UPDATED PUBLIC HEALTH GOALS FOR CHEMICALS IN CALIFORNIA DRINKING WATER

CHLOROBENZENE
ENDOTHALL
HEXACHLOROCYCLOPENTADIENE
SILVEX
TRICHLOROFLUOROMETHANE

April 2014

Director
Office of Environmental Health Hazard Assessment
George V. Alexeeff, Ph.D.

Updated Public Health Goals for Chemicals in California Drinking Water

Chlorobenzene

Endothall

Hexachlorocyclopentadiene

Silvex

Trichlorofluoromethane

April 2014

Prepared by

Pesticide and Environmental Toxicology Branch

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

LIST OF CONTRIBUTORS

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

Authors

Christopher Banks, Ph.D.

Wesley Smith, Ph.D.

Moira Sullivan, M.S.

Reviewers

Rose Cendak, M.S.

Shoba Iyer, Ph.D.

Lori Lim, Ph.D.

Nathalie Pham, Ph.D.

Rajpal Tomar, Ph.D.

Patty Wong, Ph.D.

K. Lily Wu, Ph.D.

Final Reviewers

Anna Fan, Ph.D., DABT

Elaine Khan, Ph.D.

Melanie Marty, Ph.D.

Lauren Zeise, Ph.D.

PREFACE

This Public Health Goal (PHG) technical support document provides 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. This document presents updates for five chemicals for which PHGs have been previously developed.

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SUMMARY

This document presents public health goal (PHG) updates for chlorobenzene, endothall, hexachlorocyclopentadiene (HCCPD), silvex, and trichlorofluoromethane. These chemicals are occasionally detected at low levels in public water supply wells in California.

A PHG is the concentration of a contaminant in drinking water that is estimated to pose no significant health risk to individuals consuming the water on a daily basis over a lifetime. 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.

In developing these updated PHGs, OEHHA incorporated the following practices/methods into the calculations:

1. Consideration of the most recent scientific literature
2. Toxicological evaluation and exposure assessment
3. Updated dose-response modeling, when appropriate
4. Updated drinking water ingestion rates
5. Dermal/inhalation exposures from household uses of tap water, when appropriate
6. An updated intraspecies variability factor to account for sensitive individuals.

Chlorobenzene is a halogenated aromatic hydrocarbon that is used in a variety of applications, including the manufacture of other organic chemicals and as a solvent. The original PHG of 200 parts per billion (ppb) was based on liver and serum effects in a subchronic oral toxicity study in dogs (Knapp et al., 1971). The updated PHG of 70 ppb is based on kidney effects in an oral two-generation reproductive toxicity study in rats (Nair et al., 1987). Additionally, exposure modeling for inhalation and dermal exposures, updated dose-response modeling and drinking water intake rates, and an updated intraspecies variability factor to account for sensitive individuals are incorporated into the derivation of the updated PHG.

Endothall is a pesticide used to control aquatic weeds and algal growth. The original PHG of 580 ppb was based on gastrointestinal effects observed in an oral chronic toxicity study in dogs (Keller, 1965). This study is retained as the critical study (the study on which the PHG calculation is based), and the updated PHG of 94 ppb is derived using an updated drinking water ingestion rate and an updated interspecies extrapolation factor to account for differences between dogs and humans.

Hexachlorocyclopentadiene (HCCPD) is a chemical intermediate in the synthesis of various chlorinated pesticides. The original PHG of 50 ppb was based on stomach effects in a subchronic oral toxicity study in rats and mice (Abdo et al., 1984). This study is retained as the critical study, and the updated PHG of 2 ppb is derived using exposure modeling for inhalation and dermal exposures, updated dose-response

modeling and drinking water intake rates, and an updated intraspecies variability factor to account for sensitive individuals.

Silvex is an herbicide that was used to control aquatic weeds before its use was banned in 1985. The original PHG of 25 ppb was based on liver toxicity in a chronic oral toxicity study in dogs (Mullison, 1966). This study is retained as the critical study, and the updated PHG of 3 ppb is derived using exposure modeling for inhalation and dermal exposures, updated drinking water intake rates, and an updated intraspecies variability factor to account for sensitive individuals.

