OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Public Health Goal

1,2-Dibromo-3-Chloropropane in Drinking Water

July 2020

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Prepared by

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PREFACE

Public Health Goal (PHG) technical support documents provide information on health effects from contaminants in California drinking water. PHGs are developed for chemical contaminants based on the best available data in the scientific literature and using the most current principles, practices, and methods used by public health professionals. These documents and the analyses contained therein provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

Under the California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365), the Office of Environmental Health Hazard Assessment (OEHHA) develops PHGs for drinking water contaminants in California based exclusively on public health considerations. OEHHA periodically reviews PHGs and revises them as necessary based on the availability of new scientific data and new methodologies. This document presents an update for 1,2-dibromo-3-chloropropane, for which a PHG has been previously developed.

PHGs published by OEHHA are used by the State Water Resources Control Board (SWRCB) in establishing primary drinking water standards (California Maximum Contaminant Levels, or CA MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by SWRCB are to consider economic factors and technological feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, CA MCLs established by SWRCB must be at least as stringent as the federal MCL if one exists.

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SUMMARY

This document presents an update of the public health goal (PHG) for 1,2-dibromo-3-chloropropane (DBCP). The current PHG (OEHHA, 1999) of 0.0017 µg/L (micrograms/liter) or 0.0017 ppb (parts per billion) was based on forestomach tumors in female mice (Hazleton, 1977, 1978). The updated PHG of 0.003 ppb is derived using route-specific cancer potency factors to estimate the total cancer risk from oral and inhalation exposures, as well as updated drinking water ingestion rates and age sensitivity factors to account for enhanced childhood sensitivity to carcinogens. This value is very close to the original PHG value of 0.0017 ppb and remains lower than the current California MCL of 0.2 ppb. OEHHA is also updating the 1999 health-protective concentration from 0.2 ppb to 0.5 ppb for noncancer effects based on male reproductive toxicity in rabbits (Rao et al., 1982).

INTRODUCTION

The Office of Environmental Health Hazard Assessment (OEHHA) performs health risk assessments and develops public health goals (PHGs) for drinking water contaminants in California. A PHG is a health-protective concentration developed for regulatory purposes; it is the concentration of a chemical in drinking water that is estimated to pose no significant health risks to individuals consuming the water on a daily basis over a lifetime. This document presents a proposed PHG update for 1,2-dibromo-3-chloropropane (DBCP). This update incorporates current chemical-specific toxicity information in the scientific literature and the most current risk assessment practices and methods.

DBCP (CAS No. 96-12-8) was used extensively as a soil fumigant and nematocide in the United States until its use was restricted in 1977, and its registration was cancelled in 1985. DBCP was identified by California's Proposition 65 program as both a carcinogen and a male reproductive toxicant in 1987. Before 1977, DBCP was heavily used in the San Joaquin Valley and it is still detectable in some well water samples from the area. In the past three years, there have been more than 700 detections of DBCP in California public supply wells.[1] Of these, 92% were within the Central Valley Regional Water Quality Board (Region Five) boundaries. The highest level detected was 1.6 µg/L (micrograms/liter), which is 8 times the California MCL of 0.2 µg/L or 0.2 parts per billion (ppb),[2] suggesting that exposure to DBCP through drinking water is still a health concern.

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[1] Data accessed with Geotracker GAMA (Groundwater Ambient Monitoring and Assessment Program) May 2018: http://geotracker.waterboards.ca.gov/gama/. The GeoTracker GAMA data for public water supply wells do not indicate whether the source is raw (untreated) or treated water; therefore the dataset may not be representative of water delivered to customers.

[2] CA MCL: California Maximum Contaminant Level (https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/documents/ccr/MCLsEPAvsDWP-2018-03-21.pdf)

METHODOLOGY

Development of an updated PHG for a chemical in drinking water entails a two-part process:

1. Toxicological evaluation

The toxicological evaluation of a chemical starts with a thorough review of the PHG being updated and its toxicological basis, as well as a review of the relevant scientific literature published subsequent to its issuance. Relevant studies and toxicity endpoints are identified. The data and study findings are critically evaluated and the quality of each study is assessed. In evaluating toxicity studies, consideration is given to the potential molecular and cellular mechanisms by which toxicity is induced (modes of action), corroborating data from different studies, and the relevance of toxicity endpoints to humans.

2. PHG derivation

After a review of the toxicity studies of suitable quality, the most sensitive endpoints from studies determined to be relevant to human health are selected, and analyses of the dose-response relationships are performed. The adverse effect or a physiological change that leads to an adverse effect that occurs at the lowest dose is selected as the critical effect from which a PHG is derived.

If a chemical has been identified as a human or animal carcinogen, health-protective water concentrations are determined for both cancer and noncancer endpoints.

Deriving Health-Protective Concentrations for Noncancer Effects

Calculation of a health-protective concentration for noncancer effects involves a three-step approach: determination of the point of departure (POD), estimation of an acceptable daily dose (ADD), and calculation of a health-protective drinking water concentration (C).

Point of Departure (POD)

The POD is the dose of a chemical (in units of milligrams per kilogram of body weight per day, mg/kg-day) from a study in animals or humans that is used as a starting point for calculation of the ADD. The POD is typically determined by fitting a mathemathical model to the dose-response data. OEHHA generally uses a computer program called Benchmark Dose Software (BMDS) to perform this task. The program is developed and maintained by the US Environmental Protection Agency (US EPA) and is publicly available (http://www.epa.gov/ncea/bmds/). BMDS uses mathematical models to fit the data and determines the dose (benchmark dose or BMD) that corresponds to a pre-determined level of response (benchmark response or BMR). The BMR is typically set at 5% above the background or the response of the control group for dichotomous data. For continuous data, a BMR of one standard deviation from the control mean is typically

used when there are no data to indicate what level of response is biologically significant (US EPA, 2012). In order to account for the uncertainty of the data, the model also calculates the 95% lower confidence limit of the BMD, called the BMDL (L stands for the lower confidence limit). For PHG development, OEHHA uses the BMDL as the POD for the calculation of a health-protective drinking water concentration when the data are amenable to BMD modeling. When data are not amenable to BMD modeling, OEHHA uses the traditional no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) approach in identifying the POD.

Application of BMD modeling for noncancer effects mitigates some of the limitations of the NOAEL/LOAEL approach (Davis et al., 2011), including:

- dependence on dose selection and sample size;
- inability to account for uncertainty and variability of experimental results due to the characteristics of the study design;
- the need to use an uncertainty factor when a NOAEL cannot be determined in a study; and
- inability to account for the shape of the dose-response curve.

Acceptable Daily Dose (ADD)

The ADD is the estimated maximum average daily dose of a chemical (in mg/kg-day) that can be consumed by a human for an entire lifetime without adverse effects. This is similar to the term "reference dose" used by US EPA. To determine the ADD, the POD is adjusted by factors that account for uncertainties and variabilities in the risk assessment, such as differences between animals and humans, and differences among humans in response to a chemical exposure. This combined factor is referred to as the total uncertainty factor (UF).

Uncertainty and Variability Factors

When developing health-protective levels for noncancer effects based on animal toxicity studies, OEHHA generally applies a combined UF of 300 (OEHHA, 2008).

These UFs are:

- 10 for interspecies extrapolation, accounting for possible differences in the way laboratory animals and humans respond to the chemical, consisting of
    - $\sqrt{10}$ for pharmacodynamics
    - $\sqrt{10}$ for pharmacokinetics

- 30 for intraspecies variability, which accounts for some human subpopulations, such as children and the elderly, possibly being more sensitive to the chemical than the general population, consisting of
    - $\sqrt{10}$ for pharmacodynamics
    - 10 for pharmacokinetics.

These default factors are applied unless data support an alternative value. A table of default UFs for ADD derivation is presented in Appendix V. Additional adjustments may be included depending on the limitations of available data.

The ADD is calculated using the following equation:

$$ADD = \frac{POD}{UF}$$

Daily Water Intake Equivalent

To calculate a PHG for a chemical, the ADD is converted to a concentration in drinking water that accounts for the total exposure to the chemical that people receive from using tap water. It includes intake from ingestion as well as inhalation and dermal contact with the chemical in tap water from household uses (e.g., drinking, cooking, bathing, and showering). Inhalation exposure can take place when the chemical volatilizes out of the water during cooking or showering. Dermal absorption of the chemical can occur during bathing and other household uses of tap water.

The daily water intake (DWI) is expressed in units of liters or liter equivalents per kilogram of body weight per day (L/kg-day or L_{eq}/kg-day, respectively). Liter equivalents represent the equivalent of the amount of tap water one would have to drink to account for the exposure to a chemical in tap water through oral, inhalation, and dermal routes.

For oral intake rates, the PHG program uses age-specific water ingestion estimates (OEHHA, 2012) derived from a nationwide survey of food and beverage intake from approximately 20,000 people (US Department of Agriculture's Continuing Survey of Food Intake of Individuals 1994-1996, 1998 dataset). These age-specific intake rates are normalized to body weight and expressed as L/kg-day. The updated water ingestion rates indicate that drinking water ingestion per unit body weight is higher in infants than in adults. Previous PHGs using ingestion rates of 2 L/day for adults and 1 L/day for a 10 kg child are being updated with these more refined estimates. For noncancer endpoints, the time-weighted average daily water ingestion rate for a 70-year lifetime for the general population is generally used. However, if there is a particularly sensitive age group or other subgroup, the high end estimates of the age-specific water ingestion rate for the subgroup will be used in the PHG calculations (OEHHA, 2012). OEHHA is mandated to consider sensitive subgroups, such as children and infants, who may be at greater risk of adverse health effects due to their greater exposure to drinking water contaminants on a body weight basis than the general population.

As noted above, exposure to a chemical in tap water can occur from pathways such as inhalation and dermal absorption while bathing or showering, in addition to oral intake. For example, volatile organic compounds (VOCs) are released from tap water in the shower and can be inhaled by the person showering. In previous PHG documents, OEHHA assumed that inhalation and dermal exposures to volatile contaminants in tap water were equivalent to the exposure from drinking 2 L/day of water. However, studies have shown that exposures to volatile chemicals from routes other than oral ingestion

may be as large as or larger than exposure from ingestion alone (McKone, 1987). To estimate inhalation and dermal exposures to chemicals in tap water, OEHHA uses equations extracted from the CalTOX 4.0[3] multimedia total exposure model developed for the California Department of Toxic Substances Control by Lawrence Berkeley National Laboratory. The equations, parameters, and inputs used in calculating multiroute exposures are described in Appendix II.

Relative Source Contribution

The relative source contribution (RSC) is the proportion of exposures to a chemical attributed to tap water, as part of total exposure from all sources (including food and air). The RSC values typically range from 20% to 80% (expressed as 0.20 to 0.80), and are determined based on available environmental monitoring data. For certain PHGs, the RSC can be as high as 1.0 (tap water is the only source of the chemical) when it is deemed appropriate. OEHHA uses this approach to ensure that the PHG identifies a level of a drinking water contaminant that would pose no significant health risk after taking into account exposures to all other sources.

PHG Derivation

Following the determination of the ADD, the health-protective concentration (C, in milligrams/liter, mg/L or in micrograms/liter, µg/L) in drinking water can be derived by incorporating the DWI and RSC of the chemical:

$$C = \frac{ADD \times RSC}{DWI}$$

Deriving Health-Protective Concentrations for Cancer Effects

Calculation of a health-protective concentration for cancer effects involves a three-step approach: determination of a cancer potency, estimation of an average daily dose, and calculation of a health-protective drinking water concentration (C).

Cancer Dose-Response Analyses and Cancer Potency Derivation

Standard methods for estimation of lifetime theoretical cancer risks are employed in the development of cancer potencies based on animal studies (OEHHA, 2009; US EPA, 2005; US EPA, 2012). The estimated cancer potency, also referred to as the cancer slope factor (CSF), is a measure of the carcinogenic potential of a compound. It is often reported in units of 1/(mg/kg-day) or $(mg/kg\text{-}day)^{-1}$ and is derived by fitting a linear low-dose extrapolation using US EPA's BMDS Multistage-Cancer model (US EPA, 2012) to the tumor incidence data from an animal carcinogenicity bioassay.

[3] Available at: https://dtsc.ca.gov/caltox-download-instructions/

Method for Calculating Cancer Potency

Development of cancer potency estimates from animal bioassays includes consideration of:

- the quality, suitability, and sensitivity of the available animal bioassay studies; for example, the thoroughness of experimental protocol, the temporal exposure pattern, the degree to which dosing resembles the expected manner of human exposure, the duration of the study, the purity of test material, the number and size of exposed groups, and the extent of tumor occurrence
- the cancer sites and types from the selected experiments most appropriate for characterizing the cancer potency; where there are multiple sites with significant tumor findings in a selected experiment, a multisite analysis is performed to describe the overall carcinogenic potential
- whether a dose-response model that assumes the absence of a carcinogenic threshold dose should be used or whether there are compelling mechanistic data to support an alternative approach
- interspecies scaling of animal cancer potency to human cancer potency
- physiologic, pharmacokinetic and metabolic information for possible use in extrapolating from test animals to humans, from high to low dose, and from one exposure route to another.

Calculating Average Daily Dose

A mathematical model is fit to dose-response data from animal studies. For studies that do not involve daily administration of a fixed mg/kg amount, an average daily dose "d" (in units of mg/kg-day) is calculated. This is done by adjusting the administered or nominal dose, accounting for days of dosing during the week and total dosing weeks during the experimental period. For studies using variable doses, the weighted mean dose is calculated considering the dosing frequency and duration of the various administered doses.

Dose-Response Model

Information on the mode of action involved in the carcinogenesis of a chemical is evaluated to determine whether human cancer risk should be estimated using the default assumption of low dose linearity or otherwise. Unless there is sufficiently compelling evidence, OEHHA uses a non-threshold approach and a linearized multistage (LMS) cancer model to calculate the chemical's cancer slope factor, or potency, expressed as the CSF. This is accomplished by using the BMDS Multistage-Cancer model developed by US EPA (BMDS version 2.5). The model calculates the lifetime probability of developing a tumor (p) induced by an average daily dose (d) using the following equation:

$$p(d) = \beta + (1- \beta) \times \exp[-(q_1 d + q_2 d^2 + ... + q_i d^i)]$$

The q_i are parameters of the model, which are taken to be constants and are estimated from the animal cancer bioassay data. As recommended by US EPA (2012), $q_i \geq 0$ for all i. For example, with four dose groups, the Multistage-Cancer model can have a maximum of four parameters, β, q_1, q_2, and q_3. When dose is expressed in units of mg/kg-day, q_1 is given in units of $(mg/kg\text{-}day)^{-1}$. The q_1 parameter is, for small doses, the ratio of excess lifetime cancer risk to the average daily dose received. The parameter β provides the basis for estimating the background lifetime probability of the tumor (i.e., when dose d is zero, the probability of cancer, p, is equal to β).

The Multistage-Cancer model defines the probability of developing a tumor at a single site. For carcinogens that induce tumors at multiple sites and/or in different cell types at the same site in a particular species and sex, US EPA's BMDS can be used to derive maximum likelihood estimates (MLEs) for the parameters of the multisite carcinogenicity model by summing the MLEs for the individual multistage models from the different sites and/or cell types. This multisite model provides a basis for estimating the cancer potency of a chemical that causes tumors at multiple sites.

Adjusting for Human-Animal Differences

In the absence of reliable pharmacokinetic information, the human cancer slope factor (CSF_{human}) is estimated by assuming the chemical dose per body weight scaled to the three-quarters power produces the same degree of effect in different species. Under this assumption, the CSF_{animal} is multiplied by the ratio of human to animal body weights raised to the one-fourth power when animal cancer potency is expressed in units of $(mg/kg\text{-}day)^{-1}$:

$$CSF_{(human)} = CSF_{(animal)} \times (\text{body weight}_{(human)} \div \text{body weight}_{(animal)})^{1/4}$$

When data are available, separate oral and inhalation cancer potencies may be calculated and they are applied to each specific exposure route. Since it is unusual to have a cancer bioassay through dermal exposure, OEHHA generally uses the oral cancer potency for estimating cancer risk through the dermal route. Similarly, when an inhalation cancer potency is not available, the oral cancer potency is used to estimate cancer risk through the inhalation route. If only an inhalation cancer potency is available, then it will be applied to all routes when determining the PHG.

Accounting for Increased Susceptibility during Early-in-Life Exposures

When determining cancer risk, OEHHA applies age sensitivity factors (ASFs, unitless) to account for the increased susceptibility of infants and children to carcinogens (OEHHA, 2009). A weighting factor of 10 is applied for exposures that occur from the 3rd trimester to <2 years of age, and a factor of 3 is applied for exposures that occur from 2 through 15 years of age (Table 1). These factors are applied regardless of the mechanism of action, unless chemical-specific data exist to better guide the risk assessment.

Table 1. Duration and age sensitivity factors of different life stages

Life Stage	Fractional Duration[a] (d)	Age Sensitivity Factor (ASF)[b]
3rd Trimester	0.25/70	10
Infant (0-2 yr)	2/70	10
Child (2-16 yr)	14/70	3
Adult (16-70 yr)	54/70	1

[a]An average lifetime of 70 years is assumed for the general population
[b]Age sensitivity factors for different life stages adopted by OEHHA (2009)

ASFs for each life stage are multiplied by the fractional duration (d) of each life stage and the daily water intake (DWI, in L/kg-day or L_{eq}/kg-day if accounting for inhalation and dermal exposures). This generates the ASF-adjusted exposure at each life stage, as shown in Appendix VI. The sum of the ASF-adjusted exposures across all life stages is the lifetime exposure value for the chemical.

