

NO SIGNIFICANT RISK LEVEL (NSRL) FOR THE PROPOSITION 65 CARCINOGEN PHENYL GLYCIDYL ETHER

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SUMMARY OF FINDINGS

The cancer potency of phenyl glycidyl ether was estimated from dose-response data for nasal cavity epidermoid tumors among male Charles River-CD Sprague-Dawley rats exposed via inhalation (Lee *et al.*, 1983; EI du Pont de Nemours and Company [du Pont], 1986). The cancer potency estimate corresponds to the upper 95 percent confidence bound on the linear term of the multistage model fit to cancer dose-response data in experimental animals. The potency derivation takes into account body size differences between humans and experimental animals. The Proposition 65 “no significant risk level” (NSRL) is defined in regulation as the daily intake level posing a 10^{-5} lifetime risk of cancer. The cancer potency estimate and corresponding NSRL are given in Table 1.

Table 1. Cancer Potency and NSRL for Phenyl Glycidyl Ether.

Chemical	Cancer Potency (mg/kg-day) ⁻¹	NSRL (µg/day)
Phenyl glycidyl ether	0.14	5.0

INTRODUCTION

This report describes the derivation of the cancer potency value and no significant risk level (NSRL) for phenyl glycidyl ether (CAS number 122-60-1, molecular weight 150.18). “Phenyl glycidyl ether” was listed on October 1, 1990 as a chemical known to the State to cause cancer under Proposition 65 (California Health and Safety Code 25249.5 *et seq.*). Phenyl glycidyl ether is used mainly in industry to increase storage time and stability of halogenated chemicals because of its effectiveness as an acid acceptor (Lee *et al.*, 1983) and as a “chain stopper” or reaction inhibitor in the production of epoxy resins (IARC, 1989).

This document discusses the studies available for cancer dose-response assessment, and summarizes the derivation of the cancer potency estimate and NSRL. A description of the methodology is provided in the Appendix.

STUDIES SUITABLE FOR DOSE-RESPONSE ASSESSMENT

Lee *et al.* (1983; du Pont, 1986) exposed groups of 100 male and 100 female Charles River Sprague-Dawley rats to phenyl glycidyl ether (99.6% purity) via inhalation at 0, 1, or 12 ppm for six hours per day, five days per week, for 24 months. The study design included an interim sacrifice of 10 animals per dose group at 12 months. Significant increases in the incidence of nasal epidermoid carcinoma were observed in both males and females exposed to 12 ppm phenyl glycidyl ether. Male rats were more sensitive to the tumorigenic effects of phenyl glycidyl ether than female rats. The dose-response data for male and female rats are summarized in Tables 2 and 3.

Table 2. Incidence of Nasal Epidermoid Carcinoma in Male Charles River-CD Sprague-Dawley Rats Treated With Phenyl Glycidyl Ether Via Inhalation (Lee *et al.*, 1983; du Pont, 1986).

Chamber Concentration ¹ (ppm)	Average Dose ² (mg/kg-day)	Tumor Incidence ³
0	0	1/74
1	0.559	0/66
12	6.71	9/61 ⁴

¹ Administered six hours per day, five days per week, for two years.

² Details on the dose calculation are provided in Appendix A.

³ The number of tumor-bearing animals/animals alive at first occurrence of tumor in any of the three groups. This was determined from individual animal data reported by du Pont (1986).

⁴ Significantly different from controls by Fisher exact test, $p < 0.01$.

Table 3. Incidence of Nasal Epidermoid Carcinoma in Female Charles River-CD Sprague-Dawley Rats Treated With Phenyl Glycidyl Ether Via Inhalation (Lee *et al.*, 1983; du Pont, 1986).

Chamber Concentration¹ (ppm)	Average Dose² (mg/kg-day)	Tumor Incidence³
0	0	0/62
1	0.659	0/47
12	7.91	4/57 ⁴

¹ Administered six hours per day, five days per week, for two years.

² Details on the dose calculation are provided in Appendix A.

³ The number of tumor-bearing animals/animals alive at first occurrence of tumor in any of the three groups. This was determined from individual animal data reported by du Pont (1986).

⁴ Significantly different from controls by Fisher exact test, $p < 0.05$.

APPROACH TO DOSE-RESPONSE ANALYSIS

Phenyl glycidyl ether was positive in bacterial mutagenesis assays and *in vitro* mammalian transformation assays (IARC, 1999). Adducts of phenyl glycidyl ether with thymidine and 2'-deoxyadenosine formed *in vitro* (IARC, 1999). These findings suggest that a genotoxic mode of action is plausible. The precise mechanism of carcinogenicity is not sufficiently understood to permit the development of a biologically based model for cancer potency estimation. Data are not available to support dose adjustments based on pharmacokinetic models. Therefore, the default approach (*i.e.*, a linearized multistage model and interspecies scaling) has been applied. The approach is described in detail in Appendix A.

DOSE-RESPONSE ASSESSMENT

Cancer potency estimates were derived for phenyl glycidyl ether based on the data for male and female rats from the study of Lee *et al.* (1983) and du Pont (1986). The human cancer potency is estimated to be $0.14 \text{ (mg/kg-day)}^{-1}$ based on the data for male rats, the more sensitive sex.