Trichlorofluoromethane is a chlorofluorocarbon that was primarily used as a solvent, refrigerant, and aerosol propellant. The original PHG of 700 ppb was based on liver effects and changes in blood chemistry in a subchronic inhalation toxicity study in dogs (Jenkins et al., 1970). The updated PHG of 1300 ppb is based on increased incidences of mortality in a chronic oral study in rats (NCI, 1978). Additionally, exposure modeling for inhalation and dermal exposures, updated drinking water intake rates, and an updated intraspecies variability factor to account for sensitive individuals are incorporated into the derivation of the PHG.

The updated PHGs and associated changes, along with a comparison with original PHG values are shown in Table 1.

Table 1. Updated PHGs and associated changes

Chemical	Original PHG in ppb[a]	Updated PHG in ppb	CA MCL[b] in ppb	Endpoint[c]	Change(s)
Chlorobenzene	200 (OEHHA, 2003)	70	70	kidney effects	• Different critical study and endpoint • Updated dose-response modeling • Updated inhalation and dermal exposure estimates • Updated water intake rate • Updated intraspecies variability factor
Endothall	580 (OEHHA, 1997)	94	100	gastrointestinal effects	• Updated water intake rate • Updated intraspecies variability factor
Hexachlorocyclo-pentadiene (HCCPD)	50 (OEHHA, 1999)	2	50	stomach effects	• Updated dose-response modeling • Updated inhalation and dermal exposure estimates • Updated water intake rate • Updated intraspecies variability factor
Silvex (2,4,5-TP)	25 (OEHHA, 2003)	3	50	liver effects	• Updated inhalation and dermal exposure estimates • Updated water intake rate • Updated intraspecies variability factor
Trichlorofluoro-methane (FC-11)	700 (OEHHA, 1997)	1300	150	increased mortality	• Different critical study and endpoint • Updated inhalation and dermal exposure estimates • Updated water intake rate • Updated intraspecies variability factor

[a]ppb: parts per billion
[b]CA MCL: California Maximum Contaminant Level
[c]This is the endpoint identified for PHG calculation; more information on effects can be found in the review for each chemical.

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 the concentration of a contaminant in drinking water that is estimated to pose no significant health risk to individuals consuming the water on a daily basis over a lifetime. This document presents PHG updates for the five chemicals listed in Table 2. These updates incorporate a thorough review of the current scientific literature and the most current risk assessment practices and methods, as well as relevant chemical-specific toxicity data.

Table 2. Chemical limits and occurrence in California

Chemical	CAS No.[a]	Original PHG in ppb[b]	CA MCL[c] in ppb	Concentration Range of Detections[d] in ppb
Chlorobenzene	108-90-7	200 (OEHHA, 2003)	70	0.85 to 1.4
Endothall	145-73-3	580 (OEHHA, 1997)	100	64[e]
Hexachlorocyclo-pentadiene (HCCPD)	77-47-4	50 (OEHHA, 1999)	50	0.006[e]
Silvex (2,4,5-TP)	93-72-1	25 (OEHHA, 2003)	50	not detected
Trichlorofluoromethane (FC-11)	75-69-4	700 (OEHHA, 1997)	150	0.15 to 102

[a]CAS No.: Chemical Abstracts Service Registry Number
[b]ppb: parts per billion
[c]CA MCL: California Maximum Contaminant Level
[d]Based on California Department of Public Health monitoring data over the last three years for water supply wells, accessed with GeoTracker GAMA (http://geotracker.waterboards.ca.gov/gama/). The data do not indicate whether the source is raw (untreated) water or treated water; therefore, the results in the dataset may not be representative of the water delivered to customers.
[e]Single detection in the last three years

These chemicals have been detected with relatively low occurrence in California public water supply wells within the last three years. Monitoring data for these chemicals are provided by the California Department of Public Health (CDPH) and can be accessed with GeoTracker GAMA (http://geotracker.waterboards.ca.gov/gama/). The levels of each chemical detected were generally quite low, with no detections exceeding the California Maximum Contaminant Level (MCL).

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 conclusions 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 determining the sensitive 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 measure of response that leads to an adverse effect, that occurs at the lowest dose is selected as the critical effect from which the PHG is derived.

A PHG can be derived using general equations for calculating health-protective concentrations in drinking water. The five chemicals presented in this document have not been shown to be carcinogenic; therefore, their respective PHGs are calculated using equations for non-cancer endpoints.

