

Author(s): Hester, T. Roderick Jr. M.D.; Ford, Neville F. M.D., Ph.D.; Gale, P. Jane Ph.D.; Hammett, Janis L. B.S., M.B.A.; Raymond, Ralph M.S.; Turnbull, Duncan D.Phil., D.A.B.T.; Frankos, Vasilios H. Ph.D.; Cohen, Marvin B. Ph.D.

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Institution(s): From The Emory Clinic, the Departments of Clinical Pharmacology, Metabolism and Pharmacokinetics, and Biostatistics and Data Management, Bristol-Myers Squibb Pharmaceutical Research Institute, and Environ Corporation.

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Reprint requests to: Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, N.J. 08543-4000.

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Abstract

The objective of this matched case-control study was to determine whether women with Même or Replicon polyurethane-covered silicone breast implants are exposed to clinically significant levels of free 2,4-TDA from biodegradation of the polyurethane foam. Urine and serum samples were obtained from 61 patients with Même or Replicon breast implants and 61 controls on two separate occasions separated by 10 ± 3 days. Free TDA was analyzed by gas chromatography combined with negative chemical ionization mass spectrometry with lower limit of quantitation in both urine and serum of 10 pg/ml. The results were correlated with the length of time since implantation. No patients or controls had detectable free 2,4-TDA in their sera. Thirty patients had quantifiable levels of free 2,4-TDA, and 18 had detectable levels in their urine. Controls had no quantifiable levels, but 7 subjects had detectable levels. The biodegradative half-life of the polyurethane foam was estimated to be 2 years. A risk assessment using the cancer potency estimate calculated by the FDA from rat data and the National Academy of Sciences methodology provided a theoretical lifetime risk of approximately one in one million. It was concluded that the polyurethane foam cover on the Même and Replicon breast implants biodegrades. The risk assessment of approximately one in one million derived from this study strengthens earlier conclusions by the Health Protection Branch (Canada) that there is no significant risk of cancer from

Graphics

exposure to the 2,4-TDA formed from this biodegradation.

Polyurethane foam-covered breast implants, such as the Même or Replicon, significantly reduce the incidence of postoperative capsular contractures relative to silicone breast implants without a polyurethane foam covering.[1,2] The polyester polyurethane used was a flexible, porous, reticulated foam, which was produced from the polymerization of polydiethylene glycol adipate with a 4:1 mixture of 2,4- and 2,6- toluene diisocyanate.

Because there was evidence suggesting that the polyurethane covers biodegraded,[3] this study was undertaken at the request of the Food and Drug Administration (FDA) to determine whether women would be exposed to free 2,4-toluenediamine (2,4-TDA) as a consequence of this biodegradation. 2,4-TDA has been reported to be carcinogenic in rats and female mice in a National Cancer Institute (NCI) bioassay.[4] There is, however, no evidence that 2,4-TDA is carcinogenic in humans, and epidemiological studies of workers at two large European manufacturing sites have not shown any increased incidence of malignancies.[5,6]

Very careful in vitro studies of 2,4-TDA, 2,6-TDA, and 4-acetyl-TDA (a metabolite of 2,4-TDA) in serum and urine were carried out to establish conditions under which the aromatic amines could be stabilized in these matrices (P. J. Gale, Ph.D., unpublished results). It was therefore possible to stabilize the clinical samples, as they were collected at the Emory Clinic, and permit their shipment to the Bristol-Myers Squibb bioanalytical laboratory. The accurate analysis of free 2,4-TDA was essential so that a dosimetry could be derived from a population pharmacokinetic method. The dosimetry could then be used for an appropriate risk assessment.[7] Analyses of 2,6-TDA and 4-acetyl-TDA were also carried out. These values provided insights into the biodegradation process. In a study by Chan et al.[8] of one patient with a Même implant, no free 2,4-TDA was detected in the patient's urine. However, following reflux in 6 *N* hydrochloric acid, measurable levels of 2,4-TDA were observed. For comparison purposes, the urines and sera in the present study were hydrolyzed by strong acid using a procedure similar to that of Chan et al.[8,9]

Methods

Study Subjects

A total of 129 women, ranging in age from 23 to 62 years, were enrolled in the study. Sixty-six were patients with Même or Replicon breast implants for cosmetic purposes. Sixtythree were control subjects, matched by age (±2 years) and race. All women were recruited by the Emory Clinic in Atlanta, Ga.; the patients were from the Plastic Surgery Clinic, and the control subjects were from the Emory University community. Each study participant gave written informed consent.

