NO SIGNIFICANT RISK LEVEL (NSRL) FOR THE PROPOSITION 65 CARCINOGEN GLYCIDOL

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SUMMARY OF FINDINGS

The human cancer potency of glycidol was estimated and used to calculate a "No Significant Risk Level" (NSRL). The human cancer potency was estimated from dose-response data for multiple treatment-related tumor sites in female F344/N rats exposed to glycidol via oral gavage (National Toxicology Program [NTP], 1990; Irwin *et al*., 1996). In modeling the dose response data, the Weibull form of the multistage model was used because of the high mortality in the study due to tumor onset. An overall estimate of cancer potency associated with all treatment-related tumors observed in the study was derived using a multisite statistical approach. The potency derivation takes into account differences in body size between humans and experimental animals. The human cancer potency estimate for glycidol is 1.3 $(mg/kg\text{-}day)^{-1}$.

The Proposition 65 NSRL is defined in regulation as the daily intake level posing a 10^{-5} lifetime risk of cancer. The NSRL for glycidol is calculated to be 0.54 μg/day.

Table 1. Cancer Potency and NSRL for Glycidol.

Chemical	Cancer potency $(mg/kg\text{-}day)^{-1}$	NSRL (μg/day)
Glycidol	1.3	0.54

INTRODUCTION

This report describes the derivation of a human cancer potency estimate and NSRL for glycidol (CAS No. 556-52-5). Glycidol was listed on July 1, 1990 as a chemical known to the State to cause cancer under Proposition 65 (formally known as the Safe Drinking Water and Toxic Enforcement Act of 1986; California Health and Safety Code 25249.5 *et seq*.).

Glycidol is a synthetic aliphatic epoxide used as a stabilizer in vinyl polymers, an intermediate in pharmaceuticals synthesis, an additive for lubricating oil and synthetic hydraulic fluids, and a diluent for epoxy resins. Occupational exposures occur among workers in the related industries. Glycidol has been released into the environment through various waste streams (IARC, 2000; NTP, 2007).

The studies available for cancer dose response assessment and the derivations of the cancer potency estimate and NSRL are discussed below. A detailed description of the methodology used is provided in the Appendix.

STUDIES SUITABLE FOR DOSE-RESPONSE ASSESSMENT

There are no human carcinogenicity studies of glycidol. Both long- and shorter-term cancer bioassays of glycidol have been conducted in rodents. The National Toxicology Program (NTP, 1990; Irwin *et al*., 1996) conducted two-year cancer bioassays of glycidol in F344/N rats and $B6C3F_1$ mice of both sexes. The shorter term studies consist of a 520-day skin painting study in female mice (Van Duuren *et al*. 1967, as cited by IARC, 2000), 60-week gavage studies in male and female Syrian golden hamsters (Lijinsky and Kovatch, 1992, as cited by IARC, 2000), and 40-week gavage studies in male and female genetically modified haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice (NTP, 2007). The designs and results for these studies are detailed below.

In the NTP 1990 carcinogenicity bioassays, groups of 50 male and female rats and mice were administered glycidol by gavage for five days per week for 103 weeks. Doses administered to rats were 0, 37.5, or 75 mg/kg glycidol per gavage treatment. Doses administered to mice were 0, 25, or 50 mg/kg per gavage treatment. The average daily doses were calculated by multiplying the administered dose by 5/7 to account for the 5 days per week dosing schedule and 103/104 to account for the less-than-lifetime duration of dosing. The resulting average daily doses are 0, 26.5, and 53.1 mg/kg-day in male and female rats, and 0, 17.7, and 35.4 mg/kg-day in male and female mice.

The NTP found clear evidence of the carcinogenicity of glycidol in male and female rats and mice (NTP, 1990). The NTP conclusion for male rats was based on tumors observed in the following sites: brain, forestomach, intestine, mammary gland, skin, thyroid gland, tunica vaginalis and Zymbal's gland. In female rats, the NTP conclusion was based on leukemia and tumors observed in the following sites: brain, clitoral gland, forestomach, mammary gland, oral mucosa and thyroid gland. In male mice, the NTP conclusion was based on tumors observed in the following sites: forestomach, Harderian gland, liver, lung and skin. In female mice, the NTP conclusion was based on tumors observed in the following sites: Harderian gland, mammary gland, skin, subcutaneous tissue and uterus.