Calculation of health-protective concentrations 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 a 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 established by fitting a dose-response model to the data. This is done using the United States Environmental Protection Agency's (U.S. EPA) Benchmark Dose Software (BMDS) when appropriate. This software is publicly available (http://www.epa.gov/ncea/bmds/). When using benchmark dose (BMD) modeling, the POD is the 95% lower confidence limit of a modeled dose (the BMD) resulting in a pre-determined level of response above background (typically 5%), known as the BMDL (L stands for lower confidence limit). Traditionally a no-observed-adverse-effect level (NOAEL) or a lowest-observed-adverse-effect level (LOAEL) has served as the POD, where low-dose extrapolation begins. This approach

is still used when data are not amenable to BMD modeling. Application of BMD modeling for non-cancer 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 an estimated maximum daily dose of a chemical (in milligrams per kilogram of body weight per day, mg/kg-day) that can be consumed by humans for an entire lifetime without toxic effects. This is similar to the term "reference dose" used by the U.S. EPA. To determine the ADD, the POD is divided by factors which account for uncertainties in the risk assessment, such as differences between animals and humans, and differences among humans in response to the toxicant. This combined factor is referred to as a total uncertainty factor (UF).

Uncertainty and Variability Factors

When developing health-protective levels for non-cancer effects based on animal toxicity studies, OEHHA generally applies a combined UF of 300: 10 for interspecies extrapolation, consisting of √10 for pharmacodynamics and √10 for pharmacokinetics; 30 for intraspecies variability, consisting of √10 for pharmacodynamics and 10 for pharmacokinetics, which accounts for diversity in these factors among humans (OEHHA, 2008). These default factors are applied unless data support an alternative value. A table of default uncertainty factors for ADD derivation is presented in Appendix III. Additional adjustments may be included depending on the limitations of available data.

The ADD is calculated using the following equation:

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

Daily Water Intake Equivalent

To calculate a drinking water public health goal, the ADD is converted to a concentration level in drinking water that accounts for the amount of exposure to the chemical people receive from using tap water. It includes intake from multiple routes of exposure (including oral ingestion, inhalation, and dermal contact) to contaminants in tap water from household uses (e.g., drinking, cooking, bathing, and showering). This is

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

For oral ingestion 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 individuals (U.S. 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 liters of water ingested per kilogram of body weight per day (L/kg-day). The updated water ingestion rates indicate that drinking water ingestion per unit body weight is higher in infants than in adults (see Table 6 below). Previous PHGs using ingestion rates of 2 liters per day for adults and 1 liter per day for a 10 kg child are being updated with these more refined estimates. For non-cancer 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 exposure to drinking water contaminants than the general population. These improvements in water ingestion estimates are crucial to the assessment of risk to these sensitive subgroups as well as 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 ingestion. For example, volatile organic compounds (VOCs) are released from tap water in the shower and the person showering can breathe them in. In some previous PHG documents, OEHHA assumed that inhalation and dermal exposures to volatile contaminants in tap water were equivalent to drinking 2 liters of water per day. 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 is using the CalTOX 4.0 multimedia total exposure model developed for the California Department of Toxic Substances Control by Lawrence Berkeley National Laboratory.[1] Details on model inputs used in calculating PHGs are described in Appendix I.

[1]Available at http://energy.lbl.gov/ied/era/caltox/index.html

Relative Source Contribution

The relative source contribution (RSC) is the proportion of exposures to a chemical attributed to tap water (including inhalation and dermal exposures, e.g., during showering), as part of total exposure from all sources (including food and air pollution). The RSC values typically range from 20 to 80 percent (expressed as 0.20 to 0.80), and are determined based on available exposure data. The lowest RSC applied for PHG derivation is 20 percent.

PHG Derivation

Following the determination of the ADD, the health-protective concentration (C, in milligrams/liter, mg/L) in drinking water can be derived by incorporating the drinking water intake of the chemical (DWI) and the relative amount of the chemical obtained from tap water (RSC):

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

If the health effects are only non-cancer endpoints, then the health-protective concentration, C, is the PHG

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UPDATED PHG FOR CHLOROBENZENE

Chlorobenzene (mono-chlorobenzene) belongs to a group of chemicals called halogenated aromatic hydrocarbons. Chlorobenzene is used in the manufacture of organic chemicals, dyestuffs and insecticides. It is also used as a solvent for adhesives, drugs, rubber, paints, dry cleaning, and as a fiber-swelling agent in textile processing.

