

NO SIGNIFICANT RISK LEVEL (NSRLS) FOR THE PROPOSITION 65 CARCINOGENS 3,3'-DIMETHYLBENZIDINE AND 3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE

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SUMMARY OF FINDINGS

The cancer potencies of 3,3'-dimethylbenzidine (commonly called *o*-tolidine) and 3,3'-dimethylbenzidine dihydrochloride were estimated from dose-response data for multiple treatment-responding tumor sites among male rats exposed orally to 3,3'-dimethylbenzidine dihydrochloride via drinking water (NTP, 1991). These sites included liver, lung, preputial gland, oral cavity, skin, small intestines, large intestines, and Zymbal's gland. NTP (1991) noted other sites that may have been associated with treatment, but they were judged likely to contribute only minimally to the overall potency estimate and thus were not included in the analyses. For each of the tumor sites contributing to the potency calculation, a probability distribution of cancer potency estimates was derived using likelihood theory. The linear term (q_1) of the multistage model fit to dose response data for a given site represents the cancer potency for that site. The cancer potencies for the affected sites were summed probabilistically, according to their distributions, to obtain a combined distribution. This combined distribution representing cancer potency for all selected sites affected by 3,3'-dimethylbenzidine dihydrochloride was derived through Monte Carlo analysis. The upper 95 percent confidence bound indicated by the combined distribution for these treatment-related tumor sites was taken as the cancer potency for 3,3'-dimethylbenzidine dihydrochloride.

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 obtained from studies of 3,3'-dimethylbenzidine dihydrochloride was used as the basis for the 3,3'-dimethylbenzidine cancer potency after adjusting for differences in molecular weight. Cancer potency estimates and the corresponding NSRLs are given in Table 1.

Table 1. Cancer Potencies and NSRLs for 3,3'-Dimethylbenzidine and Its Dihydrochloride.

Chemical	Cancer Potency (mg/kg-day) ⁻¹	NSRL (µg/day)
3,3'-Dimethylbenzidine	16	0.044
3,3'-Dimethylbenzidine dihydrochloride	12	0.059

INTRODUCTION

This report describes the derivation of cancer potency values and no significant risk levels (NSRLs) for 3,3'-dimethylbenzidine (CAS No. 119-93-7, molecular weight 212.28) and 3,3'-dimethylbenzidine dihydrochloride (CAS No. 612-82-8, molecular weight 285.2). “3,3'-Dimethylbenzidine” and “3,3'-dimethylbenzidine dihydrochloride” were listed on January 1, 1988 and April 1, 1992, respectively, as chemicals known to the State to cause cancer under Proposition 65 (California Health and Safety Code 25249.5 *et seq.*). 3,3'-Dimethylbenzidine has been used mainly as an intermediate in the production of dyes (IARC, 1971). 3,3'-Dimethylbenzidine dihydrochloride is used mainly as an intermediate in the production of bisazobiphenyl dyes (NTP, 1991).

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

STUDIES SUITABLE FOR DOSE-RESPONSE ASSESSMENT

A human cancer study of dye manufactures or dye workers with exposures to 3,3'-dimethylbenzidine or its dihydrochloride was reported by Ouellet-Hellstrom and Rench (1996). However, this study could not be used to derive cancer potency estimates since the exposure concentrations were not reported. Additionally, Frumin *et al.* (1990) published descriptions of six cases of bladder cancer among textile dyeing and printing workers. Relative risk or other measures of response required for dose response analysis could not be derived from the information provided; thus, this study could not be used for potency estimation.

Several animal carcinogenicity studies of 3,3'-dimethylbenzidine or its dihydrochloride have been conducted (Griswold *et al.*, 1968; Pliss, 1963; Pliss, 1965; Pliss and Zabezhinsky, 1970; Spitz *et al.*, 1950; Schieferstein *et al.*, 1989; NTP, 1991). The studies prior to 1989 were considered the least suitable for potency evaluation compared to later studies for various reasons including: route used, limited number of animals tested, lack of concurrent control data, and poor survival (as reviewed by NTP, 1991). More recently, Schieferstein *et al.* (1989) exposed BALB/c mice of both sexes to 3,3'-dimethylbenzidine dihydrochloride in the drinking water. An increase in the incidence of lung adenocarcinomas was observed in male mice. However, the increase was only in the highest dose group of six treatment groups, and the combined incidence of lung adenomas and adenocarcinomas was not significantly increased. NTP (1991) conducted studies in which 3,3'-dimethylbenzidine dihydrochloride was administered by the oral route (drinking water) to male and female F344/N rats. Both the Schieferstein *et al.* and NTP studies used adequate numbers of animals per group (at least 50), performed complete histopathology, and provided thorough reporting. Rats are clearly the more sensitive species based on a

qualitative and quantitative examination of the data (Schieferstein *et al.*, 1989; NTP, 1991). For this reason, the NTP studies in rats are selected as the basis of the potency derivation.