In addition, the NTP identified other neoplasms in these two-year studies that may have been related to glycidol exposure, namely glandular stomach fibrosarcomas in female rats, and urinary bladder carcinomas and subcutaneous tissue sarcomas in male mice. The dose-response data for tumor sites affected by treatment in the NTP 1990 bioassays are presented in Tables 2-5.

In the 520-day female mouse skin painting study, 5% glycidol in acetone was applied to the dorsal skin of 20 ICR/Ha Swiss mice three times per week for 520 days (Van Duuren *et al*. 1967, as cited by IARC, 2000). The study included vehicle and untreated controls. No treatment-related increase in skin tumors was observed (IARC, 2000). This study is of limited usefulness for dose response assessment because of the small group size, the inclusion of only one dose group, the less-than-lifetime exposure and

study duration, and the difficulty associated with extrapolating from dermal to other routes.

In the gavage studies in male and female Syrian golden hamsters, groups of 20 animals of each sex received glycidol in ethyl acetate/corn oil by gavage twice per week (~100 mg glycidol/kg body weight per gavage treatment) for 60 weeks, and were observed until death (Lijinsky & Kovatch, 1992, as cited by IARC, 2000). Groups of 12 animals of each sex served as vehicle controls, receiving the ethyl acetate/corn oil vehicle by gavage twice per week for 90 weeks. Spleen hemangiosarcomas were slightly elevated in treated animals of both sexes (2/19 in males and 4/20 in females compared with 0/12 and 0/12 in male and female controls, respectively) (IARC, 2000). No statistically significant increases in the incidence of treatment-related tumors were observed. These studies are not suitable for dose response assessment because the dosing duration is substantially shorter than the animal lifetime for hamsters (Gold and Zeiger, 1997). Additional limitations include the small group sizes and the inclusion of only one dose group.

In 2007 the NTP conducted 40-week gavage studies in male and female genetically modified mice lacking two tumor suppressor genes (*i.e.*, haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice) (NTP, 2007). In the studies, groups of 15 animals/dose/sex received glycidol in distilled water by gavage five times per week. Fifteen animals per sex served as vehicle controls. The NTP concluded that there was clear evidence of carcinogenic activity in males based on the occurrence of histiocytic sarcomas and alveolar/bronchiolar adenomas. The NTP concluded there was some evidence of carcinogenic activity in female mice based on the occurrence of alveolar/bronchiolar adenomas, and that the increase in forestomach papillomas in females may have been treatment related. The NTP's genetically modified mice studies (NTP, 2007) were less suitable for dose-response assessment than the Program's two-year bioassays (NTP, 1990) for a number of reasons, including the considerably less-than-lifetime study duration, the small number of animals used per treatment group, and limited understanding of how dose-response relationships observed in genetically modified animals correspond with those observed in standard long-term carcinogenicity bioassays.

In consideration of the studies identified above, the most suitable carcinogenicity data for human cancer potency assessments come from the two-year studies conducted in F344/N rats and $B6C3F_1$ mice by NTP (1990).

Table 2. Tumor incidences in male F344/N rats exposed to glycidol (NTP, 1990).

