NO SIGNIFICANT RISK LEVELS (NSRLS) FOR PROPOSITION 65 CARCINOGENS:

p-CHLOROANILINE (CAS No. 106-47-8) AND *p*-CHLOROANILINE HYDROCHLORIDE (CAS No. 20265-96-7)

February 2010

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SUMMARY OF FINDINGS

The human cancer potency of *p*-chloroaniline hydrochloride was estimated using the linearized multistage model from dose-response data for multiple treatment-responding tumor sites in male F344/N rats exposed via oral gavage (National Toxicology Program [NTP], 1989). To provide the basis for developing the cancer risk for *p*-chloroaniline hydrochloride, an estimate of cancer potency associated with all treatment-related tumors was derived using a multisite statistical approach. The potency derivation takes into account body size differences between humans and experimental animals. Cancer potency for *p*-chloroaniline is obtained by adjusting for the molecular weight difference between this compound and its hydrochloride. The human cancer potency estimates for *p*-chloroaniline hydrochloride and *p*-chloroaniline are 0.37 and 0.48 $(mg/kg\text{-}day)^{-1}$.

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 NSRLs for *p*-chloroaniline hydrochloride and *p*-chloroaniline are calculated to be 1.9 μg/day and 1.5 μg/day, respectively.

Table 1. Cancer Potencies and NSRLs.

Chemical	Cancer potency $(mg/kg\text{-}day)^{-1}$	NSRL (μg/day)
p-chloroaniline hydrochloride	0.37	1.9
p-chloroaniline	0.48	1.5

INTRODUCTION

This report describes the derivation of human cancer potency estimates and NSRLs for *p*-chloroaniline (CAS number 106-47-8) and *p*-chloroaniline hydrochloride (CAS number

20265-96-7). *p*-Chloroaniline was listed on October 1, 1994 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*.). *p*-Chloroaniline hydrochloride was listed on May 15, 1998.

p-Chloroaniline is an aromatic amine that is not known to occur as a natural product (IARC, 1993). It is widely used in dye, textile, rubber, pharmaceutical and agricultural chemical manufacturing. *p*-Chloroaniline and its hydrochloride salt are detected as degradation products in some herbicides, fungicides and pharmaceutical preparations (NTP, 1989; IARC, 1993).

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 *p*-chloroaniline or *p*-chloroaniline hydrochloride. The National Cancer Institute (NCI, 1979) conducted animal cancer bioassays of *p*-chloroaniline and the National Toxicology Program (NTP, 1989) performed animal cancer bioassays of its hydrochloride. The design and results for these studies are detailed below. As discussed below, the most suitable carcinogenicity data for human cancer potency assessment come from the studies conducted by NTP (1989).

In the carcinogenicity bioassays of *p*-chloroaniline hydrochloride conducted by the NTP (1989), groups of 50 male and female rats and mice were administered *p*-chloroaniline hydrochloride by gavage for five days per week for 103 weeks. Doses administered to rats were 0, 2, 6, or 18 mg/kg per gavage treatment. Doses administered to mice were 0, 3, 10, or 30 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 shorter duration of dosing. The resulting average daily doses are 0, 1.41, 4.24, and 12.7 mg/kg-day in male and female rats, and 0, 2.12, 7.07 and 21.2 mg/kg-day in male and female mice.

NTP (1989) reported clear evidence of carcinogenicity in male rats based on increases in spleen sarcomas and adrenal gland pheochromocytomas and some evidence of carcinogenicity in male mice based on increases in liver and spleen hemangiosarcomas and combined hepatocellular adenomas and carcinomas. NTP (1989) found equivocal evidence in female rats based on sarcomas of the spleen and adrenal gland pheochromocytomas. There was no evidence of carcinogenicity in female mice. Male rats and male mice were therefore more sensitive than the females in their species in the NTP bioassays. Dose-response data for tumor sites affected by treatment are presented in Table 2.

Table 2. Incidence of tumors in animals exposed to *p*-chloroaniline hydrochloride via gavage (NTP, 1989).