Historically, the major source of chlorobenzene in drinking water has been discharge from chemical and agricultural chemical factories. Chlorobenzene was once used as an intermediate in production of the pesticide DDT (p,p'-dichlorodiphenyltrichloroethane). Since the banning of DDT in 1972, the use of chlorobenzene has decreased significantly and, according to the U.S. EPA's 2010 Toxics Release Inventory (TRI)[2] Chemical Report, 72 pounds of chlorobenzene were discharged into surface waters nationally, whereas on- and off-site disposal and other releases totaled 282,256 pounds. In moist soil, the majority of chlorobenzene should volatize to the atmosphere. Chlorobenzene is relatively mobile in sandy soil, where it biodegrades slowly or not at all, and is expected to leach into groundwater (OEHHA, 2003). Monitoring data from the past three years show that chlorobenzene has been detected in public water supply wells throughout California, with results ranging from < 0.5 to < 5 ppb[3], well below the California MCL of 70 ppb (CDPH, 2008), the original PHG of 200 ppb (OEHHA, 2003), and the updated PHG of 70 ppb.

2003 PHG

In 2003, OEHHA developed a PHG of 200 µg/L (200 ppb) for chlorobenzene in drinking water. The PHG was based on a subchronic oral toxicity study in dogs (Knapp et al*.,* 1971; erroneously cited as 1979 in OEHHA, 2003*)*. Male and female beagle dogs were given chlorobenzene orally by gelatin capsule at doses of 0, 27, 54, or 272 mg/kg-day, 5 days/week, for 13 weeks. A NOAEL for liver changes and changes in serum enzyme chemistry was identified as 27 mg/kg-day (19 mg/kg-day when adjusted for conversion of the 5 days/week dosing schedule to 7 days/week). Calculation of the PHG incorporated a total UF of 300 (10 for interspecies extrapolation, 10 for intraspecies variability, and, because the LOAELs for liver effects in subchronic and chronic studies in different species were fairly consistent, a UF of 3 was used to extrapolate from subchronic study results to lifetime exposure). The exposure evaluation assumed a 70 kg adult body weight, a multi-route water consumption rate of 4 L_{eq}/kg-day, and an RSC of 20 percent. There was inadequate evidence of chlorobenzene-induced

[2]Accessed at: http://iaspub.epa.gov/triexplorer/tri_release.chemical

[3]Data accessed with GeoTracker GAMA: http://geotracker.waterboards.ca.gov/gama/. The CDPH data for water supply wells accessed with GeoTracker GAMA do not indicate whether the source is raw (untreated) water or treated water; therefore, the results in the dataset may not be representative of the water delivered to customers.

carcinogenicity, thus the PHG was based on a non-cancer endpoint. Additionally, chlorobenzene did not cause developmental or reproductive toxicity in the available developmental/reproductive toxicity studies conducted with animals.

Recent Literature

A thorough review of the literature for chlorobenzene did not identify any critical new studies that could be used to derive a PHG value. One new in vivo animal toxicity study, however, suggests that chlorobenzene is a mutagen in rats (Siddiqui et al., 2006). Intraperitoneal administration of sublethal doses of chlorobenzene induced significant cytogenetic damage in bone marrow cells, leading to micronucleus induction and other chromosomal abnormalities. The clastogenic effects were both dose- and time-dependent. This study supports the positive findings of a limited number of previous in vivo studies on the genotoxicity of chlorobenzene in mice (Mohtashamipur et al., 1987), rats (Grilli et al., 1985), and occupationally exposed humans (Major et al., 1992-1993). However, the effects observed in the animal studies were seen at relatively high concentrations while bacterial mutagenicity tests were clearly negative, suggesting that chlorobenzene may have marginal genotoxic potential (OEHHA, 2003). This limited finding does not impact OEHHA's earlier determination that there is inadequate evidence of carcinogenicity for chlorobenzene. This is also consistent with U.S. EPA's designation of chlorobenzene as a Group D carcinogen ("not classifiable as to human carcinogenicity") (U.S. EPA, 1989).