Tumor site, type, and first occurrence	Administered dose (mg/kg)	Average daily dose[1] (mg/kg-day)	Tumor incidence[2]	Statistical significance[3]
Brain glioma (week 65)	0	0	0/46	p = 0.002[4]
	37.5	26.5	5/50	p = 0.035
	75	53.1	6/30	p = 0.003
Forestomach papilloma or carcinoma (week 64)	0	0	1/46	p = 0.007[4]
	37.5	26.5	2/50	NS
	75	53.1	6/32	p = 0.017
Intestine adenomatous polyp or adenocarcinoma (week 73)	0	0	0/45	p < 0.001[5]
	37.5	26.5	1/39	NS
	75	53.1	4/17	p = 0.004
Mammary gland fibroadenoma (week 73)	0	0	3/45	p = 0.001[4]
	37.5	26.5	8/39	p = 0.060
	75	53.1	7/17	p = 0.003
Skin sebaceous gland adenoma or adenocarcinoma, basal cell tumor (week 72)	0	0	0/45	p = 0.003[4]
	37.5	26.5	5/41	p = 0.022
	75	53.1	4/18	p = 0.005
Thyroid gland follicular cell adenoma or carcinoma (week 71)	0	0	1/46	p < 0.001[4]
	37.5	26.5	4/42	NS
	75	53.1	6/19	p = 0.002
Tunica vaginalis / peritoneum mesothelioma (week 49)	0	0	3/49	p < 0.001[4]
	37.5	26.5	34/50	p < 0.001
	75	53.1	39/47	p < 0.001
Zymbal's gland carcinoma (week 47)	0	0	1/49	p = 0.033[4]
	37.5	26.5	3/50	NS
	75	53.1	6/48	p = 0.053

[1] The average daily dose was calculated as described in the Appendix.
[2] The denominator represents the number of animals alive at the time of the first occurrence of the tumor.
[3] p-values from pairwise comparison with controls (Fisher Exact Test), as reported by NTP (1990). NS is not significant.
[4] Cochran-Armitage trend test p-values, as reported by NTP (1990).
[5] The Cochran-Armitage trend test value calculated by OEHHA.

Table 3. Tumor incidences in female F344/N rats exposed to glycidol (NTP, 1990).

Tumor site, type, and first occurrence	Administered dose (mg/kg)	Average daily dose[1] (mg/kg-day)	Tumor incidence[2]	Statistical significance[3]
Brain glioma (week 65)	0	0	0/49	p = 0.052[4]
	37.5	26.5	4/46	p = 0.051
	75	53.1	4/46	p = 0.051
Clitoral gland adenoma, adenocarcinoma or carcinoma (week 60)	0	0	5/49	p = 0.027[4]
	37.5	26.5	9/47	NS
	75	53.1	12/45	p = 0.035
Forestomach papilloma or carcinoma (week 77)	0	0	0/47	p < 0.001[4]
	37.5	26.5	4/38	p = 0.036
	75	53.1	11/30	p < 0.001
Hematopoietic system leukemia (week 67)	0	0	13/49	p = 0.020[4]
	37.5	26.5	14/44	NS
	75	53.1	20/41	p = 0.025
Mammary gland fibroadenoma or adenocarcinoma (week 56)	0	0	14/50	p < 0.001[4]
	37.5	26.5	34/48	p < 0.001
	75	53.1	37/48	p < 0.001
Oral mucosa papilloma or carcinoma (week 79)	0	0	1/46	p = 0.001[4]
	37.5	26.5	3/37	NS
	75	53.1	7/26	p = 0.003
Thyroid gland follicular cell adenoma or carcinoma (week 73)	0	0	0/49	p = 0.034[4]
	37.5	26.5	1/38	NS
	75	53.1	3/35	p = 0.069

[1] The average daily dose was calculated as described in the Appendix.
[2] The denominator represents the number of animals alive at the time of the first occurrence of the tumor.
[3] p-values from pairwise comparison with controls (Fisher Exact Test), as reported by NTP (1990). NS is not significant.
[4] Cochran-Armitage trend test p-values, as reported by NTP (1990).

Table 4. Tumor incidences in male $B6C3F_1$ mice exposed to glycidol (NTP, 1990).

