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

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SUMMARY OF FINDINGS

The cancer potency of naphthalene was estimated from dose-response data for benign and malignant tumors among male rats exposed via inhalation to naphthalene by the National Toxicology Program (NTP, 2000). The male rat was the most sensitive sex and species tested by NTP (1992; 2000) in the inhalation carcinogenesis studies of naphthalene. NTP considered the increased incidences in male rats of nasal respiratory epithelial adenoma and nasal olfactory epithelial neuroblastoma, which are rare tumors, to provide clear evidence of the carcinogenic activity of naphthalene. A cancer potency of 0.12 $(mg/kg\text{-}day)^{-1}$ was derived based on the potential for male rats to develop either nasal respiratory epithelial adenoma or nasal olfactory epithelial neuroblastoma. The potency derivation takes into account body size differences between humans and experimental animals.

Cancer potency was taken to be the sum of potencies associated with the two types of tumors in the male rat. Because of the statistical uncertainty in individual estimates of potency for each site, the terms were summed statistically, using Monte Carlo techniques. The upper 95 percent confidence bound on the summed linear terms was taken as cancer potency. The Proposition 65 "no significant risk level" (NSRL) is the daily intake level posing a 10^{-5} lifetime risk of cancer, based on this cancer potency. The cancer potency estimate and the corresponding NSRL are given in Table 1.

Table 1. Cancer potency and NSRL for naphthalene.

Chemical	Cancer Potency $(mg/kg\text{-}day)^{-1}$	NSRL (μg/day)
Naphthalene	0.12	5.8

INTRODUCTION

This report describes the derivation of a cancer potency estimate and NSRL for naphthalene (CAS No. 91-20-3; molecular weight 128.2). "Naphthalene" was listed on April 19, 2002, as a chemical known to the State to cause cancer under Proposition 65 (California Health and Safety

Code 25249.5 *et seq*.). The National Toxicology Program (NTP, 2004) has listed naphthalene as "reasonably anticipated to be a human carcinogen" based on sufficient evidence from studies in experimental animals.

This document discusses the studies available for cancer dose-response assessment, and summarizes the derivation of the cancer potency estimate and NSRL.

STUDIES SUITABLE FOR DOSE-RESPONSE ASSESSMENT

~~The National Toxicology Program (~~NTP~~)~~ conducted inhalation cancer studies of naphthalene using male and female $B6C3F_1$ mice (NTP, 1992). Animals were exposed to 0 (70 males, 69 females), 10 (69 males, 65 females) or 30 ppm naphthalene (135 males, 135 females) for six hours/day, five days/week for 104 weeks.

The survival rates of exposed female mice were similar to that of controls (86%, 88% and 76% for controls, 10 and 30 ppm exposure groups, respectively). However, survival of male control mice was significantly less than that of exposed male mice (37%, 75% and 89% for controls, 10 and 30 ppm exposure groups, respectively). NTP stated that the reduced control survival was due to wound trauma and secondary infections due to fighting among the group-housed mice.

Almost all of the male and female mice in the NTP 1992 mouse inhalation studies demonstrated an increased incidence of nasal respiratory epithelium hyperplasia and olfactory epithelium metaplasia.

Increased incidences of alveolar/bronchiolar adenomas and carcinomas were observed in male $B6C3F_1$ mice. Alveolar/bronchiolar adenoma or carcinoma incidences in the male mice as cited by NTP were 7/70, 17/69 and 31/135 for controls, and the 10 and 30 ppm exposure groups, respectively. The increased tumor incidences observed for the 10 and 30 ppm groups were significant when a pairwise comparison to control was performed using the Fisher exact test (p = 0.019 and 0.016 for the 10 and 30 ppm groups, respectively). However, NTP noted that an evaluation of the dose-response trend (p = 0.530) and pairwise comparisons between the controls and exposure groups (p = 0.212 and 0.394 for the 10 and 30 ppm exposure groups, respectively) using a logistic regression test indicated a lack of statistical significance. This was explained by NTP as being the result of the early control mortality due to fighting which lowered considerably the number of control animals at risk of developing lung tumors. NTP also noted that the alveolar/bronchiolar adenoma and carcinoma incidence (adjusted rate 26% in the high dose group) was within the historical control range for male $B6C3F_1$ mice (total incidence 19.7%, range 10-30%). NTP therefore concluded that the marginally increased alveolar / bronchiolar adenoma and carcinoma incidence in the male mice was more likely to be related to survival difference between exposed and control groups, than directly related to naphthalene exposure.

