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

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SUMMARY OF FINDINGS

The carcinogenic potency of nitromethane was estimated from dose-response data for multiple treatment-responding tumor sites in female $B6C3F_1$ mice exposed to nitromethane via inhalation (National Toxicology Program [NTP], 1997). These sites were lung, liver and Harderian gland. To provide the basis for determining the cancer risk for this compound, an estimate of cancer potency associated with all treatment-related tumors was derived using a multisite statistical approach. 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 human cancer potency estimate for nitromethane is 0.18 $(mg/kg\text{-}day)^{-1}$ and the corresponding NSRL is 39 µg/day.

Table 1. Cancer Potency and NSRL for Nitromethane.

Chemical	Cancer Potency $(mg/kg\text{-}day)^{-1}$	NSRL (µg/day)
Nitromethane	0.18	39

INTRODUCTION

This report describes the derivation of a human cancer potency estimate and NSRL for nitromethane (CAS number 75-52-5; molecular weight 61.04; synonym nitrocarbol). "Nitromethane" was listed on May 1, 1997 as 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*.). Nitromethane was considered a high priority to assess due to the large quantities produced or imported per year in the U.S. (10-50 million pounds in 2002) and the potential for human exposure (U.S. EPA, 2002; NTP, 1997). Nitromethane is a fuel used for rockets and engines, a chemical intermediate for agricultural fumigants, biocides and other products, a solvent, an explosive used in mining, oil well drilling and seismic exploration, and has been detected in air, surface and drinking water and cigarette smoke (NTP, 1997).

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

STUDIES SUITABLE FOR DOSE-RESPONSE ASSESSMENT

The International Agency for Research on Cancer (IARC, 2000) identified the studies of NTP (1997) and Griffin *et al.* (1996) as the only available carcinogenicity data on nitromethane. Subsequent to the IARC (2000) review, NTP (2005) published cancer bioassays for nitromethane in fish models (guppies and medaka). A literature search did not identify any human studies or any additional animal studies that may be suitable for dose-response assessment. Griffin *et al.* (1996) exposed Long-Evans rats to nitromethane for two years via inhalation and found no evidence of carcinogenicity. The NTP (2005) bioassays in male and female guppies and medaka were characterized as either inadequate (male guppies) or negative (all others). The studies of Griffin *et al.* (1996) and the studies in fish by NTP (2005) provide no useful information for dose-response analysis. Therefore, the NTP inhalation bioassays in male and female F344/N rats and $B6C3F_1$ mice (NTP, 1997) are the only cancer bioassays suitable for estimating the potency of nitromethane.

NTP (1997) exposed groups of 50 male and 50 female F344/N rats and 50 male and 50 female $B6C3F_1$ mice to nitromethane via inhalation for six hours and twelve minutes per day, five days per week, for 103 weeks, with sacrifice occurring at week 105. Nitromethane exposure concentrations were 0, 94, 188 or 375 ppm for rats, and 0, 188, 375, or 750 ppm for mice. The survival of the exposed male and female rats was not significantly different from the controls for each sex. Male rats had similar body weights as chamber control rats throughout the study. Female rats exposed at 375 ppm weighed slightly more than chamber controls at the end of the study (NTP, 1997). The survival rates in the exposed male mice were similar to that of the chamber control mice; however, the survival in the female mice was marginally greater than that of the chamber controls (NTP, 1997). The exposed female mice were generally slightly heavier than the controls during the study, but body weights of all groups were similar at the end of the study. Exposed male mice had similar body weights to the controls for the entire study length.