Tumor site, type, and first occurrence	Administered dose (mg/kg)	Average daily dose[1] (mg/kg-day)	Tumor incidence[2]	Statistical significance[3]
Alveolar / bronchiolar adenoma or carcinoma (week 73)	0	0	13/46	$p = 0.034$[4]
	25	17.7	11/46	NS
	50	35.4	21/44	$p = 0.046$
Forestomach squamous cell papilloma or carcinoma (week 71)	0	0	1/47	$p < 0.001$[4]
	25	17.7	2/47	NS
	50	35.4	10/46	$p = 0.003$
Harderian gland adenoma or adenocarcinoma (week 72)	0	0	8/47	$p < 0.001$[4]
	25	17.7	12/47	NS
	50	35.4	22/45	$p = 0.001$
Hepatocellular adenoma or carcinoma (week 52)	0	0	24/48	$p = 0.020$[4]
	25	17.7	31/50	NS
	50	35.4	35/49	$p = 0.025$
Skin squamous cell papilloma or carcinoma (week 90)	0	0	0/41	$p = 0.006$[5]
	25	17.7	0/37	NS
	50	35.4	4/38	$p = 0.049$

[1] Average daily dose calculated as described in the Appendix.
[2] The denominator represents the number of animals alive at the time of the first occurrence of the tumor.
[3] p-values from pairwise comparison with controls (Fisher Exact Test), calculated by OEHHA. NS is not significant.
[4] Exact trend test p-values calculated by OEHHA.
[5] The Cochran-Armitage trend test p-value calculated by OEHHA.

Table 5. Tumor incidences in female B6C3F$_1$ mice exposed to glycidol (NTP, 1990).

Tumor site, type, and first occurrence	Administered dose (mg/kg)	Average daily dose[1] (mg/kg-day)	Tumor incidence[2]	Statistical significance[3]
Harderian gland adenoma or adenocarcinoma (week 88)	0	0	4/42	$p < 0.001$[4]
	25	17.7	11/38	$p = 0.026$
	50	35.4	17/35	$p < 0.001$
Mammary gland adenoma, fibroadenoma, or adenocarcinoma (week 55)	0	0	2/49	$p < 0.001$[4]
	25	17.7	6/50	NS
	50	35.4	15/49	$p < 0.001$
Skin squamous cell papilloma or carcinoma (week 98)	0	0	0/35	$p = 0.024$[5]
	25	17.7	0/30	NS
	50	35.4	2/24	NS
Subcutaneous tissue sarcoma or fibrosarcoma (week 70)	0	0	0/48	$p < 0.001$[4]
	25	17.7	3/48	NS
	50	35.4	9/44	$p < 0.001$
Uterus carcinoma or adenocarcinoma (week 97)	0	0	0/36	$p = 0.063$[4]
	25	17.7	3/30	$p = 0.089$
	50	35.4	3/28	$p = 0.079$

[1] Average daily dose calculated as described in the Appendix.
[2] The denominator represents the number of animals alive at the time of the first occurrence of the tumor.
[3] p-values from pairwise comparison with controls (Fisher Exact Test), calculated by OEHHA. NS is not significant.
[4] Exact trend test p-values calculated by OEHHA.
[5] The Cochran-Armitage trend test p-value calculated by OEHHA.

APPROACH TO DOSE-RESPONSE ANALYSIS

This section briefly reviews the information on genotoxicity and other data relevant to possible mechanisms of glycidol carcinogenicity for the purpose of determining the most appropriate approach for dose-response analysis.

The genetic toxicity of glycidol has been reviewed by IARC (2000). Glycidol gave uniformly positive responses in various mutation assays in *Salmonella typhimurium, Escherichia coli,* fungal, *Drosophila melanogaster*, and mammalian cell systems without

metabolic activation. Glycidol was positive in all *in vitro* clastogenic tests, including sister chromatid exchange, chromosomal aberration, and micronucleus assays. Glycidol induced unscheduled DNA synthesis in human fibroblasts in the presence of metabolic activation (IARC, 2000). Glycidol possesses a reactive epoxide moiety, and has been shown in a number of *in vitro* studies to directly alkylate DNA (IARC, 2000). IARC concluded: "Glycidol has been shown to be genotoxic using assays covering a wide range of endpoints. *In vitro*, it did not require metabolic activation to elicit positive responses."

No pharmacokinetic information was found suggesting dose-dependent or species dependent adjustments to the dose response analysis should be done.