Increased incidences of alveolar/bronchiolar adenomas and carcinomas were also observed in female $B6C3F_1$ mice. The incidences of alveolar/bronchiolar adenoma or carcinoma, combined, in the female mice as cited by NTP were 5/69, 2/65 and 29/135 for controls, and the 10 and 30 ppm exposure groups, respectively. The tumors were primarily adenomas; one carcinoma was observed in high dose female mice. The increased tumor incidence in the 30 ppm exposure group females was statistically significant when compared to controls. NTP concluded that this provided some evidence of carcinogenicity.

These results were generally considered at the time to provide only equivocal evidence of carcinogenic activity, when considered in conjunction with earlier studies by various routes,

which, although of lower power, also had nonpositive or equivocal results (Adkins *et al*., 1986; Kennaway, 1930; Schmahl, 1955). However, the observation of possible tumor responses in the mice prompted the NTP to undertake naphthalene inhalation cancer studies in rats.

NTP (2000) exposed groups of 49 male and female Fischer 344N (F344) rats to naphthalene by inhalation at concentrations of 0, 10, 30 or 60 ppm for 6.2 hours/day, five days/week for 105 weeks. Survival of the male and female exposure groups was similar to that of controls.

These studies found clear evidence of carcinogenic activity in male and female rats, based on increased incidences of rare tumors, respiratory epithelial adenoma and olfactory epithelial neuroblastoma of the nose, in both sexes. Respiratory epithelial adenoma incidence occurred with a positive dose-response trend in male rats and was significantly increased in all exposed male rat groups. Male rat respiratory epithelial adenoma incidence as cited by NTP was 0/49, 6/49, 8/48 and 15/48 for controls, and the 10, 30 and 60 ppm exposure groups, respectively. Respiratory epithelial adenoma incidences in female rats exposed to 30 or 60 ppm were also increased, but the increase in the 60 ppm animals was not significant, and the increase in the 30 ppm animals was of borderline significance ($p = 0.053$ by Poly-3 test). Female rat respiratory epithelial adenoma incidence as cited by NTP was 0/49, 0/49, 4/49 and 2/49 for controls, and the 10, 30 and 60 ppm exposure groups, respectively.

Olfactory epithelial neuroblastomas occurred in males exposed to 30 and 60 ppm naphthalene and in all dose groups of naphthalene-exposed females. Neuroblastoma incidences occurred with positive dose-response trends in males and females. The incidence in females exposed to 60 ppm was significantly greater ($p < 0.001$ by Poly-3 test) than that in controls. Male rat olfactory epithelial neuroblastoma incidence as cited by NTP was 0/49, 0/49, 4/48 and 3/48 for controls, and the 10, 30 and 60 ppm exposure groups, respectively. Female rat olfactory epithelium neuroblastoma incidence as cited by NTP was 0/49, 2/49, 3/49 and 12/49 for controls, and the 10, 30 and 60 ppm exposure groups, respectively.

NTP also noted that nasal olfactory epithelial neuroblastomas and nasal respiratory epithelial adenomas have not been observed in male or female control rats in the NTP historical control database for animals fed NIH-07 feed in two-year inhalation studies or in the more recent, smaller database for control rats fed NTP-2000 feed. Additionally, almost all of the male and female mice in the NTP 1992 inhalation studies demonstrated increased nasal respiratory epithelium hyperplasia and olfactory epithelium metaplasia. These tissue types correspond to the tumor sites observed in rats exposed to naphthalene by inhalation.

DOSE RESPONSE ASSESSMENT

Cancer potency values for naphthalene were calculated based on data in female mice, male rats and female rats from the studies of NTP (1992, 2000) using the methodology described below.

Data

The mouse lung alveolar/bronchiolar adenoma or carcinoma incidence data, rat nasal respiratory epithelial adenoma data and nasal olfactory epithelial neuroblastoma data used to calculate cancer potency values are listed in Tables 2, 3 and 4, respectively.