The health-protective water concentration (C) for carcinogenic effects that addresses the inhalation, oral, and dermal routes of exposure can be calculated using the following equation, which combines the separate calculations for each exposure period (shown in Appendix VI) into a single bracket:

$$C = \frac{R}{CSF_{oral} \times (\sum_j [ASF_j \times d_j \times DWI^{oral}_j]) + CSF_{inh} \times (\sum_j [ASF_j \times d_j \times DWI^{inh}_j])}$$

Where:

R	=	default risk level of one in one million, or 10^{-6}
CSF_{oral}	=	oral cancer slope factor, in $(mg/kg\text{-}day)^{-1}$
CSF_{inh}	=	inhalation cancer slope factor, in $(mg/kg\text{-}day)^{-1}$
$\sum_j$	=	sum of contributions at each age range
ASF_i	=	age sensitivity factors for the 3rd trimester + infants, children, and adults
d_j	=	duration of exposure for the 3rd trimester + infant, child, and adult life stages
$DWI^{inh/oral}_j$	=	equivalent water exposure values for each age range.

Water consumption rates and multiroute exposure calculations are described in the noncancer methodology section, and the underlying principles do not change when examining cancer endpoints.

BASIS FOR THE 1999 PHG

A PHG of 1.7 parts per trillion (1.7 ppt or 0.0017 µg/L) for DBCP was developed by OEHHA in 1999 based on the occurrence of squamous cell carcinomas in female mice following oral exposure to DBCP (Hazleton Laboratories, 1978). In this study, 50 Swiss mice/sex/dose group were exposed to time-weighted average doses of 0, 0.48, 1.6, or 4.8 mg/kg-day DBCP in their feed for 78 weeks. Squamous cell carcinomas in the stomach or forestomach were observed in 19/50 female mice exposed to the high dose. Incidence rates for the low and mid-doses were not reported. In addition to carcinomas, squamous cell papillomas were also observed in the stomach of these mice. A cancer potency factor of 7 $(mg/kg\text{-}day)^{-1}$ derived previously by OEHHA to calculate the Proposition 65 No Significant Risk Level (CDHS, 1988), and a default value for lifetime excess individual cancer risk of one in one million (10^{-6}) were used in calculating the PHG. A drinking water intake rate of 6 liter equivalents (L_{eq}) per day (2 L for oral ingestion, 2 L_{eq} to account for dermal exposure, 2 L_{eq} to account for inhalation exposure) was applied, based on a 2 L/day default ingestion rate and previous studies citing oral ingestion as one-third the total exposure to DBCP from household uses of tap water (OEHHA, 1999). This resulted in a PHG of 1.7 ppt.

For the noncancer effects of DBCP, a health-protective concentration of 0.2 parts per billion (ppb) was calculated based on a male reproductive toxicity study in rabbits. Rao et al. (1982) exposed groups of 10 male New Zealand white rabbits to 0, 0.1, or 1.0 part per million (ppm) DBCP via inhalation (6 hours/day, 5 days/week for 14 weeks). Another group was exposed to 10 ppm but the exposure lasted only 8 weeks due to mortality in half of the group. Semen was evaluated after the exposure period and at periodic intervals for 32-38 weeks post-exposure. DBCP exposures of 1.0 and 10 ppm resulted in decreased sperm count, motility, and viability, and 10 ppm also caused male infertility when the rabbits were mated during week 14 (6 weeks post-exposure). Testicular atrophy was observed in approximately 50% of rabbits exposed to 1.0 ppm for 14 weeks. Nearly complete bilateral testicular atrophy was observed in a single rabbit after 8 weeks of exposure to 10 ppm DBCP. The NOAEL for this study was 0.1 ppm, based on decreased sperm production and testicular atrophy. After accounting for compound purity (97.3%), and conversion from intermittent to continuous exposure, the NOAEL of 0.1 ppm was calculated to be 0.17 mg/m^3. An equivalent human daily dose of 0.025 mg/kg-day was calculated based on a default 70 kg body weight, 20 m^3/day inhalation rate, and an estimated 50% absorption via inhalation (OEHHA, 1999). Using these estimates, OEHHA derived a health-protective concentration of 0.2 ppb for the noncancer effects of DBCP by applying a total uncertainty factor of 1,000 (10 for interspecies extrapolation, 10 for extrapolation from subchronic to chronic exposure, and 10 to account for variability among individuals), a relative source contribution (RSC) of 80% since the main anticipated source of exposure was ground water (OEHHA, 1999), and a daily water intake rate of 6 L_{eq}/day.

UPDATED TOXICOLOGICAL REVIEW

A thorough search of recent literature revealed relatively few new toxicity studies since the 1999 PHG document. There are three studies focused on the effects of DBCP on sperm. Foote (2002) treated isolated human sperm with 0, 0.05, or 1 mg/mL DBCP and observed a statistically significant ($p<0.05$) difference in motility at both doses. While treated sperm were unable to penetrate zona-free hamster oocytes at both concentrations, this effect was not statistically different from controls (Foote, 2002). A study in rats using a single subcutaneous (s.c.) injection of DBCP showed Leydig cell degeneration at 50 mg/kg and morphological changes in seminiferous tubules at 75 mg/kg (Yoshida et al., 1998). In addition, altered expression of luteinizing hormone receptor was observed following treatment. Meistrich et al. (2003) observed oligospermia (reduced sperm count) in rats, which persisted for up to 20 weeks following s.c. injection of 87.5 mg/kg-day DBCP for 4 days.

There are four studies focused on the genotoxic potential of DBCP. An in vivo study used a micronucleus test to evaluate DNA damage in mice (Sasaki, 1998). Following a single oral exposure to 100 mg/kg DBCP, DNA damage was detected in the stomach, liver, kidney, lung, and bone marrow. Hachiya and Motohashi (2000) used a mouse strain carrying a *lacZ* transgene to assay DNA mutagenesis in liver and testis cells. Following a single intraperitoneal (i.p.) injection of 40 mg/kg DBCP, slight increases in mutation frequency were induced in the testis but not the liver. An in vitro study (Ryu et al., 2002) using a transgenic rat fibroblast cell line showed DBCP caused a significant dose-dependent increase in mean mutation frequencies, with G:C → A:T transition as the most common mutation. Holzer et al. (2008) observed increased DNA damage in both rat and human isolated nasal mucosa cells, although rat cells were much more sensitive to genotoxic effects from DBCP exposure.

Two epidemiological studies on workers handling DBCP were published. Slutsky et al. (1999) utilized a database of information collected on 21,857 DBCP applicators working on pineapple and banana plantations in 12 countries in Latin America, the Caribbean, Africa, and Asia. The mean duration of occupational exposure to DBCP was 5 years, during which time the applicators received no health hazard warnings or safety training, and were not required to wear personal protective equipment. The degree of adverse reproductive outcome varied by country, with workers in Latin America and the Philippines showing oligospermia or azoospermia (absence of sperm) in 50% and 90% of semen samples, respectively. In some cases, semen samples were collected more than 10 years after the last exposure to DBCP, suggesting that adverse reproductive effects persist in humans.

Hofmann et al. (2006) examined mortality in a cohort of 40,959 banana plantation workers from Costa Rica. Employment records from 1972 to 1979, a period of high DBCP use at these plantations, were cross-referenced with mortality registry entries through 1999. Of the 3,316 reported deaths, non-significant increases in the rates of testicular and penile cancers and Hodgkin's and Parkinson's diseases were observed in males, and non-significant increases in cervical and lung cancers were observed in

females. While all causes of mortality were examined, the study design did not account for incidences of non-fatal cancer.

A review paper by Clark and Snedeker (2005) evaluated DBCP carcinogenicity. The authors concluded that, "[T]he induction of a variety of tumors by multiple routes of exposure in two rodent species provides clear evidence of a DBCP tumorigenic response. In vitro, in vivo and human genotoxicity studies indicate that DBCP is capable of acting as a mutagen and clastogen." OEHHA agrees with this determination.

US EPA has not updated its risk assessment for DBCP since the 1999 PHG was published. The World Health Organization (WHO) (2003) republished its 1996 risk assessment for DBCP in drinking water, and concluded that DBCP is possibly carcinogenic to humans (Group 2B)[4] based on sufficient evidence of carcinogenicity in animals, and is also a reproductive toxicant in humans and animals.

DOSE-RESPONSE ASSESSMENT

Noncancer Effects

Several studies on male reproductive toxicity were reviewed for the 1999 PHG and a 14-week inhalation study in rabbits (Rao et al., 1982) was selected to calculate a health-protective concentration for noncancer effects at that time. This study was chosen because it was adequately reported, the results were comparable to other studies, and it provided the lowest NOAEL of 0.1 ppm based on multiple testicular effects. This selection is still valid for the current evaluation.

OEHHA's current review of the reproductive toxicity studies for DBCP has identified a data set from the Rao et al. (1982) study that could be modeled with BMDS (Benchmark Dose Software, US EPA, version 2.5) to derive a POD for noncancer effects. Fourteen weeks of DBCP exposure resulted in ultrastructural abnormalities in rabbit spermatozoa. Following a 32-week recovery period, a statistically significant increase in abnormal spermatozoa was still observed in the 1.0 ppm exposure group (Table 2), suggesting the adverse effects may be irreversible. A higher dose group, exposed to 10 ppm, was not included in this analysis due to increased mortality and a shortened exposure time (8 weeks) with a longer recovery period (38 weeks) relative to other dose groups.

[4] IARC Monographs *Supplement 7* (1987) https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-Supplements/Overall-Evaluations-Of-Carcinogenicity-An-Updating-Of-IARC-Monographs-Volumes-1%E2%80%9342-1987

Table 2. Percent abnormal spermatozoa in rabbits following inhalation exposure to DBCP for 14 weeks plus 32 weeks recovery (Rao et al., 1982)

DBCP Concentration	Number of Animals	% Abnormal Spermatozoa (mean ± SD)
0 ppm	6	5 ± 3%
0.1 ppm	3	6 ± 2%
1.0 ppm	3	24 ± 10%*

Statistical significance: * ($p<0.01$) compared to control using unpaired t-test.

BMD modeling of the dataset in Table 2, using continuous models with a BMR of one standard deviation (SD) from the control mean, produced two models with adequate fit and $BMDL_{1SD}$ values of 0.17 ppm and 0.08 ppm. Modeling results are presented in Appendix I.

The $BMDL_{1SD}$ of 0.08 ppm is very close to the NOAEL of 0.1 ppm selected as the POD for the 1999 health-protective concentration. While BMD modeling is OEHHA's preferred approach for dose-response analysis when possible, there are some limitations to moving from the NOAEL of 0.1 ppm for multiple testicular effects to modeling the single endpoint of abnormal spermatozoa presented in Table 2. A detailed description of the methods for histological evaluation was not provided for this study, leading to uncertainty regarding the sensitivity of identifying abnormalities across dose groups. For example, the study did not indicate the number of sections, tubules, and cells from each tubule that were evaluated and did not indicate what stage of the seminiferous epithelium cycle was evaluated. Thus, the NOAEL of 0.1 ppm based on multiple observed testicular effects, is retained as the POD for this study.

OEHHA's current review of the reproductive toxicity studies for DBCP has identified an additional study from which a POD for noncancer effects could be derived. Foote et al. (1986) showed sperm toxicity when male rabbits were exposed to 0, 0.94, 1.88, 3.75, 7.5, or 15 mg/kg-day DBCP in drinking water, 5 days per week for 10 weeks. There was no change in body weight over the dosing period but there was a significant decrease in testis weight at the highest dose. The mean number of primary spermatocytes per Stage I seminiferous tubular cross section decreased in a dose-dependent manner. In particular, the mean number of round spermatids decreased significantly, to approximately 25% of the control mean at the highest dose (Table 3).

Table 3. Mean number of round spermatids per cross-section for male rabbits exposed to DBCP in drinking water for 10 weeks (Foote et al., 1986)

Dose (mg/kg-day)	Adjusted Dose[a] (mg/kg-day)	Number of Animals	Mean # of Round Spermatids (% ↓ from control)	Standard Deviation[b]
0.00	0.00	5	141.3	24.6
0.94	0.67	5	128.5 (9%)	24.6
1.88	1.34	6	121.8* (14%)	24.7
3.75	2.68	6	84.8** (40%)	24.7
7.50	5.36	6	55.2** (61%)	24.7
15.00	10.71	4	36.6** (74%)	24.6

[a] Dose adjusted for 5/7 days per week exposure.

[b] Standard error of the mean (SEM) was converted to standard deviation (SD) using: SD=SEM x √number of animals.

Statistical significance: * ($p<0.05$), ** ($p<0.01$) compared to control using unpaired t-test.

While the data presented in Table 3 indicates a NOAEL of 0.67 mg/kg-day, BMD modeling of these data, using continuous models with a BMR of 1 SD above or below the control mean, results in a $BMDL_{1SD}$ of 0.55 mg/kg-day from Exponential Model 4 (Appendix I) after doses are adjusted from five days per week to daily exposure.

In comparison to Rao et. al. (1982), the study by Foote et al. (1986) exposed animals through drinking water, had more dose groups, and used more animals per dose group. However, the study duration was 10 weeks, as opposed to 14 weeks, and the study is less sensitive (i.e., has a higher NOAEL) than Rao et al. (1982). The study by Rao et al. (1982) showed multiple adverse effects and is the most sensitive study deemed to be of sufficient quality. It remains the most health-protective and the NOAEL of 0.1 ppm or 0.044 mg/kg-day is retained as the noncancer POD.

Using current OEHHA methodology, the noncancer POD is converted from an air concentration (ppm) to an oral dose (mg/kg-day) as follows:

POD in mg/kg-day = [NOAEL in ppm × UC × P × ETA × EFA × BR × AE] ÷ BW
= 0.044 mg/kg-day

Where:

NOAEL in ppm = 0.1 ppm

UC = unit conversion factor, 9.67 (mg/m^3)/ppm

P = compound purity, 97.3%

ETA = exposure time adjustment, 6 hr/24 hr (unitless)

EFA = exposure frequency factor, 5 days/7 days (unitless)

BR = rabbit breathing rate, 1.979 m^3/day (US EPA, 1994)

AE = absorption efficiency, 50%

BW = body weight of New Zealand white rabbit, 3.76 kg (rabbit body weight for chronic studies, US EPA, 1994).

Cancer Effects

Due to the physicochemical properties of DBCP, in addition to oral ingestion, inhalation is also an important route of exposure. For this reason, OEHHA has derived two cancer slope factors, one for the oral route and another for the inhalation route, both from animal cancer studies.

Oral Cancer Slope Factor

In the 1999 PHG, a CSF of 7 $(mg/kg\text{-}day)^{-1}$ was derived using the multistage polynomial model (CDHS, 1988) fit to the incidence data for squamous cell carcinomas in the stomach or forestomach of female HaM/ICR mice after exposure to 0, 0.48, 1.6, or 4.8 mg/kg-day DBCP in the feed for 78 weeks. The results were from an unpublished study sponsored by Dow Chemical Company (Hazleton Laboratories, 1978) and only data for the control and high-dose groups of male and female mice were reported (Table 4). Data for the low and mid-dose groups of mice were not available.

In a corresponding rat study performed by Hazleton Laboratories (1977), squamous cell carcinomas in the stomach or forestomach, hepatocellular carcinomas, and renal tubule cell carcinomas and adenomas were observed in rats (reported as Charles River rats, no strain given) following exposure to 0, 0.24, 0.80, or 2.39 mg/kg-day DBCP for 104 weeks (Table 4). The original data for this rat study were not obtainable. Information from the summary of the original study and the data described in the 1999 PHG are used in this update. Available information does not indicate early mortality or overt signs of toxicity, with the exception of a significant decrease in mean body weight gain in the high dose group of male rats. Cancer incidence data of rats and mice are summarized in Table 4.

Table 4. Tumor incidences in rats and mice administered DBCP in the diet for 104 and 78 weeks, respectively (Hazleton Laboratories, 1977 and 1978, as cited in OEHHA, 1999)

Sex/ Species	Tumor site and type	Dose (mg/kg-day)			
		Control	0.24	0.80	2.39
Male Rat	Squamous cell carcinoma or papilloma of stomach or forestomach	0/48***	0/46	3/46	21/41**
	Hepatocellular carcinoma	0/48**	1/46	2/46	5/41*
	Renal tubular cell carcinoma or adenoma	0/48***	1/46	4/46	15/41**
Female Rat	Squamous cell carcinoma or papilloma of stomach or forestomach	0/48***	0/45	0/47	10/43**
	Hepatocellular carcinoma	0/48	1/45	3/47	0/43

	Renal tubular cell carcinoma or adenoma	0/48***	1/45	0/47	12/43**
		Control	**0.48**	**1.6**	**4.8**
Male Mice	Squamous cell carcinoma of stomach or forestomach	0/50***	N/A	N/A	26/49**
	Squamous cell papilloma of stomach or forestomach	0/50*			5/49*
Female Mice	Squamous cell carcinoma of stomach or forestomach	0/50***			19/50**
	Squamous cell papilloma of stomach or forestomach	0/50**			6/50*

Statistical significance for trend using Cochran-Armitage trend test is indicated at the control incidence. Difference from control using Fisher's exact test is indicated at the treated incidence;
* ($p<0.05$), ** ($p<0.01$), *** ($p<0.005$)
N/A, data not available

In this update of the 1999 DBCP PHG, BMD modeling is performed on the data for individual tumor types in male rats shown in Table 4, using the BMDS Multistage-Cancer model with a BMR of 5% extra risk. The tumor incidence rates of males were generally higher than those of females, thus CSFs are derived from data in the males. A multisite analysis is also performed, which provides an estimate of the cumulative risk for all treatment-related tumors. The multisite model calculates the risk for developing any combination of tumors at any site when more than one tumor type is observed, and assumes the tumors are independent of one another. Tumor types are first modeled individually to determine the best fit model, then are combined to derive a multisite potency factor. Modeling results are shown in Appendix I and summarized in Table 5.