NTP (1997) found clear evidence of carcinogenicity in female rats and male and female mice exposed to nitromethane. No treatment-related tumors were observed in male rats. For female rats, the incidence of mammary fibroadenoma, adenoma or carcinoma (combined) increased with concentration and was significantly greater compared to chamber controls in the two highest exposure groups. NTP observed a positive trend in the incidence of Harderian gland adenoma or carcinoma (combined) with increasing concentration in male and female mice. The incidence of Harderian gland tumors was significantly greater in the two highest exposure groups compared to controls for both males and females. There were also significantly higher incidences of alveolar/bronchiolar carcinoma in the highest exposure group compared to controls in male mice and alveolar/bronchiolar adenomas or carcinomas (combined) in female mice. Female mice also showed significant increases in the incidence of hepatocellular adenomas or carcinomas (combined). The dose-response data from the NTP studies in female F344/N rats and the male and female $B6C3F_1$ mice are presented by tumor site in Table 2 and Tables 3a-c, respectively.

Table 2. Incidence of Mammary Tumors in Female Rats Exposed to Nitromethane via Inhalation for Two Years (NTP, 1997).

Sex, strain, species	Chamber concentration (ppm)	Lifetime average dose[1] (mg/kg-day)	Mammary fibroadenoma, adenoma or carcinoma (combined)[2]	Statistical significance
Female F344/N rats	0	0	21/50	$p < 0.001$[4]
	94	29.4	25/50	$p = 0.274$[3]
	188	58.8	34/50	$p = 0.008$[3]
	375	117	41/49	$p < 0.001$[3]

[1] Nitromethane was administered six hours and twelve minutes per day, five days per week, for 103 weeks, with sacrifice at week 105. Lifetime average dose was calculated as described in the Appendix.

[2] Number of tumor-bearing animals/number of animals alive at first occurrence of mammary tumor in any of the dose groups. The first mammary fibroadenoma, adenoma or carcinoma occurred on day 425.

[3] The *p*-values from pairwise comparison with controls (Fisher Exact Test).

[4] Trend test *p*-values as reported in NTP (1997) from life table test, logistic regression test and Cochran-Armitage test (Table B3; NTP, 1997).

Table 3a. Incidence of Harderian Gland Tumors in Mice Exposed to Nitromethane via Inhalation for Two Years (NTP, 1997).

Sex, strain, species	Chamber concentration (ppm)	Lifetime average dose[1] (mg/kg-day)	Harderian gland adenoma or carcinoma (combined)[2]	Statistical significance
Male $B6C3F_1$ mice	0	0	10/49	$p < 0.001$[4]
	188	97	11/49	$p = 0.500$[3]
	375	193	25/48	$p = 0.001$[3]
	750	386	37/48	$p < 0.001$[3]
Female $B6C3F_1$ mice	0	0	6/43	$p = 0.010$ < 0.001 < 0.001[4]
	188	99	9/44	$p = 0.303$[3]
	375	197	20/48	$p = 0.003$[3]
	750	394	21/48	$p = 0.002$[3]

[1] Nitromethane was administered six hours and twelve minutes per day, five days per week, for 103 weeks, with sacrifice at week 105. Lifetime average dose was calculated as described in the Appendix.

[2] Number of tumor-bearing animals/number of animals alive at first occurrence of Harderian tumor in any of the dose groups. The first Harderian gland adenoma/carcinoma occurred on day 436 for male mice and on day 498 for female mice.

[3] The *p*-values from pairwise comparison with controls (Fisher Exact Test).

[4] Trend test *p*-values as reported in NTP (1997) from the life table test, logistic regression test and Cochran-Armitage test, respectively (Table C3 for male mice and Table D3 for female mice; NTP, 1997).

Table 3b. Incidence of Alveolar/Bronchiolar Tumors in Mice Exposed to Nitromethane via Inhalation for 103 Weeks (NTP, 1997).

Sex, strain, species	Chamber concentration (ppm)	Lifetime average dose[1] (mg/kg-day)	Alveolar/bronchiolar adenoma or carcinoma (combined)[2]	Statistical significance
Male $B6C3F_1$ mice	0	0	13/49	p = 0.032 = 0.059 = 0.063[4]
	188	97	13/48	p = 0.566[3]
	375	193	12/47	p = 0.548N[3]
	750	386	20/48	p = 0.087[3]
Female $B6C3F_1$ mice	0	0	3/46	p = 0.042 = 0.007 = 0.007[4]
	188	99	6/47	p = 0.254[3]
	375	197	6/47	p = 0.254[3]
	750	394	12/49	p = 0.015[3]

[1] Nitromethane was administered six hours and twelve minutes per day, five days per week, for 103 weeks, with sacrifice at week 105. Lifetime average dose was calculated as described in the Appendix.