Table 3. Human Cancer Potency Estimates for Phenyl Glycidyl Ether Based on Lee *et al.* (1983) and du Pont (1986).

Sex, Species	Tumor	Cancer Potency Estimate (mg/kg-day)⁻¹
Male rat	Nasal epidermoid carcinoma	0.14
Female rat	Nasal epidermoid carcinoma	0.091

NO SIGNIFICANT RISK LEVEL

The NSRL for Proposition 65 is the intake associated with a lifetime cancer risk of 10⁻⁵. The cancer potency estimate of 0.14 (mg/kg-day)⁻¹ based on nasal epidermoid carcinoma in male rats was used to calculate the NSRL of 5.0 µg/day for phenyl glycidyl ether.

REFERENCES

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APPENDIX: DEFAULT METHODOLOGY USED TO DERIVE THE NSRL FOR PHENYL GLYCIDYL ETHER

Procedures for the development of Proposition 65 NSRLs are described in regulation (California Code of Regulations, Title 22, Sections 12701 and 12703). Consistent with these procedures, the specific methods used to derive the NSRL for phenyl glycidyl ether are outlined in this Appendix.

A.1 Cancer Potency as Derived from Animal Data

"Multistage" polynomial

For regulatory purposes, the lifetime probability of dying with a tumor (p) induced by an average daily dose (d) is often assumed to be (CDHS, 1985; U.S. EPA, 1996; Anderson *et al.*, 1983):

$$p(d) = 1 - \exp[-(q_0 + q_1d + q_2d^2 + \dots + q_id^i)] \quad (1)$$

with constraints,

$$q_i \geq 0 \text{ for all } i.$$

The q_i are parameters of the model, which are taken to be constants and are estimated from the data. The parameter q_0 represents the background lifetime incidence of the tumor. The parameter q_1 , or some upper bound, is often called the cancer potency, since for small doses it is the ratio of excess lifetime cancer risk to the average daily dose received. For the present discussion, cancer potency will be defined as q_1^* , the upper 95% confidence bound on q_1 (CDHS, 1985), estimated by maximum likelihood techniques. When dose is expressed in units of mg/kg-day, the parameters q_1 and q_1^* are given in units of (mg/kg-day)⁻¹. Details of the estimation procedure are given in Crump (1984) and Crump *et al.* (1977). To estimate potency in animals (q_{animal}) from experiments of duration T_e , rather than the natural life span of the animals (T), it is assumed that the lifetime incidence of cancer increases with the third power of age:

$$q_{\text{animal}} = q_1^* \cdot (T/T_e)^3 \quad (2)$$

Following Gold and Zeiger (1997) and the U.S. Environmental Protection Agency (U.S. EPA, 1988), the natural life span of mice and rats is assumed to be two years, so that for experiments lasting T_e weeks in these rodents:

$$q_{\text{animal}} = q_1^* \cdot (104/T_e)^3 \quad (3)$$

To estimate risk at low doses, potency is multiplied by average daily dose. The risk estimate obtained is referred to by the U.S. EPA (Anderson *et al.*, 1983) as "extra risk", and is equivalent to that obtained by using the Abbott (1925) correction for background incidence.

Calculation of the average daily dose

Lifetime average doses in units of mg/kg-day were calculated by multiplying the chamber concentrations of phenyl glycidyl ether by a conversion factor (6.14 [mg/m³]/ppm), by the inhalation rate for rats, by 6/24, to account for the 6 hours per day exposure, and by 5/7, to account for the 5 days per week exposure and then by dividing by the average body weight for rats. The inhalation rates were calculated using a formula given by Anderson *et al.* (1983) for rats:

$$I = 0.105 \cdot (bw_a / 0.113)^{2/3} \quad (5)$$

Average body weights of 0.682 kg for male rats and 0.416 kg for female rats were determined based on data from du Pont (1986). Using these body weights in equation (4) gave inhalation rates of 0.348 m³/day for male rats and 0.250 m³/day for female rats.

A.2 Interspecies Scaling

Once a potency value is estimated in animals following the techniques described above, human potency is estimated. As described in the California risk assessment guidelines (CDHS, 1985), a dose in units of milligram per unit surface area is assumed to produce the same degree of effect in different species in the absence of information indicating otherwise. Under this assumption, scaling to the estimated human potency (q_{human}) can be achieved by multiplying the animal potency (q_{animal}) by the ratio of human to animal body weights (bw_h / bw_a) raised to the one-third power when animal potency is expressed in units (mg/kg-day)⁻¹:

$$q_{\text{human}} = q_{\text{animal}} \cdot (bw_h / bw_a)^{1/3} \quad (5)$$

A.3 Risk-Specific Intake Level Calculation

The intake level (I, in mg/day) associated with a cancer risk R, from exposure is:

$$I = \frac{R \cdot bw_h}{q_{\text{human}}} \quad (6)$$

where bw_h is the body weight, and q_{human} the theoretical cancer potency estimate for humans.

Daily intake levels associated with lifetime cancer risks above 10⁻⁵ exceed the no significant risk level for cancer under Proposition 65 (Title 22 California Code of Regulations, Section 12703). Thus for a 70 kg person, the NSRL is given by:

$$\text{NSRL} = \frac{10^{-5} \cdot 70\text{kg}}{q_{\text{human}}} \quad (7)$$

APPENDIX REFERENCES

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