Table 5. BMD modeling results for tumor incidences in male rats following exposure to DBCP in the diet for 104 weeks (Hazleton Laboratories, 1977)

Sex/ Species	Tumor Site and Type	$BMDL_{05(animal)}$ (mg/kg-day)	CSF_{animal} $(mg/kg\text{-}day)^{-1}$	CSF_{human}[a,b] $(mg/kg\text{-}day)^{-1}$	Model p-value	Polynomial Degree[c]
Male Rat	Stomach or forestomach squamous cell carcinoma or papilloma	0.44	0.11	0.38	0.94	2nd
	Hepatocellular carcinoma	0.52	0.096	0.33	0.97	1st
	Renal tubular cell adenoma or carcinoma	0.25	0.20	0.69	0.99	2nd
	Multisite tumor analysis	**0.17**	**0.29**	**1.0**	n/a[d]	n/a

[a] Calculations are shown in Appendix III.

[b] Assumes a male rat body weight of 0.5 kg and default human body weight of 70 kg

[c] Degree of polynomial in the Multistage-Cancer model that best characterizes the dose-response relationship

[d] n/a, not applicable

The CSF is calculated as follows:

$$CSF_{animal} = BMR \div BMDL_{05\ (animal)} = 0.05 \div BMDL_{05\ (animal)}$$

Calculations used to derive the CSF for male rats are shown in Appendix III. From male rat data in this study (Hazleton Laboratories, 1977), the estimated human multisite CSF is 1.0 $(mg/kg\text{-}day)^{-1}$.

In addition to the chronic dietary studies conducted by the Hazleton Laboratories, the National Cancer Institute (NCI, 1978) also studied chronic effects of DBCP in rats and mice. Osborne-Mendel rats were administered 0, 10.7, or 20.7 mg/kg-day DBCP by gavage for 62-83 weeks. Increased incidences of squamous cell carcinomas were observed in the forestomach of both sexes, and adenocarcinomas in the mammary gland of female rats (Table 6). Male and female B6C3F1 mice were administered 0, 81.4, or 156.4 mg/kg-day and 0, 78.6, or 149.3 mg/kg-day DBCP, respectively, by gavage for 47-60 weeks. Both sexes of mice developed squamous cell carcinomas in the forestomach, with over 90% incidence rates for both the low and high doses (Table 7).

Table 6. Tumor incidence in rats following exposure to DBCP via oral gavage (NCI, 1978)

Tumor Site and Type	Dose (mg/kg-day)		
	Control	10.7	20.7
Females			
Forestomach squamous cell carcinoma	0/20*	38/50*	29/49*
Mammary adenocarcinoma	0/20*	24/50*	31/50*
Males			
Forestomach squamous cell carcinoma	0/20*	47/50*	47/50*

Statistical significance for trend using Cochran-Armitage trend test is indicated at the control incidence. Difference from control using Fisher's exact test is indicated at the treated incidence; *, $p<0.05$

Table 7. Tumor incidence in mice following exposure to DBCP via oral gavage (NCI, 1978)

Tumor Site and Type	Dose (mg/kg-day)		
Females	**Control[a]**	**78.6**	**149.3**
Forestomach squamous cell carcinoma	0/20*	50/50*	47/48*
Males	**Control[a]**	**81.4**	**156.4**
Forestomach squamous cell carcinoma	0/20*	43/46*	47/49*

Statistical significance for trend using Cochran-Armitage trend test is indicated at the control incidence. Difference from control using Fisher's exact test is indicated at the treated incidence; *, $p<0.001$

The NCI studies had high mortality, a shortened dosing period, and the high dose was ten-fold higher than that in the Hazleton (1978) study. Tumor incidence rates for both rats and mice lack adequate dose-response information for lower dose ranges, thus CSFs are not estimated for these studies.

The oral CSF of 1.0 $(mg/kg\text{-}day)^{-1}$, based on multi-site tumor analysis in male rats exposed to DBCP in the diet (Hazleton Laboratories, 1977), is determined to be the most appropriate value for oral exposure. OEHHA analyzed this dataset using current methodology, which includes changing the default body scaling factor from the ratio of animal to human body weight to the ⅔ power to the same animal-human body weight ratio to the ¾ power,[5] and using BMD modeling software. This updated oral cancer potency factor is based on a more complete data set with multiple doses and also considers multiple tumor sites.

Inhalation Cancer Slope Factor

For this PHG update, OEHHA has derived a CSF for the inhalation route using the only inhalation cancer bioassays available. The inhalation CSF is based on the National Toxicology Program (NTP, 1982) studies in which Fischer 344/N rats and B6C3F1 mice were exposed to 0, 0.6 or 3.0 ppm DBCP in air for 6 hours per day, 5 days per week. Male and female rats were exposed for 84 and 103 weeks at the high and low concentrations, respectively. Female mice were exposed for 74 and 103 weeks at the high and low concentrations, respectively, and male mice were exposed for 76 weeks at both concentrations. In male and female rats, high mortality associated with treatment-related respiratory tract tumors was observed at the high dose only. In male mice, high mortality was reported in all dose groups, including the control group, likely due to urinary tract infections. Mammary gland tumors in female rats, and tumors in the stomach or forestomach of both mouse sexes were identified but the incidences were

[5] OEHHA (2009) adopted the use of body weight scaling to the ¾ power rather than to the ⅔ power, consistent with guidance from US EPA (2005), to estimate from animal data a human equivalent dose that would result in an equal lifetime risk of cancer.

not significantly different from controls. Tumor incidences were highest in the male rats. Thus, data from the male rats (Table 8) are chosen to derive the inhalation CSF.

A common method used to determine the effective number of animals at risk for developing tumors is to count the number of animals alive on the first week the tumor is observed. The poly-3 adjustment (Bailer and Portier, 1988) is another method that adjusts the data to more accurately reflect the number of animals at risk for developing tumors when there is high treatment-related early mortality. If an animal has the specified tumor type at the time of death or does not die prior to the end of the study, it is counted as 1; if an animal dies prior to the end of the study but does not exhibit the tumor type of interest, then the contribution towards animal number (N) is calculated as:

$$\text{Contribution to N} = \left(\frac{\text{Week number at death}}{\text{Total weeks in study}}\right)^3.$$

For this assessment, poly-3 mortality adjustments are applied to the male rat data to account for the high mortality observed in the high concentration group (Table 8).

Table 8. Mortality-adjusted tumor incidences[a] in male Fischer 344/N rats following exposure to DBCP via inhalation for 84 or 103 weeks (NTP, 1982)

Site	Tumor type	Adjustment Type[a]	Exposure (ppm)		
			Control	0.6	3.0
Nasal Cavity	Squamous cell carcinoma	Effective	0/50***	2/50	11/41***
		Poly-3	0%	4.2%	49.6%
	Squamous cell papilloma	Effective	0/50*	7/50*	3/18*
		Poly-3	0%	14.7%	17.3%
	Combined[b]	Effective	0/50***	12/50***	14/41***
		Poly-3	0%	25.2%	58.9%
Nasal Cavity	Adenoma (NOS[c])	Effective	0/50	9/50***	1/26
		Poly-3	0%	18.9%	6.1%
	Adenocarcinoma (NOS[c])	Effective	0/50	8/50**	6/47*
		Poly-3	0%	16.7%	30.0%
	Carcinoma (NOS[c])	Effective	0/50***	2/50	22/49***
		Poly-3	0%	4.2%	70.7%
	Combined	Effective	0/50***	18/50***	28/49***
		Poly-3	0%	37.4%	79.6%
Tongue	Squamous cell carcinoma	Effective	0/50***	0/50	3/35
		Poly-3	0%	0%	17.1%
	Squamous cell papilloma	Effective	0/50***	1/50	8/45***

		Poly-3	0%	2.1%	38.9%
	Combined	Effective	0/50***	1/50	11/45**
		Poly-3	0%	2.1%	48.8%

Statistical significance for trend using Cochran-Armitage trend test is indicated at the control incidence. Difference from control using Fisher's exact test is indicated at the treated incidence; * ($p<0.05$), ** ($p<0.01$), *** ($p<0.005$)

[a]For effective animal, the numerator indicates number of animals with tumor, denominator indicates number of animals alive on the first week the first tumor was found in any treatment group. For Poly-3, percentage of tumor incidence in animals, adjusted for survival using poly-3 mortality adjustment.

[b] Includes turbinate and septum tumor incidences

[c] NOS, not otherwise specified

Multisite tumor analysis, using the BMDS Multistage-Cancer model with a BMR of 5%, is performed on the data presented in Table 8. Model run outputs are shown in Appendix I. The resulting BMDLs for individual tumor types are converted from ppm to mg/kg-day as shown in Appendix III, and adjusted for exposure times and rat inhalation rates (Appendix IV) to achieve adjusted $BMDL_{05(animal)}$ values, summarized in Table 9. The finding of tumors at multiple sites in addition to the nasal cavity and tongue (NTP, 1982) implies that these cancers are due to systemic, rather than local effects, of DBCP.

Table 9. Modeling results for survival adjusted tumor incidences in male Fischer 344/N rats following exposure to DBCP via inhalation for 84 or 103 weeks, data from NTP (1982)

Tumor Site and Type	$BMDL_{05(animal)}$[a] (mg/kg-day)	CSF_{animal}[a] $(mg/kg\text{-}day)^{-1}$	CSF_{human}[a] $(mg/kg\text{-}day)^{-1}$	Model p-value	Polynomial Degree[b]
Nasal cavity squamous cell carcinoma or papilloma	0.085	0.59	2.2	0.46	1st
Nasal cavity (NOS[c]) adenoma, adenocarci-noma, or carcinoma	0.053	0.94	3.5	0.47	1st
Tongue squamous cell carcinoma or papilloma	0.18	0.28	1.0	0.13	1st
Multisite tumor analysis	**0.028**	**1.76**	**6.5**	n/a[d]	n/a

[a] Calculations are shown in Appendix III. The $BMDL_{05(animal)}$ conversion from ppm to mg/kg-day for multisite tumor analysis is shown in the text below.

[b] Degree of polynomial in the Multistage-Cancer model that best characterizes the dose-response relationship.

[c] NOS, not otherwise specified

[d] n/a, not applicable

The $BMDL_{05(animal)}$ is converted from ppm to mg/kg-day using the following equation.

$BMDL_{05(animal)}$ in mg/kg-day = [$BMDL_{05(animal)}$ in ppm × UC × ETA × EFA × BR × AE]÷BW
= 0.0284 mg/kg-day

Where:

$BMDL_{05(animal)}$ in ppm = 0.034 ppm

UC = unit conversion factor, 9.67 (mg/m^3)/ppm

ETA = exposure time adjustment, 6 hr/24 hr (unitless)

EFA = exposure frequency factor, 5 days/7 days (unitless)

BR = breathing rate of rat, 0.368 m^3/day (calculated in Appendix III)

AE = absorption efficiency, 50%

BW = body weight of male Fischer 344 rat, 0.380 kg

Using the poly-3 mortality adjustment, the inhalation CSF is 6.5 $(mg/kg\text{-}day)^{-1}$ based on the male rat data reported by NTP (1982). For comparison, if the effective number of animals at risk approach were used, the inhalation CSF would have been 3.2 $(mg/kg\text{-}day)^{-1}$. The inhalation CSF of 6.5 $(mg/kg\text{-}day)^{-1}$ is more health-protective and is selected for PHG derivation for this route.

HEALTH-PROTECTIVE DRINKING WATER CONCENTRATIONS

Noncancer Effects

The NOAEL of 0.1 ppm based on testicular effects reported by Rao et al. (1982) is retained as the POD for the noncancer effects of DBCP. In the 1999 health-protective concentration derivation, a default UF of 10 was applied in extrapolating from less than 8% of lifetime exposure in the Rao et al. (1982) study to lifetime exposure (see Appendix V for details on default UFs). Morton (1988) suggested that exposure to a toxicant for at least 6 cycles of the seminiferous epithelium (each cycle is 10.7 days), or 64 days, would be sufficient to evaluate spermatogenesis in male rabbits, which indicates that a subchronic to chronic UF may not be necessary for a 14-week study reporting sperm effects. Rao et al. (1982) reported testicular atrophy in approximately 50% of rabbits in the 1 ppm dose group after 14 weeks of exposure. Furthermore, they also found a significant increase in abnormal spermatozoa in the 1 ppm dose group even after 32 weeks of recovery. These data indicate the injury to the male reproductive system may be severe and not entirely reversible. Similar observations have been reported in humans. For example, semen samples taken from farm workers whose last exposure to DBCP was more than 10 years earlier still showed highly elevated rates of oligospermia or azoospermia (Slutsky et al., 1999). There are also animal data indicating greater sensitivity to testicular damage following DBCP exposure during fetal and neonatal development, which may persist into adulthood (Lui and Wysocki, 1987; Sod-Moraih et al., 1990; Warren et al., 1988), although the nature of these studies precludes their use for dose-response analysis. Nonetheless, there are deficiencies in the reproductive toxicity database for DBCP, including a lack of: 1) long-term studies that focus on the reversibility (or irreversibility) of sperm effects and testicular damage in animals; 2) studies characterizing the doses that result in irreversible effects; 3) studies involving larger groups of animals. This, coupled with the

observation in both animals and humans that DBCP causes potentially irreversible effects on the testis, supports the use of a database uncertainty factor of √10.

Inhalation and dermal exposures to DBCP from household uses of tap water are calculated for individual life stages using equations extracted from the CalTOX 4.0 multimedia total exposure model developed for the California Department of Toxic Substances Control by the Lawrence Berkeley National Laboratory. The estimated relative contributions from each route at different life stages are shown in Table 10. Detailed parameters and equations used are presented in Appendix II.

Table 10. Estimated relative contributions of multiple routes of exposure to DBCP in tap water at different life stages

Life Stage	Oral Ingestion (%)	Inhalation (%)	Dermal (%)
Fetus (pregnancy)	59	33	8
Infant	94	0[a]	6
Child	49	43	8
Adult	62	29	9

[a] It is anticipated that infants are not exposed to chemicals in tap water via inhalation because they typically do not shower or flush toilets. These are the predominant inhalation exposure scenarios; therefore the inhalation pathway is excluded for infants.

From studies of similar compounds in human volunteers, absorption via inhalation is assumed to be 50% (Astrand, 1975, as cited in OEHHA, 1999), while absorption via dermal and ingestion routes is assumed to be 100%. Liter equivalent (L_{eq}) values for inhalation and dermal exposures (Table 11) are calculated using life stage-specific oral ingestion rates (OEHHA, 2012) and the relative contributions of the routes of exposure listed in Table 10.

Table 11. Liter equivalent values for multiroute exposure to DBCP in tap water

Life Stage	Fractional Duration	Oral Ingestion (L/kg-day)	Inhalation[a,b] (L_{eq}/kg-day)	Dermal[a] (L_{eq}/kg-day)	Total Exposure (L_{eq}/kg-day)
Fetus (pregnancy)	0.75/70	0.047	0.013	0.006	0.066
Infant	2/70	0.196	0	0.013	0.209
Child	14/70	0.061	0.027	0.010	0.098
Adult	54/70	0.045	0.010	0.007	0.062
Time-weighted average over lifetime					**0.074**[c]

[a] Inhalation and dermal estimates are calculated using life stage-specific oral ingestion rates (OEHHA, 2012) and relative contributions of multiple routes of exposure.

[b] L_{eq} for inhalation assumes 50% absorption in the lung (OEHHA, 1999).

[c] Multiroute lifetime tap water exposure = [(0.75 × 0.066) + (2 × 0.209) + (14 × 0.098) + (54 × 0.062)]÷70 = 0.074 L_{eq}/kg-day.

The default relative source contribution (RSC) of 0.80 used in the 1999 PHG is retained. Since DBCP was banned from agricultural uses in 1985, tap water was anticipated to be the major source of exposure and this has not changed (OEHHA, 1999).

Table 12 presents a side-by-side comparison of the parameters used in calculating the noncancer health-protective concentration in 1999 and the parameters derived with current methodology in this update.

Table 12. Noncancer health-protective concentration parameters

Parameter	1999	Current
Critical Study and Endpoint	Rao et al. (1982), decreased sperm production and testicular atrophy	Rao et al. (1982), decreased sperm production and testicular atrophy
Point of Departure (POD)	NOAEL of 0.1 ppm[a] (equivalent to 0.025 mg/kg-day)[b]	NOAEL of 0.1 ppm[a] (equivalent to 0.044 mg/kg-day)[b]
Total Uncertainty Factor	1,000 (10 for interspecies extrapolation, 10 for intraspecies variability, 10 for extrapolating from subchronic to chronic exposure)	1,000 (10 for interspecies extrapolation, 30 for intraspecies variability, $\sqrt{10}$ for database uncertainty around irreversibility of testicular effects in animals and humans; need for larger studies)
Drinking Water Intake	6 L_{eq}/day (assuming an adult body weight of 70 kg, equivalent to 0.086 L_{eq}/kg-day)	0.074 L_{eq}/kg-day
Relative Source Contribution	0.80	0.80

[a] Concentration of DBCP in air

[b] The difference between the 1999 POD and the current POD is due to updated methodology for converting ppm to mg/kg-day.