Sex, strain, species	Tumor site and first occurrence	Administered dose (mg/kg)	Average daily dose[1] (mg/kg-day)	Tumor incidence[2]	Statistical significance[3]
Male F344/N rats	Spleen sarcomas (day 494)	0	0	0/44	$p < 0.001$[4]
		2	1.41	1/49	NS
		6	4.24	3/46	NS
		18	12.7	38/48	$p < 0.0001$
	Adrenal gland pheochromo-cytomas (day 476)	0	0	13/44	$p = 0.0015$[4]
		2	1.41	14/48	NS
		6	4.24	15/46	NS
		18	12.7	26/47	$p = 0.011$
Male $B6C3F_1$ mice	Hemangiosarcomas of the liver and the spleen (day 399)	0	0	4/50	$p = 0.011$[4]
		3	2.12	4/49	NS
		10	7.07	1/50	NS
		30	21.2	10/50	$p = 0.074$
	Hepatocellular adenomas and carcinomas (day 432)	0	0	11/50	$p = 0.092$[4]
		3	2.12	21/47	$p = 0.015$
		10	7.07	20/48	$p = 0.030$
		30	21.2	21/49	$p = 0.022$

[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 at that site.
[3] *p*-values from pairwise comparison with controls (Fisher Exact Test). NS is not significant.
[4] Exact trend test *p*-values.

In the long-term carcinogenicity bioassays of *p*-chloroaniline conducted by the National Cancer Institute (NCI, 1979), groups of 50 F344/N rats and B6C3F1 mice of both sexes were administered *p*-chloroaniline in feed for 78 weeks. Rats were fed a diet containing 250 or 500 mg/kg *p*-chloroaniline for 78 weeks followed by an observation period of 24 weeks. Mice were fed with diet containing 2500 or 5000 mg/kg *p*-chloroaniline for 78 weeks followed by an observation period of 13 weeks. Twenty animals of each sex and species were placed on test as controls. OEHHA calculated the average daily doses by multiplying the concentration in the feed by the percent of body weight consumed as feed each day, and then by adjusting for the

shorter duration of dosing, as detailed in the Appendix. The resulting average daily doses are 7.65 and 15.3 mg/kg-day in male rats, 9.56 and 19.1 mg/kg-day in female rats, 257 and 514 mg/kg-day in male mice, and 279 and 557 mg/kg-day in female mice. NCI found that there was a significant positive association between concentration and mortality in male rats, but not in female rats or mice of either sex.

NCI (1979) reported a significant positive association between compound dosing and incidences of splenic tumors including fibromas, fibrosarcomas, sarcomas, hemangiosarcomas, and osteosarcomas in male rats. These unusual tumors were combined for analysis by NCI based on the rationale that they are all derived from cells of similar origin, and the fibromas are considered to be a benign form of sarcoma. NCI considered the findings in male rats strongly suggestive of carcinogenicity because of the rarity of these tumors in the spleens of control rats. In female mice, incidences of hemangiomas and hemangiosarcomas of spleen, liver, kidney, and other organs were found elevated when compared to historical controls. In male mice, hemangiomas and hemangiosarcomas were also elevated in treated animals. While NCI found these not to be significant for trend at the 0.05 level, the International Agency for Research on Cancer (IARC, 1993) and OEHHA found significant trend by the same test. NCI concluded that sufficient evidence was not found to establish the carcinogenicity of *p*-chloroaniline in rats or mice under the conditions of these studies. The dose-response data from the NCI studies in male rats and mice of both sexes are summarized in Table 3. The later NTP (1989) study reported similar tumor types at similar sites.

Table 3. Incidence of tumors in animals exposed to *p*-chloroaniline via feed (NCI, 1979).

Sex, strain, species	Tumor site and first occurrence	Administered dose (mg/kg)	Average daily dose[1] (mg/kg-day)	Tumor incidence[2]	Statistical significance[3]
Male F344/N rats	Fibromas, fibrosarcomas, hemangiosarcomas, osteosarcomas or sarcomas of spleen (week 74)	0	0	0/20	p=0.001[4]
		250	7.65	0/49	NS
		500	15.3	10/49	p = 0.024
Male $B6C3F_1$ mice	Hemangiosarcomas or hemangiomas of all sites (week 72)	0	0	2/20	p = 0.046[5]
		2500	257	10/50	NS
		5000	514	14/50	p = 0.092
Female $B6C3F_1$ mice	Hemangiosarcomas or hemangiomas of all sites (week 89)	0	0	0/18	p = 0.012[4]
		2500	279	3/49	NS
		5000	557	8/42	p = 0.046

[1] The average daily dose was calculated from ppm or mg/kg in the diet, as described in Appendix.
[2] The denominator represents the number of animals alive at the first occurrence of tumor at that site.
[3] *p*-values from pairwise comparison with controls (Fisher Exact Test). NS is not significant.
[4] Cochran-Armitage trend test *p*-values, as reported by NCI (1979).
[5] Cochran-Armitage trend test *p*-values calculated by OEHHA.