Sixty patients and 61 control subjects completed the study per protocol. One of the formal violators was identified after she had completed the study. As the medication she had taken did not seem to interfere with the analyses, she was included. Sixty-one patients and their controls were analyzed. Five patients and two subjects were discontinued from the study for the following reasons: urines positive for cannabis (one patient, one control), inability to complete visit (one patient), wrong type of implants (two patients), and need for intercurrent therapy (one patient, one control).

Evaluation

Prior to study entry, each participant provided a brief occupational history and a complete medical history, including information on parity. Patients were also asked to complete a brief questionnaire specifying the type and position of breast implants; the duration of implantation; the occurrence of postoperative complications, such as rash, infection, or contractures; the occurrence of pregnancy postimplantation; and whether they had nursed with implants in place. Information on previous implants, if any, was also elicited. Another part of the questionnaire focused on reasons for the implantation and was adapted from an independent survey of women with breast augmentation by the American Society of Plastic and Reconstructive Surgeons.[10]

Patients and controls were screened with clinical laboratory tests and a physical examination including vital signs. The following exclusion criteria were applied: breast implants for reasons other than augmentation, recent environmental or occupational exposure to industrial or agricultural chemicals, a positive pregnancy test, positive results of drug screening or history of drug or alcohol abuse, history of smoking or smoking cessation within the past year, clinically significant abnormal laboratory values; fever (>101°F) on either day of the study or between study days, other standard exclusionary criteria, and known contact with polyurethane (e.g., use of the Today contraceptive sponge or implanted devices such as pacemakers with polyurethane-coated leads, heart valves, or vascular shunts).

Conduct of the Study

The study protocol and informed consent document were approved by the Emory University School of Medicine Institutional Review Board. Patients and controls presented to the clinic in a fasted state for sample collection on two

mornings separated by 10 ± 3 days. All participants were instructed to refrain from alcohol- or caffeine-containing beverages for at least 12 h before sample collection; those taking regular daily medications deferred their dose on the mornings of the study until after urine and serum samples had been collected. Initiation of new drug therapy during the study was prohibited. Patients who were noncompliant were considered nonevaluable and were replaced by new patients enrolled according to the protocol.

Collection of Biological Samples for Screening

At the time of screening, each participant provided a blood sample for clinical laboratory tests. At screening and on both study days, a 20-ml sample of freshly voided urine was obtained from each participant for urinalysis and determination of creatinine concentration.

Collection of Biological Samples for Measurement of 2,4-TDA, 2,6-TDA, and 4-Acetyl-TDA

On both study days, two serum samples (each 10-ml blood sample yielded 4 ml of serum) were collected from each participant. The samples were stabilized with a citric acid/sodium citrate buffer. Randomized labeling ensured that analysts were blinded to sample identity.

To prevent degradation of TDA, serum samples were stabilized at a pH of approximately 3 to 3.5 with a citric acid/sodium citrate buffer (967 mg of citric acid and 244 mg of dibasic sodium citrate per 15-ml Falcon tube) within a few minutes of collection. The citrated samples were vortexed and frozen for storage at -20°C.

From approximately 50 ml of freshly voided, clean-catch urine obtained from each patient on each study day, a 10-ml aliquot was transferred within 10 min of the void to each of two 50-ml Falcon tubes containing the citrate buffer (2.44 g of citric acid and 0.61 g of dibasic sodium citrate).