NTP (1991) administered 3,3'-dimethylbenzidine dihydrochloride to groups of 50 male and 50 female F344/N rats via drinking water continuously at concentrations of 0, 30, 70, or 150 ppm for 14 months. The survival of the two highest dose groups was significantly lower than that of controls. The reduced survival was primarily due to neoplasia.

Among male rats, significant increases with increasing dose in the incidences of skin basal cell and sebaceous gland carcinomas or adenomas (combined), skin squamous cell carcinomas or papillomas (combined), skin keratoacanthomas, Zymbal's gland carcinomas or adenomas (combined), preputial gland carcinomas or adenomas (combined), adenocarcinomas or adenomatous polyps of the small and large intestines (combined), hepatocellular carcinomas or neoplastic nodules (combined), oral cavity squamous cell carcinomas or papillomas (combined), lung alveolar/bronchiolar carcinomas or adenomas (combined) and mesothelioma were reported (NTP, 1991). These data are summarized in Table 2. In addition, NTP (1991) observed an increase in brain neoplasms in the two highest dose groups of male rats which they considered as possibly related to exposure to 3,3'-dimethylbenzidine dihydrochloride.

Table 2. Incidences of Neoplastic Lesions Among Male F344/N Rats Treated with 3,3'-Dimethylbenzidine Dihydrochloride in Drinking Water for 14 Months.¹

Tumor site	Average Dose ² (mg/kg-day)				Trend ³
	0	1.8	4.0	11.2	
Hepatocellular carcinomas or neoplastic nodules	0/60	0/45	35/72	33/55	p < 0.001
Lung alveolar/bronchiolar carcinomas or adenomas	1/60	0/45	8/73	6/57	p = 0.013
All organs, mesothelioma (benign or malignant)	0/60	0/44	3/67	4/58	p = 0.003
Preputial gland carcinomas or adenomas	2/60	4/44	6/72	9/49	p = 0.008
Oral cavity squamous cell carcinomas or papillomas	0/60	0/44	4/67	5/32	p < 0.001
Skin basal cell or sebaceous gland carcinomas or adenomas	0/60	11/44	54/72	30/45	p < 0.001
Skin squamous cell carcinomas or papillomas	0/60	2/45	17/74	27/59	p < 0.001
Skin keratoacanthomas	1/60	1/44	8/67	5/27	p < 0.001
Small intestine adenocarcinomas or adenomatous polyps	0/60	0/45	4/74	8/59	p < 0.001
Large intestine adenocarcinomas or adenomatous polyps	0/60	0/45	6/67	15/38	p < 0.001
Zymbal's gland carcinomas or adenomas	1/60	3/45	32/74	36/50	p < 0.001

¹ Incidence data shown are based on effective rates: the number of animals with tumor/effective number of animals (i.e., number of animals alive at first occurrence of tumor in any group). Rates obtained from NTP (1991), Table A3

² Average doses as reported by NTP (1991).

³ Cochran-Armitage trend test.

Among female rats, significant increases with increasing dose in the incidences of skin basal cell carcinomas or adenomas (combined), skin squamous cell carcinomas or papillomas (combined), Zymbal's gland carcinomas or adenomas (combined), clitoral gland carcinomas or adenomas (combined), adenocarcinomas or adenomatous polyps of the small and large intestines (combined), liver neoplasms, oral cavity squamous cell carcinomas or papillomas (combined), mammary gland adenocarcinomas, and lung alveolar/bronchiolar carcinomas or adenomas (combined) were reported (NTP, 1991). These data are summarized in Table 3. NTP (1991) noted that the increases in brain neoplasms and mononuclear cell leukemia seen in female rats may have been treatment-related (data not shown).

