Public Health Goal

FIRST PUBLIC REVIEW DRAFT

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

March 2019

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
Proposed Public Health Goal for 1,2-Dibromo-3-Chloropropene in Drinking Water

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Prepared by
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Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
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.
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 proposed updated PHG of 0.002 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 is essentially the same as the original PHG value of 0.0017 ppb rounded and remains lower than the current California MCL of 0.2 ppb. OEHHA also proposes to retain the 1999 health-protective concentration of 0.2 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. 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), 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.

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 mathematical 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, 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
  - √10 for pharmacodynamics
  - √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
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 Leq/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 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

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\(^3\) Available at: [https://www.dtsc.ca.gov/AssessingRisk/caltox.cfm](https://www.dtsc.ca.gov/AssessingRisk/caltox.cfm)
reduced to the form reported in units of 1/(mg/kg-day) or (mg/kg-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.

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 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:

\[ p(d) = \beta + (1 - \beta) \times \exp\left[-(q_1d + q_2d^2 + \ldots + q_id^i)\right] \]

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, \( \beta, q_1, q_2, \) and \( q_3 \). When dose is expressed in units of mg/kg-day, \( q_1 \) is given in units of \((\text{mg/kg-day})^{-1}\). The \( q_1 \) parameter is, for small doses, the ratio of excess lifetime cancer risk to the average daily dose received. The parameter \( \beta \) 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 \( \beta \)).

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\(_{\text{human}}\)) 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\(_{\text{animal}}\) 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 \((\text{mg/kg-day})^{-1}\):

\[ \text{CSF}_{\text{human}} = \text{CSF}_{\text{animal}} \times \left(\frac{\text{body weight}_{\text{human}}}{\text{body weight}_{\text{animal}}}\right)^{1/4} \]

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

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Fractional Duration(^a) (d)</th>
<th>Age Sensitivity Factor (ASF)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3(^{rd}) Trimester</td>
<td>0.25/70</td>
<td>10</td>
</tr>
<tr>
<td>Infant (0-2 yr)</td>
<td>2/70</td>
<td>10</td>
</tr>
<tr>
<td>Child (2-16 yr)</td>
<td>14/70</td>
<td>3</td>
</tr>
<tr>
<td>Adult (16-70 yr)</td>
<td>54/70</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^a\)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 Leq/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:

\[
C = \frac{R}{CSF_{oral} \times (\sum_i[ASF_i \times d_i \times DWI_{oral,i}]) + CSF_{inh} \times (\sum_i[ASF_i \times d_i \times DWI_{inh,i}])}
\]

Where:

- \(R\) = default risk level of one in one million, or \(10^{-6}\)
- \(CSF_{oral}\) = oral cancer slope factor, in (mg/kg-day\(^{-1}\))
- \(CSF_{inh}\) = inhalation cancer slope factor, in (mg/kg-day\(^{-1}\))
- \(\sum_i\) = sum of contributions at each age range
- \(ASF_i\) = age sensitivity factors for the 3\(^{rd}\) trimester + infants, children, and adults
- \(d_i\) = duration of exposure for the 3\(^{rd}\) trimester + infant, child, and adult life stages
- \(DWI_{inh/oral,i}\) = 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-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 (Leq) per day (2 L for oral ingestion, 2 Leq to account for dermal exposure, 2 Leq 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 Leq/day.
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 found sperm were unable to penetrate zona-free hamster oocytes at both concentrations and motility was low at the highest concentration (p<0.05). 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 a Group 2B4 carcinogen (possible human carcinogen) based upon 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. This selection is still valid for the current evaluation.

 Although the Rao et al. (1982) data set in Table 2 were used to derive the POD in 1999, the reported effect lacked statistical significance for either dose group when compared to the control group (one-way ANOVA, p=0.19). However, OEHHA's current dose-response analysis with benchmark dose software (BMDS version 2.5, US EPA) demonstrates that these data can be modeled. Using continuous models with a BMR of one standard deviation (SD) from the control mean and modeled variance, the resulting BMDL1SD is 0.07 ppm (Appendix I), which is very close to the NOAEL of 0.1 ppm.

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

<table>
<thead>
<tr>
<th>DBCP Concentration</th>
<th>Number of Animals</th>
<th>% Abnormal Spermatozoa (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ppm</td>
<td>2</td>
<td>5 ± 3%</td>
</tr>
<tr>
<td>0.1 ppm</td>
<td>4</td>
<td>10 ± 3%</td>
</tr>
<tr>
<td>1.0 ppm</td>
<td>4</td>
<td>18 ± 12%</td>
</tr>
</tbody>
</table>

OEHHA’s current review of the reproductive toxicity studies for DBCP has identified a second data set from the same study (Rao et al., 1982) that could be used to derive the POD for noncancer effects. Fourteen weeks of DBCP exposure resulted in ultrastructural abnormalities in rabbit spermatozoa, as shown in Tables 2 and 3. Following a 32-week recovery period, a statistically significant increase in abnormal spermatozoa was still observed in the 1.0 ppm exposure group (Table 3), 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.

Table 3. Percent abnormal spermatozoa in rabbits following inhalation exposure to DBCP for 14 weeks plus 32 weeks recovery (Rao et al., 1982)

<table>
<thead>
<tr>
<th>DBCP Concentration</th>
<th>Number of Animals</th>
<th>% Abnormal Spermatozoa (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ppm</td>
<td>6</td>
<td>5 ± 3%</td>
</tr>
<tr>
<td>0.1 ppm</td>
<td>3</td>
<td>6 ± 2%</td>
</tr>
<tr>
<td>1.0 ppm</td>
<td>3</td>
<td>24 ± 10%*</td>
</tr>
</tbody>
</table>

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

BMD modeling of the dataset with the 32-week recovery period (Table 3) produced two models with adequate fit (Appendix I). Although Exponential Model 2 has the lowest AIC value, the Linear model produces the more health protective BMDL, with an AIC that is relatively close to the one for Exponential Model 2. Furthermore, the BMDL_{1SD} of 0.08 ppm from this data set (Table 3), which shows statistical significance at the high dose, is supported by the BMDL_{1SD} of 0.07 ppm derived from the dataset with no recovery period (Table 2). The BMDL_{1SD} of 0.08 ppm is very close to the NOAEL of 0.1 ppm used to derive the previous POD for the 1999 health-protective concentration. Modeling results and the Linear model output are presented in Appendix I.

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 cancer slope factor (CSF) of 7 (mg/kg-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.

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)

<table>
<thead>
<tr>
<th>Sex/Species</th>
<th>Tumor site and type</th>
<th>Dose (mg/kg-day)</th>
<th>Control</th>
<th>0.24</th>
<th>0.80</th>
<th>2.39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Rat</td>
<td>Squamous cell carcinoma or papilloma of stomach or forestomach</td>
<td>0/48***</td>
<td>0/46</td>
<td>3/46</td>
<td>21/41**</td>
<td></td>
</tr>
<tr>
<td>Female Rat</td>
<td>Squamous cell carcinoma or papilloma of stomach or forestomach</td>
<td>0/48***</td>
<td>0/45</td>
<td>0/47</td>
<td>10/43**</td>
<td></td>
</tr>
<tr>
<td>Male Mice</td>
<td>Squamous cell carcinoma of stomach or forestomach</td>
<td>0/50***</td>
<td>N/A</td>
<td>N/A</td>
<td>26/49**</td>
<td></td>
</tr>
<tr>
<td>Female Mice</td>
<td>Squamous cell carcinoma of stomach or forestomach</td>
<td>0/50***</td>
<td>0/50*</td>
<td>N/A</td>
<td>5/49*</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Sex/Species</th>
<th>Tumor Site and Type</th>
<th>BMDL_{05(\text{animal})} (mg/kg-day)</th>
<th>CSF_{\text{animal}} (mg/kg-day)\textsuperscript{a}</th>
<th>CSF_{\text{human}}\textsuperscript{a,b} (mg/kg-day)\textsuperscript{a}</th>
<th>Model p-value</th>
<th>Polynomial Degree\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Rat</td>
<td>Stomach or forestomach squamous cell carcinoma or papilloma</td>
<td>0.44</td>
<td>0.11</td>
<td>0.39</td>
<td>0.94</td>
<td>2\textsuperscript{nd}</td>
</tr>
<tr>
<td>Male Rat</td>
<td>Hepatocellular carcinoma</td>
<td>0.52</td>
<td>0.096</td>
<td>0.33</td>
<td>0.97</td>
<td>1\textsuperscript{st}</td>
</tr>
<tr>
<td>Male Rat</td>
<td>Renal tubular cell adenoma or carcinoma</td>
<td>0.25</td>
<td>0.20</td>
<td>0.69</td>
<td>0.99</td>
<td>2\textsuperscript{nd}</td>
</tr>
<tr>
<td>Male Rat</td>
<td>Multisite tumor analysis</td>
<td>0.17</td>
<td>0.29</td>
<td>1.0</td>
<td>n/a\textsuperscript{d}</td>
<td>n/a</td>
</tr>
<tr>
<td>Male Mice</td>
<td>Squamous cell carcinoma of the stomach or forestomach</td>
<td>0.24</td>
<td>0.21</td>
<td>3.2\textsuperscript{e}</td>
<td>1</td>
<td>1\textsuperscript{st}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Calculations are shown in Appendix III.

\textsuperscript{b} Assumes a male rat body weight of 0.5 kg,\textsuperscript{5} male mouse body weight of 0.041 kg, and default human body weight of 70 kg

\textsuperscript{c} Degree of polynomial in the Multistage-Cancer model that best characterizes the dose-response relationship

\textsuperscript{d} n/a, not applicable

\textsuperscript{e} Includes adjustment of (104/78)\textsuperscript{3} to account for early mortality

\textsuperscript{5} The strain of rat is listed as “Charles River rats.” Because of the time period in which the study was conducted, it is likely referencing Wistar rats. Based on growth charts available from Charles River Laboratories, the mean body weight of an adult male Wistar rat is 0.5 kg.
BMD modeling was performed on the data for individual tumor types in male and female rats and mice shown in Table 4, using the BMDS Multistage-Cancer model with a BMR of 5%. 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 was also performed and included all significant tumor types in male rats. Multisite analyses are used to calculate the risk for developing any combination of tumors at any site when more than one tumor type is observed, and assume 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.