Sample Analysis

For the assay of free TDA in each fluid, 1-ml portions of serum and urine were removed from one of each pair of duplicate tubes. They were buffered with ammonium phosphate to approximately neutral pH and extracted with toluene. The extracts were derivatized with perfluoropropionic anhydride and analyzed by gas chromatography combined with negative chemical ionization mass spectrometry. The lower limit of quantification for the assays of 2,4-TDA and 2,6-TDA in serum and urine was 10 pg/ml, the lower limit of detection was 2 pg/ml for serum and 3 pg/ml for urine. The lower limit of quantification for the assay of 4-acetyl-TDA in serum and urine was 100 pg/ml; the lower limits of detection were 20 pg/ml (serum) and 30 pg/ml (urine).[11]

Serum and urine samples were removed from the other pair of duplicate tubes. After addition of 1 ml of 6 *N* HCl, the samples were heated at 110°C for 1 h. When cool, the samples were made basic by addition of 10 *N* NaOH and extracted. The extracts were derivatized and analyzed for TDAs as described above.

Risk Assessment

The urinary free 2,4-TDA data were used to estimate an upper limit of potential excess lifetime cancer risk following the standard methodology for risk assessment formalized by the National Academy of Sciences [12] and used by the FDA.[13] Under this procedure, the upper limit of lifetime risk is calculated as upper limit of risk = lifetime average daily dose × potency, where the lifetime average daily dose is the cumulative dose of the chemical averaged over the lifetime, and potency is the risk per unit of dose calculated for the chemical from the available carcinogenic data,[4] assuming a linear relation between dose and risk. The FDA previously performed a risk assessment for 2,4-TDA in polyurethane-coated breast implants based on data from an in vitro extraction study of the polyurethane foam.[13] In that assessment, the FDA used a potency estimate for 2,4-TDA of 0.21 (mg per kg per day)$^{-1}$, derived from the results of the NCl bioassay of 2,4-TDA,[4] and we have used that potency estimate in this assessment. 2,6-TDA was not carcinogenic in the NCl bioassay and is therefore not included in the assessment.[14]

The lifetime average daily dose is calculated in a series of steps. First, the mean creatinine-corrected urinary concentration of 2,4-TDA is used to estimate a total daily urinary excretion of 2,4-TDA for each patient, assuming a constant daily excretion of creatinine of 15.5 mg per kilogram of body weight per day.[15] Because 2,4-TDA is extensively metabolized, the amount excreted in the urine represents only a small fraction of the total daily dose released from the foam.[16] The corresponding estimate of total daily dose of TDA is back-calculated, assuming the same fraction (0.41 percent) of the daily dose was excreted unchanged in the urine of the patients as in rats receiving a single subcutaneous dose of 2,4-TDA (M. B. Cohen, Ph.D., unpublished results). This fraction is similar to that reported in the literature.[16] The resultant estimates of log (total daily dose of TDA) were then plotted against time after implantation, and the best-fitting regression to these data was used to determine the area under the daily dose-time curve. The resultant estimate of the total cumulative dose of TDA was divided by the number of days in a lifetime (365 days per year × 70 years) to derive the lifetime average daily dose for 2,4-TDA. This form of dose averaging is usually used as the appropriate measure of risk.[17]

Results

Patient Surveys

On the basis of the completed survey, the patients enrolled in our study were demographically representative of the breast-augmentation population at large, according to recently published FDA findings.[18] The mean age of our patients

was 39 years; all were from the southern United States; 98 percent were white; only 15 percent were full-time homemakers; and 92 percent were of small to medium build. They differed from the FDA population in that only 60 percent had their original implants.

Among our patients, time after implantation ranged from 16 to 102 months. Implant positions were submuscular (40 patients), subglandular (20 patients), and unknown (1 patient). Postoperative contractures were reported by 11 of 61 patients. Two patients had a postoperative rash, but in only one was the rash severe enough to require oral and topical steroids. One postoperative infection occurred. In our patients, reasons for breast augmentation closely resembled those in the 385 patients previously studied by the American Society of Plastic and Reconstructive Surgeons.[10]

Serum Analysis

No patients or controls had detectable levels of free 2,4-TDA, 2,6-TDA, or 4-acetyl-TDA in their sera.