Table 3. Incidences of Neoplastic Lesions among Female F344/N Rats Treated with 3,3'-Dimethylbenzidine Dihydrochloride in Drinking Water for 14 Months.¹

Tumor site	Average Dose ² (mg/kg-day)				Trend ³
	0	3.0	6.9	12.9	
Clitoral gland carcinomas or adenomas	0/60	14/45	42/73	32/58	p < 0.001
Large intestine adenocarcinomas or adenomatous polyps	0/60	1/45	7/70	4/46	p = 0.021
Hepatocellular carcinomas or neoplastic nodules	0/60	0/45	7/58	4/36	p = 0.004
Lung alveolar/bronchiolar carcinomas or adenomas	1/60	1/45	3/63	4/41	p = 0.033
Mammary gland adenocarcinomas	0/60	1/45	3/71	6/51	p = 0.002
Oral cavity squamous cell carcinomas or papillomas	0/60	3/45	9/73	13/59	p < 0.001
Skin basal cell carcinomas or adenomas	0/60	3/45	10/69	9/46	p < 0.001
Skin squamous cell carcinomas or papillomas	0/60	3/45	9/72	12/55	p < 0.001
Small intestine adenocarcinomas or adenomatous polyps	0/60	1/45	3/72	5/57	p = 0.011
Zymbal's gland carcinomas or adenomas	0/60	6/45	32/74	42/59	p < 0.001

¹ Incidence data shown are based on effective rates: the number of animals with tumor/effective number of animals (i.e., number of animals alive at first occurrence of tumor in any group). Rates obtained from NTP (1991), Table B3.

² Average doses as reported by NTP (1991).

³ Cochran-Armitage trend test.

APPROACH TO DOSE-RESPONSE ANALYSIS

3,3'-Dimethylbenzidine was mutagenic in *Salmonella* and in mouse L5178Y lymphoma cells, induced unscheduled DNA synthesis, DNA repair, sister chromatid exchange, and chromosomal aberrations in mammalian cells *in vitro*, and micronuclei in rat bone marrow *in vivo* (NTP, 1991). 3,3'-Dimethylbenzidine dihydrochloride was mutagenic in *Salmonella*, induced sister chromatid exchange and chromosomal aberrations in mammalian cells *in vitro*, and sex-linked recessive lethal mutations in germ cells of male *Drosophila* (NTP, 1991). These findings, coupled with the observed mutagenicity of closely related structural analogs, are strongly suggestive that a genotoxic mode of action is operative. Given this information on mode of

action for 3,3'-dimethylbenzidine and the dihydrochloride, a linear multistage model was used to estimate the slope of the dose-response in the low dose region.

In the rat bioassays (NTP, 1991), treatment resulted in significant early mortality, which was primarily due to cancers at different sites. In males, the multistage model did not fit well at one site. The incidence in the high-dose group (50%) was lower than in the mid-dose group (72%) for skin basal cell carcinomas and adenomas (combined), apparently due to competing causes of death. Similarly, at one site in the females the model did not fit well. The lower incidence of clitoral gland carcinomas and adenomas (combined) in high dose females compared to those in the mid-dose group was consistent with the effects of competing causes of death. As described in more detail below and in the Appendix, standard procedures (Anderson *et al.*, 1983) that partially address the potential underestimation of potency due to early death were applied in modeling the incidence data for male skin tumors and female clitoral gland and Zymbal's gland tumors.

Since 3,3'-dimethylbenzidine dihydrochloride induced tumors at multiple sites in both male and female rats, cancer potency estimates based on a single tumor site will not fully represent the overall cancer risks due to exposure to the compound; thus, a combined cancer potency estimate was derived for male rats (the more sensitive sex) for treatment-related cancer sites judged likely to contribute to the overall cancer potency using Monte Carlo analysis (see below).

There are insufficient data to support dose adjustments based on pharmacokinetic models. Therefore, the default approach (*i.e.*, a linearized multistage model, adjustments for less than lifetime study duration, and interspecies scaling) has been applied. The approach used is described in detail in the Appendix.