PHG Derivation

Re-evaluation of the Knapp et al. (1971) subchronic dog study, which was summarized in a meeting abstract, showed that it is not the optimal study for the development of a PHG. Hazleton Laboratories performed the study for the Monsanto Company in 1967, but the full report cannot be located. The U.S. EPA Integrated Risk Information System (IRIS) based its 1989 oral reference dose (RfD) for chlorobenzene (U.S. EPA, 1989) on the unpublished 1967 Monsanto report and briefly described the study. Knapp et al. (1971) reported no consistent signs of chlorobenzene-induced toxicity at the intermediate- and low-dose levels, but the U.S. EPA review (1989) concluded that chlorobenzene-related hepatotoxicity was observed among dogs in the intermediate-dose group (54 mg/kg-day) and identified a NOAEL at 27 mg/kg-day (19 mg/kg-day when adjusted for 5 days/week exposure). Based on this NOAEL, OEHHA (2003) developed the original PHG of 200 ppb for chlorobenzene in drinking water.

Among the available toxicity studies on chlorobenzene, the present update determined that results from a 2-generation reproductive toxicity study in rats (Nair et al., 1987) provide the best data for the development of the PHG for chlorobenzene. OEHHA had previously used this study as the basis for the chlorobenzene reference exposure level in air (OEHHA, 2000). Nair and associates (1987) exposed groups of 30 male and 30 female Sprague-Dawley rats (the F_0 generation) to 0, 50, 150 or 450 parts-per-million (ppm) chlorobenzene vapor 6 hours/day, 7 days/week, for 10 weeks prior to mating and during mating, gestation, and lactation. Dams were not exposed from gestation day 20

to lactation day 4 in order to reduce the stress to dams at parturition and to pups early in lactation. Thirty animals/sex of the offspring (the F_1 generation) were then exposed to the same concentrations of chlorobenzene as the F_0 generation, beginning one week post-weaning and lasting for 11 weeks before mating, and through mating, gestation, and lactation. Liver, kidneys, pituitary gland, and reproductive organs were examined microscopically in F_0 and F_1 controls and 450 ppm animals, and liver, kidneys, and testes were examined in male rats exposed to 50 and 150 ppm chlorobenzene. Brain weights of F_0 and F_1 adults were recorded but not presented and neither were the histological data for the pituitary gland, suggesting there were no observable adverse effects in these organs. The authors reported that hepatocellular hypertrophy and renal changes (tubular dilation with eosinophilic material, interstitial nephritis, and foci of regenerative epithelium) were observed among F_0 and F_1 male rats exposed to 150 and 450 ppm chlorobenzene (Table 3). These changes were also observed in the highest-dose females, whereas observations for lower dose females were not reported. Therefore, only data from the male rats are presented here.

Table 3. Toxicity data for male rats exposed to chlorobenzene via inhalation in a 2-generation study (Nair et al., 1987)

Generation	Endpoint	Control	50 ppm	150 ppm	450 ppm
F_0	renal interstitial nephritis-bilateral	1/30[a]	2/30	7/30*	9/30*
F_0	renal tubular dilation-bilateral with eosinophilic material	0/30	1/30	4/30	15/30*
F_0	renal changes (foci of regenerative epithelium-bilateral)	0/30	1/30	5/30*	8/30*
F_1	renal interstitial nephritis-bilateral	0/30	1/30	6/30*	11/30*
F_1	increased mean relative liver weight (g/100g body weight)[b]	3.47 ± 0.32[c]	3.73 ± 0.36**	4.15 ± 0.46**	4.44 ± 0.40**

[a]Number of animals affected/total number of animals examined
[b]30 animals/dose
[c]Mean ± standard deviation
* Significantly different from control, p≤0.05, calculated by OEHHA using Fisher's exact test
** Significantly different from control, p≤0.05, using the parametric Dunnett test (Nair et al. 1987)

The study data show that the mean relative liver weight for F_1 males in the lowest exposure group of 50 ppm was statistically significantly elevated (p≤0.05) compared to the control group. The authors reported there was no adverse effect of treatment on body weight or food consumption. In addition, there were signs of a dose-dependent increase in kidney changes (interstitial nephritis, focal epithelial regeneration) in the F_0

generation after exposure to >50 ppm chlorobenzene. Furthermore, the incidence of dilated renal pelvis was elevated in all treated groups among F_1 adults when compared to controls.