Urine Analysis

None of the control subjects had quantifiable levels of free 2,4-TDA. However, seven had detectable levels on one but not both study days. In view of these low levels and random incidence, no effort was made to correct for background 2,4-TDA levels.

Quantifiable levels of free 2,4-TDA were found in the urine samples of 30 patients and detectable levels in a further 18 patients. The value calculated for each study day was the mean of two determinations. The concentrations of the two patients with double implants were halved. All values were then normalized based on the urinary creatinine concentration for each study day.[19] The normalized concentrations were comparable between study days. A mean of these normalized concentrations was used for data analysis. The statistical treatment required nonzero values for concentrations below the limits of quantification (less than the lower limit of quantification) and detection (less than the lower limit of detection). Assuming a uniform distribution of values between the two limits, concentrations less than the lower limit of quantification were assigned a value of 6.5 pg/ml, the median value between the limits of quantification and detection; nondetectable concentrations were assigned the value 1.5 pg/ml assuming a similar distribution of values between the lower limit of detection and zero.

For patients with TDA urine concentrations at or near the limits of detection, cases in which one day's results were less than the lower limit of quantification and the other day's results were nondetectable, the mean value was considered less than the lower limit of quantification. For patients with one value less than the lower limit of quantification or nondetectable and one value quantifiable, a mean was calculated from the assigned and measured values. These data for the patients and controls are presented in Table I. The group differences are highly significant ($p < 0.001$).

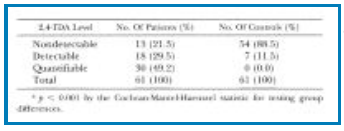

TABLE I: Frequency (Percent) of Patients and Control Subjects That Had Nondetectable, Detectable, and Quantifiable Levels of Free 2,4-TDA in Urine on at Least One of the Study Days*

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A plot of free 2,4-TDA against the time since implantation indicated a decrease in 2,4-TDA concentrations with time. A one-compartment model was fit to these data (Fig. 1). The goodness of fit was determined by the ratio of the regression sum of squares to the total sum of squares (Rss/Tss = 0.66). An extra sum-of-squares analysis indicated no statistically significant improvement in fit ($p = 0.89$) with the addition of a second compartment. A linear regression model was fit to the log-transformed data (Fig. 2). From the slope of the regression, an estimate of the half-life of biodegradation of the polyurethane foam of 24 months was obtained.

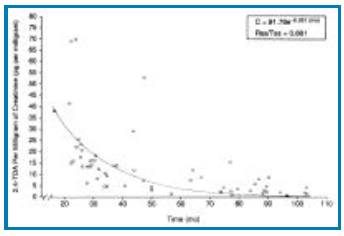

Fig. 1. One-compartment model of amount of free 2,4-TDA excreted per milligram of creatinine in collection (pg per milligram) over time.

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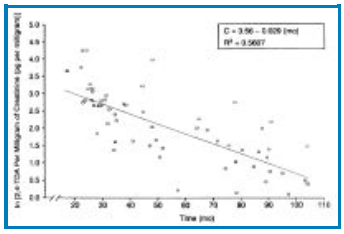

Fig. 2. Amount of 2,4-TDA excreted per milligram of creatinine in collection (pg per milligram)-log transformed.

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The relationships of free 2,4-TDA to 2,6-TDA and to its metabolite 4-acetyl-TDA were assessed with linear regression analyses. The slope of the regression line was 1.27, and the coefficient of determination (r^2) was 0.95 for 2,6-TDA and 2.53 and 0.61 for 4-acetyl-TDA, respectively. All statistical analyses were performed with SAS. All tests of significance were carried out at the 0.05 level.

Serum and Urine Analyses After Acid Hydrolysis

The analysis of serum and urine samples posthydrolysis was the same as that for free TDA in urine. No correction for free TDA in either matrix was made, as none was found in serum and only small (1 to 2 percent) amounts in urine. Data were fit to one-compartment models, and from the linear regression of the log transform of these data, estimates of halflife for degradation of the polyurethane foam were made. These estimates are compared with the half-life estimate obtained from the analysis of free TDA in urine in Table II.

