

## Cancer Risk Assessment P020023

Restylane gel contains 1,4-butanediol diglycidyl ether (BDDE), a compound that has been shown to be mutagenic in various assay systems and may have been associated with tumor formation in mice following topical application in one study. Consequently, it is prudent to assess the potential carcinogenic risk of BDDE in patients who receive injections of Restylane gel. The excess cancer risk in humans was determined using two approaches: 1) simple linear extrapolation of the dose associated with  $10^{-6}$  risk from the tumor incidence at the lowest dose of BDDE that produced an increased tumor incidence in the mouse study, with conversion of this dose to a human equivalent dose; and 2) use of dose-response models to estimate the 10% tumor incidence, with subsequent application of uncertainty factors to estimate the dose associated with  $10^{-6}$  risk in humans. The human equivalent doses associated with  $10^{-6}$  excess cancer risk derived using either approach were then compared to the dose of BDDE estimated to be received by patients treated with Restylane.

### Linear Extrapolation Method

BDDE is indeed mutagenic in the Ames and other genotoxicity assays; however, the dose-response data for total tumors presented in the Ciba-Geigy mouse carcinogenicity study do not lend themselves to quantitative risk assessment. The incidence of total tumors following topical application of the negative control vehicle (acetone) is greater than the incidence of tumors following application of either dose of BDDE. Therefore, extrapolation of the dose associated with either a *de minimus* or acceptable level of risk is not possible from these results.

In contrast, there was a statistically significant increase in the incidence of lymphoblastic lymphosarcomas in female mice in the Ciba-Geigy study.

Topically administered dose	Acetone control	0.05% BDDE	0.2% BDDE
Tumor incidence	2/100 (2%)	3/49 (6.1%)	5/50 (10%)

These data can be used to conduct a quantitative risk assessment for BDDE; however doing so requires estimation of the absorbed dose of BDDE (route-to-route extrapolation), estimation of a human equivalent dose of BDDE (interspecies extrapolation), and estimation of the dose of BDDE associated with an acceptable level of risk, or conversely, estimation of the excess cancer risk associated with the upper-bound dose of BDDE that patients may receive (low dose extrapolation).

### Route-to-Route Extrapolation

Data are not available to conduct a quantitative route-to-route extrapolation of BDDE to estimate the absorbed dose of the compound following topical administration. The degree to which glycidyl ethers are absorbed across the skin varies greatly and is determined by their lipophilicity and their molecular weight (Boogaard et al., 2000). The estimated log octanol-water partition coefficient for BDDE is -0.15 (Syracuse Research Corporation, 2003), indicating that the compound is not especially lipophilic, and therefore, is not expected to be readily absorbed by the skin, compared to other glycidyl ethers. Nevertheless, the acetone vehicle in the topical application studies could be expected to facilitate absorption of the compound. In the absence of data on the extent to which BDDE was absorbed in the Ciba-Geigy mouse study, a default value of 10% will be used, based on the default values recommended by this reviewer for other routes of exposure (Brown and Stratmeyer, 2003).

#### Interspecies Extrapolation

The total dose of BDDE administered to mice at the low dose in the Ciba-Geigy study is estimated to be:

$$0.1 \text{ mg/application} \times 2 \text{ applications/week} \times 104 \text{ weeks} = 20.8 \text{ mg}/0.025 \text{ kg} = 832 \text{ mg/kg}$$

The total absorbed dose, using the default route-to-route extrapolation factor of 0.1, is 83.2 mg/kg. The human equivalent dose, based on surface area scaling consideration, associated with the absorbed dose of 83.2 mg/kg is 6.7 mg/kg.

#### Low dose extrapolation

Given the findings in mutagenicity tests for BDDE, it's appropriate to assume low-dose linearity for carcinogenic effects. In lieu of using statistical models to conduct the low dose extrapolation, it's possible to use a simple linear extrapolation approach to estimate the risk associated with the upper-bound dose of BDDE that could be received by patients injected with Restylane gel.