APPROACH TO DOSE-RESPONSE ANALYSIS

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

NTP (1989) and IARC (1993) summarized results from a series of genotoxicity assays on *p*-chloroaniline. *p*-Chloroaniline was mutagenic in *S. typhimurium* strain TA98 in the presence of exogenous metabolic activation (i.e., rat liver and hamster liver S9) and in TA100 in the presence of hamster liver S9; it was not mutagenic in other strains of *S. typhimurium*. A positive mutagenic response was found in the fungus *Aspergillus nidulans* mutagenicity assay, in the absence of exogenous metabolic activation. *p*-Chloroaniline was mutagenic in the mouse $L5178Y/TK^{+/-}$ lymphoma cell assay in the absence or presence of rat liver S9. *p*-Chloroaniline increased sister chromatid exchanges in the absence or presence of rat liver S9 and chromosomal aberrations in the presence of rat liver S9 in Chinese hamster ovary cells (IARC, 1993). Induction of mitotic recombination was not observed in *Saccharomyces cerevisiae*. This agent is positive in the *in vivo* mouse bone marrow micronucleus assay (NTP, 1998). In the *E. coli* $polA^+/polA^-$ assay, *p*-chloroaniline induced DNA damage, measured as growth inhibition, and induced unscheduled DNA synthesis (UDS) in primary rat hepatocytes (NTP, 1989). In

addition, *p*-chloroaniline transformed primary cultures of Syrian hamster embryo cells in one of two studies (IARC, 1993).

p-Chloroaniline is metabolized similarly in humans and in experimental animals (IARC, 1993). Activation of *p*-chloroaniline to reactive electrophiles capable of binding covalently with cellular macromolecules is thought to occur as a result of N-oxidation, e.g. the formation of *p*-chloro-*N*-hydroxyaniline (NTP, 1989). A non-N-hydroxy metabolite thought to form reactive electrophiles is *p*-aminophenol. Both *p*-chloro-*N*-hydroxyaniline and *p*-aminophenol have been reported to be *p*-chloroaniline metabolites in studies in rabbits (NTP, 1989).

Because *p*-chloroaniline causes methemoglobinemia, it has been speculated that splenic tumors may have resulted from hematotoxicity (NTP, 1989; 1998). On the other hand, *p*-chloroaniline has been shown in multiple *in vitro* assays to be genotoxic. Moreover, as noted by NTP (1989), there are strong similarities between the toxic and carcinogenic effects of *p*-chloroaniline and the structurally similar carcinogen aniline. Both cause methemoglobinemia, and both induce sarcomas of the spleen and pheochromocytomas of the adrenal gland in male rats. Both are genotoxic, and both are thought to undergo metabolic activation to reactive electrophiles capable of binding to macromolecules. Aniline binds covalently with protein and RNA, and, to a lesser extent, with DNA. DNA binding studies have not been conducted with *p*-chloroaniline.

While the precise mechanism of carcinogenicity is unknown, genotoxicity is likely to play a major role in the carcinogenicity of *p*-chloroaniline. Therefore, the default approach using a linearized multistage model is applied to derive a cancer potency estimate for each treatment-related tumor site. The default procedures 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 model to the dose-response data of the NTP studies (Table 2) for male rats and male mice are shown in Table 4. 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 bodyweight in humans (assumed to be 70 kilograms) to the body weight of the experimental animal. The average body weights of 0.427 kg for male rats and 0.0398 kg for male mice were calculated based on the data reported by NTP (1989) for control animals.

As shown in Table 4, the human cancer potency derived from the male rat study, 0.37 $(mg/kg\text{-}day)^{-1}$, is slightly higher than that derived from the male mouse study. This value was selected as the human cancer potency estimate for *p*-chloroaniline hydrochloride.

As detailed in the Appendix, a molecular weight adjustment was applied to the cancer potency estimate of *p*-chloroaniline hydrochloride to obtain the cancer potency value for *p*-chloroaniline. The human cancer potency estimate for *p*-chloroaniline is 0.48 $(mg/kg\text{-}day)^{-1}$.

Table 4. Human cancer potency estimates for *p*-chloroaniline hydrochloride based on NTP (1989) studies.