ADD = noncancer POD ÷ UF = 0.044 mg/kg-day ÷ 1,000

= 0.044 µg/kg-day.

The health-protective concentration, C, incorporates the amount of exposure from drinking water and the average drinking water intake over a lifetime (DWI), and is calculated as:

$$C = \frac{ADD \times RSC}{DWI} = \frac{0.044\ \mu g/kg\text{-}day \times 0.80}{0.074\ L_{eq}/kg\text{-}day} = 0.48\ \mu g/L = 0.5\ \mu g/L \text{ or } 0.5\ ppb.$$

As shown in Table 12, OEHHA applied various methodological updates to the data from the Rao et al. (1982) critical study. Thus, OEHHA is updating the health-protective concentration to 0.5 ppb for noncancer effects based on male rabbit reproductive toxicity.

Cancer Effects

The 1999 PHG for DBCP used a single CSF for all routes of exposure. This update utilizes both an oral and an inhalation CSF to estimate cancer risk. In addition, age sensitivity factors (ASFs) are included to further protect sensitive subpopulations, specifically infants and children, who have been shown to be more sensitive to the effects of carcinogens during early-in-life exposures (Tables 13 and 14).

Table 13. ASF-adjusted oral/dermal exposures from tap water use

Life Stage	Age Sensitivity Factor (ASF)[a]	Fractional Duration (d)	Daily Water Intake (DWI, Leq/kg-day)[b]	ASF x d x DWI (Leq/kg-day)
3rd trimester Fetus	10	0.25/70	0.053	0.002
Infant (0-2 yr)	10	2/70	0.209	0.060
Child (2-16 yr)	3	14/70	0.071	0.043
Adult (16-70 yr)	1	54/70	0.052	0.040
			Total Lifetime Exposure	**0.145**

[a] OEHHA (2009), Appendix VI

[b] DWI values are obtained by adding oral ingestion and dermal tap water exposure values in Table 11

Table 14. ASF-adjusted inhalation exposure from tap water use

Life Stage	Age Sensitivity Factor (ASF)[a]	Fractional Duration (d)	Daily Water Intake (DWI, L_{eq}/kg-day)[b]	ASF x d x DWI (L_{eq}/kg-day)
3rd trimester Fetus	10	0.25/70	0.013	0.00046
Infant (0-2 yr)	10	2/70	0[c]	0
Child (2-16 yr)	3	14/70	0.027	0.0162
Adult (16-70 yr)	1	54/70	0.010	0.0077
			Total Lifetime Exposure	**0.0244**

[a] OEHHA (2009), Appendix VI

[b] Values taken from Table 11; assumes 50% inhalation absorption (OEHHA, 1999).

[c] It is anticipated that infants are not exposed to chemicals in tap water via inhalation because they typically do not shower or flush toilets. These are the predominant inhalation exposure scenarios, therefore, the inhalation pathway is excluded for infants.

Life stage-specific exposure is determined by multiplying ASFs by the fractional duration and daily water intake for each life stage. Life stage exposures are then summed to determine a total lifetime exposure for each exposure route (Appendix VI). The health-protective concentration (C) of DBCP for cancer endpoints is:

$$C = \frac{10^{-6}}{(1.0\ (mg/kg\text{-}day)^{-1} \times 0.145\ L_{eq}\ /kg\text{-}day) + (6.5\ (mg/kg\text{-}day)^{-1} \times 0.0244\ L_{eq}/kg\text{-}day)}$$

$$= \frac{10^{-6}}{0.145 + 0.159}$$

= 0.0000033 mg/L = 0.0033 µg/L or 0.003 ppb (rounded)

The updated PHG for DBCP is 0.003 ppb based on an estimated lifetime cancer risk of one in one million. This is very similar to the original PHG value of 0.0017 ppb rounded and remains lower than the current California MCL of 0.2 ppb. Although a number of methodological updates, including the use of exposure route-specific cancer potency estimates, age-sensitivity factors and age-specific water intake rates, resulted in a slightly higher PHG value, these more refined estimates also provided higher confidence in the derivation of the PHG. Since this value is lower than the health-protective concentration of 0.5 ppb derived for noncancer effects, the PHG of 0.003 ppb should protect against both cancer and noncancer effects of DBCP.

RISK CHARACTERIZATION

In this report, OEHHA analyzed the noncancer (sperm) data, updated the previously developed oral CSF to 1.0 $(mg/kg\text{-}day)^{-1}$ and developed a new inhalation CSF. The updated PHG incorporates updated drinking water ingestion rates, CalTOX equations, a new equation for calculating rat breathing rates, and ASFs to protect infants and children exposed to carcinogens.

The proposed PHG of 0.003 ppb was calculated based on the carcinogenic effects of DBCP. Since this value is lower than the health-protective concentration of 0.5 ppb derived for noncancer effects, the PHG of 0.003 ppb should protect against both cancer and noncancer effects of DBCP.

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APPENDIX I. Benchmark Dose Modeling

This appendix provides the BMD modeling outputs for DBCP toxicity data that were amenable to dose-response modeling. All models are run with default parameters and a benchmark response of 5% for dichotomous data and one standard deviation from the control mean for continuous data. The models for abnormal sperm in rabbits (Figure A1) are run with modeled variance instead of the default constant variance. Model selection criteria when comparing outputs of different models for the same endpoint/dataset are: scaled residual ≤ the absolute value of two, goodness of fit p-value ≥ 0.05,[6] the Akaike's information criterion (AIC), and visual inspection of the dose-response curve. The lower limit of the 95% confidence interval of the BMD resulting in the benchmark response, the BMDL, is selected as the POD. The model selected for each study to derive the POD is presented below.

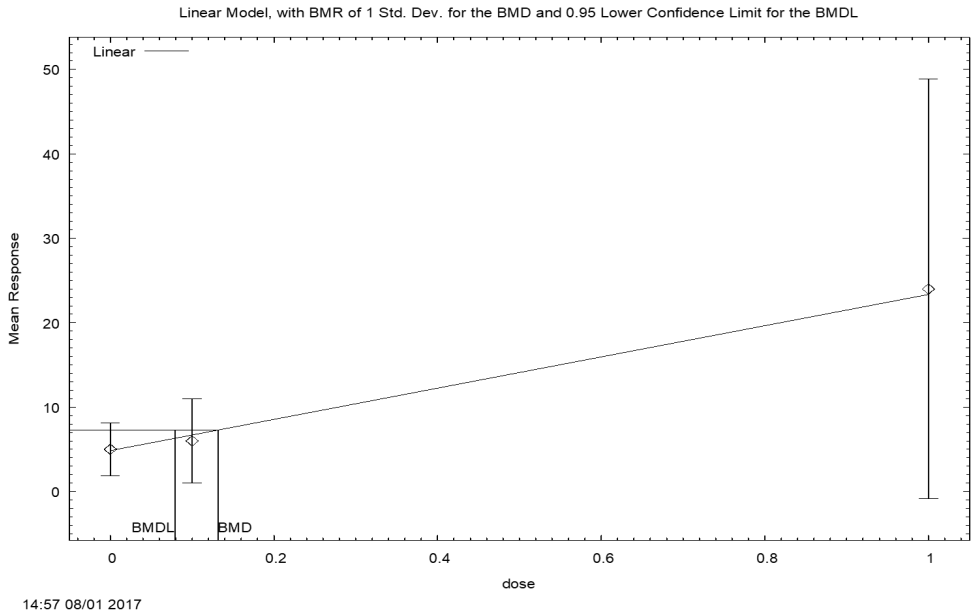
Table A1. BMD modeling of percent abnormal spermatozoa for male rabbits exposed to DBCP by inhalation for 14 weeks followed by a 32-week recovery period (Rao et al., 1982)

Model[a]	Scaled Residual	Model p-value	AIC	BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)
Exponential2	0.07	0.72	48.99	0.25	0.17
Linear	-0.39	0.36	49.69	0.13	**0.08**

[a] All models were run with modeled variance and a benchmark response of 1 standard deviation (SD) from the control mean.
[b] Exponential3 model produced the same results.
[c] Power and second degree polynomial models produced the same results.

[6] US EPA's Benchmark Dose Technical Guidance (2012) suggests using a goodness of fit p-value ≥ 0.1; however, models with less adequate fit (goodness of fit p-value ≥ 0.05) may be used when other criteria are taken into account, such as variability in the endpoint and visual fit.

Figure A1. Linear model output for increase in percentage of ultrastructurally abnormal spermatozoa in male rabbits exposed to DBCP for 14 weeks followed by a 32-week recovery period (Rao et al., 1982)




```
==========================================================================
Polynomial Model. (Version: 2.20;  Date: 10/22/2014)
Input Data File: K:/PHGs/DBCP/BMDS/072517
noncancer/lin_RaoTable7nohi_noncancer_opt_1SD_NCV.(d)
Gnuplot Plotting File:  K:/PHGs/DBCP/BMDS/072517
noncancer/lin_RaoTable7nohi_noncancer_opt_1SD_NCV.plt
Tue Aug 01 14:57:30 2017
 ========================================================================
BMDS Model Run
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The form of the response function is:

Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 +

Dependent variable = Mean
  Independent variable = Dose
  Signs of the polynomial coefficients are not restricted
  The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

  Total number of dose groups = 3
  Total number of records with missing values = 0
  Maximum number of iterations = 500
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

lalpha =	3.33616
rho =	0
beta_0 =	4.55495
beta_1 =	19.3956

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	beta_0	beta_1
lalpha	1	-0.95	0.0095	0.047
rho	-0.95	1	0.002	-0.063
beta_0	0.0095	0.002	1	-0.31
beta_1	0.047	-0.063	-0.31	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	-0.517054	1.26866	-3.00357	1.96947
rho	1.45711	0.58551	0.309537	2.60469
beta_0	4.84617	0.899559	3.08307	6.60927
beta_1	18.5449	4.53775	9.65104	27.4387

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	5	4.85	3	2.44	0.155
0.1	3	6	6.7	2	3.09	-0.393
1	3	24	23.4	10	7.68	0.137

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-24.290897	4	56.581794
A2	-19.815511	6	51.631021
A3	-20.431288	5	50.862576
fitted	-20.844092	4	49.688184
R	-32.766644	2	69.533288

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)

Test 2: Are Variances Homogeneous? (A1 vs A2)

Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)

(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	25.9023	4	<.0001
Test 2	8.95077	2	0.01139
Test 3	1.23155	1	0.2671
Test 4	0.825608	1	0.3635

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

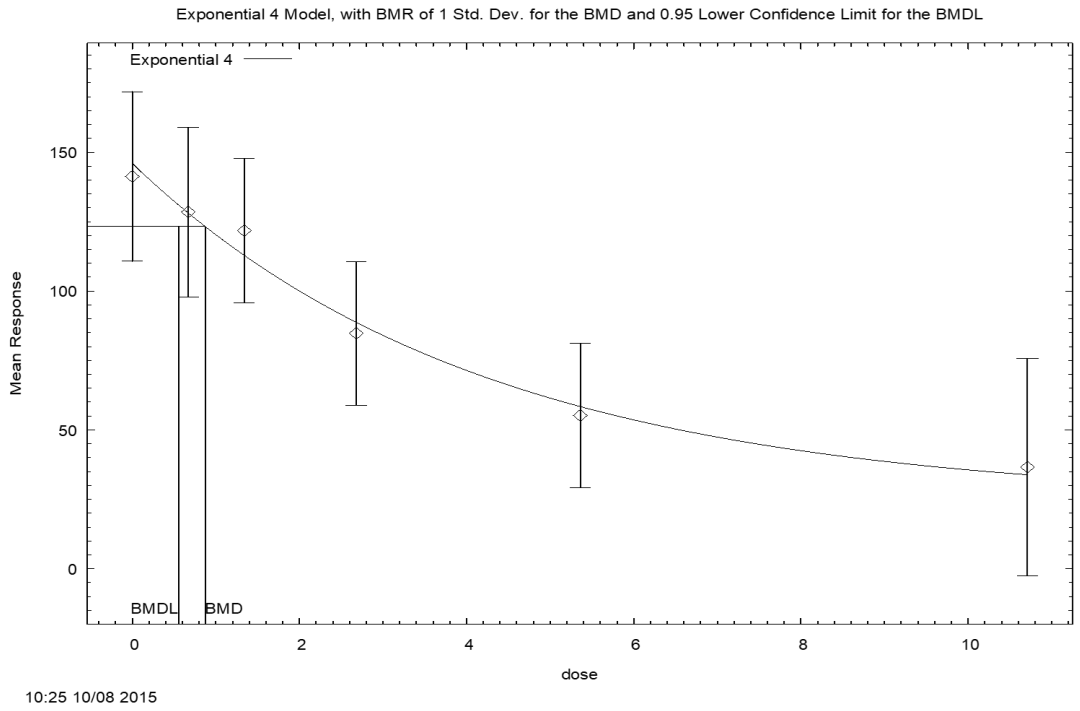
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.131478

BMDL = 0.0788347

Figure A2. Exponential 4 model output for decrease in mean number of round spermatids per cross-section of male rabbits exposed to DBCP for 10 weeks (Foote et al., 1986)



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Exponential Model. (Version: 1.10; Date: 01/12/2015)
Input Data File: K:/PHGs/12dibromo3chloropropane/BMDS/data/exp_Foote86spermatid.(d)
Gnuplot Plotting File:
Thu Oct 08 12:01:21 2015

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BMDS Model Run

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The form of the response function by Model:
Model 2: Y[dose] = a * exp{sign * b * dose}
Model 3: Y[dose] = a * exp{sign * (b * dose)^d}
Model 4: Y[dose] = a * [c-(c-1) * exp{-b * dose}]
Model 5: Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

Note: Y[dose] is the median response for exposure = dose;
sign = +1 for increasing trend in data;
sign = -1 for decreasing trend.

Model 2 is nested within Models 3 and 4.
Model 3 is nested within Model 5.
Model 4 is nested within Model 5.
~~~~~~~~~~

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	6.20254
rho	0 Specified
a	148.365
b	0.19607
c	0.123344
d	1 Specified

Parameter Estimates

Variable	Model 4	Std. Err.
lnalpha	6.25045	129.562
a	146.002	8.16012
b	0.236976	0.0828923
c	0.165886	0.123881

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	5	141.3	24.6
0.67	5	128.5	24.6
1.34	6	121.8	24.7
2.68	6	84.8	24.7
5.36	6	55.2	24.7
10.71	4	36.6	24.6

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	146	22.77	-0.4619
0.67	128.1	22.77	0.037
1.34	112.9	22.77	0.961
2.68	88.75	22.77	-0.4251
5.36	58.41	22.77	-0.3458
10.71	33.84	22.77	0.2422

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model R: Yij = Mu + e(i)
Var{e(ij)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-115.2407	7	244.4814
A2	-115.2289	12	254.4579
A3	-115.2407	7	244.4814
R	-136.6341	2	277.2683
4	-116.0073	4	240.0145

Additive constant for all log-likelihoods = -29.41. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	42.81	10	< 0.0001
Test 2	0.02349	5	1
Test 3	0.02349	5	1
Test 6a	1.533	3	0.6746

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than 1. A homogeneous variance model appears to be appropriate here.