Matrix/Treatment	Equation for Predicted 2,4-TDA Concentration	Goodness of Fit (R_{adj}/T_{adj})	Half-life Estimate (Mo)
Urine, free	$91.38e^{-0.031t}$	0.66	24
Serum, posthydrolysis	$2.81e^{-0.033t}$	0.64	19
Urine, posthydrolysis	$12.2e^{-0.032t}$	0.77	21

TABLE II: Polyurethane Foam Half-life Estimation from 2,4-TDA Concentrations

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An analysis of the homogeneity of the slopes of the three log-linear models was performed. There was no statistically significant difference (p = 0.26), indicating consistency across the three biological matrices for which data were obtained, (i.e., free TDA in urine, posthydrolysis TDA in urine, and posthydrolysis TDA in serum). The mean of the three half-lives, 21 months, may therefore be considered a reasonable point estimate.

The relationship between acid hydrolysisderived 2,4-TDA and 2,6-TDA in each matrix was also assessed with a linear regression analysis. The results are compared with those obtained for free 2,4-TDA and 2,6-TDA in urine in Table III.

Matrix/Treatment	Slope of Regression	Coefficient of Determination (r^2)
Urine, free	1.27	0.95
Serum, posthydrolysis	2.45	0.99
Urine, posthydrolysis	1.92	0.95

TABLE III: Results of Linear Regression Analyses for Free and Acid-Hydrolysis-derived 2,4- and 2,6-TDA

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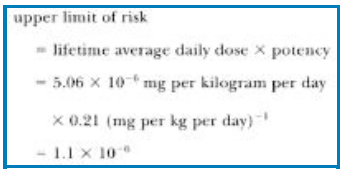
Risk Assessment

The amounts of free 2,4-TDA in urine relative to time since implantation were used to estimate the lifetime average daily dose of TDA resulting from biodegradation of the foam, as described under Methods. The estimate of lifetime average daily dose was 5.06×10^{-6} mg per kilogram per day. Applying the cancer potency estimate used previously by the FDA 14 yields the following estimate of the upper limit of excess lifetime risk resulting from the implants: Equation



Equation 1A

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This represents a theoretical lifetime risk of 1.1 in one million, resulting from a single pair of polyurethane foam-covered breast implants, assuming the animal data are relevant to humans and that the risk is linearly related to dose at very low doses.

Discussion

This study shows that the amount of free 2,4-TDA excreted into the patient's urine is inversely related to time since implantation, as one may expect if the 2,4-TDA is generated either directly or indirectly from a biodegradation process of the polyurethane foam.[20] Our estimated half-life of 21 months for this process is similar to the estimate of 2 to 3 years (C. Kerrigan, M.D., personal communication) from a study of explanted polyurethane foam-covered breast implants.[21]

The biodegradation of the polyester polyurethane foam used to cover the breast implants will initially involve cleavage at the ester bonds.[20] In this polymer, which is not extensively cross-linked, cleavage of just a few urethane, urea, or amide bonds could then liberate low molecular weight oligomers containing TDAs. These oligomers would be expected to be protein bound. The small fraction that was unbound, however, would be filterable at the glomerulus, and oligomers would be excreted in the urine.

The approximately 70-fold increase in TDA levels on treatment of the urine under strongly acidic conditions is then most probably due to the hydrolysis of these oligomers and their biotransformation products. Comparison of our posthydrolysis data, by extrapolation back to time zero (i.e., concentration = $12.2e^{-0.07t}$ when t = 0, concentration = 12.2 ng/mg of creatinine), yields a value very similar to those (12.1 and 13.8 ng/mg of creatinine) reported by Chan et al. for their patient soon after implantation.[9] Furthermore, the ratio of 2,4-TDA to 2,6-TDA of 1.92 in the urines posthydrolysis in our study is similar to the 2.10 derivable from the data in the Chan paper, and both differ from the original ratio of 4.0 in the polyurethane foam. The strong acid treatment of the serum samples also liberates TDA from hydrolysis of the oligomers and their biotransformation products that are present in the serum. This 2,4-TDA liberated ex vivo by strong acid from urine and serum is material to which the patient has not been exposed in vivo and thus is not relevant for a risk assessment.