The CSF is calculated as follows:

\[
CSF = \frac{\text{BMR}}{\text{BMDL}05} = \frac{0.05}{\text{BMDL}05}.
\]

Calculations used to derive the CSF for both male rats and male mice are shown in Appendix III. From male rat data in this study (Hazleton Laboratories, 1977), the estimated human multisite cancer potency is 1.0 (mg/kg-day)⁻¹. For male mice, an adjustment was included to account for the reduced study time of 78 weeks. The estimated human cancer potency based on squamous cell carcinomas of the stomach or forestomach in male mice is 3.2 (mg/kg-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 stomach, 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)

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

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)

<table>
<thead>
<tr>
<th>Tumor Site and Type</th>
<th>Dose (mg/kg-day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control(^a)</td>
</tr>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>Forestomach squamous cell carcinoma</td>
<td>0/20(^*)</td>
</tr>
<tr>
<td>Males</td>
<td>Control(^a)</td>
</tr>
<tr>
<td>Forestomach squamous cell carcinoma</td>
<td>0/20(^*)</td>
</tr>
</tbody>
</table>

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 are much higher than the BMR of 5%, thus CSFs are not estimated for these studies.

The oral CSF of 7.0 (mg/kg-day\(^{-1}\)) (CDHS, 1988; OEHHA, 1999) used in the 1999 PHG calculation was based on squamous cell carcinomas in the stomach or forestomach in male mice exposed to DBCP in the diet (Hazleton Laboratories, 1977). OEHHA re-analyzed this dataset using current methodology, which included changing the default body scaling factor from the ratio of animal to human body weight to the \(\frac{3}{2}\) power to the same animal-human body weight ratio to the \(\frac{3}{4}\) power,\(^6\) and using benchmark dose modeling software. The current methodologies, when applied to the same dataset, give an updated oral CSF of 3.2 (mg/kg-day\(^{-1}\)).

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

---

\(^6\) OEHHA (2009) adopted the use of body weight scaling to the \(\frac{3}{4}\) power rather than to the \(\frac{3}{2}\) 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 (NTP, 1982)

<table>
<thead>
<tr>
<th>Site</th>
<th>Tumor type</th>
<th>Exposure (ppm)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control(^a)</td>
<td>0.6</td>
</tr>
<tr>
<td>Nasal Cavity</td>
<td>Squamous cell carcinoma</td>
<td>0/48.49***</td>
<td>2/47.57</td>
</tr>
<tr>
<td></td>
<td>Squamous cell papilloma</td>
<td>0/48.49</td>
<td>7/47.57**</td>
</tr>
<tr>
<td></td>
<td>Combined(^b)</td>
<td>0/48.49***</td>
<td>12/47.57</td>
</tr>
<tr>
<td>Nasal Cavity</td>
<td>Adenoma (NOS(^c))</td>
<td>0/48.49</td>
<td>9/47.57***</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma (NOS(^c))</td>
<td>0/48.49*</td>
<td>8/47.92***</td>
</tr>
<tr>
<td></td>
<td>Carcinoma (NOS(^c))</td>
<td>0/48.49***</td>
<td>2/47.83</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>0/48.49***</td>
<td>18/48.19***</td>
</tr>
<tr>
<td>Tongue</td>
<td>Squamous cell carcinoma</td>
<td>0/48.49**</td>
<td>0/47.57</td>
</tr>
<tr>
<td></td>
<td>Squamous cell papilloma</td>
<td>0/48.49***</td>
<td>1/48.10</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>0/48.49***</td>
<td>1/48.10</td>
</tr>
</tbody>
</table>

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)

\(^a\)Numerator indicates number of animals with tumor, denominator indicates number of animals adjusted for survival using poly-3 mortality adjustment

\(^b\)Includes turbinate and septum (NOS) 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 species specific inhalation rates (US EPA, 1994) to achieve adjusted BMDL\textsubscript{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, data from NTP (1982)

<table>
<thead>
<tr>
<th>Tumor Site and Type</th>
<th>BMDL\textsubscript{05(animal)}\textsuperscript{a} (mg/kg-day)</th>
<th>CSF\textsubscript{animal}\textsuperscript{a} (mg/kg-day)\textsuperscript{d}</th>
<th>CSF\textsubscript{human}\textsuperscript{a} (mg/kg-day)\textsuperscript{d}</th>
<th>Model p-value</th>
<th>Polynomial Degree\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal cavity squamous cell carcinoma or papilloma</td>
<td>0.085</td>
<td>0.59</td>
<td>2.2</td>
<td>0.46</td>
<td>1\textsuperscript{st}</td>
</tr>
<tr>
<td>Nasal cavity (NOS\textsuperscript{c}) adenoma, adenocarcinoma, or carcinoma</td>
<td>0.053</td>
<td>0.94</td>
<td>3.5</td>
<td>0.47</td>
<td>1\textsuperscript{st}</td>
</tr>
<tr>
<td>Tongue squamous cell carcinoma or papilloma</td>
<td>0.18</td>
<td>0.28</td>
<td>1.0</td>
<td>0.13</td>
<td>1\textsuperscript{st}</td>
</tr>
<tr>
<td>Multisite tumor analysis</td>
<td><strong>0.028</strong></td>
<td><strong>1.76</strong></td>
<td><strong>6.5</strong></td>
<td>n/a\textsuperscript{d}</td>
<td>n/a</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Calculations are shown in Appendix III. The BMDL\textsubscript{05(animal)} conversion from ppm to mg/kg-day for multisite tumor analysis is shown in the text below.
\textsuperscript{b} Degree of polynomial in the Multistage-Cancer model that best characterizes the dose-response relationship.
\textsuperscript{c} NOS, not otherwise specified
\textsuperscript{d} n/a, not applicable

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

BMDL\textsubscript{05(animal)} in ppm = \[\text{BMDL}_{05}\text{(animal)} \text{ in ppm} \times \text{UC} \times \text{ETA} \times \text{EFA} \times \text{BR} \times \text{AE}\]/\text{BW} = 0.0284 mg/kg-day

Where:
BMDL\textsubscript{05(animal)} in ppm = 0.034 ppm
UC = unit conversion factor, 9.67 (mg/m\textsuperscript{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\textsuperscript{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-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-day)-1. The inhalation CSF of 6.5 (mg/kg-day)-1 is more health-protective and is selected for PHG derivation for this route.

**HEALTH-PROTECTIVE DRINKING WATER CONCENTRATIONS**

*Noncancer Effects*

A POD of 0.08 ppm (Appendix I) is derived from benchmark dose modeling of the abnormal spermatozoa data following a recovery period reported by Rao et al. (1982). 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. However, 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 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).

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 apparently 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

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Oral Ingestion (%)</th>
<th>Inhalation (%)</th>
<th>Dermal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetus (pregnancy)</td>
<td>59</td>
<td>33</td>
<td>8</td>
</tr>
<tr>
<td>Infant</td>
<td>94</td>
<td>0a</td>
<td>6</td>
</tr>
<tr>
<td>Child</td>
<td>49</td>
<td>43</td>
<td>8</td>
</tr>
<tr>
<td>Adult</td>
<td>62</td>
<td>29</td>
<td>9</td>
</tr>
</tbody>
</table>

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 (Leq) 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

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Fractional Duration</th>
<th>Oral Ingestion (L/kg-day)</th>
<th>Inhalationa,b (Leq/kg-day)</th>
<th>Dermala (Leq/kg-day)</th>
<th>Total Exposure (Leq/kg-day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetus (pregnancy)</td>
<td>0.75/70</td>
<td>0.047</td>
<td>0.013</td>
<td>0.006</td>
<td>0.066</td>
</tr>
<tr>
<td>Infant</td>
<td>2/70</td>
<td>0.196</td>
<td>0</td>
<td>0.013</td>
<td>0.209</td>
</tr>
<tr>
<td>Child</td>
<td>14/70</td>
<td>0.061</td>
<td>0.027</td>
<td>0.010</td>
<td>0.098</td>
</tr>
<tr>
<td>Adult</td>
<td>54/70</td>
<td>0.045</td>
<td>0.010</td>
<td>0.007</td>
<td>0.062</td>
</tr>
</tbody>
</table>

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 Leq 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 Leq/kg-day.

A default relative source contribution (RSC) of 0.80 is used because DBCP was banned from agricultural uses in 1985 and tap water is anticipated to be the major source of exposure (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. As shown in Table 12, application of various methodological updates to the data from the Rao et al. (1982) critical study did not change the main calculation parameters considerably. Thus, OEHHA is retaining the 1999 health-protective concentration of 0.2 ppb for noncancer effects based on male rabbit reproductive toxicity.
Table 12. Noncancer health-protective concentration parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1999</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical Study and Endpoint</td>
<td>Rao et al. (1982), decreased sperm production and testicular atrophy</td>
<td>Rao et al. (1982), abnormal spermatozoa</td>
</tr>
<tr>
<td>Point of Departure (POD)</td>
<td>NOAEL of 0.1 ppm</td>
<td>BMDL_{1SD} of 0.08 ppm</td>
</tr>
<tr>
<td>Total Uncertainty Factor</td>
<td>1,000 (10 for interspecies extrapolation, 10 for intraspecies variability, 10 for extrapolating from subchronic to chronic exposure)</td>
<td>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)</td>
</tr>
<tr>
<td>Drinking Water Intake</td>
<td>6 L_{eq}/day</td>
<td>0.074 L_{eq}/kg-day (5.2 L_{eq}/day for a 70 kg adult)</td>
</tr>
<tr>
<td>Relative Source Contribution</td>
<td>0.80</td>
<td>0.80</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Age Sensitivity Factor (ASF)^a</th>
<th>Fractional Duration (d)</th>
<th>Daily Water Intake (DWI, L_{eq}/kg-day)^b</th>
<th>ASF \times d \times DWI (L_{eq}/kg-day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd trimester Fetus</td>
<td>10</td>
<td>0.25/70</td>
<td>0.053</td>
<td>0.002</td>
</tr>
<tr>
<td>Infant (0-2 yr)</td>
<td>10</td>
<td>2/70</td>
<td>0.209</td>
<td>0.060</td>
</tr>
<tr>
<td>Child (2-16 yr)</td>
<td>3</td>
<td>14/70</td>
<td>0.071</td>
<td>0.043</td>
</tr>
<tr>
<td>Adult (16-70 yr)</td>
<td>1</td>
<td>54/70</td>
<td>0.052</td>
<td>0.040</td>
</tr>
<tr>
<td>Total Lifetime Exposure</td>
<td></td>
<td></td>
<td></td>
<td>0.145</td>
</tr>
</tbody>
</table>