[2] Number of tumor-bearing animals/number of animals alive at first occurrence of alveolar/bronchiolar tumor in any dose group. The first alveolar/bronchiolar carcinoma/adenoma occurred on day 449 for male mice and day 426 for female mice.

[3] The *p*-values from pairwise comparison with controls (Fisher Exact Test). An "N" after the *p*-value signifies that the incidence in the dose group is lower than that in the control group.

[4] Trend test *p*-values as reported in NTP (1997) from the life table test, logistic regression test and Cochran-Armitage test, respectively (Table C3 for male mice and Table D3 for female mice; NTP, 1997).

Table 3c. Incidence of Hepatocellular Tumors in Mice Exposed to Nitromethane via Inhalation for Two Years (NTP, 1997).

Sex, strain, species	Chamber concentration (ppm)	Lifetime average dose[1] (mg/kg-day)	Hepatocellular adenoma or carcinoma (combined)[2]	Statistical significance
Female $B6C3F_1$ mice	0	0	19/46	p = 0.095 = 0.001 < 0.001[4]
	188	99	34/46	p = 0.001[3]
	375	197	22/47	p = 0.372[3]
	750	394	40/49	p < 0.001[3]

[1] Nitromethane was administered six hours and twelve minutes per day, five days per week, for 103 weeks, with sacrifice at week 105. Lifetime average dose was calculated as described in the Appendix.

[2] Number of tumor-bearing animals/number of animals alive at first occurrence of hepatocellular tumor in any dose group. The first occurrence of hepatocellular adenoma/carcinoma occurred on day 426 in female mice.

[3] The *p*-values from pairwise comparison with controls (Fisher Exact Test).

[4] Trend test *p*-values as reported in NTP (1997) from the life table test, logistic regression test and Cochran-Armitage test, respectively (Table D3; NTP, 1997).

APPROACH TO DOSE-RESPONSE ANALYSIS

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

IARC (2000) summarized the available data on the genotoxicity of nitromethane. Nitromethane was not mutagenic in bacterial test systems with or without metabolic activation or in *Drosophila melanogaster* (IARC, 2000). Nitromethane was also negative in *in vitro* assays for sister chromatid exchanges and chromosomal aberrations. Micronuclei were not induced in bone marrow erythrocytes from mice exposed to nitromethane via intraperitoneal injection or in peripheral blood erythrocytes from mice exposed to nitromethane via inhalation. No micronuclei induction was observed in Syrian hamster embryo cells *in vitro*. IARC (2000) noted that an *in vitro* cell transformation assay in Syrian hamster embryo cells showed positive results at high concentration (4000 and 5000 µg/mL; Kerckaert *et al*., 1996). IARC (2000) concluded that "The results of short-term tests on nitromethane do not indicate that the compound has genotoxic activity." An additional study not reviewed by IARC found that nitromethane was negative in an *in vitro* p53 induction assay (Duerksen-Hughes *et al.*, 1999).

NTP (1997) reviewed structure-activity information relevant to the mechanism of carcinogenicity for the series of nitroalkanes and concluded that "It is not known whether the generation of reactive radicals directly or indirectly is involved in the mechanism of toxicity or carcinogenicity for some primary nitroalkanes and for nitromethane in particular." No additional relevant information was located on the mechanism of nitromethane carcinogenicity.