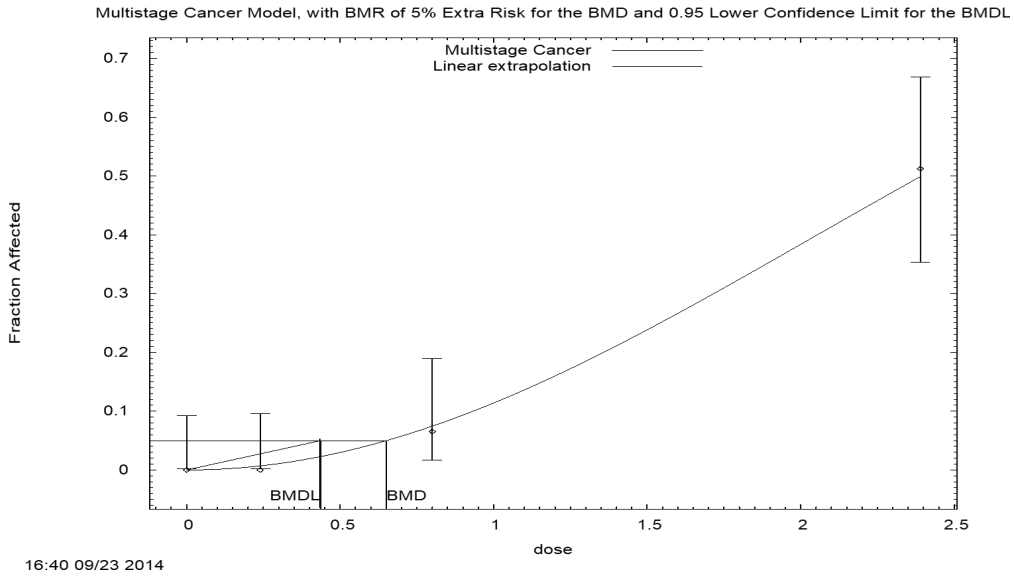
The p-value for Test 3 is greater than 1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than 1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:
Specified Effect = 1.000000
Risk Type = Estimated standard deviations from control
Confidence Level = 0.950000
BMD = 0.873254
BMDL = 0.554776

Figure A3. Multistage-Cancer model outputs and multisite analysis of tumors in male rats following chronic dietary exposure to DBCP (Hazleton, 1977)

Squamous cell carcinomas or papillomas in the stomach of male rats following dietary exposure to DBCP (Hazleton, 1977)



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MS_COMBO. (Version: 1.8 Beta; Date: 04/30/2014)
Input Data File: K:\PHGs\12dibromo3chloropropane\BMDS\091814 DBCP feed\ratmulti3bestpoly.(d)
Gnuplot Plotting File: K:\PHGs\12dibromo3chloropropane\BMDS\091814 DBCP feed\ratmulti3bestpoly.plt
Fri Oct 03 11:24:58 2014

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BMDS_Model_Run

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The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2)]

The parameter betas are restricted to be positive
~~~~~~~~~~

Dependent variable = Col3
Independent variable = Col1
Data file name = maleratsccpstom.dax

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 3
Total number of specified parameters = 0
Degree of polynomial = 2

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
Background = 0
Beta(1) = 0
Beta(2) = 0.12671

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background -Beta(1)
have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	Beta(2)
Beta(2)	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.120915	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-39.4969	4			
Fitted model	-39.8618	1	0.729763	3	0.8662
Reduced model	-70.8241	1	62.6544	3	<.0001

AIC: 81.7236

Log-likelihood Constant 35.94619047318114

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	48.000	0.000
0.2400	0.0069	0.319	0.000	46.000	-0.567
0.8000	0.0745	3.425	3.000	46.000	-0.239
2.3900	0.4988	20.449	21.000	41.000	0.172

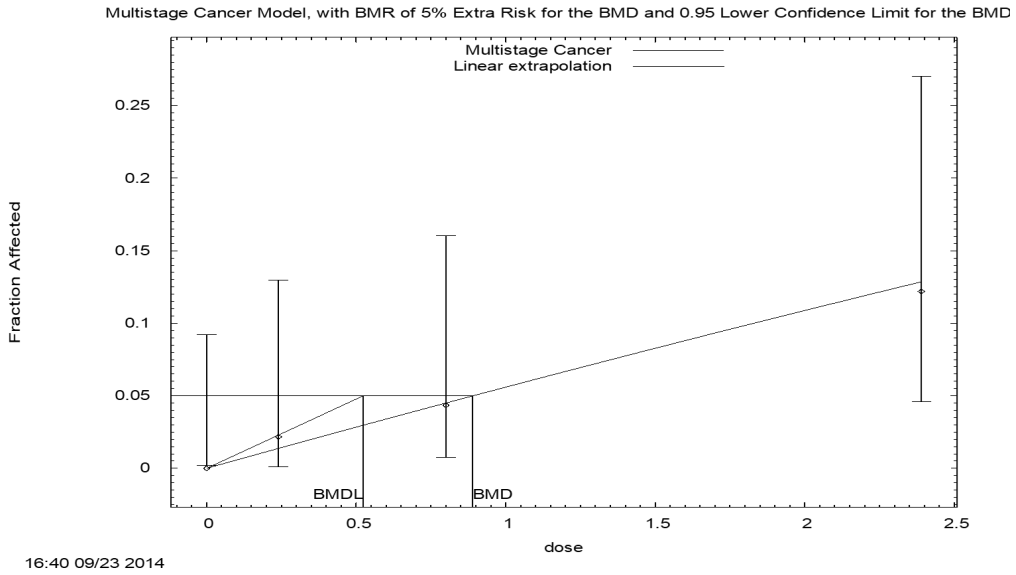
Chi^2 = 0.41 d.f. = 3 P-value = 0.9385

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 0.651314
BMDL = 0.436768
BMDU = 0.780095

Taken together, (0.436768, 0.780095) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.114477

Hepatocellular carcinomas in male rats following dietary exposure to DBCP (Hazleton, 1977)



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MS_COMBO. (Version: 1.8 Beta; Date: 04/30/2014)
Input Data File: K:\PHGs\12dibromo3chloropropane\BMDS\091814 DBCP feed\ratmulti3bestpoly.(d)

Gnuplot Plotting File: K:\PHGs\12dibromo3chloropropane\BMDS\091814 DBCP feed\ratmulti3bestpoly.plt
Fri Oct 03 11:24:58 2014
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BMDS_Model_Run
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The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(-beta1*dose^1)]

The parameter betas are restricted to be positive
Dependent variable = Col3
Independent variable = Col1
Data file name = maleratHC.dax

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
Background = 0.00382698
Beta(1) = 0.0528124

Asymptotic Correlation Matrix of Parameter Estimates
(*** The model parameter(s) -Background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	Beta(1)
Beta(1)	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.0576405	*	*	*

* - Indicates that this value is not calculated.
~~~~~~~~~~

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-28.2471	4			0.9769
Fitted model	-28.3493	1	0.204357	3	
Reduced model	-32.773	1	9.05169	3	0.02861

AIC: 58.6986

Log-likelihood Constant 24.297823598725294

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	48.000	0.000
0.2400	0.0137	0.632	1.000	46.000	0.466
0.8000	0.0451	2.073	2.000	46.000	-0.052
2.3900	0.1287	5.276	5.000	41.000	-0.129

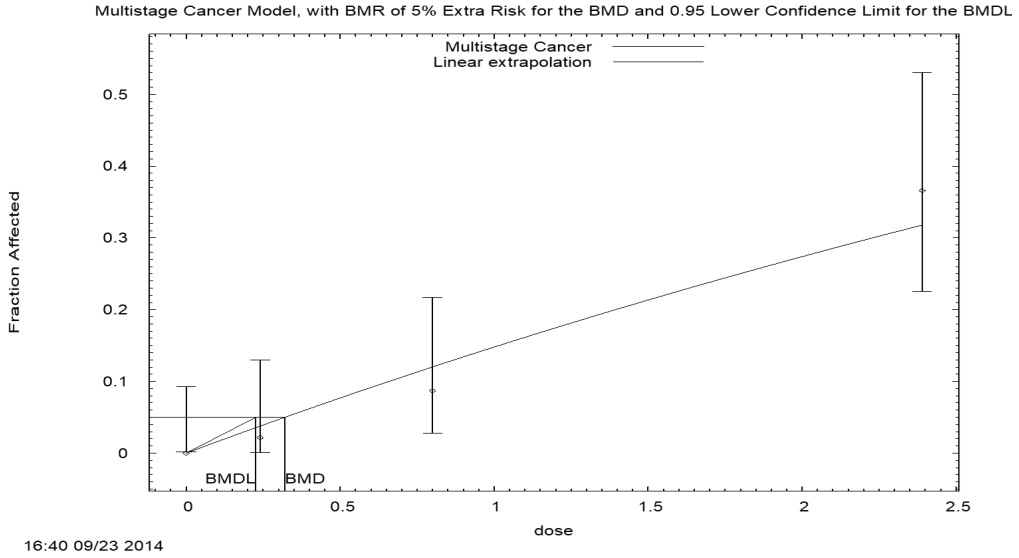
Chi^2 = 0.24 d.f. = 3 P-value = 0.9715

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 0.889883
BMDL = 0.523478
BMDU = 2.09375

Taken together, (0.523478, 2.09375) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.095515

Renal tubular cell adenomas or carcinomas in male rats following dietary exposure to DBCP (Hazleton, 1977)



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MS_COMBO. (Version: 1.8 Beta; Date: 04/30/2014)
Input Data File: K:\PHGs\12dibromo3chloropropane\BMDS\091814 DBCP feed\ratmulti3bestpoly.(d)
Gnuplot Plotting File: K:\PHGs\12dibromo3chloropropane\BMDS\091814 DBCP feed\ratmulti3bestpoly.plt
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BMDS_Model_Run

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The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2)]

The parameter betas are restricted to be positive

Dependent variable = Col3
Independent variable = Col1
Data file name = maleratRTCA.dax

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 3
Total number of specified parameters = 0
Degree of polynomial = 2

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
~~~~~~~~~~

Default Initial Parameter Values

Background = 0.000477217

Beta(1) = 0.0748296

Beta(2) = 0.048341

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	Beta(1)	Beta(2)
Beta(1)	1	-0.96
Beta(2)	-0.96	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.0774699	*	*	*
Beta(2)	0.0472006	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-45.3331	4			
Fitted model	-45.3339	2	0.00168058	2	0.9992
Reduced model	-62.9072	1	35.1483	3	<.0001

AIC: 94.6679

Log-likelihood Constant 40.704519838631398

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	48.000	0.000
0.2400	0.0211	0.970	1.000	46.000	0.031
0.8000	0.0881	4.051	4.000	46.000	-0.026
2.3900	0.3654	14.982	15.000	41.000	0.006

Chi^2 = 0.00 d.f. = 2 P-value = 0.9992

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 0.506068
BMDL = 0.248973
BMDU = 0.894824

Taken together, (0.248973, 0.894824) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.200825

BMDS multisite analysis of male rat tumors from Hazleton Laboratories (1977)

**** Start of combined BMD and BMDL Calculations.****

Combined Log-Likelihood -113.54502895102657

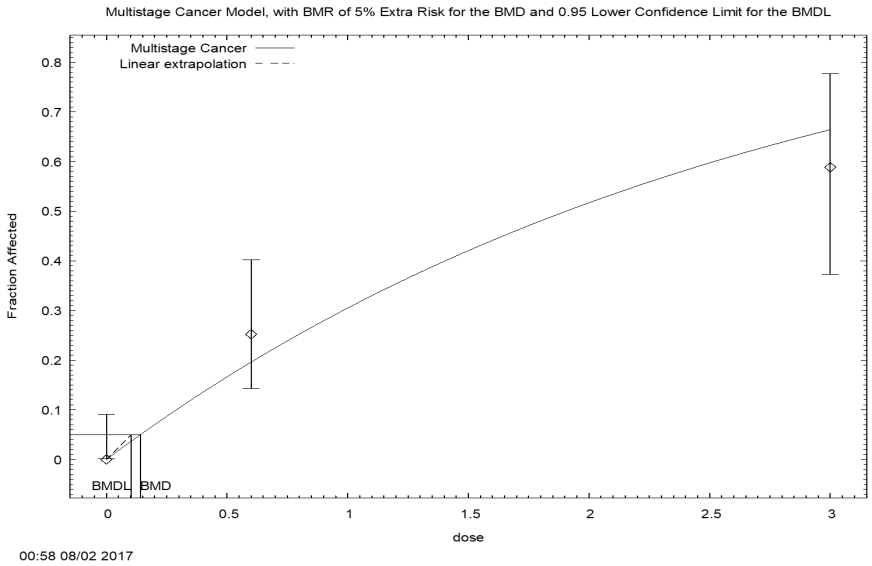
Combined Log-likelihood Constant 100.94853391053783

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 0.281229
BMDL = 0.172821

Multistage Cancer Slope Factor = 0.289316

Figure A4. Multistage-Cancer model outputs and multisite analysis of tumors observed in male rats following chronic inhalation exposure to DBCP (NTP, 1982)

Squamous cell carcinomas or papillomas of the nasal cavity in male rats following exposure to DBCP via inhalation (NTP, 1982)



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MS_COMBO. (Version: 1.9; Date: 05/20/2014)
Input Data File: K:\PHGs\DBCP\BMDS\072517 cancer\multisite_malerat_poly3.(d)
Gnuplot Plotting File: K:\PHGs\DBCP\BMDS\072517 cancer\multisite_malerat_poly3.plt
Wed Aug 02 01:03:46 2017

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BMDS_Model_Run

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The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(-beta1*dose^1)]

The parameter betas are restricted to be positive

Dependent variable = Effect
Independent variable = Dose
Data file name = maleratsccp_nascav_104wk.dax

Total number of observations = 3
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1
~~~~~~~~~~

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
Background = 0.0523868
Beta(1) = 0.282716

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	Beta(1)
Beta(1)	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.364139	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-42.9743	3			
Fitted model	-43.715	1	1.48123	2	0.4768
Reduced model	-62.6797	1	39.4107	2	<.0001

AIC: 89.4299
Log-likelihood Constant 39.145590523823344

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	48.490	0.000
0.6000	0.1963	9.336	12.000	47.570	0.972
3.0000	0.6646	15.804	14.000	23.780	-0.784

Chi^2 = 1.56 d.f. = 2 P-value = 0.4585

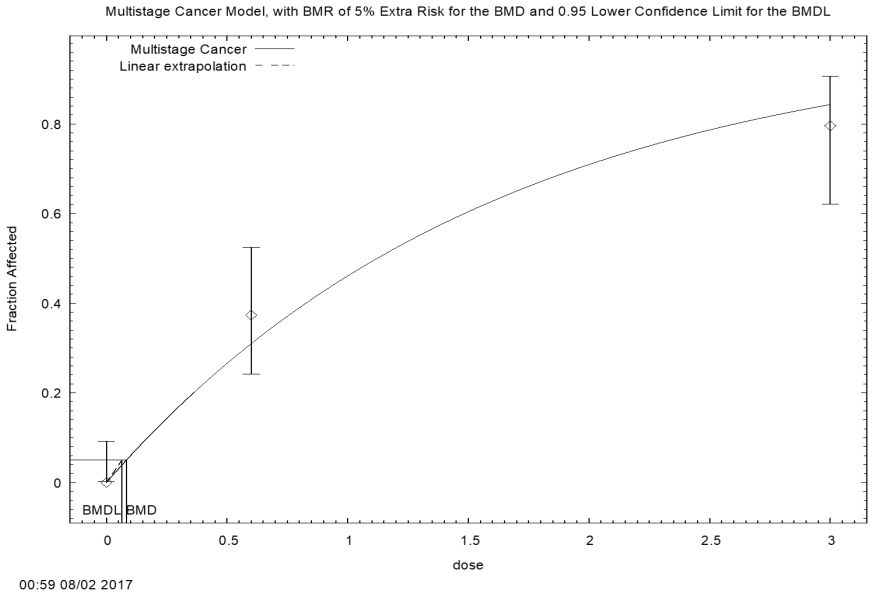
Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95

BMD = 0.140862
BMDL = 0.102709
BMDU = 0.199645

Taken together, (0.102709, 0.199645) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.486812

Adenomas, adenocarcinomas, or carcinomas of the nasal cavity in male rats following inhalation exposure to DBCP (NTP, 1982)



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MS_COMBO. (Version: 1.9; Date: 05/20/2014)
Input Data File: K:\PHGs\DBCP\BMDS\072517 cancer\multisite_malerat_poly3.(d)
Gnuplot Plotting File: K:\PHGs\DBCP\BMDS\072517 cancer\multisite_malerat_poly3.plt
Wed Aug 02 01:03:46 2017

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BMDS_Model_Run

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The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(-beta1*dose^1)]

The parameter betas are restricted to be positive

Dependent variable = Effect
Independent variable = Dose
Data file name = malerat_nascavnos_104wk.dax