^a OEHHA (2009), Appendix VI
^b DWI values are obtained by adding oral ingestion and dermal tap water exposure values in Table 11
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:

\[
C = \frac{10^{-6}}{(3.2 \text{ (mg/kg-day)}^{-1} \times 0.145 \text{ L}_{eq}/\text{kg-day}) + (6.5 \text{ (mg/kg-day)}^{-1} \times 0.0244 \text{ L}_{eq}/\text{kg-day})}
\]

\[
= \frac{10^{-6}}{0.464 + 0.159}
\]

\[
= 0.0000016 \text{ mg/L} = 0.0016 \mu\text{g/L} \text{ or } 0.002 \text{ ppb (rounded)}
\]

The updated PHG for DBCP is 0.002 ppb based on an estimated lifetime cancer risk of one in one million. This is essentially the same as the original PHG value of 0.0017 ppb rounded and remains lower than the current California MCL of 0.2 ppb. While a number of methodological updates were applied, including using exposure route-specific cancer potency estimates, and applying age-sensitivity factors and age-specific intake rates in the derivation, these changes did not result in an appreciable change in the final PHG value. Since this value is lower than the health-protective concentration of 0.2 ppb derived for noncancer effects, the PHG of 0.002 ppb should protect against both cancer and noncancer effects of DBCP.

**RISK CHARACTERIZATION**

In this report, OEHHA reanalyzed the noncancer (sperm) data, updated the previously developed oral CSF to 3.2 (mg/kg-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 0.002 ppb was calculated based on the carcinogenic effects of DBCP. Since this value is lower than the health-protective concentration of 0.2 ppb derived for noncancer effects, the PHG of 0.002 ppb should protect against both cancer and noncancer effects of DBCP.

References


Hachiya N, Motohashi Y (2000). Examination of lacZ mutant induction in the liver and testis of Muta Mouse following injection of halogenated aliphatic hydrocarbons classified as human carcinogens. *Ind Health* 38(2), 213-220.


NTP (1982). Carcinogenesis bioassay of 1,2-dibromo-3-chloropropane in F344 rats and B6C3F1 mice (inhalation study). National Toxicology Program Technical Report Series No. 206, National Toxicology Program, Bethesda, MD.

OEHHA (1999). Public health goal for 1,2-dibromo-3-chloropropane (DBCP) in drinking water. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA. 


Ryu JC, Kim YJ, Chai YG (2002). Mutation spectrum of 1,2-dibromo-3-chloropropane, an endocrine disruptor, in the lacI transgenic Big Blue Rat2 fibroblast cell line. *Mutagenesis* 17(4), 301-307.


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: the Akaike’s information criterion (AIC), goodness of fit p-value ≥ 0.05, scaled residual ≤ the absolute value of two, 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 (Rao et al., 1982)

<table>
<thead>
<tr>
<th>Modela</th>
<th>Goodness of Fit</th>
<th>Scaled Residual</th>
<th>BMD1SD (ppm)</th>
<th>BMDL1SD (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AIC</td>
<td>p-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Recovery Period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exponential2b</td>
<td>50.75</td>
<td>0.146</td>
<td>1.00</td>
<td>0.37</td>
</tr>
<tr>
<td>Linearc</td>
<td>50.28</td>
<td>0.20</td>
<td>1.03</td>
<td>0.21</td>
</tr>
<tr>
<td>32-Week Recovery Period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exponential2</td>
<td>48.99</td>
<td>0.72</td>
<td>0.07</td>
<td>0.25</td>
</tr>
<tr>
<td>Linear</td>
<td>49.69</td>
<td>0.36</td>
<td>-0.39</td>
<td>0.13</td>
</tr>
</tbody>
</table>

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.
Figure A1. Linear model output for increase in percentage of ultrastructurally abnormal spermatozoa in male rabbits exposed to DBCP for 14 weeks (Rao et al., 1982)

![Linear model output for increase in percentage of ultrastructurally abnormal spermatozoa in male rabbits exposed to DBCP for 14 weeks (Rao et al., 1982)](image-url)
Asymptotic Correlation Matrix of Parameter Estimates

\[
\begin{pmatrix}
  lalpha & rho & beta_0 & beta_1 \\
  lalpha & 1 & -0.98 & 0.21 & -0.34 \\
rho & -0.98 & 1 & -0.21 & 0.34 \\
beta_0 & 0.21 & -0.21 & 1 & -0.49 \\
beta_1 & -0.34 & 0.34 & -0.49 & 1
\end{pmatrix}
\]

Parameter Estimates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Std. Err.</th>
<th>Lower Conf. Limit</th>
<th>Upper Conf. Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>lalpha</td>
<td>-3.19888</td>
<td>2.54728</td>
<td>-8.19146</td>
<td>1.79371</td>
</tr>
<tr>
<td>rho</td>
<td>2.64927</td>
<td>1.0326</td>
<td>0.625414</td>
<td>4.67314</td>
</tr>
<tr>
<td>beta_0</td>
<td>7.02227</td>
<td>1.39394</td>
<td>4.2902</td>
<td>9.75434</td>
</tr>
<tr>
<td>beta_1</td>
<td>12.5976</td>
<td>5.93511</td>
<td>0.964969</td>
<td>24.2302</td>
</tr>
</tbody>
</table>

Table of Data and Estimated Values of Interest

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Obs Mean</th>
<th>Est Mean</th>
<th>Obs Std Dev</th>
<th>Est Std Dev</th>
<th>Scaled Res.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>5</td>
<td>7.02</td>
<td>3</td>
<td>2.67</td>
<td>-1.07</td>
</tr>
<tr>
<td>0.1</td>
<td>4</td>
<td>10</td>
<td>8.28</td>
<td>3</td>
<td>3.32</td>
<td>1.03</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>18</td>
<td>19.6</td>
<td>12</td>
<td>10.4</td>
<td>-0.311</td>
</tr>
</tbody>
</table>

Model Descriptions for likelihoods calculated

Model A1: \( Y_{ij} = \mu(i) + e(ij) \)
\Var{e(ij)} = \Sigma^2

Model A2: \( Y_{ij} = \mu(i) + e(ij) \)
\Var{e(ij)} = \Sigma(i)^2

Model A3: \( Y_{ij} = \mu(i) + e(ij) \)
\Var{e(ij)} = \exp(lalpha + rho*ln(\mu(i)))

Model A3 uses any fixed variance parameters that were specified by the user

Model R: \( Y_i = \mu + e(i) \)
\Var{e(i)} = \Sigma^2

Likelihoods of Interest

<table>
<thead>
<tr>
<th>Model</th>
<th>Log(likelihood)</th>
<th># Param's</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>-24.229416</td>
<td>4</td>
<td>56.458832</td>
</tr>
<tr>
<td>A2</td>
<td>-19.687425</td>
<td>6</td>
<td>51.374850</td>
</tr>
<tr>
<td>A3</td>
<td>-20.315780</td>
<td>5</td>
<td>50.631561</td>
</tr>
<tr>
<td>fitted</td>
<td>-21.142223</td>
<td>4</td>
<td>50.284447</td>
</tr>
<tr>
<td>R</td>
<td>-26.422069</td>
<td>2</td>
<td>56.844138</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Test</th>
<th>-2*log(Likelihood Ratio)</th>
<th>Test df</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>13.4693</td>
<td>4</td>
<td>0.009196</td>
</tr>
<tr>
<td>Test 2</td>
<td>9.08398</td>
<td>2</td>
<td>0.01065</td>
</tr>
<tr>
<td>Test 3</td>
<td>1.25671</td>
<td>1</td>
<td>0.2623</td>
</tr>
<tr>
<td>Test 4</td>
<td>1.65289</td>
<td>1</td>
<td>0.1986</td>
</tr>
</tbody>
</table>

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.

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28
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 = 0.212013
BMDL = 0.072176
BMDU = 1.24214

Figure A2. 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)
The form of the response function is:

\[ Y[dose] = \beta_0 + \beta_1 \times \text{dose} + \beta_2 \times \text{dose}^2 + \ldots \]

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

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

\[
\begin{align*}
\text{lalpha} &= 3.33616 \\
\rho &= 0 \\
\beta_0 &= 4.55495 \\
\beta_1 &= 19.3956 \\
\end{align*}
\]

Asymptotic Correlation Matrix of Parameter Estimates

\[
\begin{array}{cccc}
& \text{lalpha} & \rho & \beta_0 & \beta_1 \\
\text{lalpha} & 1 & -0.95 & 0.0095 & 0.047 \\
\rho & -0.95 & 1 & 0.002 & -0.063 \\
\beta_0 & 0.0095 & 0.002 & 1 & -0.31 \\
\beta_1 & 0.047 & -0.063 & -0.31 & 1 \\
\end{array}
\]

Parameter Estimates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Std. Err.</th>
<th>Lower Conf. Limit</th>
<th>Upper Conf. Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>lalpha</td>
<td>-0.517054</td>
<td>1.26866</td>
<td>-3.00357</td>
<td>1.96947</td>
</tr>
<tr>
<td>rho</td>
<td>1.45711</td>
<td>0.58551</td>
<td>0.309537</td>
<td>2.60469</td>
</tr>
<tr>
<td>beta_0</td>
<td>4.84617</td>
<td>0.899559</td>
<td>3.08307</td>
<td>6.60927</td>
</tr>
<tr>
<td>beta_1</td>
<td>18.5449</td>
<td>4.53775</td>
<td>9.65104</td>
<td>27.4387</td>
</tr>
</tbody>
</table>

Table of Data and Estimated Values of Interest

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Obs Mean</th>
<th>Est Mean</th>
<th>Obs Std Dev</th>
<th>Est Std Dev</th>
<th>Scaled Res.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
<td>5</td>
<td>4.85</td>
<td>3</td>
<td>2.44</td>
<td>0.155</td>
</tr>
<tr>
<td>0.1</td>
<td>3</td>
<td>6</td>
<td>6.7</td>
<td>2</td>
<td>3.09</td>
<td>-0.393</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>24</td>
<td>23.4</td>
<td>10</td>
<td>7.68</td>
<td>0.137</td>
</tr>
</tbody>
</table>