Assuming the BDDE concentration in the gel is 2 ug/ml, that 2 injections can be received per visit (3 ml/visit), that 2 visits can occur/year, and that injections can take place for 15 years, the upper-bound lifetime dose of BDDE from this product is:

$$2 \text{ ug/ml} \times 3 \text{ ml/visit} \times 2 \text{ visits/year} \times 15 \text{ years} = 180 \text{ ug} \text{ or } 3 \text{ ug/kg for a 60 kg patient.}$$

Based on the lymphoblastic lymphosarcoma data from the Ciba-Geigy study, the excess cancer risk associated with the human equivalent dose of 6700 ug/kg is 0.041 (difference between treated and control incidence). Consequently, the excess cancer risk associated with a lifetime patient dose of 3 ug/kg is  $1.8 \times 10^{-5}$ . This value is likely to be conservative (high) since: 1) a conservative assumption was used regarding the absorbed dose in the animal study, 2) a conservative interspecies scaling approach was used (surface area scaling), 3) the lack of a threshold was assumed, and 4) the upper-bound concentration of BDDE in the gel was assumed. In addition, the dosing regimen in patients involves 6-month

periods between exposures, compared to dosing two times per week in the mouse study.

Total tumor data from the Ciba-Geigy study of BDDE cannot be used to determine the excess cancer risk associated with BDDE in Restylane gel; however, application of route-to-route, interspecies, and linear low dose extrapolation methods to the data on lymphoblastic lymphosarcoma from the Ciba-Geigy study indicate that the excess cancer risk for the amount of BDDE received by patients from this device is on the order of  $1 \times 10^{-5}$ . The true excess cancer risk is unknown, but the estimation is likely to be conservative (high) based on conservative assumptions made about the amount of BDDE absorbed in the animal study, the way in which BDDE dose scales across species, the mechanism by which BDDE exerts its carcinogenic effect, and the concentration of BDDE in the gel.

Since negative results were obtained in the mutagenicity studies of Restylane, and since the estimated excess cancer risk is in the range determined to be acceptable for compounds released from medical devices (based on ISO 10993-17), it is unlikely that BDDE-associated carcinogenic effects would be observed in patients who receive this product.

### Dose-Response Models

Using the Lifetime Average Daily Dose (LADD) and EPA Benchmark Dose software provides a more accurate estimate of the cancer risk of BDDE released from Restylane gel using dose-response modeling that takes into account the tumor incidence at both doses and uses the approach developed by Gaylor et al (1999) that describes a unified approach for cancer and noncancer risk assessment.

The dose-response data for lymphoblastic lymphosarcomas in female mice in the Ciba-Geigy study is summarized in the table below.

Topically administered concentration	Acetone control	0.05% BDDE	0.2% BDDE
Total administered dose <sup>1</sup> (mg/kg/day)	0	1.14	4.56
Total absorbed dose <sup>2</sup> (mg/kg/day)	0	0.114	0.456
Tumor incidence	2/100 (2%)	3/49 (6.1%)	5/50 (10%)

<sup>1</sup>0.1 mg/application x 2 applications/week x week/7days ÷ 0.025 kg

<sup>2</sup>Assuming 10% absorption of dermal dose

The Benchmark Dose (dose associated with a 10% response) and the lower limit of a one-sided 95% confidence interval on the BMD (BMDL) were derived using the assumed absorbed dose and tumor incidence from the Ciba-Geigy study.