Total number of observations = 3
~~~~~~~~~~

Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
Background = 0.0688508
Beta(1) = 0.511892

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)
Beta(1)	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.618032	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-49.6461	3			
Fitted model	-50.3671	1	1.44215	2	0.4862
Reduced model	-85.2785	1	71.2648	2	<.0001

AIC: 102.734
Log-likelihood Constant 45.707440336524073

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	48.490	0.000
0.6000	0.3098	14.931	18.000	48.190	0.956
3.0000	0.8434	29.671	28.000	35.180	-0.775

Chi^2 = 1.52 d.f. = 2 P-value = 0.4688

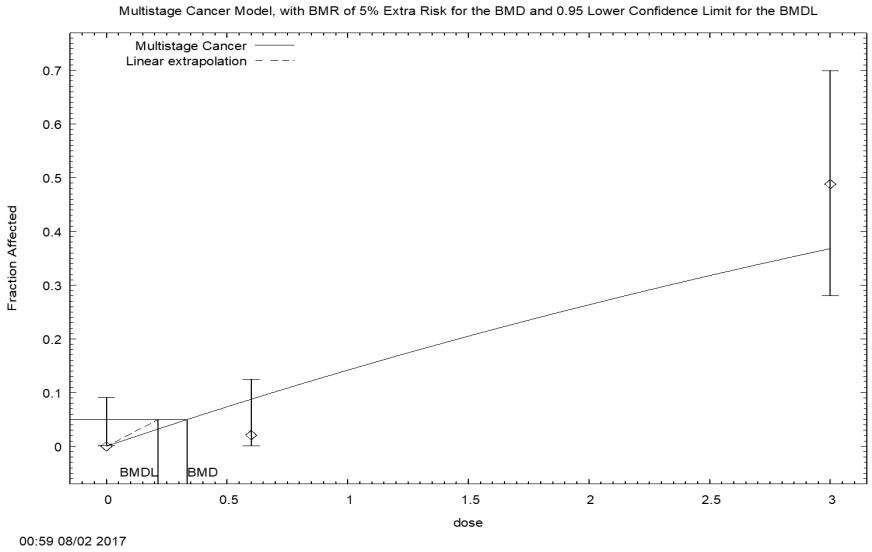
Benchmark Dose Computation

Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 0.0829946
BMDL = 0.0642637
BMDU = 0.108927

Taken together, (0.0642637, 0.108927) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.778045

Carcinomas or papillomas of the tongue in male rats following exposure to DBCP via inhalation (NTP, 1982)



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MS_COMBO. (Version: 1.9; Date: 05/20/2014)
Input Data File: K:\PHGs\DBCP\BMDS\072517 cancer\multisite_malerat_poly3.(d)
Gnuplot Plotting File: K:\PHGs\DBCP\BMDS\072517 cancer\multisite_malerat_poly3.plt
Wed Aug 02 01:03:46 2017

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BMDS_Model_Run

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The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(-beta1*dose^1)]

The parameter betas are restricted to be positive

Dependent variable = Effect
Independent variable = Dose
Data file name = maleratsccp_tongue_104wk.dax

Total number of observations = 3
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
Background = 0
Beta(1) = 0.236596

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Beta(1)
Beta(1)	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.15303	*	*	*

* - Indicates that this value is not calculated.
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Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-20.4799	3			
Fitted model	-23.0482	1	5.13662	2	0.07666
Reduced model	-38.9179	1	36.8761	2	<.0001

AIC: 48.0964

Log-likelihood Constant 17.696104219104107

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	48.490	0.000
0.6000	0.0877	4.220	1.000	48.100	-1.641
3.0000	0.3681	8.298	11.000	22.540	1.180

Chi^2 = 4.09 d.f. = 2 P-value = 0.1297

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 0.335184
BMDL = 0.2149
BMDU = 0.563137

Taken together, (0.2149 , 0.563137) is a 90% two-sided confidenceinterval for the BMD

Multistage Cancer Slope Factor = 0.232666

BMDS multisite analysis of male rat tumors from NTP (1982)

**** Start of combined BMD and BMDL Calculations.****

Combined Log-Likelihood -117.13029238287254

Combined Log-likelihood Constant 102.54913507945153

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 0.0451843
BMDL = 0.0336165

Multistage Cancer Slope Factor = 1.48736

APPENDIX II. Determination of Multiroute Exposures

Human exposure to chemical contaminants in tap water can occur via oral ingestion, as well as inhalation or dermal contact while performing common household activities, such as bathing, showering, and flushing toilets. This appendix describes the multiroute exposure assessment of chemicals in drinking water using equations extracted from CalTOX.[7] CalTOX is a multimedia total exposure model with built-in physicochemical property values for over 200 chemicals and mathematical equations to calculate total human exposure to contaminants in the environment (air, soil, and water).

For PHG development, exposures to chemicals in tap water over a lifetime (70 years) are considered. Exposure estimates differ across life stages (fetus, infant, child, and adult) due to physiological and activity pattern changes. CalTOX equations are used to calculate how much each route (oral, inhalation, and dermal) contributes to total daily exposure to a contaminant in tap water. The relative contributions of the different routes are then used to estimate a daily drinking water intake equivalent (DWI, in L_{eq}/kg-day) of multiroute exposure to tap water for each life stage. The lifetime daily multiroute intake rate of tap water in L_{eq}/kg-day is the time-weighted average of these life-stage specific tap water intake rates.[8] The liter equivalent (L_{eq}/kg-day) value represents the equivalent of how much water a person would have to drink to account for exposures via ingestion, inhalation and dermal uptake. Table A1 shows the descriptions and values of parameters applied in the exposure equations. Tables A2 and A3 show life-stage specific exposure parameter values.

Table A2. Descriptions and Values of Model Defaults, Chemical-Specific and Exposure-Specific Parameters

Symbol	Parameter	Value	Unit	Source
Inputs and Calculated Outputs				
$Intake_{oral}$	chemical intake via oral ingestion of tap water	-	mg/kg-day	calculated
$Intake_{inh}$	chemical intake via inhalation	-	mg/kg-day	calculated
$Uptake_{dermal}$	chemical uptake via dermal contacts	-	mg/kg-day	calculated
C_{tap_water}	chemical concentration in tap water	100[a]	mg/L	input
C_{air}	chemical concentration in indoor air	-	mg/m^3	calculated
C_{bath_air}	chemical concentration in bathroom air	-	mg/m^3	calculated

[7] A multimedia total exposure model developed for the Department of Toxic Substances Control, California Environmental Protection Agency (Cal/EPA), by the Lawrence Berkeley National Laboratory (2002, Version 4.0 Beta available at https://www.dtsc.ca.gov/caltox).

[8] A 0.75-yr exposure duration for the fetus is used to derive the time-weighted average for the lifetime daily exposure rate (e.g., 0.75/70*0.047+2/70*0.196+14/70*0.061+54/70*0.045=0.053 L/kg-day for exposure via oral ingestion) in calculating the noncancer health-protective concentration. A 0.25-yr duration (3rd trimester) is applied as the life-stage-specific exposure of the fetus in calculating the age sensitivity factor (ASF)-adjusted life-stage-specific exposures to tap water.

Symbol	Parameter	Value	Unit	Source
Exposure Parameters				
Ifl	fluid (water) intake, normalized to body weight	0.045 to 0.196[b]	L/kg-day	OEHHA, 2012
BR_a	active breathing rate, normalized to body weight	0.012 to 0.045[b]	m^3/kg-hr	OEHHA, 2012
BR_r	resting breathing rate, normalized to body weight	0.012 to 0.045[b]	m^3/kg-hr	OEHHA, 2012
SA_b	surface area, normalized to body weight	0.029 to 0.059[b]	m^2/kg	OEHHA, 2012
ET_{ai}	exposure time, active indoors	5.71 to 8	hr/day	model default
ET_{ri}	exposure time, resting indoors	8 to 11	hr/day	model default
ET_{sb}	exposure time, in shower or bath	0.27	hr	model default
δ_{skin}	skin thickness	0.0025	cm	model default
f_s	fraction of skin in contact of water during showering or bathing	0.80	unitless	model default
CF	conversion factor for dermal uptake calculation	10	L/cm-m^2	calculated
Physicochemical and Other Parameters				
W_{house}	Water use in the house	40	L/hr	model default
VR_{house}	Room ventilation rate, house	750	m^3/hr	model default
W_{shower}	Water use in the shower	8	L/min	model default
VR_{bath}	Room ventilation rate, bathroom	1	m^3/min	model default
D_{water}	Diffusion coefficient in pure water	chemical specific	m^2/day	literature
D_{air}	Diffusion coefficient in pure air	chemical specific	m^2/day	literature
Z_{water}	fugacity capacity of pure water	volatiles=1/H semivolatiles=1 (H: Henry's Law constant)	mole/Pa-m^3	literature
R_{gas}	gas constant	8.31	Pa-m^3/mol-K	literature
t_{lag}	diffusion lag time in skin	chemical specific	hr	calculated
K_m	skin-water partition coefficient	chemical specific	unitless	literature
K_p^w	steady-state skin permeability coefficient	chemical specific	cm/hr	literature
MW	molecular weight	chemical specific	g/mole	literature
K_{ow}	octanol/water partition coefficient	chemical specific	unitless	literature

[a] As long as the chemical concentration in tap water is low (well below the saturation concentration in water), the input value of C_{tap_water} does not affect the calculation of relative contributions from the multiroute exposures and 100 ppm is an arbitrarily assigned low value.
[b] See Table A3 for life-stage specific values.

Table A3. OEHHA Calculated Exposure Parameters (OEHHA, 2012[9])

Life Stage	Water Intake Rate[a] (L/kg-day)	Breathing Rate[b] (m^3/kg-hr)	Surface Area[c] (m^2/kg)
Infant (0<2 yrs)	0.196	0.045	0.059
Child (2<16 yrs)	0.061	0.031	0.045
Adult (16-70 yrs)	0.045	0.012	0.029
Fetus[d]	0.047	0.015	0.029

[a] 95th percentile water intake rates (L/kg-day) are obtained from Table 8.1 of OEHHA (2012) risk assessment guidelines.
[b] 95th percentile breathing rates (L/kg-day) are obtained from Table 3.1 of OEHHA (2012) risk assessment guidelines and converted to m^3/kg-hr. The same life stage-specific breathing rate is used for BR_a and BR_r.
[c] 95th percentile values for total body surface area over body weight (m^2/kg) are obtained from Table 6.5 of OEHHA (2012) risk assessment guidelines.
[d] In utero exposure dose of the fetus is assumed to be the same as that of the pregnant mothers. Therefore the breathing rate and water intake rate for pregnant women are applied in the exposure estimates for fetuses (OEHHA, 2012). Pregnant women are assumed to have the same total body surface area over body weight as adults. Therefore, the total body surface area per body weight for adults is applied in the fetal dermal exposure estimation.

Table A4. CalTOX Model Default Exposure Durations

Life Stage	CalTOX Exposure Factors Set[a]	Exposure Time, Active Indoors (hr/day)	Exposure Time, Resting Indoors (hr/day)	Exposure Time, Shower or Bath (hr/day)
Infant (0<2 yrs)	Female 0-1	5.71	11.01	0.27
Child (2<16 yrs)	Female 7-9	5.71	11.01	0.27
Adult (16-70 yrs)	Female 19+	8.00	8.00	0.27
Fetus	Female 19+	8.00	8.00	0.27

[a] These Exposure Factors Sets provide the best estimates of the multiroute exposure for the corresponding life stages. Between the age groups within a particular life stage, the differences in relative contribution of a particular route are negligible, predominantly well below 1%. Within the same age group, the male and female inputs provide almost the same model outputs. Therefore, for internal consistency, use of the female Exposure Factor Sets is recommended for all life stages.

A. Oral Intake: Ingestion of Tap Water

Oral intake through ingestion of tap water can be calculated as follows:[10]

$$\mathbf{Intake_{oral}} = \mathbf{C_{tap\_water}} \times \mathbf{Ifl}$$

[9] OEHHA (2012). Air Toxics Hot Spots Program Risk Assessment Guidelines: Technical Support Document for Exposure Assessment and Stochastic Analysis. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, California.
[10] Abbreviations and symbols used in equations are defined in Table A2.

B. Inhalation Intake: Inhalation of Indoor Air in Active State, Resting State, and Shower/Bath

Chemicals in tap water can be transferred to indoor air during domestic activities such as showering, bathing, and toilet flushing. The total inhalation intake ($Intake_{inh}$) for a chemical in indoor air is obtained by summing the inhalation intakes in the active state, resting state, and in the shower/bath for each life-stage, as shown in the following equation:

$$\mathbf{Intake_{inh}} = \mathbf{C_{air}} \times (\mathbf{BR_a} \times \mathbf{ET_{ai}} + \mathbf{BR_r} \times \mathbf{ET_{ri}} - \mathbf{BR_a} \times \mathbf{ET_{sb}}) + \mathbf{C_{bath\_air}} \times \mathbf{BR_a} \times \mathbf{ET_{sb}}$$

The chemical concentration in indoor air and bathroom air are derived from the two equations below:

$$\mathbf{C_{air}} = \frac{\mathbf{3 \times 10^6 \times 0.7 \times \left(\frac{W_{house}}{VR_{house}}\right) \times C_{tap\_water}}}{\frac{\mathbf{2.5}}{\mathbf{(D_{water}/86400)^{2/3}}} + \frac{\mathbf{R_{gas} \times 298 \times Z_{water}}}{\mathbf{(D_{air}/86400)^{2/3}}}}$$

and

$$\mathbf{C_{bath\_air}} = \frac{\mathbf{3 \times 10^6 \times 0.6 \times \left(\frac{W_{shower}}{VR_{bath}}\right) \times C_{tap\_water}}}{\frac{\mathbf{2.5}}{\mathbf{(D_{water}/86400)^{2/3}}} + \frac{\mathbf{R_{gas} \times 298 \times Z_{water}}}{\mathbf{(D_{air}/86400)^{2/3}}}}$$

C. Dermal Uptake: Dermal Exposure to Tap Water during Shower/Bath

Dermal uptake of a chemical is dependent on exposure time and chemical-specific parameters, including diffusion through the skin. As a result, the dermal uptake of chemicals in tap water while showering or bathing are derived from one of the following equations:

1. When exposure time < diffusion lag time in skin[11] (t_{lag}):

   a. Exposure time << diffusion lag time, i.e. $\frac{t_{lag} \times 2}{ET_{sb}} > 3$:

$$\mathbf{Uptake_{dermal}} = \mathbf{C_{tap\_water}} \times \left(\frac{\mathbf{\delta_{skin} \times K_m}}{\mathbf{2}}\right) \times \mathbf{f_s} \times \mathbf{CF} \times \mathbf{SA_b} \times \frac{\mathbf{ET_{sb}}}{\mathbf{2 \times tlag}} \times \frac{\mathbf{1\ event}}{\mathbf{day}}$$

   b. For $1 \leq \frac{t_{lag} \times 2}{ET_{sb}} \leq 3$:

[11] Diffusion lag time in the skin is the amount of time it takes a chemical to permeate through the skin until it reaches a steady state of diffusion.

$$\mathbf{Uptake_{dermal}} = \mathbf{C_{tap\_water}} \times \left(\frac{\delta_{\mathbf{skin}} \times \mathbf{K_m}}{\mathbf{2}}\right) \times \mathbf{f_s} \times \mathbf{CF} \times \mathbf{SA_b} \times \frac{\mathbf{1\ event}}{\mathbf{day}}$$

2. When exposure time > diffusion lag time, i.e. $\frac{t_{lag} \times 2}{ET_{sb}} < 1$:

$$\mathbf{Uptake_{dermal}} = \mathbf{C_{tap\_water}} \times \left[\frac{\delta_{\mathbf{skin}} \times \mathbf{K_m}}{\mathbf{2}} + \left(\frac{\mathbf{ET_{sb}}}{\mathbf{2}} - \mathbf{t_{lag}}\right) \times \mathbf{K_p^w}\right] \times \mathbf{f_s} \times \mathbf{CF} \times \mathbf{SA_b} \times \frac{\mathbf{1\ event}}{\mathbf{day}}$$

where the chemical-specific t_{lag} is obtained from:

$$\mathbf{t_{lag}} = \frac{\delta_{\mathbf{skin}} \times \mathbf{K_m}}{\mathbf{6} \times \mathbf{K_p^w}}$$

For chemicals with no steady-state skin permeability coefficient (K_p^w) and skin/water partition coefficient (K_m) available in the literature, these values are derived from the following equations, using chemical molecular weight (MW) and octanol/water partition coefficient (K_{ow}):

1. K_p^w is calculated using one of the equations below:

   a. Chemicals with MW < 280 g/mole:

$$\mathbf{K_p^w} = \frac{1}{(\mathbf{MW})^{0.6}} \times \frac{2.4\times10^{-6}+3\times10^{-5}\times(\mathbf{K_{ow}})^{0.8}}{\delta_{\mathbf{skin}}}$$

   b. Chemicals with MW ≥ 280 g/mole:

$$\mathbf{K_p^w} = 0.0019\times(\mathbf{K_{ow}})^{0.71}\times10^{(-0.0061\times\mathbf{MW})}$$

   c. Chemicals with calculated K_p^w > 1:

$$\mathbf{K_p^w} = 1$$

2. K_m is calculated using this equation:

$$\mathbf{K_m} = 0.64+0.25\times(\mathbf{K_{ow}})^{0.8}$$

D. Relative Contributions from Each Route of Exposure