Model Descriptions for likelihoods calculated

Model A1: \( Y_{ij} = \mu(i) + e(ij) \)
Var\(e(ij)) = \text{Sigma}^2

Model A2: \( Y_{ij} = \mu(i) + e(ij) \)
Var\(e(ij)) = \text{Sigma}(i)^2

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Model A3: \( Y_{ij} = \mu(i) + e_{ij} \)  
\( \text{Var}(e_{ij}) = \exp(\alpha + \rho \ln(\mu(i))) \)  
Model A3 uses any fixed variance parameters that were specified by the user

Model R: \( Y_i = \mu + e(i) \)  
\( \text{Var}(e(i)) = \sigma^2 \)

Likelihoods of Interest

<table>
<thead>
<tr>
<th>Model</th>
<th>Log(likelihood)</th>
<th># Param's</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>-24.290897</td>
<td>4</td>
<td>56.581794</td>
</tr>
<tr>
<td>A2</td>
<td>-19.815511</td>
<td>6</td>
<td>51.631021</td>
</tr>
<tr>
<td>A3</td>
<td>-20.431288</td>
<td>5</td>
<td>50.862576</td>
</tr>
<tr>
<td>fitted</td>
<td>-20.844092</td>
<td>4</td>
<td>49.688184</td>
</tr>
<tr>
<td>R</td>
<td>-32.766644</td>
<td>2</td>
<td>69.533288</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Test</th>
<th>-2*\log(\text{Likelihood Ratio})</th>
<th>Test df</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>25.9023</td>
<td>4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Test 2</td>
<td>8.95077</td>
<td>2</td>
<td>0.01139</td>
</tr>
<tr>
<td>Test 3</td>
<td>1.23155</td>
<td>1</td>
<td>0.2671</td>
</tr>
<tr>
<td>Test 4</td>
<td>0.825608</td>
<td>1</td>
<td>0.3635</td>
</tr>
</tbody>
</table>

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 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)

The form of the probability function is:

\[ P[\text{response}] = \text{background} + (1-\text{background})*[1-\exp(-\beta_1*\text{dose}^1-\beta_2*\text{dose}^2)] \]

The parameter betas are restricted to be positive

| Dependent variable = Col3
| Independent variable = Col1
| Data file name = maleratstccpстом.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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Std. Err.</th>
<th>Lower Conf. Limit</th>
<th>Upper Conf. Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>0</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Beta(1)</td>
<td>0</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Beta(2)</td>
<td>0.120915</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

* - Indicates that this value is not calculated.

Analysis of Deviance Table

<table>
<thead>
<tr>
<th>Model</th>
<th>Log(likelihood)</th>
<th># Param's</th>
<th>Deviance</th>
<th>Test d.f.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>-39.4969</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitted model</td>
<td>-39.8618</td>
<td>1</td>
<td>0.729763</td>
<td>3</td>
<td>0.8662</td>
</tr>
<tr>
<td>Reduced model</td>
<td>-70.8241</td>
<td>1</td>
<td>62.6544</td>
<td>3</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

AIC: 81.7236

Log-likelihood Constant 35.94619047318114

Goodness of Fit

<table>
<thead>
<tr>
<th>Dose</th>
<th>Est._Prob.</th>
<th>Expected</th>
<th>Observed</th>
<th>Size</th>
<th>Scaled Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0000</td>
<td>0.0000</td>
<td>0.000</td>
<td>0.000</td>
<td>48.000</td>
<td>0.000</td>
</tr>
<tr>
<td>0.2400</td>
<td>0.0069</td>
<td>0.319</td>
<td>0.000</td>
<td>46.000</td>
<td>-0.567</td>
</tr>
<tr>
<td>0.8000</td>
<td>0.0745</td>
<td>3.425</td>
<td>3.000</td>
<td>46.000</td>
<td>-0.239</td>
</tr>
<tr>
<td>2.3900</td>
<td>0.4988</td>
<td>20.449</td>
<td>21.000</td>
<td>41.000</td>
<td>0.172</td>
</tr>
</tbody>
</table>

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)
The form of the probability function is:

\[ P[\text{response}] = \text{background} + (1-\text{background})*[1-\text{EXP}\{-\text{betas}^\text{dose}\}] \]

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Std. Err.</th>
<th>Lower Conf. Limit</th>
<th>Upper Conf. Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>0</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Beta(1)</td>
<td>0.0576405</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

* - Indicates that this value is not calculated.

Analysis of Deviance Table

<table>
<thead>
<tr>
<th>Model</th>
<th>Log(likelihood)</th>
<th># Param's</th>
<th>Deviance</th>
<th>Test d.f.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>-28.2471</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitted model</td>
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<td>1</td>
<td>0.204357</td>
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</tr>
<tr>
<td>Reduced model</td>
<td>-32.773</td>
<td>1</td>
<td>9.05169</td>
<td>3</td>
<td>0.02861</td>
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<tr>
<td>AIC:</td>
<td>58.6986</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log-likelihood Constant</td>
<td>24.297823598725294</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Proposed Public Health Goal for 1,2-Dibromo-3-Chloropropane in Drinking Water

March 2019
### Goodness of Fit

<table>
<thead>
<tr>
<th>Dose</th>
<th>Est. Prob.</th>
<th>Expected</th>
<th>Observed</th>
<th>Size</th>
<th>Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0000</td>
<td>0.0000</td>
<td>0.000</td>
<td>0.000</td>
<td>48.000</td>
<td>0.000</td>
</tr>
<tr>
<td>0.2400</td>
<td>0.0137</td>
<td>0.632</td>
<td>1.000</td>
<td>46.000</td>
<td>0.466</td>
</tr>
<tr>
<td>0.8000</td>
<td>0.0451</td>
<td>2.073</td>
<td>2.000</td>
<td>46.000</td>
<td>-0.052</td>
</tr>
<tr>
<td>2.3900</td>
<td>0.1287</td>
<td>5.276</td>
<td>5.000</td>
<td>41.000</td>
<td>-0.129</td>
</tr>
</tbody>
</table>

Chi^2 = 0.24  \(d.f. = 3\)  \(P\text{-value} = 0.9715\)

### Benchmark Dose Computation

- **Specified effect** = 0.05
- **Risk Type** = Extra risk
- **Confidence level** = 0.95

\[
\text{BMD} = 0.889883 \\
\text{BMDL} = 0.523478 \\
\text{BMDU} = 2.09375
\]

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)
The form of the probability function is:

\[ P[\text{response}] = \text{background} + (1-\text{background}) \times \left(1-\exp(-\text{beta1} \times \text{dose}^1-\text{beta2} \times \text{dose}^2)\right) \]

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 )

<table>
<thead>
<tr>
<th></th>
<th>Beta(1)</th>
<th>Beta(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta(1)</td>
<td>1</td>
<td>-0.96</td>
</tr>
<tr>
<td>Beta(2)</td>
<td>-0.96</td>
<td>1</td>
</tr>
</tbody>
</table>

Parameter Estimates
Proposed Public Health Goal for  
1,2-Dibromo-3-Chloropropane 
in Drinking Water

March 2019

95.0% Wald Confidence Interval

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Std. Err.</th>
<th>Lower Conf. Limit</th>
<th>Upper Conf. Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>0</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Beta(1)</td>
<td>0.0774699</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Beta(2)</td>
<td>0.0472006</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

* - Indicates that this value is not calculated.

Analysis of Deviance Table

<table>
<thead>
<tr>
<th>Model</th>
<th>Log(likelihood)</th>
<th># Param's</th>
<th>Deviance</th>
<th>Test d.f.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>-45.3331</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitted model</td>
<td>-45.3339</td>
<td>2</td>
<td>0.00168058</td>
<td>2</td>
<td>0.9992</td>
</tr>
<tr>
<td>Reduced model</td>
<td>-62.9072</td>
<td>1</td>
<td>35.1483</td>
<td>3</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

AIC: 94.6679

Log-likelihood Constant: 40.704519838631398

Goodness of Fit

<table>
<thead>
<tr>
<th>Dose</th>
<th>Est._Prob.</th>
<th>Expected</th>
<th>Observed</th>
<th>Size</th>
<th>Scaled Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0000</td>
<td>0.0000</td>
<td>0.000</td>
<td>0.000</td>
<td>48.000</td>
<td>0.000</td>
</tr>
<tr>
<td>0.2400</td>
<td>0.0211</td>
<td>0.970</td>
<td>1.000</td>
<td>46.000</td>
<td>0.031</td>
</tr>
<tr>
<td>0.8000</td>
<td>0.0881</td>
<td>4.051</td>
<td>4.000</td>
<td>46.000</td>
<td>-0.026</td>
</tr>
<tr>
<td>2.3900</td>
<td>0.3654</td>
<td>14.982</td>
<td>15.000</td>
<td>41.000</td>
<td>0.006</td>
</tr>
</tbody>
</table>

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 output for squamous cell carcinomas of the stomach or forestomach in male mice following chronic dietary exposure to DBCP (Hazleton, 1977)
BMDS_Model_Run

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background})*\left[1-\exp\left(-\beta_1\cdot\text{dose}^1\right)\right]$$

The parameter betas are restricted to be positive

Dependent variable = Effect
Independent variable = Dose

Total number of observations = 2
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) = 0.157568

Asymptotic Correlation Matrix of Parameter Estimates

<table>
<thead>
<tr>
<th></th>
<th>Beta(1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta(1)</td>
<td>1</td>
</tr>
</tbody>
</table>

Parameter Estimates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Std. Err.</th>
<th>95.0% Wald Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Beta(1)</td>
<td>0.157568</td>
<td>0.0316434</td>
<td>0.095548 - 0.219588</td>
</tr>
</tbody>
</table>

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

<table>
<thead>
<tr>
<th>Model</th>
<th>Log(likelihood)</th>
<th># Param's</th>
<th>Deviance</th>
<th>Test d.f.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>-33.8723</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitted model</td>
<td>-33.8723</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>.1</td>
</tr>
<tr>
<td>Reduced model</td>
<td>-57.0028</td>
<td>1</td>
<td>46.261</td>
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<td>&lt;.0001</td>
</tr>
</tbody>
</table>

AIC: 69.7446
**Goodness of Fit**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Est. Prob.</th>
<th>Expected</th>
<th>Observed</th>
<th>Size</th>
<th>Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0000</td>
<td>0.0000</td>
<td>0.000</td>
<td>0.000</td>
<td>50.000</td>
<td>0.000</td>
</tr>
<tr>
<td>4.8000</td>
<td>0.5306</td>
<td>26.000</td>
<td>26.000</td>
<td>49.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

\[ \text{Chi}^2 = 0.00 \quad \text{d.f.} = 1 \quad \text{P-value} = 1.0000 \]

**Benchmark Dose Computation**

- Specified effect = 0.05
- Risk Type = Extra risk
- Confidence level = 0.95

\[
\begin{align*}
\text{BMD} &= 0.325531 \\
\text{BMDL} &= 0.237622 \\
\text{BMDU} &= 0.460934
\end{align*}
\]

Taken together, (0.237622, 0.460934) is a 90% two-sided confidence interval for the BMD.