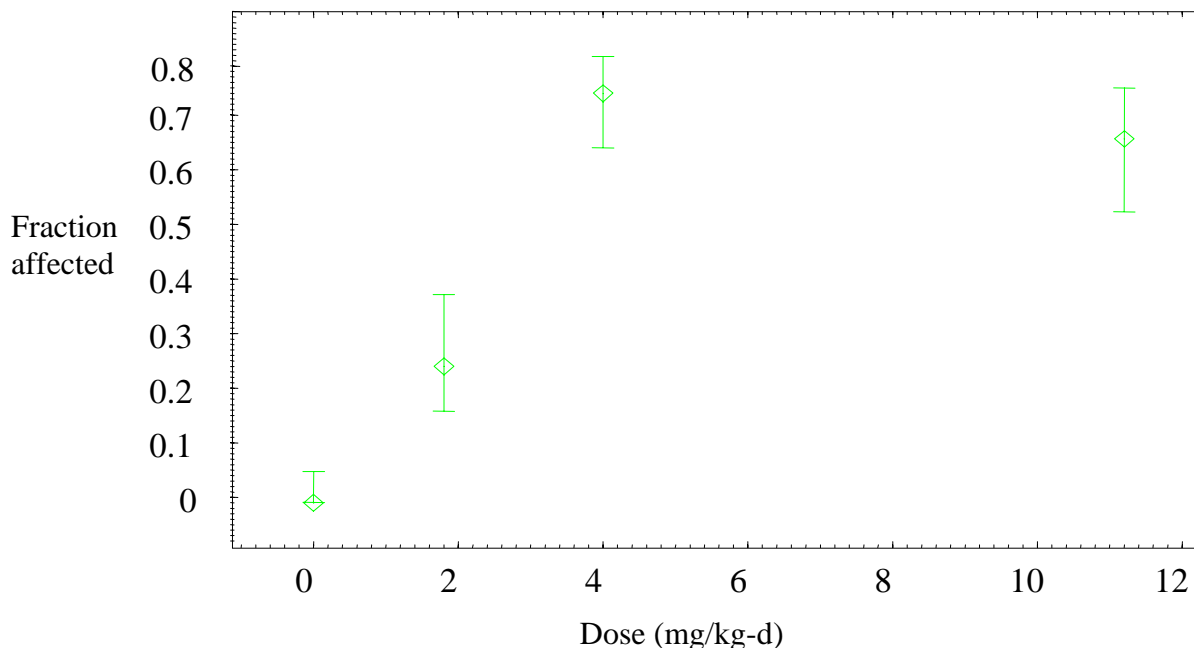
DOSE RESPONSE ASSESSMENT

Cancer potency estimates for each tumor site for male and female rats treated orally with 3,3'-dimethylbenzidine dihydrochloride were derived from the NTP studies described above (NTP, 1991), using methods described in the Appendix. The cancer potency estimates are summarized in Table 4. Potency estimates indicate that male rats are more sensitive to tumor induction by 3,3'-dimethylbenzidine dihydrochloride than female rats, but details on the calculations for both males and females are provided below.

The multistage model produced an adequate fit to the datasets, except for the tumor incidence of male rat skin basal cell carcinomas and adenomas (combined) (Table 2), and female rat clitoral gland carcinomas and adenomas (combined) (Table 3). For male rat skin basal cell tumors, the tumor incidences in the mid- and high-dose groups were high, 75 percent and 66 percent, respectively (Figure 1). Modeling all dose groups the multistage model provided a poor fit (chi-squared test, $p < 0.001$). Likewise, for female clitoral gland tumors, the tumor incidences in the mid- and high-dose groups were high, 58 percent and 55 percent, respectively. Modeling all dose groups the multistage model provided a poor fit (chi-squared test, $p = 0.018$). Following the U.S. Environmental Protection Agency (U.S. EPA) procedures described in Anderson *et al.* (1983), when the multistage model does not fit the data adequately, data at the highest dose are deleted, and the model fitted to the remaining data. This is repeated until an acceptable fit is obtained, as measured by the chi-squared goodness-of-fit test. In the case of male rat skin tumors, removal of the high-dose group resulted in a good fit. Similarly, in the case of female rat clitoral gland tumors, removal of the high-dose group resulted in an acceptable fit. Cancer potency estimates for male rat skin basal cell tumors and for female clitoral gland tumors, with

and without the high-dose groups removed from the analysis, are shown in Table 4. For male rat skin tumors, removal of the highest dose group increased the slope of the central (maximum likelihood) estimate, but reduced the upper-bound cancer potency estimate due to narrower confidence intervals surrounding the slope parameter (q_1).

Figure 1. Skin Basal Cell Carcinomas and Adenomas (Combined) Among Male Rats Fed 3,3'-Dimethylbenzidine Dihydrochloride in the Diet for 14 Months.