Table 2. Incidence of lung alveolar/bronchiolar adenoma or carcinoma in female B6C3F$_1$ mice exposed to naphthalene via inhalation (from NTP, 1992)

Chamber Concentration (ppm)	Average Concentration[a] (mg/m^3)	Lifetime Average Dose[b] (mg/kg-day)	Tumor Incidence[c] (%)	Statistical Significance[d]
0	0	0	5/67 (7)	$p < 0.001$
10	9.36	12.3	2/61 (3)	$p = 1$
30	28.1	36.8	29/129[e] (22)	$p < 0.01$

a. Average concentration calculated by multiplying chamber concentration by six hours/24 hours, five days/seven days and 5.24 mg/m^3/ppm.
b. Lifetime average doses were determined by multiplying the average concentrations during the dosing period by the female mouse breathing rate (0.038 m^3/day) divided by the female mouse body weight (0.029 kg). The dosing period of 104 weeks was equivalent to the standard lifespan of the test animals (104 weeks for rodents), so no correction for less than lifetime exposure was required.
c. Effective rate. Animals that died before the first occurrence of tumor (day 471) were removed from the denominator.
d. The *p*-value listed next to dose groups is the result of pairwise comparison with controls using the Fisher exact test. The *p*-value listed next to the control group is the result of trend tests conducted by NTP (1992) using the logistic regression, life table, and Cochran-Armitage methods (all three methods produced the same result).
e. One carcinoma was observed in the high dose group.

Table 3. Incidence of nasal respiratory epithelial adenoma in male F344/N rats exposed to naphthalene via inhalation (from NTP, 2000)

Chamber Concentration (ppm)	Average Concentration[a] (mg/m^3)	Lifetime Average Dose[b] (mg/kg-day)	Tumor Incidence[c] (%)	Statistical Significance[d]
0	0	0	0/44 (0)	$p < 0.001$
10	9.67	5.69	6/42 (14)	$p < 0.05$
30	29.0	17.1	8/44 (18)	$p < 0.01$
60	58.0	34.1	15/41 (37)	$p < 0.001$

a. Average concentration calculated by multiplying chamber concentration by 6.2 hours/24 hours, five days/seven days, and 5.24 mg/m^3/ppm.
b. Lifetime average doses were determined by multiplying the average concentrations during the dosing period by the male rat breathing rate (0.262 m^3/day) divided by the male rat body weight (0.445 kg). The dosing period of 105 weeks was at least the standard lifespan of the test animals (104 weeks for rodents), so no correction for less than lifetime exposure was required.
c. Effective rate. Animals that died before the first occurrence of tumor (day 552) were removed from the denominator.
d. The *p*-value listed next to dose groups is the result of pairwise comparison with controls using the Fisher exact test. The p-value listed next to the control group is the result of the Poly-3 trend test, as reported by NTP (2000).

Table 4. Incidence of nasal olfactory epithelial neuroblastoma in F344/N rats exposed to naphthalene via inhalation (from NTP, 2000)

Chamber Concentration (ppm)	Average Concentration[a] (mg/m^3)	Lifetime Average Dose[b] (mg/kg-day)	Tumor Incidence[c] (%)	Statistical Significance[d]
Males				
0	0	0	0/49 (0)	$p = 0.027$
10	9.67	5.69	0/48 (0)	$p = 1$
30	29.0	17.1	4/48 (8)	$p = 0.056$
60	58.0	34.1	3/48 (6)	$p = 0.117$
Females				
0	0	0	0/49 (0)	$p < 0.001$
10	9.67	6.82	2/49 (4)	$p = 0.247$
30	29.0	20.4	3/49 (6)	$p = 0.121$
60	58.0	40.9	12/48 (25)	$p < 0.001$

a. Average concentration calculated by multiplying chamber concentration by 6.2 hours/24 hours, five days/seven days, and 5.24 mg/m^3/ppm.
b. Lifetime average doses were determined by multiplying the average concentrations during the dosing period by the rat breathing rate (males: 0.262 m^3/day; females: 0.182 m^3/day) divided by the rat body weight (males: 0.445 kg; females: 0.258 kg). The dosing period was at least the standard lifespan of the test animals (104 weeks for rodents), so no correction for less than lifetime exposure was required.
c. Effective rate. Animals that died before the first occurrence of tumor (males, day 399; females, day 429) were removed from the denominator.
d. The *p*-value listed next to dose groups is the result of pairwise comparison with controls using the Fisher Exact test. The *p*-value listed next to the control group is the result of the Poly-3 trend test, as reported by NTP (2000).