Sex, strain, species	Tumor sites	Animal cancer potency $(mg/kg\text{-}d)^{-1}$	Interspecies scaling factor (kg/kg)	Human cancer potency $(mg/kg\text{-}d)^{-1}$
Male F344/N rats	Sarcoma of the spleen	0.0253	$\left(70/0.427\right)^{1/3}$	0.14
	Adrenal gland pheochromocytomas	0.0555	$\left(70/0.427\right)^{1/3}$	0.30
	Multisite	0.0677	$\left(70/0.427\right)^{1/3}$	**0.37**
Male $B6C3F_1$ mice	Hemangiosarcomas of the liver & spleen	0.0066	$\left(70/0.0398\right)^{1/3}$	0.08
	Hepatocellular adenomas and carcinomas	0.0237	$\left(70/0.0398\right)^{1/3}$	0.29
	Multisite	0.0259	$\left(70/0.0398\right)^{1/3}$	0.31

Bold indicates the value selected as the basis of the NSRL.

Table 5 summarizes the animal and human cancer potency estimates for *p*-chloroaniline based on the NCI (1979) studies (see Table 3). In the absence of data from the NCI studies on animal body weights, default values of 0.5 kg for male rats, 0.03 for male mice, and 0.025 kg for female mice (See Appendix) were used to calculate the interspecies scaling factors, as shown in Table 5. The human cancer potency estimates were 0.039 $(mg/kg\text{-}day)^{-1}$ based on the data in male rats, 0.016 $(mg/kg\text{-}day)^{-1}$ for male mice, and 0.010 $(mg/kg\text{-}day)^{-1}$ for female mice. The cancer potency estimates based on the NCI (1979) studies were lower than the cancer potency estimates based on the NTP (1989) studies. In addition, the NCI studies had shorter experiment durations with high mortality in some dosing groups and had small concurrent control groups. Therefore, the potencies derived from the NTP (1989) studies are more reliable. The human cancer potency estimate derived from the NTP study of *p*-chloroaniline hydrochloride in male rats is used as the basis for calculating the NSRL.

Table 5. Human cancer potency estimates for *p*-chloroaniline based on NCI (1979) studies.

Sex, strain, species	Tumor sites	Animal cancer potency $(mg/kg\text{-}d)^{-1}$	Interspecies scaling factor (kg/kg)	Human cancer potency $(mg/kg\text{-}d)^{-1}$
Male F344/N rats	Fibromas, fibrosarcomas, hemangiosarcomas, osteo sarcomas or sarcoma of spleen	0.0077	$\left(70/0.5\right)^{1/3}$	0.039
Male $B6C3F_1$ mice	Hemangiosarcomas or hemangiomas of all sites	0.0012	$\left(70/0.03\right)^{1/3}$	0.016
Female $B6C3F_1$ mice	Combined hemangiosarcomas or hemangiomas of liver, spleen, and other organs	0.0007	$\left(70/0.025\right)^{1/3}$	0.010

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 0.37 for *p*-chloroaniline hydrochloride $(mg/kg\text{-}day)^{-1}$, based on multisite analysis in male rats, was used to calculate the NSRL for this compound. A value of 1.9 μg/day was derived as shown below:

$$\text{NSRL} = \frac{10^{-5} \times 70\,\text{kg}}{0.37\,(\text{mg/kg - day})^{-1}} \times 1000\ \mu\text{g/mg} = 1.9\ \ \mu\text{g/day}$$

The human cancer potency estimate of 0.48 $(mg/kg\text{-}day)^{-1}$ for *p*-chloroaniline was derived by adjusting for molecular weight differences between it and the hydrochloride. This potency is used to calculate the NSRL of p-chloroaniline, 1.5 μg/day.

REFERENCES

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APPENDIX: METHODOLOGY USED TO DERIVE THE NSRLS FOR *p*-CHLOROANILINE AND ITS HYDROCHLORIDE SALT

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 NSRLs for *p*-chloroaniline and *p*-chloroaniline hydrochloride 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 (California Department of Health Services [CDHS], 1985; U.S. Environmental Protection Agency [U.S. EPA], 2002; Anderson *et al.*, 1983):

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

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 four dose groups, as is the case with the NTP 1989 studies of *p*-chloroaniline hydrochloride, the default linearized multistage model defaults to three stages, or four parameters, q_0, q_1, q_2, and q_3. The parameter q_0 provides the basis for estimating the background lifetime probability of the tumor (i.e., - 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. 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. 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 equation 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.

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:

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

In the NTP 1989 studies, the overall study duration was two years. 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. A correction factor to extrapolate to two years or 104 weeks was not required. Therefore, for the two-year NTP 1989 studies $q_{animal} = q_{1(UCB)}$.

In the NCI 1979 studies, the overall study duration was 102 weeks for the studies in rats, and 91 weeks for the studies in mice. Thus, adjustments to $q_{1(UCB)}$ are necessary to account for the less than lifetime experiment duration.