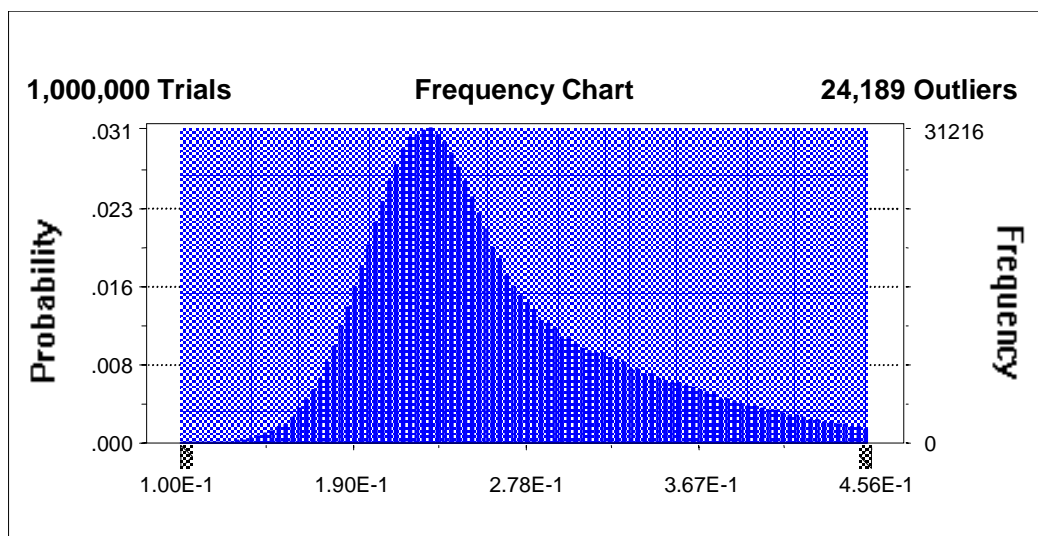


Since 3,3'-dimethylbenzidine dihydrochloride induced tumors at multiple sites in male rats, a combined potency estimate for all treatment-related tumor sites was derived for each sex, using Monte Carlo analysis. For each tumor site, a distribution of estimates corresponding to the 0.1 through 99.9 percentiles of the linear term (q_1) of the multistage model was generated with the MSTAGE computer program (Crouch, 1998), which had been modified to tabulate percentile values. A combined distribution (Figure 2) was created by adding q_1 for each tumor site, according to its distribution, through one million Monte Carlo trial simulations (Crystal Ball 2000 software, Decisioneering, Inc., Denver, Colorado). The upper 95 percent confidence bound of the combined distribution was taken as the basis of the cancer potency estimate for the combined tumor sites (Table 4).

For male rats, distributions of the cancer potency estimates were combined for the following tumor sites: hepatocellular adenoma and carcinoma (combined), lung alveolar or bronchiolar adenomas and carcinomas (combined), preputial gland adenomas and carcinomas (combined), oral cavity squamous cell papillomas or carcinomas (combined), skin basal cell adenomas and carcinomas (combined, top dose group removed), skin keratocanthomas, small intestine adenocarcinomas and adenomatous polyps (combined), large intestine adenocarcinomas and adenomatous polyps (combined), Zymbal's gland adenomas and carcinomas (combined), and

mesothelioma. The combined distribution of animal cancer potency estimates for 3,3'-dimethylbenzidine dihydrochloride in male rats is shown in Figure 2.

Figure 2. Combined Distribution of Potency Estimates for All 3,3'-Dimethylbenzidine Dihydrochloride-Related Tumor Sites Among Male Rats.¹



¹ The 95 percent upper confidence bound of this distribution, 0.414 (mg/kg-d)⁻¹, represents the 61-week animal cancer potency for all treatment-related tumors in male rats. This corresponds to a lifetime animal potency of 2.05 (mg/kg-d)⁻¹ and a human potency estimate of 11.9 (mg/kg-d)⁻¹ (see Appendix).

Using methods described in the Appendix, animal potencies derived from the 61-week study are projected to estimates of potencies associated with lifetime exposures. These lifetime values are then used to predict human cancer potency. Table 4 provides human potency estimates derived from the individual treatment-related sites in the male and female bioassays on the compound (NTP, 1991), as well as the combined estimate for the most sensitive sex. Because the values given in Table 4 are derived from the 95 percent upper confidence bounds, the sum of the values for the individual sites does not correspond to the combined estimate. The estimate for all treatment-related cancers corresponds to the upper 95 percent confidence bound on the distribution obtained through the Monte Carlo simulation (Figure 2).

Table 4. Human Cancer Potency Estimates for 3,3'-Dimethylbenzidine Dihydrochloride.