Methodology

The default approach, as originally delineated by CDHS (1985), is based on a linearized form of the multistage model of carcinogenesis (Armitage and Doll, 1954). Cancer potency is estimated from the upper 95% confidence bound, q_1^*, on the linear coefficient q_1 in a model relating lifetime probability of cancer (*p*) to dose (d):

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

The parameter q_1^* is estimated by fitting the above model to dose response data using MSTAGE (Crouch, 1992). This default linear approach is used for naphthalene because a genotoxic mechanism of action is plausible, as discussed in OEHHA (2004), and an alternative mechanism of action has not been established.

For a given chemical, the model is fit to one or more data sets. The default approach is to select the data for the most sensitive species and sex. For carcinogens that induce tumors at multiple sites, or at the same site but arising from different cell types, in a particular species and sex, cancer potency is taken to be the sum of potencies from the different sites or cell types. This approach assumes that tumors arising at different sites or from different cell types are

independent. Because of the statistical uncertainty in individual estimates of potency, the terms are summed statistically as follows. A distribution of estimates corresponding to the 0.1 through 99.9 percentiles of the linear term (q_1) of the multistage model (Equation 1) is generated for each treatment-related tumor site in a given species and sex using the computer program MSTAGE (Crouch, 1992), modified to tabulate percentile values. (Distributional values stem from the assumption that twice the log likelihood function is χ^2 distributed). The discretized distributions were used to obtain a distribution of the sum of q_1s for each site affected by the chemical using Monte Carlo simulation (100,000 trials; Crystal Ball 2000 software, Decisioneering, Inc., Denver, Colorado). The upper 95 percent confidence bound on the summed q_1s is taken as q_1* for the combined tumor sites.

To estimate animal potency, q_{animal}, the parameter q_1* is adjusted to account for short duration of an experiment by assuming that the lifetime incidence of cancer increases with the third power of age. However, the durations of the studies examined here (NTP, 1992; 2000) were at least the standard lifespan of the test animals (104 weeks for rodents), so this correction was not required. Thus, for the calculations based on the NTP (1992; 2000) studies, q_1* is equivalent to q_{animal}.

Interspecies extrapolation from experimental animals to humans is normally based on the following relationship (Anderson *et al*., 1983), where bw_h and bw_a are human and animal body weights, respectively, and potency (e.g., q_{animal}) is expressed on a dose per body weight basis:

$$q_{human} = q_{animal} \times \left(\frac{bw_h}{bw_a} \right)^{\frac{1}{3}} \qquad (2)$$

Alternatively, when performing calculations based on applied dose in terms of air concentrations, the assumption has sometimes been made that air concentration values are equivalent between species (CDHS, 1985). However, using the interspecies scaling factor shown above is preferred because it is assumed to account not only for pharmacokinetic differences (*e.g.*, breathing rate, metabolism), but also for pharmacodynamic considerations. Therefore, lifetime average doses in mg/kg-day were determined (details provided below) and used in the calculation of q_{animal} in $(mg/kg\text{-}day)^{-1}$. The interspecies scaling factor was applied to q_{animal} to obtain q_{human} in $(mg/kg\text{-}day)^{-1}$.

Male and female rats (NTP, 2000) were exposed 6.2 hours/day, five days/week for 105 weeks. Female mice (NTP 1992) were exposed six hours/day, five days/week for 104 weeks. Average concentrations during the dosing period were calculated by multiplying the reported chamber concentrations by 6 or 6.2 hours/24 hours, five days/seven days and 5.24 mg/m^3/ppm. The average body weight of female mice was estimated to be approximately 0.029 kg based on data for controls reported by NTP (1992). The average body weights of male and female rats were calculated to be 0.445 kg and 0.258 kg, respectively, based on data for controls reported by NTP (2000). Inhalation rates (I) in m^3/day for mice and rats were calculated based on Anderson *et al.* (1983):

$$I_{mice} = 0.0345 \times (bw_{mice}/0.025)^{2/3} \qquad (3)$$

$$I_{rats} = 0.105 \times (bw_{rats}/0.113)^{2/3} \qquad (4)$$

Breathing rates were calculated to be 0.038 m^3/day for female mice, 0.262 m^3/day for male rats, and 0.182 m^3/day for female rats. Lifetime average doses were determined by multiplying the average concentrations during the dosing period by the appropriate animal breathing rate divided by the corresponding animal body weight. The dosing periods in the NTP studies were at least the standard lifespan of the test animals (104 weeks for rodents), so no correction for less than lifetime exposure was required.