Cancer Slope Factor = 0.210418

**Figure A5. 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)
BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

The form of the probability function is:

\[ P[\text{response}] = \text{background} + (1-\text{background}) \times [1-\exp(-\text{beta1} \times \text{dose}^1)] \]

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 )

<table>
<thead>
<tr>
<th></th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta(1)</td>
<td>1</td>
</tr>
</tbody>
</table>

95.0% Wald Confidence Interval

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Std. Err.</th>
<th>Lower Conf. Limit</th>
<th>Upper Conf. Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>0</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Beta(1)</td>
<td>0.364139</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Model</th>
<th>Log(likelihood)</th>
<th># Param's</th>
<th>Deviance</th>
<th>Test d.f.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>-42.9743</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitted model</td>
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<td>1.48123</td>
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<td>0.4768</td>
</tr>
<tr>
<td>Reduced model</td>
<td>-62.6797</td>
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<td>39.4107</td>
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<td>&lt;.0001</td>
</tr>
</tbody>
</table>

AIC: 89.4299

Log-likelihood Constant 39.145590523823344

Goodness of Fit

<table>
<thead>
<tr>
<th>Dose</th>
<th>Est._Prob.</th>
<th>Expected</th>
<th>Observed</th>
<th>Size</th>
<th>Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0000</td>
<td>0.0000</td>
<td>0.000</td>
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<td>48.49</td>
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<td>0.6000</td>
<td>0.1963</td>
<td>9.336</td>
<td>12.000</td>
<td>47.57</td>
<td>0.972</td>
</tr>
<tr>
<td>3.0000</td>
<td>0.6646</td>
<td>15.804</td>
<td>14.000</td>
<td>23.78</td>
<td>-0.784</td>
</tr>
</tbody>
</table>

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)

The form of the probability function is:

\[ P[\text{response}] = \text{background} + (1-\text{background}) \times (1 - \exp(-\beta_1 \times \text{dose}^1)) \]

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Std. Err.</th>
<th>Lower Conf. Limit</th>
<th>Upper Conf. Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>0</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Beta(1)</td>
<td>0.618032</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

* - Indicates that this value is not calculated.

Analysis of Deviance Table

<table>
<thead>
<tr>
<th>Model</th>
<th>Log(likelihood)</th>
<th># Param's</th>
<th>Deviance</th>
<th>Test d.f.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitted model</td>
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<td>1.44215</td>
<td>2</td>
<td>0.4862</td>
</tr>
<tr>
<td>Reduced model</td>
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<td>&lt;.0001</td>
</tr>
</tbody>
</table>

AIC: 102.734

Log-likelihood Constant 45.707440336524073

Goodness of Fit

<table>
<thead>
<tr>
<th>Dose</th>
<th>Est._Prob.</th>
<th>Expected</th>
<th>Observed</th>
<th>Size</th>
<th>Scaled Residual</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.0000</td>
<td>0.000</td>
<td>0.000</td>
<td>48.490</td>
<td>0.000</td>
</tr>
<tr>
<td>0.6000</td>
<td>0.3098</td>
<td>14.931</td>
<td>18.000</td>
<td>48.190</td>
<td>0.956</td>
</tr>
<tr>
<td>3.0000</td>
<td>0.8434</td>
<td>29.671</td>
<td>28.000</td>
<td>35.180</td>
<td>-0.775</td>
</tr>
</tbody>
</table>

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
Proposed Public Health Goal for 1,2-Dibromo-3-Chloropropane (DBCP) in Drinking Water

March 2019

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)

The form of the probability function is:

\[ P[\text{response}] = \text{background} + (1-\text{background}) \times [1-\text{EXP(-betal*dose^1})] \]

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Std. Err.</th>
<th>Lower Conf. Limit</th>
<th>Upper Conf. Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>0</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Beta(1)</td>
<td>0.15303</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

* - Indicates that this value is not calculated.

Analysis of Deviance Table

<table>
<thead>
<tr>
<th>Model</th>
<th>Log(likelihood)</th>
<th># Param's</th>
<th>Deviance</th>
<th>Test d.f.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>-20.4799</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitted model</td>
<td>-23.0482</td>
<td>1</td>
<td>5.13662</td>
<td>2</td>
<td>0.07666</td>
</tr>
<tr>
<td>Reduced model</td>
<td>-38.9179</td>
<td>1</td>
<td>36.8761</td>
<td>2</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

AIC: 48.0964

Log-likelihood Constant: 17.696104219104107

Goodness of Fit

Scaled
<table>
<thead>
<tr>
<th>Dose</th>
<th>Est. Prob.</th>
<th>Expected</th>
<th>Observed</th>
<th>Size</th>
<th>Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0000</td>
<td>0.0000</td>
<td>0.000</td>
<td>0.000</td>
<td>48.490</td>
<td>0.000</td>
</tr>
<tr>
<td>0.6000</td>
<td>0.0877</td>
<td>4.220</td>
<td>1.000</td>
<td>48.100</td>
<td>-1.641</td>
</tr>
<tr>
<td>3.0000</td>
<td>0.3681</td>
<td>8.298</td>
<td>11.000</td>
<td>22.540</td>
<td>1.180</td>
</tr>
</tbody>
</table>

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 confidence interval for the BMD

Multistage Cancer Slope Factor = 0.23266

**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

---

Proposed Public Health Goal for
1,2-Dibromo-3-Chloropropane in Drinking Water

March 2019
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. 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. 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 A1. Descriptions and Values of Model Defaults, Chemical-Specific and Exposure-Specific Parameters

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inputs and Calculated Outputs</td>
<td>chemical intake via oral ingestion of tap water</td>
<td>-</td>
<td>mg/kg-day</td>
<td>calculated</td>
</tr>
<tr>
<td>Intake oral</td>
<td>chemical intake via inhalation</td>
<td>-</td>
<td>mg/kg-day</td>
<td>calculated</td>
</tr>
<tr>
<td>Intake inh</td>
<td>chemical uptake via dermal contacts</td>
<td>-</td>
<td>mg/kg-day</td>
<td>calculated</td>
</tr>
<tr>
<td>Uptake dermal</td>
<td>chemical concentration in tap water</td>
<td>100^a</td>
<td>mg/L</td>
<td>input</td>
</tr>
<tr>
<td>C tap water</td>
<td>chemical concentration in indoor air</td>
<td>-</td>
<td>mg/m^3</td>
<td>calculated</td>
</tr>
<tr>
<td>C air</td>
<td>chemical concentration in bathroom air</td>
<td>-</td>
<td>mg/m^3</td>
<td>calculated</td>
</tr>
<tr>
<td>C bath air</td>
<td>chemical concentration in tap water</td>
<td>100^a</td>
<td>mg/L</td>
<td>input</td>
</tr>
</tbody>
</table>

---

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/AssessingRisk/caltox.cfm](https://www.dtsc.ca.gov/AssessingRisk/caltox.cfm)).
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 non-cancer 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.
## Exposure Parameters

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifl</td>
<td>fluid (water) intake, normalized to body weight</td>
<td>0.045 to 0.196&lt;sup&gt;b&lt;/sup&gt;</td>
<td>L/kg-day</td>
<td>OEHHA, 2012</td>
</tr>
<tr>
<td>BRa</td>
<td>active breathing rate, normalized to body weight</td>
<td>0.012 to 0.045&lt;sup&gt;b&lt;/sup&gt;</td>
<td>m&lt;sup&gt;3&lt;/sup&gt;/kg-hr</td>
<td>OEHHA, 2012</td>
</tr>
<tr>
<td>BRc</td>
<td>resting breathing rate, normalized to body weight</td>
<td>0.012 to 0.045&lt;sup&gt;b&lt;/sup&gt;</td>
<td>m&lt;sup&gt;3&lt;/sup&gt;/kg-hr</td>
<td>OEHHA, 2012</td>
</tr>
<tr>
<td>SAb</td>
<td>surface area, normalized to body weight</td>
<td>0.029 to 0.059&lt;sup&gt;b&lt;/sup&gt;</td>
<td>m&lt;sup&gt;2&lt;/sup&gt;/kg</td>
<td>OEHHA, 2012</td>
</tr>
<tr>
<td>ET&lt;sub&gt;ai&lt;/sub&gt;</td>
<td>exposure time, active indoors</td>
<td>5.71 to 8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>hr/day</td>
<td>model default</td>
</tr>
<tr>
<td>ET&lt;sub&gt;n&lt;/sub&gt;</td>
<td>exposure time, resting indoors</td>
<td>8 to 11&lt;sup&gt;c&lt;/sup&gt;</td>
<td>hr/day</td>
<td>model default</td>
</tr>
<tr>
<td>ET&lt;sub&gt;sb&lt;/sub&gt;</td>
<td>exposure time, in shower or bath</td>
<td>0.27&lt;sup&gt;c&lt;/sup&gt;</td>
<td>hr</td>
<td>model default</td>
</tr>
<tr>
<td>δskin</td>
<td>skin thickness</td>
<td>0.0025</td>
<td>cm</td>
<td>model default</td>
</tr>
<tr>
<td>fs</td>
<td>fraction of skin in contact of water during showering or bathing</td>
<td>0.80</td>
<td>unitless</td>
<td>model default</td>
</tr>
<tr>
<td>CF</td>
<td>conversion factor for dermal uptake calculation</td>
<td>10</td>
<td>L/cm-m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>calculated</td>
</tr>
</tbody>
</table>