In male rats, $q_{animal} = q_{1(UCB)} \times (104/102)^3$

In male and female mice, $q_{animal} = q_{1(UCB)} \times (104/91)^3$

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, 1989), 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).

For the NTP 1989 studies:

average daily dose (mg/kg-day) = administered dose (mg/kg) × (5/7) × (103/104)

Table A-1. Calculated average daily doses in NTP gavage studies (1989).

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
	2	5/7	103/104	1.41
	6	5/7	103/104	4.24
	18	5/7	103/104	12.7
Male & female $B6C3F_1$ mice	0	5/7	103/104	0
	3	5/7	103/104	2.12
	10	5/7	103/104	7.07
	30	5/7	103/104	21.2

In the NCI diet studies (NCI, 1979), the feed was available every day '*ad libitum*'. Both rats and mice were exposed to *p*-chloroaniline in feed for 78 weeks followed by a 24 week observation period for rats and a 13 week observation period for mice. The average daily dose received during the experimental period (D, in mg/kg-day) can be calculated from the administered feed concentration (C, in mg/kg) and the amount of feed consumed per body weight, expressed as fraction (F) of body weight consumed each day. When dosing does not occur throughout the duration of the study, adjustment is also made for dosing duration (T_d) during the experimental period (T_e) (See Table A-2).

$$D \text{ (mg/kg-day)} = C \text{ (mg/kg)} \times F \times (T_d/T_e)$$

Values for food intake as percent body weight per day were obtained from Gold et al. (1984), and are 4% for male rats, 5% for female rats, 12% for male mice, and 13% for female mice.

For example, in male rats,

$$D \text{ (mg/kg-day)} = C \text{ (mg/kg)} \times 0.04 \times (78/102)$$

In female mice,

$$D \text{ (mg/kg-day)} = C \text{ (mg/kg)} \times 0.13 \times (78/91)$$

Table A-2. Calculated average daily doses used in NCI feeding studies (1979).

Sex, strain, species	Administrated dose (mg/kg)	Food intake as % bodyweight	Weeks dosed/ weeks on study	Average daily dose (mg/kg-day)
Male F344/N rats	0	4%	78/102	0
	250	4%	78/102	7.65
	500	4%	78/102	15.3
Female F344/N rats	0	5%	78/102	0
	250	5%	78/102	9.56
	500	5%	78/102	19.1
Male $B6C3F_1$ mice	0	12%	78/91	0
	2500	12%	78/91	257
	5000	12%	78/91	514
Female $B6C3F_1$ mice	0	13%	78/91	0
	2500	13%	78/91	279
	5000	13%	78/91	557

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 1989 NTP studies, average body weights of 0.427 kg for male rats and 0.0398 kg for male mice were calculated based on data reported for control animals; the default human body weight is 70 kg. An example derivation of human cancer potency from the male rat cancer potency of $0.0677\ (mg/kg\text{-}day)^{-1}$ is shown below:

$$q_{human} = 0.0677\ (mg/kg\text{-}day)^{-1} \times (70\ kg\ /0.427\ kg\ )^{1/3} = 0.37\ (mg/kg\text{-}day)^{-1}$$

In the 1979 NCI studies, body weight data of rats and mice were not available. Default values as described by Gold and Zeiger (1997) were used. The default body weights for male and female rats are 0.5 kg and 0.35 kg, and for male and female mice are 0.03 kg and 0.025 kg, respectively. Again, the default human body weight is 70 kg.

A.3 Molecular Weight Adjustment

To obtain the cancer potency for the parent compound *p*-chloroaniline, a molecular weight adjustment was applied to the cancer potency estimate for the hydrochloride salt (HCl), *p*-chloroaniline hydrochloride, using the following relationship:

$$q_{human}\ (\text{parent compound}) = q_{human}\ (HCl) \times \left(\frac{\text{MW (HCl)}}{\text{MW (parent compound)}} \right)$$

The molecular weights of the parent compound and its hydrochloride are 127.5 and 164.1 g/mol, respectively. The human cancer potency for *p*-chloroaniline is calculated below as 0.48 $(\text{mg/kg-day})^{-1}$:

$$q_{human}\ (\text{parent}) = 0.37\ (\text{mg/kg - day})^{-1} \times \left(\frac{164.1\ \text{g/ mol}}{127.5\ \text{g/mol}} \right) = 0.48\ (\text{mg/kg - day})^{-1}$$

A.4 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:

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

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