Genotoxicity is likely to play a major role in the carcinogenicity of glycidol. IARC, in concluding that glycidol is "probably carcinogenic to humans" took into consideration that "glycidol is a direct acting agent that is mutagenic in a wide range of *in vivo* and *in vitro* test systems." Thus, it is assumed that at low doses, glycidol cancer risk is linearly related to dose. For male mice, a linearized multistage model is used to derive a cancer potency estimate for each treatment-related tumor site. For male rats, female rats, and female mice, glycidol significantly affected survival due to tumorgenicity. A Weibull form of the multistage model was used to take into account the mortality in these studies in estimating potency for each treatment-related tumor site. The default procedures for deriving cancer potency estimates are outlined in Title 27, California Code of Regulations, section 25703. A description of the methodology used is given in the Appendix.

DOSE RESPONSE ASSESSMENT

The results of fitting the multistage models to the dose-response data of the NTP studies (Tables 2-5) for rats and mice are shown in Tables 6-8. The fitting results in an animal cancer potency estimate, as described in the Appendix. Multiplying by the applicable interspecies scaling factor gives an estimate of human cancer potency for each treatment-related tumor site. Overall cancer potency estimates are based on the sum of potency estimates when multiple tumor types were observed within a given experiment on a particular species and sex. This was done using a Monte Carlo approach to statistically sum the potencies, as described in the Appendix.

The interspecies scaling factor is derived from the ratio of body weight in humans (assumed to be 70 kilograms [kg]) to the body weight of the experimental animals as explained in the Appendix. The average body weights of 0.433 and 0.257 kg for male and female rats, and 0.043 and 0.042 kg for male and female mice were calculated based on the data reported by the NTP (1990) for control animals.

As shown in Table 7, the multisite human cancer potency of 1.3 $(mg/kg\ day)^{-1}$ derived from the female rat study is the highest among potency estimates derived from rats and mice of both sexes. The human cancer potency estimate for female rats is used as the basis for calculating the NSRL.

Table 6. Animal and human cancer potency estimates in male F344/N rats for glycidol.

Type of neoplasm	Animal cancer potency[+] $(mg/kg\text{-}d)^{-1}$	Human cancer potency $(mg/kg\text{-}d)^{-1}$
Brain glioma	0.02631	0.14
Forestomach papilloma or carcinoma	0.01899	0.10
Intestine adenomatous polyp or adenocarcinoma	0.009578	0.052
Mammary gland fibroadenoma or adenocarcinoma	0.06535	0.36
Skin sebaceous gland adenoma or adenocarcinoma, or basal cell tumor	0.05606	0.31
Thyroid gland follicular cell adenoma or carcinoma	0.03604	0.20
Tunica vaginalis / peritoneum mesothelioma	0.05859	0.32
Zymbal's gland carcinoma	0.02299	0.13
Multisite	0.1450	0.79

[+] Derived using the multistage Weibull model.

Table 7. Animal and human cancer potency estimates in female F344/N rats for glycidol.

Type of neoplasm	Animal cancer potency^{+} $(mg/kg\text{-}d)^{-1}$	Human cancer potency $(mg/kg\text{-}d)^{-1}$
Brain glioma	0.01269	0.082
Clitoral gland adenoma, adenocarcinoma, or carcinoma	0.03209	0.21
Forestomach papilloma or carcinoma	0.01448	0.094
Hematopoietic system leukemia	0.02579	0.17
Mammary gland fibroadenoma or adenocarcinoma	0.1681	1.1
Oral mucosa papilloma or carcinoma	0.01314	0.085
Thyroid gland follicular cell adenoma or carcinoma	0.004393	0.024
Multisite	0.2009	**1.3**

Bolding indicates value selected as the basis of the NSRL.
$^{+}$ Derived using the multistage Weibull model.

Table 8. Animal and human cancer potency estimates in $B6C3F_1$ mice for glycidol.