Model	BMD <sup>3</sup>	BMDL <sup>4</sup>	BMDL/10 <sup>5</sup>
Quantal-linear	0.203	0.127	1.27 x 10 <sup>-5</sup>
Weibull	0.203	0.127	1.27 x 10 <sup>-5</sup>

<sup>3</sup>Based on 10% response using estimated absorbed dose

<sup>4</sup>Lower limit of a one-sided 95% confidence interval on the BMD

Gaylor et al. (1999) have proposed a unified approach for cancer and noncancer risk assessment based on application of uncertainty factors to the benchmark dose. For severe, irreversible effects (like tumors), they recommend dividing the LED<sub>10</sub> (or BMDL) by 10,000 to derive an estimate of dose in animals that corresponds to a risk of less than 10<sup>-5</sup>. Since experimental animals are generally thought to be more sensitive than humans to a given dose of a compound, this dose is expected to correspond to a risk in humans of about 10<sup>-6</sup>. Based on the tumor incidence data from the Ciba-Geigy study and the assumption that 10% of the applied dose was absorbed, the dose of BDDE associated with a 10<sup>-6</sup> excess cancer risk in humans is 1.27 x 10<sup>-5</sup> mg/kg/day, using the Gaylor et al. (1999) approach. This value is likely to be conservative based on the conservative assumptions that only 10% of the applied dose as absorbed and that the dose-response relationship is linear at low doses.

Assuming the BDDE concentration in the gel is 2 µg/ml, that 2 injections can be received per visit (3 ml/visit), that 2 visits can occur/year, and that injections can take place for 15 years, the upper-bound lifetime dose of BDDE from this product is:

$$2 \mu\text{g/ml} \times 3 \text{ ml/visit} \times 2 \text{ visits/year} \times 15 \text{ years} = 180 \mu\text{g} \text{ or } 3 \mu\text{g/kg for a 60 kg patient.}$$

This dose is equivalent to a LADD of 1.2 x 10<sup>-7</sup> mg/kg/day for a 70 year lifespan (0.003 mg/kg ÷ 25,000 days).

Since a dose of about 1.2 x 10<sup>-5</sup> mg/kg/day is assumed to correspond to an excess cancer risk in humans of 10<sup>-6</sup> (as calculated above), the LADD for BDDE

received from Restylane corresponds to an excess cancer risk of about  $10^{-8}$ . Although this approach is somewhat different, the conclusion remains the same as the original, specifically that it is unlikely that BDDE-associated carcinogenic effects would be observed in patients who receive this product.

## Summary

Use of the first approach yields a total lifetime dose of BDDE associated with  $10^{-6}$  excess cancer risk in mice of 1 ug/kg. The equivalent human dose (assuming surface area scaling) is 0.08 ug/kg. In comparison, the total estimated dose of BDDE received by patients treated with Restylane is 3 ug/kg. This dose is equivalent to an excess cancer risk about  $4 \times 10^{-5}$ . In other words, the total (presumably upper-bound) risk of BDDE that could be received by a patient undergoing treatment with Restylane is about 4 in 100,000. This risk is generally considered to be acceptable for compounds released from medical devices using the criteria outlined in the ISO 10993-17 standard. In addition, negative results were obtained in the mutagenicity studies of Restylane, providing further support to the conclusion that BDDE-associated carcinogenic effects are unlikely in patients who receive this product.

The second approach was used to derive a Lifetime Average Daily Dose (LADD) associated with a  $10^{-6}$  excess cancer risk from BDDE. Based on the data from the mouse carcinogenicity study, the LADD associated with  $10^{-6}$  excess cancer risk in humans is  $1.27 \times 10^{-5}$  mg/kg/day. If the total dose of BDDE from Restylane is averaged over a 70 year lifespan, the LADD for patients is  $1.2 \times 10^{-7}$  mg/kg/day, a dose that is about 2 orders of magnitude less than the LADD associated with  $10^{-6}$  excess cancer risk. Either approach suggests that the cancer risk from exposure of patients to BDDE in Restylane is minimal.

Boogaard PJ, Denneman MA, Van Sittert NJ (2000) Dermal penetration and metabolism of five glycidyl ethers in human, rat and mouse skin. *Xenobiotica* 30(5):469-83.

Brown, RP and Stratmeyer, ME (2003) Conversion Factors for Deriving Interim Parenteral Tolerable Intake (TI) Values from Oral Toxicity Data. FDA Science Forum

Syracuse Research Corporation (2003) Online Log P calculation  
<http://esc.syrres.com/interkow/kowdemo.htm>