Finally, the relative contributions of chemical exposure to tap water via multiple routes are derived from the $Intake_{oral}$, $Intake_{inh}$, and $Uptake_{dermal}$ as follows:

Relative Contribution from Oral Ingestion (%)

$$= \frac{\mathbf{Intake_{oral}}}{\mathbf{Intake_{oral} + Intake_{inh} + Uptake_{dermal}}} \times \mathbf{100\%}$$

Relative Contribution from Inhalation[12] (%)

$$= \frac{\mathbf{Intake_{inh}}}{\mathbf{Intake_{oral} + Intake_{inh} + Uptake_{dermal}}} \times \mathbf{100\%}$$

Relative Contribution from Dermal Uptake (%)

$$= \frac{\mathbf{Uptake_{dermal}}}{\mathbf{Intake_{oral} + Intake_{inh} + Uptake_{dermal}}} \times \mathbf{100}\%$$

[12] Infant exposure to chemicals in tap water via inhalation are anticipated to be negligible, compared to the other exposure pathways, because they typically do not shower or flush toilets. Thus, the relative contribution from inhalation is zero for infants.

APPENDIX III. Cancer Slope Factor Calculations

This appendix provides detailed calculations used to derive the human cancer slope factor based on animal data, including breathing rates for animal models, exposure adjustments, and body weight scaling.

Calculations for Table 5:

Cancer slope factor (CSF) calculation for squamous cell carcinomas or papillomas in male rat stomach or forestomach following exposure to DBCP via feed (Hazleton 1977, 1978):

CSF_{animal} = 0.05/0.44 mg/kg-day = 0.11 $(mg/kg\text{-}day)^{-1}$

$CSF_{human} = CSF_{animal} \times (BW_h/BW_a)^{1/4}$

$CSF_{human} = 0.11 \times (70\ kg/0.50\ kg)^{1/4} = 0.38\ (mg/kg\text{-}day)^{-1}$

CSF calculation for male rat hepatocellular carcinomas following exposure to DBCP via feed (Hazleton 1977, 1978):

$CSF_{animal} = 0.05/0.52 = 0.096\ (mg/kg\text{-}day)^{-1}$

$CSF_{human} = 0.096 \times (70/0.50)^{1/4} = 0.33\ (mg/kg\text{-}day)^{-1}$

CSF calculation for male rat renal tubular cell adenomas or carcinomas following exposure to DBCP via feed (Hazleton 1977, 1978):

$CSF_{animal} = 0.05/0.25 = 0.20\ (mg/kg\text{-}day)^{-1}$

$CSF_{human} = 0.20 \times (70/0.50)^{1/4} = 0.69\ (mg/kg\text{-}day)^{-1}$

CSF calculations for male rat multisite tumor analysis following exposure to DBCP via feed (Hazleton 1977, 1978):

CSF_{animal} = 0.05/0.17 mg/kg-day = 0.29 $(mg/kg\text{-}day)^{-1}$

$CSF_{human} = 0.29 \times (70/0.50)^{1/4} = 1.0\ (mg/kg\text{-}day)^{-1}$

Calculations for Table 9:

Inhalation rate (Appendix IV) for F344 rats is calculated as:

$I = 0.702 \times BW^{2/3}\ m^3/day$
$I = 0.702 \times (0.380)^{2/3}$
$I = 0.702 \times 0.525$
$I = 0.368\ m^3/day$

CSF calculation for F344/N male rat nasal cavity squamous cell carcinomas or papillomas following inhalation exposure to DBCP (NTP, 1982):

$BMDL_{05(animal)}$ = [0.103 ppm × 9.67 (mg/m^3)/ppm × 6 hours/24 hours × 5 days/7 days × 0.368 m^3/day × 50% absorption]/0.380 kg

= 0.085 mg/kg-day

CSF_{animal} = 0.05/0.085 mg/kg-day = 0.59 $(mg/kg\text{-}day)^{-1}$

CSF_{human} = 0.59 × $(70/0.38)^{1/4}$ = 2.2 $(mg/kg\text{-}day)^{-1}$

CSF calculation for F344/N male rat nasal cavity adenomas, adenocarcinomas, or carcinomas following inhalation exposure to DBCP (NTP, 1982):

$BMDL_{05(animal)}$ = [0.0643 ppm × 9.67 (mg/m^3)/ppm × 6 hours/24 hours × 5 days/7 days × 0.368 m^3/day × 50% absorption]/0.380 kg

= 0.0533 mg/kg-day

CSF_{animal} = 0.05/0.0533 = 0.94 $(mg/kg\text{-}day)^{-1}$

CSF_{human} = 0.94 × $(70/0.38)^{1/4}$ = 3.5 $(mg/kg\text{-}day)^{-1}$

CSF calculation for F344/N male rat tongue squamous cell carcinomas or papillomas following inhalation exposure to DBCP (NTP, 1982):

$BMDL_{05(animal)}$ = [0.215 ppm × 9.67 (mg/m^3)/ppm × 6 hours/24 hours × 5 days/7 days × 0.368 m^3/day × 50% absorption]/0.380 kg

= 0.178 mg/kg-day

CSF_{animal} = 0.05/0.178 = 0.28 $(mg/kg\text{-}day)^{-1}$

CSF_{human} = 0.28 × $(70/0.38)^{1/4}$ = 1.0 $(mg/kg\text{-}day)^{-1}$

CSF calculation for F344/N male rat multisite tumor analysis following inhalation exposure to DBCP (NTP, 1982):

CSF_{animal} = 0.05/0.0284 mg/kg-day = 1.76 $(mg/kg\text{-}day)^{-1}$

CSF_{human} = 1.76 × $(70/0.38)^{1/4}$ = 6.5 $(mg/kg\text{-}day)^{-1}$

APPENDIX IV. Calculation of Rat Breathing Rate Based on Body weight

Rat breathing rate is a sensitive parameter in models used to characterize health risks, and predictive models of minute volume in rats are available in the peer-reviewed literature and in government reports. A comprehensive analysis of rat minute volume data has not been undertaken since 1988, and since that time, new methods to assess experimental animal breathing rates have been developed and implemented; these methods may more accurately reflect true resting rates of inhalation. Several programs within the Office of Environmental Health Hazard Assessment (OEHHA) use breathing rate equations to calculate doses from inhalation studies in rats based on the body weights of the animals studied. In an effort to refine and update the approach used to calculate rat breathing rates for use in dose response assessments, OEHHA:

- reviewed the data used to derive the primary equations previously used by OEHHA programs
- conducted a focused literature search for recent studies containing information on inhalation rates
- identified the subset of high-quality study data (defined below) from literature search results and from the set of previously reviewed studies that best captures breathing rates of rats at rest
- used the high-quality data subset to derive a new inhalation rate equation by fitting a model of the form

  $$I = a \times (bw)^{2/3},$$

  where a is a parameter to be estimated and *bw* represents body weight.

While the initial effort of the working group was limited to studies in rats, OEHHA anticipates conducting similar efforts to develop equations for calculating breathing rates for other species.

Review of previously used equations

There are two primary equations that have been used by OEHHA programs to calculate inhalation rates in rats. Anderson et al. (1983) derived the equation

$$I = 0.105 \times \left(\frac{bw}{0.113}\right)^{2/3}$$ in m^3/day

based on data from Guyton et al. (1947), which showed that rats with an average weight of 0.113 kg breathe 105 L/day (= 0.105 m^3/day). The US Environmental Protection Agency (US EPA 1988a and 1994) derived the equation $I = 0.80 \times bw^{0.8206}$ in m^3/day by fitting a linear model of the form $\ln IR = \beta_0 + \beta_1 \times \ln bw$ to data from several studies in rats, the most recent of which was published in 1986.

The working group identified several key limitations inherent in these equations:

- The Anderson et al. (1983) equation was informed by data from a single study.

- Some of the data used for the US EPA (1988a and 1994) equation included transcription errors (e.g., duplicates, typographical errors).
- Both equations lack data from recent studies (i.e., studies conducted in the last 31 years).
- Some data used in the derivation of both equations come from studies which employed methods that are thought to alter normal physiological conditions, such as anesthetization, cannulation, and restraint.

In light of these issues, OEHHA concluded that a thorough examination of the data used to derive the Anderson et al. (1983) and US EPA (1988a and 1994) equations should be undertaken, and that a literature search should be conducted to identify any new studies.

Literature search

A literature search was conducted to identify recent studies reporting rat inhalation rates under normal physiological conditions. Searches were conducted in PubMed and in targeted journals, including Inhalation Toxicology, Journal of Applied Physiology, Journal of Physiology, Journal of Toxicology and Environmental Health, Respiration Physiology, Respiratory Physiology & Neurobiology, and Toxicological Sciences. Literature was identified using relevant search terms including “ventilation rates,” “minute volume,” “minute ventilation,” “inhalation rates,” and “rats.”

Selection of studies for new subset

An initial set of studies was compiled that included the studies in the US EPA 1988a (Blackburn) report, studies in the US EPA 1988b (Arms and Travis) report, and studies from the literature search described above. From the search results, a set of 250 articles published by December 2017 was retrieved for detailed review.

The working group determined that the highest quality data for analysis of rat inhalation rates would measure breathing in rats under as normal physiological conditions as possible. In order to be considered for inclusion, a study must have reported average body weight measured in temporal proximity to minute volume. High quality studies would include indicators that the animals were quiet and breathing evenly. The highest quality data would include adult animals from strains typical of toxicity studies. Adult animals were considered to be those approximately seven weeks of age or older. In the absence of reported age of animals, OEHHA decided to include the studies where the average body weight clearly indicates adulthood for that strain and gender. In consideration of these factors, most studies in which animals were very young or of strains not commonly used in toxicity testing or genetically modified to be pre-disposed for certain diseases were excluded, as were most studies in which animals were anesthetized during measurements and/or underwent tracheal cannulation prior to measurements. Prior anesthesia and prior surgical procedures were acceptable, so long as the procedures were minor and there was sufficient recovery time for animals prior to inhalation rate measurements. Generally, data from studies involving restrained

animals were included only if the authors indicated that an acclimation period took place following restraint, or otherwise established stable ventilation. Other factors that may influence inhalation rates, such as room temperature, relative humidity, lighting conditions, and others, were not consistently reported across studies and consequently were not part of the criteria considered for inclusion in the high quality data subset.

The working group identified some studies that did not meet a strict application of the previous criteria, but were included where it could be established that the animals reached a reasonably normal physical condition for at least some measurements. For example, the working group decided to include data from Whitehead et al. (1999) in which animals were subjected to light anesthesia. Data from a study conducted by Olson and Dempsey (1978) were also included despite the fact that the animals underwent a cannulation procedure[13] because the authors stated that the animals had a two-week recovery period following cannulation before inhalation rate measurements were recorded. The working group evaluated 250 studies for inclusion using the criteria described previously. Ultimately, 49 studies were determined to contain data that met the selection criteria and 88 data points from these studies were used for modeling. Note that where studies included repeat measures on the same animals in close temporal proximity, a single data point was selected. Listed below are the final subset of studies included in this analysis:

Bairam et al., 2009
Bavis et al., 2006
Chen et al., 1989
Colman and Miller, 2001
Cummings and Heitcamp, 1981
Cyphert et al., 2015
Cyphert et al., 2016
Donovan et al., 2011
Doperalski et al., 2008
Dye et al., 2015
Forster et al., 2003
Gamboa et al., 2003
Genest et al., 2004
Goineau et al., 2010
Gordon et al., 2010
Gordon et al., 2013
Guyton, 1947
Haouzi et al., 2009
Henderson et al., 2014
Hodges et al., 2013
Holley et al., 2012
Iiyori et al., 2003
Kuo et al., 2011
Lai et al., 1978
Leavens et al., 2006
Leong et al., 1964
Lin et al., 1983
Liu et al., 2011
Olson and Dempsey, 1978
Mantilla et al., 2011
Mauderly et al., 1979
Mauderly, 1986
Mautz and Bufalino, 1989
Pauluhn and Thiel, 2007
Polianski et al., 1984
Schlenker, 2016
Seifert and Mortola, 2002
Shore et al., 2000
Silva et al., 2017
Snow et al., 2017
Soulage et al., 2004
Strohl et al., 1997
Tsuji et al., 2011
Walker et al., 1985
Wenninger et al., 2006
Whitehead et al., 1999
Wiester et al., 1988
Xu et al., 2014
Young et al., 2013

[13] One to two weeks prior to initial control measures, rats were anesthetized and a chronically indwelling catheter was placed through the femoral artery of each rat into the abdominal aorta distal to the renal arteries and connected to an opening in the upper neck where the catheter was secured to an adhesive collar.

Model fitting

The selected model, $I = a \times bw^{2/3}$, raises the animal body weight (in kilograms, kg) from the study in question to the ⅔ power (a commonly used allometric scaling ratio), and this quantity is multiplied by a constant informed by breathing rate data (Table A5). The equation is set to intercept the origin (which is biologically appropriate when predicting inhalation rates based on body weight).

A weighted regression was used since the data being modeled in this analysis were means from samples of different sizes. In situations with aggregated data such as this, heterogeneous variance is expected, and applying weights allows the model fitting software to prioritize fit to data points with greater weights. When the variance associated with each data point is unknown (as in this case) and when heterogeneity is thought to arise from differences in sample sizes, a common approach is to base the weights on the sample sizes themselves. In this way, data points derived from studies with larger sample sizes, which are expected to have smaller variance, have greater weights than data points derived from studies with smaller sample sizes, which are expected to have larger variance. The weights used in this analysis were:

$$w_i = \frac{N \times T_i}{\sum T_i}$$

where N = number of data points and T_i = sample size for study *i*. This method ensures that the weights sum to N and studies with the same sample size have the same weight.

Analyses were performed in R (Version 3.4.2).[14] The resulting weighted regression model equation was $I = 0.702 \times bw^{2/3}$ in unit of m^3/day and body weight in kg (adjusted $R^2 = 0.8347$; see later discussion regarding additional model diagnostics).

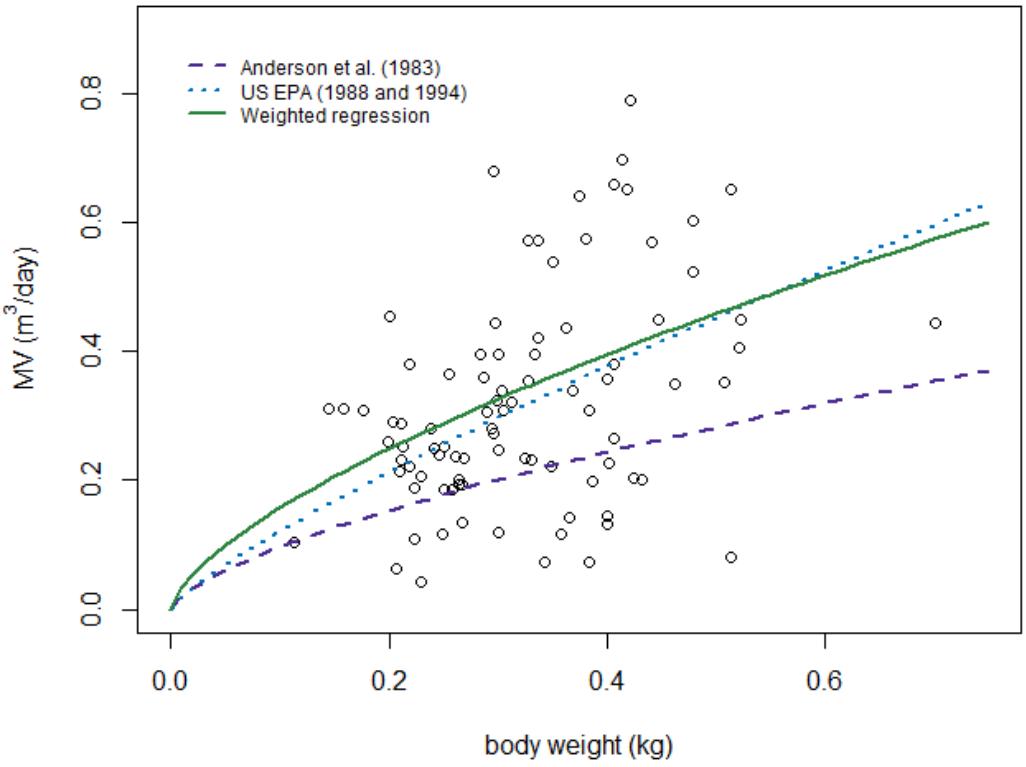
The plot below (Figure A5) shows how the fit of the equation from the weighted regression compares to the fit of the equations from Anderson et al. (1983) and US EPA (1988a and 1994) to the observations from the high quality data subset. The weighted regression equation better fits the full dataset than Anderson et al. (1983), which was based on a single data point, and provides a similar fit to the US EPA equation. OEHHA will rely on the equation below, since it is based on a robust and up-to-date set of high quality data that has been quality checked for typographical error:

$$I = 0.702 \times bw^{2/3} \text{ in } m^3/\text{day}$$