## Physicochemical and Other Parameters

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>W&lt;sub&gt;house&lt;/sub&gt;</td>
<td>Water use in the house</td>
<td>40</td>
<td>L/hr</td>
<td>model default</td>
</tr>
<tr>
<td>VR&lt;sub&gt;house&lt;/sub&gt;</td>
<td>Room ventilation rate, house</td>
<td>750</td>
<td>m&lt;sup&gt;3&lt;/sup&gt;/hr</td>
<td>model default</td>
</tr>
<tr>
<td>W&lt;sub&gt;shower&lt;/sub&gt;</td>
<td>Water use in the shower</td>
<td>8</td>
<td>L/min</td>
<td>model default</td>
</tr>
<tr>
<td>VR&lt;sub&gt;bath&lt;/sub&gt;</td>
<td>Room ventilation rate, bathroom</td>
<td>1</td>
<td>m&lt;sup&gt;3&lt;/sup&gt;/min</td>
<td>model default</td>
</tr>
<tr>
<td>D&lt;sub&gt;water&lt;/sub&gt;</td>
<td>Diffusion coefficient in pure water</td>
<td>chemical specific</td>
<td>m&lt;sup&gt;2&lt;/sup&gt;/day</td>
<td>literature</td>
</tr>
<tr>
<td>D&lt;sub&gt;air&lt;/sub&gt;</td>
<td>Diffusion coefficient in pure air</td>
<td>chemical specific</td>
<td>m&lt;sup&gt;2&lt;/sup&gt;/day</td>
<td>literature</td>
</tr>
<tr>
<td>Z&lt;sub&gt;water&lt;/sub&gt;</td>
<td>fugacity capacity of pure water</td>
<td>volatiles=1/H semivolatiles=1 (H: Henry’s Law constant)</td>
<td>mole/Pa-m&lt;sup&gt;3&lt;/sup&gt;</td>
<td>literature</td>
</tr>
<tr>
<td>R&lt;sub&gt;gas&lt;/sub&gt;</td>
<td>gas constant</td>
<td>8.31</td>
<td>Pa-m&lt;sup&gt;3&lt;/sup&gt;/mol-K</td>
<td>literature</td>
</tr>
<tr>
<td>t&lt;sub&gt;lag&lt;/sub&gt;</td>
<td>diffusion lag time in skin</td>
<td>chemical specific</td>
<td>hr</td>
<td>calculated</td>
</tr>
<tr>
<td>K&lt;sub&gt;m&lt;/sub&gt;</td>
<td>skin-water partition coefficient</td>
<td>chemical specific</td>
<td>unitless</td>
<td>literature</td>
</tr>
<tr>
<td>K&lt;sub&gt;p&lt;/sub&gt;</td>
<td>steady-state skin permeability coefficient</td>
<td>chemical specific</td>
<td>cm/hr</td>
<td>literature</td>
</tr>
<tr>
<td>MW</td>
<td>molecular weight</td>
<td>chemical specific</td>
<td>g/mole</td>
<td>literature</td>
</tr>
<tr>
<td>K&lt;sub&gt;ow&lt;/sub&gt;</td>
<td>octanol/water partition coefficient</td>
<td>chemical specific</td>
<td>unitless</td>
<td>literature</td>
</tr>
</tbody>
</table>

<sup>a</sup> As long as the chemical concentration in tap water is low (well below the saturation concentration in water), the input value of C<sub>tap_water</sub> does not affect the calculation of relative contributions from the multiroute exposures and 100 ppm is an arbitrarily assigned low value.

<sup>b</sup> See Table A2 for life-stage specific values.

<sup>c</sup> See Table A3 for life-stage specific values.
Table A2. OEHHA Calculated Exposure Parameters (OEHHA, 2012\textsuperscript{9})

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Water Intake Rate\textsuperscript{a} (L/kg\text{-}day)</th>
<th>Breathing Rate\textsuperscript{b} (m\textsuperscript{3}/kg\text{-}hr)</th>
<th>Surface Area\textsuperscript{c} (m\textsuperscript{2}/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant (0&lt;2 yrs)</td>
<td>0.196</td>
<td>0.045</td>
<td>0.059</td>
</tr>
<tr>
<td>Child (2&lt;16 yrs)</td>
<td>0.061</td>
<td>0.031</td>
<td>0.045</td>
</tr>
<tr>
<td>Adult (16-70 yrs)</td>
<td>0.045</td>
<td>0.012</td>
<td>0.029</td>
</tr>
<tr>
<td>Fetus\textsuperscript{d}</td>
<td>0.047</td>
<td>0.015</td>
<td>0.029</td>
</tr>
</tbody>
</table>

\textsuperscript{a} 95\textsuperscript{th} percentile water intake rates (L/kg\text{-}day) are obtained from Table 8.1 of OEHHA (2012) risk assessment guidelines.

\textsuperscript{b} 95\textsuperscript{th} percentile breathing rates (L/kg\text{-}day) are obtained from Table 3.1 of OEHHA (2012) risk assessment guidelines and converted to m\textsuperscript{3}/kg\text{-}hr. The same life stage-specific breathing rate is used for BR\textsubscript{a} and BR\textsubscript{r}.

\textsuperscript{c} 95\textsuperscript{th} percentile values for total body surface area over body weight (m\textsuperscript{2}/kg) are obtained from Table 6.5 of OEHHA (2012) risk assessment guidelines.

\textsuperscript{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 A3. CalTOX Model Default Exposure Durations

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>CalTOX Exposure Factors Set\textsuperscript{a}</th>
<th>Exposure Time, Active Indoors (hr/day)</th>
<th>Exposure Time, Resting Indoors (hr/day)</th>
<th>Exposure Time, Shower or Bath (hr/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant (0&lt;2 yrs)</td>
<td>Female 0-1</td>
<td>5.71</td>
<td>11.01</td>
<td>0.27</td>
</tr>
<tr>
<td>Child (2&lt;16 yrs)</td>
<td>Female 7-9</td>
<td>5.71</td>
<td>11.01</td>
<td>0.27</td>
</tr>
<tr>
<td>Adult (16-70 yrs)</td>
<td>Female 19+</td>
<td>8.00</td>
<td>8.00</td>
<td>0.27</td>
</tr>
<tr>
<td>Fetus</td>
<td>Female 19+</td>
<td>8.00</td>
<td>8.00</td>
<td>0.27</td>
</tr>
</tbody>
</table>

\textsuperscript{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:\textsuperscript{10}

\[
\text{Intake}_{\text{oral}} = C_{\text{tap\_water}} \times \text{IfI}
\]


\textsuperscript{10} Abbreviations and symbols used in equations are defined in Table A1.
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:

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

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

$$C_{air} = \frac{3 \times 10^6 \times 0.7 \times \left(\frac{W_{house}}{VR_{house}}\right) \times C_{tap\_water}}{2.5 \left(\frac{D_{water}/86400}{10^7}\right)^{2/3} + \frac{R_{gas} \times 298 \times Z_{water}}{(D_{air}/86400)^{2/3}}}$$

and

$$C_{bath\_air} = \frac{3 \times 10^6 \times 0.6 \times \left(\frac{W_{shower}}{VR_{bath}}\right) \times C_{tap\_water}}{2.5 \left(\frac{D_{water}/86400}{10^7}\right)^{2/3} + \frac{R_{gas} \times 298 \times Z_{water}}{(D_{air}/86400)^{2/3}}}$$

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. $\frac{t_{lag} \times ET_{sb}}{2} > 3$:

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

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

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

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

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

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

\[
t_{lag} = \frac{\delta_{skin} \times K_m}{6 \times K_p^w}
\]

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:
      \[
      K_p^w = \frac{1}{(MW)^{0.6}} \times \frac{2.4 \times 10^{-6} + 3 \times 10^{-5} \times (K_{ow})^{0.8}}{\delta_{skin}}
      \]
   b. Chemicals with MW ≥ 280 g/mole:
      \[
      K_p^w = 0.0019 \times (K_{ow})^{0.71} \times 10^{(-0.0061 \times MW)}
      \]
   c. Chemicals with calculated \( K_p^w > 1 \):
      \[
      K_p^w = 1
      \]

2. \( K_m \) is calculated using this equation:

\[
K_m = 0.64 + 0.25 \times (K_{ow})^{0.8}
\]

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 (%) 

\[
\text{Relative Contribution from Oral Ingestion} = \frac{\text{Intake}_{\text{oral}}}{\text{Intake}_{\text{oral}} + \text{Intake}_{\text{inh}} + \text{Uptake}_{\text{dermal}}} \times 100\%
\]

Relative Contribution from Inhalation\(^{12}\) (%) 

\[
\text{Relative Contribution from Inhalation} = \frac{\text{Intake}_{\text{inh}}}{\text{Intake}_{\text{oral}} + \text{Intake}_{\text{inh}} + \text{Uptake}_{\text{dermal}}} \times 100\%
\]

Relative Contribution from Dermal Uptake (%) 

\[
\text{Relative Contribution from Dermal Uptake} = \frac{\text{Uptake}_{\text{dermal}}}{\text{Intake}_{\text{oral}} + \text{Intake}_{\text{inh}} + \text{Uptake}_{\text{dermal}}} \times 100\%
\]

\(^{12}\) 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):

\[
\text{CSF}_{\text{animal}} = \frac{0.05}{0.44} \text{ mg/kg-day} = 0.11 \text{ (mg/kg-day)}^{-1}
\]

\[
\text{CSF}_{\text{human}} = \text{CSF}_{\text{animal}} \times (BW_h/BW_a)^{1/4}
\]

\[
\text{CSF}_{\text{human}} = 0.11 \times (70 \text{ kg}/0.50 \text{ kg})^{1/4} = 0.39 \text{ (mg/kg-day)}^{-1}
\]

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

\[
\text{CSF}_{\text{animal}} = \frac{0.05}{0.52} = 0.096 \text{ (mg/kg-day)}^{-1}
\]

\[
\text{CSF}_{\text{human}} = 0.096 \times (70/0.50)^{1/4} = 0.33 \text{ (mg/kg-day)}^{-1}
\]

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

\[
\text{CSF}_{\text{animal}} = \frac{0.05}{0.25} = 0.20 \text{ (mg/kg-day)}^{-1}
\]

\[
\text{CSF}_{\text{human}} = 0.20 \times (70/0.50)^{1/4} = 0.69 \text{ (mg/kg-day)}^{-1}
\]