An alternative dose description approach, using pharmacokinetic analyses based on models described in the literature (Willems *et al*., 2001; Quick and Shuler, 1999; Sweeney *et al*., 1996; Frederick *et al*., 1998, 2001; NTP, 2000) was evaluated. Although no data were available on the metabolism of naphthalene by rodent nasal tissues, simulations were conducted using parameters for rats and mice assuming either lung-like or liver-like scaling. The model predictions evaluated included amounts of naphthalene metabolized in each of the seven nasal compartments and their sum and the areas under the concentration × time curves (AUCs) for the olfactory and ventral respiratory compartments. Since all of these metrics appeared linear and in relative proportion to the applied doses, they did not indicate any substantial difference from the default potency analysis. If the assumptions used are correct, the concentrations used in the NTP studies were below those at which saturation of metabolism or other pharmacokinetic effects become important in the nasal and lung regions.

Application of an uptake rate for naphthalene was also considered. NTP (2000) estimated inhalation uptakes of 22 to 31 percent for rats and 65 to 73 percent for mice based on pharmacokinetic data and PBPK modeling. However, in the subsequent publication of NTP's PBPK modeling of inhaled naphthalene, uptakes are estimated to be 85 to 94 percent in rats and 92 to 96 percent in mice (Table 3 in Willems *et al*., 2001). Until more reliable estimates become available we assume there are no significant differences in uptake between mice and rats used in the NTP bioassays. Also we assume similar uptake in humans exposed to low levels of naphthalene.

The naphthalene cancer potency based on the NTP inhalation bioassays is considered relevant to all routes of exposure. Naphthalene is absorbed via inhalation, oral and dermal exposures and is metabolized at multiple sites in the body (NTP, 2000). Naphthalene induces nasal toxicity in rats and mice and respiratory toxicity in mice by intraperitoneal exposures (Buckpitt *et al*., 2002), demonstrating that biologically effective doses are achieved via non-inhalation exposures at the target sites for cancer in rodents. There are no adequate cancer bioassays for non-inhalation routes of exposure.

Results

Table 5 provides the q_{animal} and q_{human} values, calculated using the linearized multistage procedure as described above, based on data for female mice (NTP, 1992) and male and female rats (NTP, 2000). Male rats were the most sensitive sex and species.

Table 5. Cancer potency values for naphthalene derived using the linearized multistage procedure based on data from NTP (1992) and NTP (2000).

Sex, Species	Site, Tumor Type	q_{animal} (mg/kg-day)$^{-1}$	q_{human}[a] (mg/kg-day)$^{-1}$	Goodness-of-Fit Test[b]
Female mice	Lung alveolar/ bronchiolar adenoma/ carcinoma	0.004382	0.059	p = 0.1428
Male rats	Nasal respiratory epithelial adenoma	0.01919	0.10	p = 0.4192
	Nasal olfactory epithelial neuroblastoma	0.004651	0.025	p = 0.4224
	All naphthalene-related tumor types in male rats	0.02219	0.12	NA[c]
Female rats	Nasal olfactory epithelial neuroblastoma	0.007636	0.049	p = 0.6342

a. The interspecies extrapolation was applied to q_{animal} in (mg/kg-d)$^{-1}$ to determine q_{human} (mg/kg-day)$^{-1}$, as described above.
b. A p-value of greater than 0.05 for the chi-square goodness-of-fit test indicates an adequate fit.
c. Not applicable.

NO SIGNIFICANT RISK LEVEL

The NSRL for Proposition 65 is the intake associated with a lifetime cancer risk of 10^{-5}.

$$\text{NSRL} = \frac{10^{-5} \times 70\ \text{kg}}{q_{human}} \qquad (5)$$

The cancer potency estimate of 0.12 (mg/kg-day)$^{-1}$, based on all naphthalene-related tumor types observed in male rats, was used to calculate an NSRL of 5.8 μg/day.

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ATTACHMENT 2

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