A recent paper by Sepai et al.[22] describes work similar to that of Chan et al.,[8,9] with additional efforts to define the source of the 2,4-TDA formed by acid hydrolysis of plasma and urine. The study involved six women with recently implanted polyurethane foam-covered breast implants. Sepai et al. concluded that most of the 2,4-TDA formed by acid treatment of plasma arose from plasma proteins, albumin and globulin particularly. From affinity chromatography of some samples, they obtained albumin and globulin fractions, which on subsequent hydrolysis yielded 2,4-TDA. This result led them to conclude that 2,4-TDA was covalently bound to the proteins. The chemical aspects of how binding would occur, so that acid hydrolysis would liberate 2,4-TDA were not considered. Interestingly, there were no 2,4-TDA-related products obtained upon acid hydrolysis of lyzed red cells. This finding is consistent with our view that there is no free 2,4-TDA present in the circulation, only oligomers, which by virtue of their size would be unable to enter the red blood cell. In our study we have found that, in an ex vivo experiment, 2,4-TDA rapidly enters the red cell.

Our risk assessment is based on the measurement of TDA itself, using well established methodology rather than protein adducts.[12] Attempts to use protein adducts for risk assessment have not gained wide acceptance.[23] The risk assessment in the Sepai et al. paper,[22] however, is based on the measurement of purported protein adducts, and it does not conform to generally accepted guidelines for risk assessment. Our calculation of the lifetime risk of approximately one in one million, calculated from the concentrations of free 2,4-TDA relative to the time since implantation, represents an upper limit of risk because its calculation involves several conservative assumptions. In particular, it assumes a linear relationship without a threshold between dose and risk at all dose levels and treats TDA as if it were a human carcinogen, although the presently available human epidemiology data do not indicate any cancer risk.[5,6] The risk assessment strengthens earlier conclusions by the Health Protection Branch (Canada) that there is no significant risk of cancer from exposure to the TDA derived from polyurethane breast implants.[24] Based on the findings of our study, the FDA recently issued an information sheet that concurs with this view.[25]

Neville F. Ford, M.D., Ph.D.

Bristol-Myers Squibb Pharmaceutical Research Institute; P.O. Box 4000; Princeton, N.J. 08543-4000

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REFERENCES

1. Melmed, E. P. Treatment of breast contractures with open capsulotomy and replacement of the gel prosthesis with polyurethane covered implants. *Plast. Reconstr. Surg.* 86: 270, 1990. **Bibliographic Links** | [Context Link]

2. Hester, T. R., Jr., Nahai, F., Boswick, J., and Cukic, J. A 5-year experience with polyurethane-covered mammary prostheses for the treatment of capsular contracture, primary augmentation mammoplasty, and breast reconstruction. *Clin. Plast. Surg.* 15: 569, 1988. **Bibliographic Links** | [Context Link]

3. Slade, C. L., and Peterson, H. D. Disappearance of the polyurethane cover of the Ashley Natural Y prosthesis. *Plast. Reconstr. Surg.* 70: 379, 1982. **Bibliographic Links** | [Context Link]

4. National Cancer Institute Report. Bioassay of 2,4-diaminotoluene for possible carcinogenicity. DHEW/PUB/NIH-79-1718, NCI-CG-TR-162, 1980. [Context Link]

5. Sorahan, T., and Pope, D. Mortality and cancer morbidity of production workers in the UK flexible polyurethane foam industry. *Br. J. Indus. Med.* 50: 528, 1993. [Context Link]

6. Hagmar, L., Welinder, H., and Mikoczy, Z. Cancer incidence and mortality in the Swedish polyurethane foam manufacturing industry. *Br. J. Indus. Med.* 50: 537, 1993. [Context Link]

7. Henderson, R., and Bakshi, K. Pharmacokinetics: Defining dosimetry for risk assessment. *Environ. Health Perspect.* 102 (Suppl. 11): 3, 1994. [Context Link]