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

\[
\text{CSF}_{\text{animal}} = \frac{0.05}{0.17} \text{ mg/kg-day} = 0.29 \text{ (mg/kg-day)}^{-1}
\]

\[
\text{CSF}_{\text{human}} = 0.29 \times (70/0.50)^{1/4} = 1.0 \text{ (mg/kg-day)}^{-1}
\]

CSF calculations for male mouse squamous cell carcinoma of the stomach or forestomach following exposure to DBCP via feed (Hazleton 1977, 1978):

\[
\text{CSF}_{\text{animal}} = \frac{0.05}{0.24} \text{ mg/kg-day} = 0.21 \text{ (mg/kg-day)}^{-1}
\]

\[
\text{CSF}_{\text{human}} = 0.21 \times (70 \text{ kg}/0.041 \text{ kg})^{1/4} = 1.35 \text{ (mg/kg-day)}^{-1}
\]

\[
\text{CSF}_{\text{adj}} = 1.35 \text{ (mg/kg-day)}^{-1} \times (104/78)^3 = 3.21 \text{ (mg/kg-day)}^{-1}
\]
Calculations for Table 9:
Inhalation rate (Appendix IV) for F344 rats is calculated as:

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

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

\[ \text{BMDL}_{05}^{\text{(animal)}} = \frac{[0.103 \text{ ppm} \times 9.67 \text{ (mg/m}^3)/\text{ppm} \times 6 \text{ hours/24 hours} \times 5 \text{ days/7 days} \times 0.368 \text{ m}^3/\text{day} \times 50\% \text{ absorption}]}{0.380 \text{ kg}} \]
\[ = 0.085 \text{ mg/kg-day} \]
\[ \text{CSF}_{\text{animal}} = 0.05/0.085 \text{ mg/kg-day} = 0.59 \text{ (mg/kg-day)}^{-1} \]
\[ \text{CSF}_{\text{human}} = 0.59 \times (70/0.38)^{1/4} = 2.2 \text{ (mg/kg-day)}^{-1} \]

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

\[ \text{BMDL}_{05}^{\text{(animal)}} = \frac{[0.0643 \text{ ppm} \times 9.67 \text{ (mg/m}^3)/\text{ppm} \times 6 \text{ hours/24 hours} \times 5 \text{ days/7 days} \times 0.368 \text{ m}^3/\text{day} \times 50\% \text{ absorption}]}{0.380 \text{ kg}} \]
\[ = 0.0533 \text{ mg/kg-day} \]
\[ \text{CSF}_{\text{animal}} = 0.05/0.0533 = 0.94 \text{ (mg/kg-day)}^{-1} \]
\[ \text{CSF}_{\text{human}} = 0.94 \times (70/0.38)^{1/4} = 3.5 \text{ (mg/kg-day)}^{-1} \]

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

\[ \text{BMDL}_{05}^{\text{(animal)}} = \frac{[0.215 \text{ ppm} \times 9.67 \text{ (mg/m}^3)/\text{ppm} \times 6 \text{ hours/24 hours} \times 5 \text{ days/7 days} \times 0.368 \text{ m}^3/\text{day} \times 50\% \text{ absorption}]}{0.380 \text{ kg}} \]
\[ = 0.178 \text{ mg/kg-day} \]
\[ \text{CSF}_{\text{animal}} = 0.05/0.178 = 0.28 \text{ (mg/kg-day)}^{-1} \]
\[ \text{CSF}_{\text{human}} = 0.28 \times (70/0.38)^{1/4} = 1.0 \text{ (mg/kg-day)}^{-1} \]

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

\[ \text{CSF}_{\text{animal}} = 0.05/0.0284 \text{ mg/kg-day} = 1.76 \text{ (mg/kg-day)}^{-1} \]
\[ \text{CSF}_{\text{human}} = 1.76 \times (70/0.38)^{1/4} = 6.5 \text{ (mg/kg-day)}^{-1} \]
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
  \[ I = a \times \left( \frac{bw}{0.113} \right)^{2/3} \]
  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

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

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 m³/day). The US Environmental Protection Agency (US EPA 1988a and 1994) derived the equation \( I = 0.80 \times bw^{0.8206} \text{ in m}^3/\text{day} \) by fitting a linear model of the form \( \ln I = \beta_0 + \beta_1 \times \ln bw \) 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 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  Guyton, 1947  Pauluhn and Thiel, 2007
Bavis et al., 2006  Haouzi et al., 2009  Polianski et al., 1984
Chen et al., 1989  Henderson et al., 2014  Schlenker, 2016
Colman and Miller, 2001  Hodges et al., 2013  Seifert and Mortola, 2002
Cummings and Heitcamp, 1981  Holley et al., 2012  Shore et al., 2000
Cyphert et al., 2015  Iiyori et al., 2003  Silva et al., 2017
Cyphert et al., 2016  Kuo et al., 2011  Snow et al., 2017
Donovan et al., 2011  Lai et al., 1978  Souflage et al., 2004
Doperalski et al., 2008  Leavens et al., 2006  Strohl et al., 1997
Dye et al., 2015  Leong et al., 1964  Tsuji et al., 2011
Forster et al., 2003  Lin et al., 1983  Walker et al., 1985
Gamboa et al., 2003  Liu et al., 2011  Wenninger et al., 2006
Genest et al., 2004  Olson and Dempsey, 1978  Whitehead et al., 1999
Goinneau et al., 2010  Mantilla et al., 2011  Wiester et al., 1988
Gordon et al., 2010  Mauderly et al., 1979  Xu et al., 2014
Gordon et al., 2013  Mauderly, 1986  Young et al., 2013
Mautz and Bufalino, 1989

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.

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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 A4). 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:

\[
\begin{align*}
  w_i &= \frac{N \times T_i}{\sum T_i} \\
  \text{where } N &= \text{number of data points and } T_i &= \text{sample size for study } i
\end{align*}
\]

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 A6) 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.

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 A7) shows that the points

\(^{15}\) 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:
follow the solid line fairly well, with a slight but progressive divergence from the true 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 A7. Quantile-quantile plot of residuals

In Figure A8 showing the standardized residuals from the weighted regression plotted against the fitted values, the overlaid smoothing spline in teal 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.

Table A4. Data used for model fitting

<table>
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<tr>
<th>Strain</th>
<th>Sex</th>
<th>BW (kg)</th>
<th>MV observed (L/min)</th>
<th>MV observed (m3/day)</th>
<th>Sample size</th>
<th>Reference</th>
</tr>
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<td>0.311</td>
<td>10</td>
<td>Mauderly (1986)</td>
</tr>
<tr>
<td>Brown Norway</td>
<td>M</td>
<td>0.158</td>
<td>0.217</td>
<td>0.312</td>
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<td>Hodges et al. (2013)</td>
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<td>Hodges et al. (2013)</td>
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<td>BW (kg)</td>
<td>MV observed (L/min)</td>
<td>MV observed (m3/day)</td>
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### Proposed Public Health Goal for 1,2-Dibromo-3-Chloropropane in Drinking Water

- **Strain**
  - Brown Norway
  - F344
  - Wistar
  - Not specified
  - Sprague-Dawley
  - Sprague-Dawley (Kyoto)
  - Sprague-Dawley M&F
  - F344/Crl Lov
  - Brown Norway
  - Sprague-Dawley
  - Wistar
  - Sprague-Dawley
  - F344
  - Sprague-Dawley
  - Wistar
  - Sprague-Dawley
  - F344/Crl Lov
  - Brown Norway
  - F344

- **Sex**
  - M
  - F
  - M&F

- **BW (kg)**
  - 0.296
  - 0.297
  - 0.299
  - 0.300
  - 0.300
  - 0.303
  - 0.305
  - 0.312
  - 0.325
  - 0.328
  - 0.330
  - 0.334
  - 0.336
  - 0.337
  - 0.343
  - 0.349
  - 0.350
  - 0.358
  - 0.363
  - 0.365
  - 0.368
  - 0.375
  - 0.381

- **MV observed (L/min)**
  - 0.473
  - 0.309
  - 0.225
  - 0.172
  - 0.473
  - 0.236
  - 0.214
  - 0.224
  - 0.163
  - 0.246
  - 0.161
  - 0.274
  - 0.292
  - 0.398
  - 0.052
  - 0.154
  - 0.375
  - 0.081
  - 0.303
  - 0.100
  - 0.445
  - 0.400

- **MV observed (m3/day)**
  - 0.681
  - 0.445
  - 0.324
  - 0.248
  - 0.396
  - 0.120
  - 0.340
  - 0.322
  - 0.234
  - 0.354
  - 0.232
  - 0.395
  - 0.420
  - 0.573
  - 0.074
  - 0.222
  - 0.540
  - 0.117
  - 0.436
  - 0.143
  - 0.340
  - 0.641
  - 0.576

- **Sample size**
  - 12
  - 9
  - 10
  - 6
  - 48
  - 4
  - 67
  - 8
  - 14
  - 8
  - 11
  - 6
  - 10
  - 8
  - 6
  - 6
  - 24
  - 8
  - 16
  - 16
  - 24