Benchmark dose modeling (U.S. EPA BMDS, Version 2.2) of the incidence data for renal changes seen in male rats yield $BMDL_{05}$ values (as air concentrations) of 28.8 and 27.9 ppm chlorobenzene for interstitial nephritis and renal tubular dilation, respectively, observed in the F_0 generation (Table 4). The $BMDL_{05}$ is the lower limit of the 95% confidence interval of the BMD resulting in a 5% increase in response above background. Additionally, the $BMDL_{05}$ for interstitial nephritis observed in the F_1 generation is 32.2 ppm. Because there is good agreement between the $BMDL_{05}$ values for renal endpoints in both the F_0 and F_1 generations, OEHHA is selecting the lowest $BMDL_{05}$ (27.9 ppm), which has a good fit to the kidney effects data from the F_0 generation, as the POD for the PHG. This $BMDL_{05}$ concentration is equivalent to a dose of 8.9 mg/kg-day, as explained below. Details of the BMD analyses are presented in Appendix II.

Table 4. Benchmark dose modeling of endpoints in male rats (Nair et al. 1987)

Generation	Endpoint	Model[a]	BMD_{05} (ppm in air)	$BMDL_{05}$ (ppm in air)	$BMDL_{05}$ (mg/kg-day)
F_0	interstitial nephritis	LogLogistic	49.7	28.8	9.2
F_0	renal tubular dilation with eosinophilic material	Quantal-Linear	39.7	27.9	**8.9**
F_0	renal changes (foci of regenerative epithelium)	LogLogistic	55.8	34.6	11.0
F_1	renal interstitial nephritis	Gamma[b]	46.5	32.2	10.3
F_1	increased mean relative liver weight	Exponential	66.2[c]	44.6[c]	14.2[c]

[a]All models were run with default parameters.
[b]The Gamma, Multistage, Weibull, and Quantal-Linear models produced the same results.
[c]For continuous data, the benchmark response is one standard deviation above the control mean (resulting in BMD_{1SD} and $BMDL_{1SD}$, respectively).

Doses in mg/kg-day were calculated from exposure concentrations of ppm in air using estimates of body weight and inhalation rate. The average male rat body weight of 0.528 kg was calculated from the relative liver weight data presented by Nair et al. (1987), and the rat inhalation rate (I_{rat}) of 0.293 m^3/day was calculated from the equation (Anderson et al., 1983):

$$I_{rat} = 0.105 \times (BW_{rat}/0.113)^{2/3},$$

where BW is body weight.

Using a conversion factor of 4.6 mg/m^3/ppm for chlorobenzene (OEHHA, 2000), dose adjustment 6 hrs/24 hrs and 0.5 factor for the difference in absorption following inhalation versus oral exposure (Raabe, 1986; 1988, as cited in OEHHA, 2003), concentrations in ppm were converted to mg/kg-day with the following equation:

$$\frac{\text{Conc. (ppm)} \times 6/24 \times 4.6 \text{ mg/m}^3\text{/ppm} \times 0.293 \text{ m}^3\text{/day} \times 0.5}{0.528 \text{ kg}} = \text{Dose (mg/kg-day)}$$

The use of BMD modeling reduces uncertainty in the POD used in calculating the PHG. For risk assessment purposes, the $BMDL_{05}$ is used in place of the NOAEL in calculating health protective advisory levels. In this instance, the NOAEL (19 mg/kg-day) from Knapp et al. (1971) and the $BMDL_{05}$ (8.9 mg/kg-day) from Nair et al. (1987) are comparable, despite being derived using differing methodologies, different species, and different routes of exposure. Because Nair et al. (1987) is a better reported, more robust study than Knapp et al. (1971), OEHHA is selecting it as the critical study for this update.

Using the $BMDL_{05}$ of 8.9 mg/kg-day for renal toxicity in male rats derived from the Nair et al. (1987) study, the ADD is calculated as:

$$\text{ADD} = \frac{\text{POD}}{\text{UF}} = \frac{8.9 \text{ mg/kg-day}}{300} = 0.03 \text{ mg/kg-day}$$

A total UF of 300 is applied: 10 for interspecies extrapolation, and 30 for intraspecies variability. Although the animals were exposed to chlorobenzene for a less-than-lifetime duration, their total exposure duration comprised >12% of their lifetime, thus a UF for extrapolation from subchronic to chronic exposure is not necessary (OEHHA, 2008).