Tumor Site	Cancer Potency (mg/kg-day)⁻¹	
	Males	Females
Clitoral gland carcinomas or adenomas High-dose group removed	---	3.7 5.3
Large intestine adenocarcinomas or adenomatous polyps	0.75	0.55
Hepatocellular carcinomas or neoplastic nodules	3.4	0.63
Lung alveolar/bronchiolar carcinomas or adenomas	0.57	0.38
Mammary gland adenocarcinomas	---	0.44
Oral cavity squamous cell carcinomas or papillomas	0.62	0.92
Preputial gland carcinomas or adenomas	0.73	---
Skin basal cell carcinomas or adenomas High-dose group removed	6.3 5.4	0.95 NA
Skin squamous cell carcinomas or papillomas	2.0	0.93
Skin keratoacanthomas	0.93	---
Small intestine adenocarcinomas or adenomatous polyps	0.53	0.39
Zymbal's gland carcinomas or adenomas	3.9	3.1
Mesothelioma (benign or malignant, all organs)	0.37	---
All 3,3'-dimethylbenzidine dihydrochloride-related tumor sites	11.9	---

Bolding indicates values selected as the basis of the NSRL.

NA = not applicable

The cancer potency estimate for 3,3'-dimethylbenzidine was derived by multiplying the estimate for 3,3'-dimethylbenzidine dihydrochloride for male rats (the most sensitive sex) by the molecular weight of the dihydrochloride divided by the molecular weight of 3,3'-dimethylbenzidine (i.e., 285.2/212.28). The resulting cancer potency is 16.0 (mg/kg-day)⁻¹.

NO SIGNIFICANT RISK LEVEL

The NSRL for Proposition 65 is the intake associated with a lifetime cancer risk of 10⁻⁵. The cancer potency estimates derived above were used to calculate NSRLs for 3,3'-dimethylbenzidine (0.044 µg/day) and 3,3'-dimethylbenzidine dihydrochloride (0.059 µg/day), after rounding to two significant figures.

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APPENDIX: METHODOLOGY USED TO DERIVE RISK-SPECIFIC INTAKE LEVELS FOR 3,3'-DIMETHYLBENZIDINE AND 3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE

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 NSRLs for 3,3'-dimethylbenzidine and 3,3'-dimethylbenzidine dihydrochloride 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 (1981) and Crump *et al.* (1977).

Due to cancer related mortality, the dose-response data for the skin tumors in male rats (NTP, 1991) were highly supralinear (*i.e.*, the trend in tumor incidence is less than linear with increasing dose). In females, the multistage model provided adequate statistical fit for all sites except clitoral gland carcinomas and adenomas (combined). Following the U.S. Environmental Protection Agency (U.S. EPA) procedures described in Anderson *et al.* (1983), whenever the multistage model does not fit the data adequately, data at the highest dose are deleted and the model fitted to the remaining data. This is repeated until an acceptable fit is obtained, as measured by the chi-square goodness-of fit test. For analyses of the male skin tumor data and the female clitoral gland tumor data, the high-dose groups were dropped.

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:

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

Potencies from the 61 week rat bioassays (NTP, 1991) were adjusted to reflect the projected response from lifetime exposure (for the rat, assumed to be two years), *i.e.*, $q_1^* \cdot (104/61)^3$.

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 lifetime average dose

The lifetime average dose in units of mg/kg-day was calculated by NTP (1991) for each of the relevant dose groups, based on the dose level, duration and regimen described in the experiments above. Among male rats orally administered 3,3'-dimethylbenzidine dihydrochloride via the drinking water for 14 months at concentrations 0, 30, 70 or 150 ppm, NTP (1991) estimated the average dose to be 0, 1.8, 4.0 or 11.2 mg/kg-d, respectively. Among female rats orally administered 3,3'-dimethylbenzidine dihydrochloride via the drinking water for 14 months at concentrations 0, 30, 70 or 150 ppm, NTP (1991) estimated the average dose to be 0, 3.0, 6.9 or 12.9 mg/kg-d, respectively.

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:

$$q_{\text{human}} = q_{\text{animal}} \cdot (bw_h / bw_a)^{1/3} \quad (4)$$

In the calculation, the average body weights for male and female rats across dose groups, 0.36 kg and 0.21 kg, respectively, were estimated from body weight data provided by NTP (1991).

A.3 Risk-Specific Intake Level Calculation

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

$$I = \frac{R \times bw_h}{q_{\text{human}}} \quad (5)$$

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 intake levels exceeding the no significant risk level are given by:

$$NSRL = \frac{10^{-5} \times 70 \text{ kg}}{q_{\text{human}}} \quad (6)$$

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