Sex, strain, species	Type of neoplasm	Animal cancer potency[+] $(mg/kg\text{-}d)^{-1}$	Human cancer potency $(mg/kg\text{-}d)^{-1}$
Male $B6C3F_1$ mice	Alveolar/bronchiolar adenoma or carcinoma	0.01119	0.13
	Forestomach squamous cell papilloma or carcinoma	0.006139	0.079
	Harderian gland adenoma or adenocarcinoma	0.01653	0.19
	Hepatocellular adenoma or carcinoma	0.02806	0.33
	Skin squamous cell papilloma or carcinoma	0.003438	0.040
	Multisite	0.04243	0.50
Female $B6C3F_1$ mice	Harderian gland adenoma or adenocarcinoma	0.01011	0.12
	Mammary gland adenoma, fibroadenoma, or adenocarcinoma	0.01608	0.19
	Skin squamous cell papilloma or carcinoma	0.003103	0.034
	Subcutaneous tissue sarcoma or fibrosarcoma	0.01148	0.14
	Uterus carcinoma or adenocarcinoma	0.007342	0.087
	Multisite	0.04439	0.53

[+] Derived using the linearized multistage model for male mice and the multistage Weibull model for female mice.

NO SIGNIFICANT RISK LEVEL

The NSRL for Proposition 65 is the intake associated with a lifetime cancer risk of 10^{-5}. The human cancer potency estimate of 1.3 $(mg/kg\text{-}day)^{-1}$ for glycidol, based on multisite analysis in female rats, was used to calculate the NSRL for this compound. A value of 0.54 μg/day was derived as shown below:

$$NSRL = \frac{10^{-5} \times 70\,kg}{1.3\,(mg/kg\text{-}day)^{-1}} \times 1000\,\mu g/mg = 0.54\,\mu g/day$$

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APPENDIX: METHODOLOGY USED TO DERIVE THE NSRL FOR GLYCIDOL

Procedures for the development of Proposition 65 NSRLs are described in regulation in Title 27, California Code of Regulations, sections 25701 and 25703. Consistent with these procedures, the specific methods used to derive the NSRL for glycidol are outlined in this Appendix.

A.1 Cancer Potency as Derived from Animal Data

Multistage polynomial model

For regulatory purposes, the lifetime probability of dying with a tumor (p) induced by an average daily dose (d) is often assumed to be (California Department of Health Services [CDHS], 1985; U.S. Environmental Protection Agency [U.S. EPA], 2002; Anderson *et al.*, 1983):

$$\text{Probability of cancer } p(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + \cdots + q_j d^j)]$$

with constraints, $q_i \geq 0$ for all i. The q_i are parameters of the model, which are taken to be constants and are estimated from the animal cancer bioassay data. With three dose groups, as is the case with the NTP 1990 studies of glycidol, the default linearized multistage model defaults to two stages, or three parameters, q_0, q_1, and q_2. The parameter q_0 provides the basis for estimating the background lifetime probability of the tumor (*i.e.*, $1 - \exp[-(q_0)]$). The parameter q_1 is, for small doses, the ratio of excess lifetime cancer risk to the average daily dose received. The upper 95% confidence bound on q_1, estimated by maximum likelihood techniques, is referred to here as $q_{1(UCB)}$. When the experiment duration is at least the natural lifespan of the animals, the parameter $q_{1(UCB)}$ is taken as the animal cancer potency, q_{animal}. When dose is expressed in units of mg/kg-day, the parameters q_1 and $q_{1(UCB)}$ are given in units of $(\text{mg/kg-day})^{-1}$. Details of the estimation procedure are given in Crump (1984) and Crump *et al.* (1977).

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; U.S. EPA, 2002) as "extra risk", and is equivalent to that obtained by using the Abbott (1925) correction for background incidence.