This equation will be used when it is necessary to calculate the breathing rate of rats in a study, based on their body weight, and when better information of breathing rate for the rats under test is not available.

[14] R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available from: https://www.R-project.org/.

Figure A5. Rat minute volume by body weight



Additional model diagnostics

As reported earlier, the weighted linear regression model described above generated an adjusted R^2 value of 0.8347, indicating that the model explains a substantial portion of the variation in the data, and the highly significant *p*-value for the F-statistic further supports this conclusion ($p < 0.0001$).

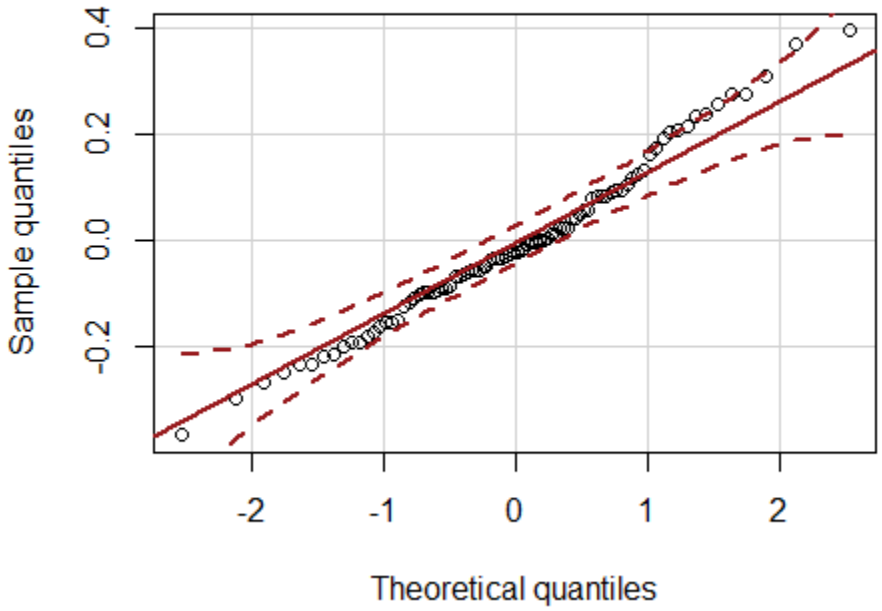
In assessing the overall suitability of the linear model and adequacy of fit, standard diagnostic plots were used to check the assumptions of normally distributed errors, independence of observations[15], linearity of relationship, and homogeneity of variance. To begin, the quantile-quantile plot of the residuals[16] (Figure A6) shows that the points follow the solid line fairly well, with a slight but progressive divergence from the true

[15] While many different studies from the literature are represented in the data used for this regression analysis, multiple values were reported and used from some studies (e.g. different rates for males and females, different rates for different strains of rat, etc.) so the independence of observations is not necessarily implied.

[16] Produced using the qqPlot() function in the 'car' package:
Fox J and Weisberg S (2011). An {R} Companion to Applied Regression, Second Edition. Thousand Oaks CA: Sage. Available from: http://socserv.socsci.mcmaster.ca/jfox/Books/Companion

normal distribution in the right tail, shown by points located on or slightly outside the dashed 95% confidence bounds. Overall, the plot does not provide strong evidence against the assumption that the errors are normally distributed.

Figure A6. Quantile-quantile plot of residuals



In Figure A7 showing the standardized residuals from the weighted regression plotted against the fitted values, the overlaid smoothing spline helps to visualize the fact that the magnitude of the standardized residuals is not changing with the level of the fitted values in an appreciable pattern or in a manner that would suggest nonlinearity or dependence. Further, the relatively evenly scattered distribution of the values around y = 0 indicates that the variance of the observed data is consistent with the weights used. There are a couple of relatively large residuals but close examination of the individual study data does not point to any reason to classify the corresponding observations as outliers and remove them from the analysis. Overall, the diagnostic plots indicate that the model fits the data adequately.

Figure A7. Standardized residuals against fitted values

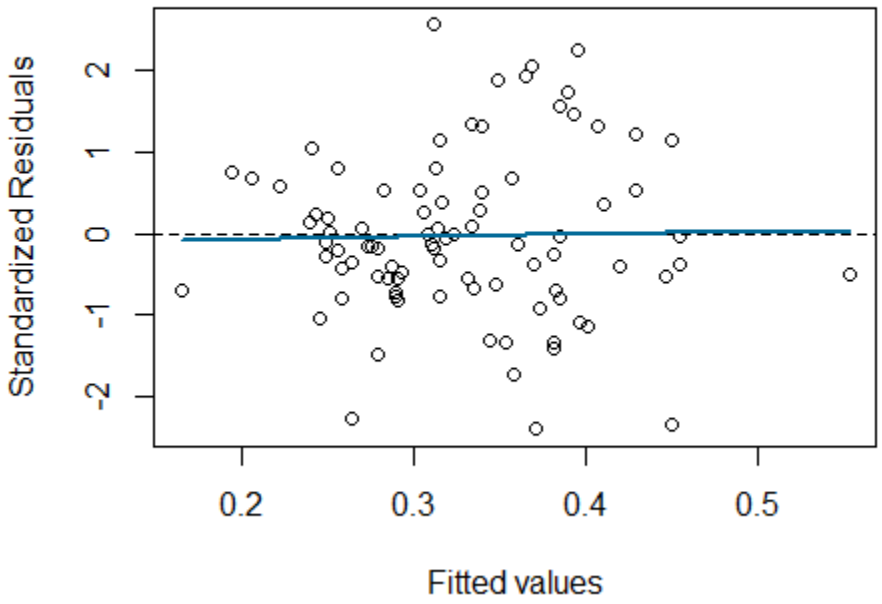


Table A5. Data used for model fitting

Strain	Sex	BW (kg)	MV observed (L/min)	MV observed (m3/day)	Sample size	Reference
White rat	Not specified	0.113	0.073	0.105	35	Guyton (1947)
F344/Crl Lov	F	0.145	0.216	0.311	10	Mauderly (1986)
Brown Norway	M	0.158	0.217	0.312	10	Hodges et al. (2013)
Brown Norway	M	0.177	0.216	0.310	11	Hodges et al. (2013)
F344/Crl Lov	F	0.199	0.181	0.261	10	Mauderly (1986)
Sprague-Dawley	F	0.200	0.315	0.454	6	Xu et al. (2014)
Sprague-Dawley	M	0.203	0.202	0.291	6	Hodges et al. (2013)
Sprague-Dawley	F	0.206	0.043	0.062	8	Schlenker (2016)
Sprague-Dawley	M	0.210	0.148	0.213	15	Seifert and Mortola (2002)
Wistar	M	0.211	0.162	0.233	10	Leong et al. (1964)
Sprague-Dawley	M	0.212	0.201	0.289	6	Hodges et al. (2013)

Strain	Sex	BW (kg)	MV observed (L/min)	MV observed (m3/day)	Sample size	Reference
Wistar	M	0.213	0.175	0.252	11	Colman and Miller (2001)
F344/Crl Lov	F	0.219	0.154	0.222	10	Mauderly (1986)
F344/Crl Lov	M	0.219	0.264	0.380	10	Mauderly (1986)
Sprague-Dawley	F	0.223	0.075	0.108	7	Holley et al. (2012)
Long-Evans	F	0.223	0.131	0.189	9	Whitehead et al. (1999)
Holzman	M	0.230	0.143	0.206	9	Gamboa et al. (2003)
Brown Norway (Mcw)	M&F	0.230	0.029	0.042	26	Forster et al. (2003)
Wistar	M&F	0.238	0.194	0.279	8	Pauluhn and Thiel (2007)
Sprague-Dawley	M	0.242	0.174	0.251	11	Cummings and Heitcamp (1981)
Fischer 344/N	F	0.246	0.167	0.240	5	Chen et al. (1989)
Brown Norway	M&F	0.250	0.081	0.117	21	Strohl et al. (1997)
Sprague-Dawley	F	0.251	0.175	0.252	11	Cummings and Heitcamp (1981)
Sprague-Dawley	F	0.251	0.130	0.187	8	Bavis et al. (2006)
F344/Crl Lov	F	0.255	0.254	0.366	10	Mauderly (1986)
Sprague-Dawley	M	0.258	0.129	0.186	8	Mautz and Bufalino (1989)
Sprague-Dawley	F	0.261	0.164	0.236	15	Genest et al. (2004)
Sprague-Dawley	M	0.264	0.139	0.193	16	Mautz and Bufalino (1989)
Sprague-Dawley	M	0.264	0.134	0.200	16	Mautz and Bufalino (1989)
Sprague-Dawley	F	0.267	0.134	0.134	7	Doperalski et al. (2008)
Sprague-Dawley	M	0.267	0.134	0.193	8	Mautz and Bufalino (1989)
CD IGS	F	0.269	0.162	0.233	16	Leavens et al. (2006)
Sprague-Dawley	M	0.284	0.276	0.397	8	Lai et al. (1978)
Sprague-Dawley	M	0.287	0.251	0.361	6	Young et al. (2013)
Sprague-Dawley	M	0.290	0.212	0.305	6	Young et al. (2013)
Sprague-Dawley	M	0.294	0.195	0.281	6	Young et al. (2013)
Sprague-Dawley	M	0.296	0.190	0.274	6	Polianski et al. (1984)

Strain	Sex	BW (kg)	MV observed (L/min)	MV observed (m3/day)	Sample size	Reference
Brown Norway	M	0.296	0.473	0.681	12	Gordon et al. (2010)
F344	M	0.297	0.309	0.445	9	Wiester et al. (1988)
Wistar	M	0.299	0.225	0.324	10	Leong et al. (1964)
Wistar	M	0.300	0.172	0.248	6	Walker et al. (1985)
Not specified	NS	0.300	0.275	0.396	48	Lin et al. (1983)
Sprague-Dawley	M	0.300	0.083	0.120	4	Mantilla et al. (2011)
Sprague-Dawley	M	0.303	0.236	0.340	67	Olson and Dempsey (1978)
Sprague-Dawley	M	0.305	0.214	0.308	8	Lai et al. (1978)
Sprague Dawley	M&F	0.312	0.224	0.322	14	Shore et al. (2000)
Wistar	M	0.325	0.163	0.234	8	Silva et al. (2017)
Sprague-Dawley	M	0.328	0.246	0.354	6	Henderson et al. (2014)
Wistar (Kyoto)	M	0.328	0.397	0.572	8	Dye et al. (2015)
Sprague-Dawley	M	0.330	0.161	0.232	11	Iiyori et al. (2003)
Sprague-Dawley	M	0.334	0.274	0.395	6	Henderson et al. (2014)
F344/Crl Lov	M	0.336	0.292	0.420	10	Mauderly (1986)
Wistar Kyoto	M	0.337	0.398	0.573	8	Dye et al. (2015)
Brown Norway	M	0.343	0.052	0.074	6	Donovan et al. (2011)
Sprague-Dawley	M	0.349	0.154	0.222	6	Liu et al. (2011)
F344	M	0.350	0.375	0.540	24	Cyphert et al. (2015)
Sprague-Dawley	M	0.358	0.081	0.117	8	Schlenker (2016)
Wistar	M	0.363	0.303	0.436	18	Snow et al. (2017)
Sprague-Dawley	M&F	0.365	0.100	0.143	16	Strohl et al. (1997)
F344/Crl Lov	M	0.368	0.236	0.340	10	Mauderly (1986)
Brown Norway	M	0.375	0.445	0.641	12	Gordon et al. (2010)
F344	M	0.381	0.400	0.576	24	Cyphert et al. (2015)
Long Evans	M&F	0.383	0.215	0.310	10	Mauderly et al. (1979)

Strain	Sex	BW (kg)	MV observed (L/min)	MV observed (m3/day)	Sample size	Reference
Sprague-Dawley (217)	Not Specified	0.384	0.050	0.072	16	Wenninger et al. (2006)
Sprague-Dawley	M	0.387	0.137	0.198	7	Holley et al. (2012)
Sprague-Dawley	M	0.400	0.248	0.357	25	Genest et al. (2004)
Wistar (Han)	M	0.400	0.092	0.132	8	Goineau et al. (2010)
Wistar (Han)	M	0.400	0.101	0.145	8	Goineau et al. (2010)
Fischer 344/N	M	0.402	0.159	0.228	5	Chen et al. (1989)
Sprague-Dawley	M	0.406	0.184	0.265	11	Bavis et al. (2006)
Wistar	M	0.406	0.459	0.661	8	Dye et al. (2015)
F344/Crl Lov	M	0.407	0.264	0.380	10	Mauderly (1986)
Wistar	M	0.414	0.484	0.698	8	Dye et al. (2015)
Sprague-Dawley	M	0.419	0.452	0.651	8	Dye et al. (2015)
Sprague-Dawley	M	0.422	0.549	0.790	8	Dye et al. (2015)
Sprague-Dawley	M	0.424	0.141	0.204	8	Kuo et al. (2011)
Sprague-Dawley	M	0.432	0.200	0.200	8	Doperalski et al. (2008)
F344	M	0.441	0.396	0.570	16	Cyphert et al. (2015)
F344	M	0.447	0.313	0.451	18	Cyphert et al. (2015)
Sprague-Dawley	M	0.462	0.243	0.350	8	Tsuji et al. (2011)
Brown Norway	M	0.479	0.419	0.524	8	Cyphert et al. (2016)
F344	M	0.479	0.364	0.603	12	Gordon et al. (2010)
Sprague-Dawley	M	0.507	0.245	0.353	8	Tsuji et al. (2011)
Brown Norway	M	0.514	0.453	0.081	10	Donovan et al. (2011)
Sprague-Dawley	M	0.514	0.056	0.652	8	Gordon et al. (2013)
Sprague-Dawley	M	0.521	0.282	0.406	15	Bairam et al. (2009)
Wistar	M	0.522	0.313	0.451	10	Soulage et al. (2004)
Sprague-Dawley	M	0.701	0.308	0.444	5	Haouzi et al. (2009)

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APPENDIX V. Default Uncertainty Factors for PHG Derivation

This appendix describes the default uncertainty factors OEHHA generally uses to calculate the Acceptable Daily Dose when deriving PHGs. When scientific evidence is compelling, these defaults are supplanted by alternative factors or modeled results. Table A6 below is adapted from OEHHA's "Technical Support Document for the Development of Noncancer Reference Exposure Levels" (OEHHA, 2008).

Table A6. Default uncertainty factors for PHG derivation, adapted from OEHHA (2008)

LOAEL uncertainty factor (UF_L)	
Values used:	10 LOAEL, any effect 1 NOAEL or BMDL used
Interspecies uncertainty factor (UF_A)	
Combined interspecies uncertainty factor (UF_A):	1 human observation √10 animal observation in nonhuman primates 10 where no data are available on toxicokinetic or toxicodynamic differences between humans and a non-primate test species
Toxicokinetic component (UF_{A-k}) of UF_A:	1 where animal and human PBPK models are used to describe interspecies differences √10 nonprimate studies with no chemical or species specific kinetic data
Toxicodynamic component (UF_{A-d}) of UF_A:	1 where animal and human mechanistic data fully describe interspecies differences (*This is unlikely to be the case.)* 2 for residual susceptibility differences where there are some toxicodynamic data √10 nonprimate studies with no data on toxicodynamic interspecies differences
Intraspecies uncertainty factor (UF_H)	
Toxicokinetic component (UF_{H-k}) of UF_H:	1 human study including sensitive subpopulations (e.g., infants and children), or where a PBPK model is used and accounts for measured interindividual variability √10 for residual susceptibility differences where there are some toxicokinetic data (e.g., PBPK models for adults only) 10 to allow for diversity, including infants and children, with no human kinetic data

Toxicodynamic component (UF_{H-d}) of UF_H:	1 human study including sensitive subpopulations (e.g., infants and children) √10 studies including human studies with normal adult subjects only, but no reason to suspect additional susceptibility of children 10 suspect additional susceptibility of children (e.g., exacerbation of asthma, neurotoxicity)
Subchronic uncertainty factor (UF_S)[1]	
Values used:	1 study duration >12% of estimated lifetime √10 study duration 8-12% of estimated lifetime 10 study duration <8% of estimated lifetime
Database deficiency factor (UF_D)	
Values used:	1 no substantial data gaps √10 substantial data gaps including, but not limited to, developmental toxicity

[1]Exposure durations of 13 weeks or less are subchronic regardless of species (OEHHA, 2008)

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APPENDIX VI. Adjustment for Early-in-Life Exposures

OEHHA accounts for the increased susceptibility of children and infants to carcinogens by applying age sensitivity factors (ASFs) to the cancer potency (OEHHA, 2009). Age-specific cancer risk is calculated for each age group by multiplying the cancer potency, age-specific exposure estimates (duration times intake rate), the concentration in drinking water and the ASF, where:

R	=	Total risk
C	=	Concentration in water
p_{oral}	=	Oral cancer potency
p_{inh}	=	Inhalation cancer potency
ASF_1	=	Age sensitivity factor for 3rd trimester + infancy, value 10
ASF_2	=	Age sensitivity factor for childhood (ages 2-16), value 3
ASF_3	=	Age sensitivity factor for adult (ages 16-70), value 1.

For this calculation, the duration (d) of sensitive periods is expressed as fractions of the standard lifetime of 70 years as follows:

d_0	=	3rd trimester, value 0.25/70
d_1	=	infancy, value 2/40
d_2	=	childhood, value 14/70
d_3	=	adult, value 54/70.

The equivalent water exposure values (Daily Drinking Water Intake or DWI, expressed in terms of L_{eq}/kg-day) for each age range are expressed as follows:

DWI^o_1	=	Oral route, infancy
DWI^o_2	=	Oral route, childhood
DWI^o_3	=	Oral route, adult
DWI^i_2	=	Inhalation route, childhood
DWI^i_3	=	Inhalation route, adult.

For the risk equation, the overall lifetime risk is the sum of the cancer risk for each age bin and route. Note that for the third trimester of pregnancy, the ASF_1 for early-in-life exposures is applicable, but the consumption rate is assumed to be that of an adult (i.e., maternal consumption). Also, infants are assumed not to take showers, but mothers do. Then,

$$
\begin{aligned}
R = {} & (p_{oral} \times ASF_1 \times d_0 \times DWI^o_3 \times C) + \\
& (p_{oral} \times ASF_1 \times d_1 \times DWI^o_1 \times C) + \\
& (p_{oral} \times ASF_2 \times d_2 \times DWI^o_2 \times C) + \\
& (p_{oral} \times ASF_3 \times d_3 \times DWI^o_3 \times C) + \\
& (p_{inh} \times ASF_1 \times d_0 \times DWI^i_3 \times C) +
\end{aligned}
$$

$$(p_{inh} \times ASF_2 \times d_2 \times DWI^i_2 \times C) +$$
$$(p_{inh} \times ASF_3 \times d_3 \times DWI^i_3 \times C) + \qquad \text{Equation 1}$$

This can be simplified by taking the common factor C outside a top-level bracket, and the common factors p_{oral} and p_{inh} can be taken outside second-level brackets:

$$R = C \times \left[p_{oral} \times \begin{pmatrix} ASF_1 \times d_0 \times DWI^o_3 + \\ ASF_1 \times d_1 \times DWI^o_1 + \\ ASF_2 \times d_2 \times DWI^o_2 + \\ ASF_3 \times d_3 \times DWI^o_3 \end{pmatrix} + p_{inh} \times \begin{pmatrix} ASF_1 \times d_0 \times DWI^i_3 + \\ ASF_2 \times d_2 \times DWI^i_2 + \\ ASF_3 \times d_3 \times DWI^i_3 + \end{pmatrix} \right]$$

Equation 2

It is important to note that the calculation cannot be simplified further to any important degree, since there are no other persistent common factors inside the second-level brackets. In other words, an accurate result cannot be achieved by summing consumption values and adjustment factors separately and then multiplying the results together.

Rearranging Equation 2:

$$C = \frac{R}{p_{oral} \times \begin{pmatrix} ASF_1 \times d_0 \times DWI^o_3 + \\ ASF_1 \times d_1 \times DWI^o_1 + \\ ASF_2 \times d_2 \times DWI^o_2 + \\ ASF_3 \times d_3 \times DWI^o_3 \end{pmatrix} + p_{inh} \times \begin{pmatrix} ASF_1 \times d_0 \times DWI^i_3 + \\ ASF_2 \times d_2 \times DWI^i_2 + \\ ASF_3 \times d_3 \times DWI^i_3 \end{pmatrix}}$$

Equation 3

The PHG is determined by solving Equation 3 for $R = 10^{-6}$.

Reference

OEHHA (2009). Technical Support Document for Cancer Potency Factors: Methodologies for Derivation, Listing of Available Values, and Adjustments to Allow for Early Life Stage Exposures. Appendix J. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.