8. Chan, S. C., Birdsell, D. C., and Gradeen, C. Y. Detection of toluenediamines in the urine of a patient with polyurethane-covered breast implants. *Clin. Chem.* 37: 756, 1991. **Bibliographic Links** | **Library Holdings** | [Context Link]

9. Chan, S. C., Birdsell, D. C., and Gradeen, C. Y. Urinary excretion of free toluene diamines in a patient with polyurethane-covered breast implants. *Clin. Chem.* 37: 2143, 1991. [Context Link]

10. American Society of Plastic and Reconstructive Surgeons. Profile: Women who have breast implantation. Arlington Heights, Ill.: ASPRS, 1990. [Context Link]

11. Gale, P.J., Muldowney, R. S., Arnold, M. E., et al. Quantitative determination of toluenediamine and an acetylated metabolite at pg/mL levels in human urine. Proceedings of the 40th ASMS Conference on Mass Spectroscopy and Allied Topics, Washington, DC, May 31-June 5, 1991. [Context Link]

12. National Academy of Sciences. Risk assessment in the federal government: Managing the process. Washington, DC: National Academy Press, 1983. [Context Link]

13. CDRH toxicology risk assessment committee report. Potential carcinogenic risk from the release of 2,4-TDA from the polyester polyurethane foam-covering of silicone gel filled breast implants. Washington, DC: Food and Drug Administration, July 22, 1991. [Context Link]

14. National Cancer Institute Report. Bioassay of 2,6-diaminotoluene for possible carcinogenicity. Report No. DHHS/PUB/NIH-80-1756, 1980. [Context Link]

15. Teitz, N. W. (Ed.) Clinical Chemistry. Philadelphia: Saunders, 1986. [Context Link]

16. Grantham, P. H., Mohan, L., Benjamin, T., Roller, P. P., Miller, J. R., and Weisburger, E. K. Comparison of the metabolism of 2,4-toluenediamine in rats and mice. *J. Environ. Pathol. Toxicol.* 3: 149, 1979. **Bibliographic Links** | [Context Link]

17. US Environmental Protection Agency. Guidelines for carcinogen risk assessment. Federal Register 1986; 51: 33992-34003. [Context Link]

18. Bright, R. A., Jeng, L. L., and Moore, R. M. National survey of self-reported breast implants. *J. Long Term Effects Med. Implants* 3: 81, 1993. [Context Link]

19. Lafolie, P., Beck, O., Blennow, G., Boreus, L., et al. Importance of creatinine analyses of urine when screening for abused drugs. *Clin. Chem.* 37: 1927, 1991. [Context Link]

20. Pinchuk, L. A review of biostability and carcinogenicity of polyurethanes in medicine. *J. Biomater Sci. Polym. Ed.* 6: 225, 1994. **Bibliographic Links** | [Context Link]

21. Sinclair, T. M., Kerrigan, C. L., and Buntic, R. Biodegradation of the polyurethane foam covering of breast implants. *Plast. Reconstr. Surg.* 92: 1003, 1993. **Bibliographic Links** | [Context Link]

22. Sepai, O., Henschler, D., Czech, S., Eckert, P., and Sabbioni, G. Exposure to toluenediamines from polyurethane-covered breast implants. *Toxicol. Lett.* 77: 371, 1995. **Bibliographic Links** | [Context Link]

23. Neumann, H. G. Haemoglobin binding in control of exposure to and risk assessment of aromatic amines. In H. Bartsch, K. Hemminki, and I. K. O'Neill (Eds.), *Methods for detecting DNA damaging agents in humans: Applications in cancer epidemiology and prevention* (IARC Scientific Publications No. 89). Lyon: International Agency for Research on Cancer, 1988. [Context Link]

24. The Expert Panel. Safety of polyurethane-covered breast implants. *Can. Med. Assoc. J.* 145: 1125, 1991. **Full Text** | **Bibliographic Links** | **Library Holdings** | [Context Link]

25. MDDI Reports: The Gray Sheet: Polyurethane foam-covered breast implant cancer risk is negligible. July 3, 1995. [Context Link]