Thus, the mechanism of carcinogenicity of nitromethane is not known at this time. Further, 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), as specified in Title 22, California Code of Regulations, section 12703, has been applied to derive cancer potency estimates for nitromethane. To account for the multisite tumorigenicity observed in both sexes of mice and to provide the basis for estimating the cumulative risk of any treatment-related tumor within each species and gender, a multisite statistical approach was used in analyzing the mouse data. Distributions of animal cancer potencies were generated for each treatment-related tumor site and probabilistically summed. The multisite animal cancer potency estimate is the upper 95 percent confidence bound on the combined distribution. To derive the human cancer potency estimate, body size differences between humans and experimental animals are taken into account. The Appendix describes the methodology in detail.

DOSE-RESPONSE ASSESSMENT

Cancer potency estimates (Table 4) were derived from the NTP (1997) studies for sites showing treatment-related effects, as discussed in detail above. These sites were mammary gland in female rats, Harderian gland and lung in male mice, and Harderian gland, lung and liver in female mice.

Both animal and human cancer potencies were determined for each site, based on the data shown in Tables 2-3c. Multisite human cancer potency estimates were generated based on data for multiple affected sites in each sex of mice as discussed above, and methods described in more detail in the Appendix.

Table 4: Animal and Human Cancer Potency Estimates for Nitromethane.

Sex, strain, species	Type of neoplasm	Animal cancer potency $(mg/kg\text{-}d)^{-1}$	Human cancer potency $(mg/kg\text{-}d)^{-1}$
Female F344/N rats	Mammary fibroadenoma, adenoma, or carcinoma (combined)	0.01423	0.089
Male $B6C3F_1$ mice	Harderian gland adenoma or carcinoma (combined)	0.002733	0.031
	Alveolar/bronchiolar adenoma or carcinoma (combined)	0.0009715	0.011
	Multisite	0.002979	0.034
Female $B6C3F_1$ mice	Harderian gland adenoma or carcinoma (combined)	0.001878	0.022
	Alveolar/bronchiolar adenoma or carcinoma (combined)	0.001020	0.012
	Hepatocellular adenoma or carcinoma (combined)	0.01323	0.16
	Multisite	0.01493	**0.18**

Bolding indicates value selected as the basis of the NSRL.

The female mouse was found to be the most sensitive species and sex tested by NTP (1997) in its carcinogenicity studies of nitromethane. The human cancer potency estimate of $0.18\ (mg/kg\text{-}d)^{-1}$ was based on the combined potency distribution for all nitromethane related tumors in female mice, as well as adjustments for rodent-to-human differences in body size.

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 $0.18\ (mg/kg\text{-}day)^{-1}$ derived above from studies in female mice was used to calculate the NSRL of 39 µg/day for nitromethane using methods described in the Appendix, with

$$\text{NSRL} = \frac{10^{-5} \times 70\ \text{kg}}{0.18\ (\text{mg/kg-day})^{-1}} \times 1000\ \mu\text{g/mg} = 39\ \mu\text{g/day}.$$

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APPENDIX: DEFAULT METHODOLOGY USED TO DERIVE THE NSRL FOR NITROMETHANE

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

A.1 Derivation of Cancer Potency 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 (California Department of Health Services [CDHS], 1985; Anderson *et al.*, 1983; U.S. Environmental Protection Agency [U.S. EPA], 2002):

$$p(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + \cdots + q_j d^j)] \quad (1)$$

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 four dose groups, as is the case with nitromethane, the linearized multistage model defaults to three stages, or four parameters (*i.e.,* q_0, q_1, q_2 and q_3). The parameter q_0 represents the background lifetime incidence of the tumor. The parameter q_1 is, for small doses, the ratio of excess lifetime cancer risk to the average daily dose received. At low doses the terms q_2d^2 and q_3d^3 contribute negligibly to excess risk, which can be approximated by q_1d. 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 life span of the animals, the parameter $q_{1(UCB)}$ is taken as the animal cancer potency. A *p*-value of greater than 0.05 for the χ^2 goodness-of-fit test was taken as an adequate model fit. When dose is expressed in units of mg/kg-day, the parameters q_1 and $q_{1(UCB)}$ are given in units of $(mg/kg\text{-}day)^{-1}$. 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.