Multistage Weibull model

When survival in the bioassay is poor, the number of animals subject to late occurring tumors is significantly reduced. In such situations, the above described default procedure can inaccurately estimate the potency. A time-dependent model fit to individual animal data (*i.e.*, tumor status and time of death for each animal under study) may provide more reliable potency estimates. When there is an indication that survival is poor, a time-dependent analysis is employed using the multistage-in-dose Weibull-in-time (multistage Weibull) model. This model is an extension of the multistage

polynomial model given above, with the probability of tumor (p(t,d)) by time t and lifetime dose rate d given as:

$$\text{Probability of cancer } p(t,d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ...)(t-t_0)^k]$$

with $q_i \geq 0$, for all i, and $0 \leq t_0 < t$, where t_0 is commonly interpreted as the latency period, and k is the age exponent. In this case, carcinogenic potency for animals is derived by applying a maximum likelihood modeling approach to estimate the parameters (q_i, t_0, and k). Using the multistage Weibull model, the animal cancer potency, q_{animal}, is defined as the upper 95% confidence bound on q_1 estimated at the assumed standard lifetime of 104 weeks for rats and mice. The age exponent k was constrained to be less than or equal to 10. The Weibull model was used to derive animal cancer potency estimates for male and female rats and female mice.

Multisite procedure

For carcinogens that induce tumors at multiple sites and/or with different cell types in a particular species and sex, the animal cancer potency is derived by probabilistically summing the potencies from the different sites and/or cell types. This is a way of taking into account the multisite carcinogenicity and provides a basis for estimating the cumulative risk of carcinogen treatment-related tumors.

The linear term (q_1) of the multistage model as described in the above equations is first estimated based on the dose-response data for each of the treatment-related tumor sites. Statistical distributions, rather than point estimates, are generated at each site for the linear term (q_1). The distributions of q_1 for each of the treatment-related sites are then statistically summed using a Monte Carlo approach and assuming independence. The sum is created by adding the linear term for each tumor site, according to its distribution, through random sampling with 100,000 trials. The upper 95 percent confidence bound on the summed distribution is taken as the multisite animal cancer potency estimate.

Calculation of the average daily dose

The average daily dose was calculated based on the daily administrated dose, dosing regimens, and total dosing duration of the study. In the gavage studies (NTP, 1990), the average daily dose (mg/kg-day) is calculated from the administered dose with adjustments for days of dosing during the week and total dosing weeks during the experimental period (see Table A-1).

$$\text{Average daily dose (mg/kg-day)} = \text{administered dose (mg/kg)} \times (5/7) \times (103/104)$$

Table A-1. Calculation of average daily doses in NTP gavage studies (1990).

Sex, strain, species	Administered dose (mg/kg)	Days dosed per week correction	Weeks dosed per experimental duration correction	Average daily dose (mg/kg-day)
Male & female F344/N rats	0	5/7	103/104	0
	37.5	5/7	103/104	26.5
	75.0	5/7	103/104	53.1
Male & female $B6C3F_1$ mice	0	5/7	103/104	0
	25.0	5/7	103/104	17.7
	50.0	5/7	103/104	35.4

A.2 Interspecies Scaling

Once a potency value is estimated in animals following the techniques described above, the human potency is estimated. As described in the California carcinogen 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}) is 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 $(mg/kg\text{-}day)^{-1}$ (see Watanabe *et al*. [1992]):

$$q_{human} = q_{animal} \times (bw_h / bw_a)^{1/3}$$

In the NTP studies (1990), based on data reported for control animals, average body weights were calculated as 0.433, 0.257, 0.043, and 0.042 kg for male and female rats, and male and female mice, respectively. The default human body weight is 70 kg. An example derivation of human cancer potency from the multisite cancer potency for female rats of 0.2009 $(mg/kg\text{-}day)^{-1}$ is shown below:

$$q_{human} = 0.2009\ (mg/kg\text{-}day)^{-1} \times (70\ kg\ /0.257\ kg\ )^{1/3} = 1.3\ (mg/kg\text{-}day)^{-1}$$

A.3 Risk-Specific Intake Level Calculation

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

$$I = \frac{R \times bw_h}{q_{human}}$$

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

Daily intake levels associated with lifetime cancer risks above 10^{-5} exceed the NSRL for cancer under Proposition 65 (Title 27 California Code of Regulations, section 25703). Thus for a 70 kg person, the NSRL is given by:

$$\text{NSRL} = \frac{10^{-5} \times 70\,\text{kg}}{q_{\text{human}}} \times 1000\,\mu\text{g/mg}.$$

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