- **Reference**
  - Gordon et al. (2010)
  - Wiester et al. (1988)
  - Leong et al. (1964)
  - Walker et al. (1985)
  - Lin et al. (1983)
  - Mantilla et al. (2011)
  - Olson and Dempsey (1978)
  - Lai et al. (1978)
  - Shore et al. (2000)
  - Silva et al. (2017)
  - Henderson et al. (2014)
  - Dye et al. (2015)
  - Iiyori et al. (2003)
  - Henderson et al. (2014)
  - Mauderly (1986)
  - Dye et al. (2015)
  - Donovan et al. (2011)
  - Liu et al. (2011)
  - Cyphert et al. (2015)
  - Cyphert (2016)
  - Snow et al. (2017)
  - Strohl et al. (1997)
  - Mauderly (1986)
  - Gordon et al. (2010)
  - Cyphert et al. (2015)
<table>
<thead>
<tr>
<th>Strain</th>
<th>Sex</th>
<th>BW (kg)</th>
<th>MV observed (L/min)</th>
<th>MV observed (m3/day)</th>
<th>Sample size</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long Evans</td>
<td>M&amp;F</td>
<td>0.383</td>
<td>0.215</td>
<td>0.310</td>
<td>10</td>
<td>Mauderly et al. (1979)</td>
</tr>
<tr>
<td>Sprague-Dawley (217)</td>
<td>Not Specified</td>
<td>0.384</td>
<td>0.050</td>
<td>0.072</td>
<td>16</td>
<td>Wenninger et al. (2006)</td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>M</td>
<td>0.387</td>
<td>0.137</td>
<td>0.198</td>
<td>7</td>
<td>Holley et al. (2012)</td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>M</td>
<td>0.400</td>
<td>0.248</td>
<td>0.357</td>
<td>25</td>
<td>Genest et al. (2004)</td>
</tr>
<tr>
<td>Wistar (Han)</td>
<td>M</td>
<td>0.400</td>
<td>0.092</td>
<td>0.132</td>
<td>8</td>
<td>Goineau et al. (2010)</td>
</tr>
<tr>
<td>Wistar (Han)</td>
<td>M</td>
<td>0.400</td>
<td>0.101</td>
<td>0.145</td>
<td>8</td>
<td>Goineau et al. (2010)</td>
</tr>
<tr>
<td>Fischer 344/N</td>
<td>M</td>
<td>0.402</td>
<td>0.159</td>
<td>0.228</td>
<td>5</td>
<td>Chen et al. (1989)</td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>M</td>
<td>0.406</td>
<td>0.184</td>
<td>0.265</td>
<td>11</td>
<td>Bavis et al. (2006)</td>
</tr>
<tr>
<td>Wistar</td>
<td>M</td>
<td>0.406</td>
<td>0.459</td>
<td>0.661</td>
<td>8</td>
<td>Dye et al. (2015)</td>
</tr>
<tr>
<td>F344/Crl Lov</td>
<td>M</td>
<td>0.407</td>
<td>0.264</td>
<td>0.380</td>
<td>10</td>
<td>Mauderly (1986)</td>
</tr>
<tr>
<td>Wistar</td>
<td>M</td>
<td>0.414</td>
<td>0.484</td>
<td>0.698</td>
<td>8</td>
<td>Dye et al. (2015)</td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>M</td>
<td>0.419</td>
<td>0.452</td>
<td>0.651</td>
<td>8</td>
<td>Dye et al. (2015)</td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>M</td>
<td>0.422</td>
<td>0.549</td>
<td>0.790</td>
<td>8</td>
<td>Dye et al. (2015)</td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>M</td>
<td>0.424</td>
<td>0.141</td>
<td>0.204</td>
<td>8</td>
<td>Kuo et al. (2011)</td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>M</td>
<td>0.432</td>
<td>0.200</td>
<td>0.200</td>
<td>8</td>
<td>Doperalski et al. (2008)</td>
</tr>
<tr>
<td>F344</td>
<td>M</td>
<td>0.441</td>
<td>0.396</td>
<td>0.570</td>
<td>16</td>
<td>Cyphert et al. (2015)</td>
</tr>
<tr>
<td>F344</td>
<td>M</td>
<td>0.447</td>
<td>0.313</td>
<td>0.451</td>
<td>18</td>
<td>Cyphert et al. (2015)</td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>M</td>
<td>0.462</td>
<td>0.243</td>
<td>0.350</td>
<td>8</td>
<td>Tsuji et al. (2011)</td>
</tr>
<tr>
<td>Brown Norway</td>
<td>M</td>
<td>0.479</td>
<td>0.419</td>
<td>0.524</td>
<td>8</td>
<td>Cyphert et al. (2016)</td>
</tr>
<tr>
<td>F344</td>
<td>M</td>
<td>0.479</td>
<td>0.364</td>
<td>0.603</td>
<td>12</td>
<td>Gordon et al. (2010)</td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>M</td>
<td>0.507</td>
<td>0.245</td>
<td>0.353</td>
<td>8</td>
<td>Tsuji et al. (2011)</td>
</tr>
<tr>
<td>Brown Norway</td>
<td>M</td>
<td>0.514</td>
<td>0.453</td>
<td>0.081</td>
<td>10</td>
<td>Donovan et al. (2011)</td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>M</td>
<td>0.514</td>
<td>0.056</td>
<td>0.652</td>
<td>8</td>
<td>Gordon et al. (2013)</td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>M</td>
<td>0.521</td>
<td>0.282</td>
<td>0.406</td>
<td>15</td>
<td>Bairam et al. (2009)</td>
</tr>
<tr>
<td>Wistar</td>
<td>M</td>
<td>0.522</td>
<td>0.313</td>
<td>0.451</td>
<td>10</td>
<td>Soulage et al. (2004)</td>
</tr>
<tr>
<td>Strain</td>
<td>Sex</td>
<td>BW (kg)</td>
<td>MV observed (L/min)</td>
<td>MV observed (m³/day)</td>
<td>Sample size</td>
<td>Reference</td>
</tr>
<tr>
<td>----------------</td>
<td>-----</td>
<td>---------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>-------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>M</td>
<td>0.701</td>
<td>0.308</td>
<td>0.444</td>
<td>5</td>
<td>Haouzi et al. (2009)</td>
</tr>
</tbody>
</table>

References


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 A5 below is adapted from OEHHA’s “Technical Support Document for the Development of Noncancer Reference Exposure Levels” (OEHHA, 2008).

Table A5. Default uncertainty factors for PHG derivation, adapted from OEHHA (2008)

<table>
<thead>
<tr>
<th>LOAEL uncertainty factor (UF_L)</th>
<th>Values used:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 LOAEL, any effect</td>
</tr>
<tr>
<td></td>
<td>1 NOAEL or BMDL used</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interspecies uncertainty factor (UF_A)</th>
<th>Values used:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined interspecies uncertainty factor (UF_A):</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 human observation</td>
</tr>
<tr>
<td></td>
<td>√10 animal observation in nonhuman primates</td>
</tr>
<tr>
<td></td>
<td>10 where no data are available on toxicokinetic or toxicodynamic differences between humans and a non-primate test species</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicokinetic component (UF_A-k) of UF_A:</th>
<th>Values used:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 where animal and human PBPK models are used to describe interspecies differences</td>
</tr>
<tr>
<td></td>
<td>√10 nonprimate studies with no chemical or species specific kinetic data</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicodynamic component (UF_A-d) of UF_A:</th>
<th>Values used:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 where animal and human mechanistic data fully describe interspecies differences (This is unlikely to be the case.)</td>
</tr>
<tr>
<td></td>
<td>2 for residual susceptibility differences where there are some toxicodynamic data</td>
</tr>
<tr>
<td></td>
<td>√10 nonprimate studies with no data on toxicodynamic interspecies differences</td>
</tr>
</tbody>
</table>
### Proposed Public Health Goal for 1,2-Dibromo-3-Chloropropane in Drinking Water

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| Intraspecies uncertainty factor (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

| 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$_S$)
| 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

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

References

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:

\[
R = \text{Total risk} \\
C = \text{Concentration in water} \\
p_{\text{oral}} = \text{Oral cancer potency} \\
p_{\text{inh}} = \text{Inhalation cancer potency} \\
\text{ASF}_1 = \text{Age sensitivity factor for 3rd trimester + infancy, value 10} \\
\text{ASF}_2 = \text{Age sensitivity factor for childhood (ages 2-16), value 3} \\
\text{ASF}_3 = \text{Age sensitivity factor for adult (ages 16-70), value 1.}
\]

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

\[
\begin{align*}
d_0 &= 3rd \text{ trimester, value } 0.25/70 \\
d_1 &= \text{infancy, value } 2/40 \\
d_2 &= \text{childhood, value } 14/70 \\
d_3 &= \text{adult, value } 54/70.
\end{align*}
\]

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:

\[
\begin{align*}
\text{DWI}_1 &= \text{Oral route, infancy} \\
\text{DWI}_2 &= \text{Oral route, childhood} \\
\text{DWI}_3 &= \text{Oral route, adult} \\
\text{DWI}_2 &= \text{Inhalation route, childhood} \\
\text{DWI}_3 &= \text{Inhalation route, adult.}
\end{align*}
\]

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 ASF1 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,

\[
R = (p_{\text{oral}} \times \text{ASF}_1 \times d_0 \times \text{DWI}_3 \times C) + \\
(p_{\text{oral}} \times \text{ASF}_1 \times d_1 \times \text{DWI}_1 \times C) + \\
(p_{\text{oral}} \times \text{ASF}_2 \times d_2 \times \text{DWI}_2 \times C)
\]
This can be simplified by taking the common factor C outside a top-level bracket, and the common factors $p_{\text{oral}}$ and $p_{\text{inh}}$ can be taken outside second-level brackets:

$$R = C \times p_{\text{oral}} \times \left( \frac{\text{ASF}_1 \times d_0 \times \text{DWI}_0^0 +}{\text{ASF}_1 \times d_1 \times \text{DWI}_1^0 +} + \frac{\text{ASF}_2 \times d_2 \times \text{DWI}_2^0 +}{\text{ASF}_3 \times d_3 \times \text{DWI}_3^0} \right) + p_{\text{inh}} \times \left( \frac{\text{ASF}_1 \times d_0 \times \text{DWI}_0^3 +}{\text{ASF}_2 \times d_2 \times \text{DWI}_2^3 +} + \frac{\text{ASF}_3 \times d_3 \times \text{DWI}_3^3}{\text{ASF}_3 \times d_3 \times \text{DWI}_3^3} \right)$$

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:

$$C = \frac{R}{p_{\text{oral}} \times \left( \frac{\text{ASF}_1 \times d_0 \times \text{DWI}_0^0 +}{\text{ASF}_1 \times d_1 \times \text{DWI}_1^0 +} + \frac{\text{ASF}_2 \times d_2 \times \text{DWI}_2^0 +}{\text{ASF}_3 \times d_3 \times \text{DWI}_3^0} \right) + p_{\text{inh}} \times \left( \frac{\text{ASF}_1 \times d_0 \times \text{DWI}_0^3 +}{\text{ASF}_2 \times d_2 \times \text{DWI}_2^3 +} + \frac{\text{ASF}_3 \times d_3 \times \text{DWI}_3^3}{\text{ASF}_3 \times d_3 \times \text{DWI}_3^3} \right)}$$

Equation 3

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

Reference