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. Using the combined potency distribution takes into account the multisite tumorigenicity and provides a basis for estimating the cumulative risk of nitromethane treatment-related tumors.

The linear term (q_1) of the multistage model (Equation 1) 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 by tracing the profile likelihood of 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 for nitromethane. The upper 95 percent confidence bound on the summed distribution is taken as the multisite animal cancer potency estimate.

Adjustments for experiments of short duration

To estimate the animal cancer potency (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:

$$q_{animal} = q_{1(UCB)} \bullet (T/T_e)^3 \quad (2)$$

Following Gold and Zeiger (1997) and the 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:

$$q_{animal} = q_{1(UCB)} \bullet (104/T_e)^3 \quad (3)$$

Because the NTP (1997) studies of nitromethane were 105 weeks in duration, a correction factor to extrapolate to 104 weeks was not required and therefore, $q_{animal} = q_{1(UCB)}$.

Calculation of the lifetime average dose

The lifetime average dose in units of mg/kg-day was calculated for each of the relevant dose groups, based on the dose level, duration and regimen described in the experiments above. Body weights for female rats (0.283 kg) and male and female mice (0.0459 kg and 0.0430 kg, respectively) were calculated from data in the NTP report (Tables 8, 15, 16 from NTP, 1997). The inhalation rates (IR) for female rats and mice of both sexes were calculated based on the equations of Anderson *et al*. (1983), which were derived using experimental data on animal breathing rates (mg/m^3) and corresponding body weights (kg):

$$IR_{mice} = 0.0345 \times (bw_{mice}/0.025)^{2/3} \quad (4)$$

$$IR_{rats} = 0.105 \times (bw_{rats}/0.113)^{2/3} \quad (5)$$

The constants 0.0345 and 0.105 are in m^3/day and 0.025 and 0.113 are in kg. The resulting inhalation rates were 0.194 m^3/day for female rats, 0.0576 m^3/day for male mice, and 0.0552 m^3/day for female mice.

The air concentration (C_{air}) in units of ppm was converted to units of mg/m^3 by multiplying the dose by 2.5 (mg/m^3)/ppm (NIOSH, 2005), the conversion factor for nitromethane. The air concentration in units (mg/m^3) was then multiplied by the inhalation rate (IR in m^3/day) for mice or rats and divided by the respective body weight, and then multiplied by 6.2/24 to account for the six hours and twelve minutes of exposure per day, by 5/7 to account for a five day per week dosing and by 103/104 to account for the less than lifetime exposure. The equation for lifetime average dose (D_{LTA}) in units (mg/kg-day) is therefore:

$$D_{LTA} = C_{air}\,(\text{ppm}) \times 2.5 \frac{(\text{mg}/\text{m}^3)}{\text{ppm}} \times \frac{IR_{rodent}}{bw_{rodent}} \frac{(\text{m}^3/\text{day})}{\text{kg}} \times \frac{6.2}{24} \times \frac{5}{7} \times \frac{103}{104} \quad (6)$$

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 $(mg/kg\text{-}day)^{-1}$ and body weight is expressed in kilograms:

$$q_{human} = q_{animal} \bullet (bw_h / bw_a)^{1/3} \tag{7}$$

A.3 Risk-Specific Intake Level Calculation

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

$$I = \frac{R \times bw_h}{q_{human}} \tag{8}$$

where bw_h is the human body weight in kilograms, and q_{human} is the theoretical cancer potency estimate for humans in units $(mg/kg\text{-}day)^{-1}$. Daily intake levels associated with lifetime cancer risks above 10^{-5} exceed the no significant risk level (NSRL) for cancer under Proposition 65 (Title 22 California Code of Regulations, Section 12703). Thus for a 70 kg person, the NSRL in units μg/day is given by:

$$NSRL = \frac{10^{-5} \times 70\,kg}{q_{human}} \times 1000\,\mu g/mg. \tag{9}$$

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