Inhalation and dermal exposures to chlorobenzene in tap water are calculated for various life stages using CalTOX modeling. Details on model inputs and outputs are presented in Appendix I. The relative contributions from each route to the overall exposure to chlorobenzene in tap water are presented in Table 5. The tap water exposure equivalencies for inhalation and dermal exposure are then calculated using life-stage-specific oral ingestion rates (OEHHA, 2012) and the relative contribution of each route (Table 6).

Table 5. CalTOX results for relative contributions of multiple routes of exposure to chlorobenzene in tap water for various life stages

Life Stage	Oral Ingestion (%)	Inhalation (%)	Dermal (%)
Fetus (Pregnancy)	51	36	13
Infant	88	0[a]	12
Child	41	46	13
Adult	53	32	15

[a]Infants are expected to be exposed to negligible levels of chemicals in tap water via inhalation (compared to other pathways) because they typically do not shower or flush toilets. These are the dominant inhalation exposure scenarios, therefore the inhalation pathway is excluded for infants.

Table 6. Total liter equivalent values for multi-route exposure to chlorobenzene in tap water

Life Stage	Age range (years)	Oral Ingestion (L/kg-day)	Inhalation[a,b] (L_{eq}/kg-day)	Dermal[a] (L_{eq}/kg-day)	Total Exposure (L_{eq}/kg-day)
Fetus (Pregnancy)	N/A[c]	0.047[d]	0.017[d]	0.012[d]	0.076
Infant	0-2	0.196	0	0.027	0.223
Child	2-16	0.061	0.034	0.019	0.114
Adult	16-70	0.045	0.014	0.013	0.072
Time-weighted average over lifetime					0.086

[a]Inhalation and dermal exposure estimates are calculated using life-stage-specific oral ingestion rates (OEHHA, 2012) and the corresponding relative contribution of the oral ingestion values.
[b]L_{eq} values for the inhalation route assumes 50% absorption in the lung (OEHHA, 2003).
[c]Not applicable; a time period of 0.75 year is used to represent the fetus in calculating the time-weighted average total exposure over a lifetime of 70 years.
[d]The fetus is assumed to be exposed to the same dose as the pregnant mother, thus the liter equivalent values for the fetus are based on exposure parameters for the pregnant woman as shown in Table A1 of Appendix I.

A default RSC of 0.20 is used because oral intake from drinking water is believed to be relatively minor compared to inhalation exposure from ambient air, which is anticipated to be the predominant exposure route (OEHHA, 2003). The health-protective concentration, C, is calculated as follows:

$$C = \frac{0.03 \text{ mg/kg-day} \times 0.20}{0.086 \text{ } L_{eq}\text{/kg-day}} = 0.070 \text{ mg/L} = 70 \text{ } \mu\text{g/L or 70 ppb}$$

Thus 70 ppb is being adopted as the updated PHG. It is based on kidney effects observed in the 2-generation inhalation study in rats by Nair et al. (1987), and is approximately 3-fold lower than the original PHG value of 200 µg/L (or 200 ppb) for chlorobenzene (OEHHA, 2003). U.S. EPA's Maximum Contaminant Level Goal (MCLG) for chlorobenzene is 100 ppb, based on liver effects in the dog study discussed above and an uncertainty factor of 1,000 (10 for interspecies extrapolation, 10 for intraspecies variability, and 10 for subchronic to chronic extrapolation), an RSC of 0.20,

and a drinking water intake rate of 2 L/day.[4] The updated PHG is based on a peer-reviewed published study, applies BMD modeling for low-dose extrapolation, and confirms the findings of several other studies using different species and exposure routes. Therefore, there is less uncertainty in the updated PHG value.

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UPDATED PHG FOR ENDOTHALL

Endothall is an herbicide and algaecide used to kill aquatic weeds and control algal growth. It also acts as a defoliant in cotton production. Endothall is actively used in California, with the California Department of Pesticide Regulation (DPR) reporting that 11,749 pounds of the dipotassium salt and 2,433 pounds of the mono [N,N-dimethyl alkylamine] salt were applied in 2010 (DPR, 2010). Monitoring data from the past three years show endothall has been detected in water supply wells across California, but all detected levels were below the state and federal MCL of 100 ppb (CDPH, 2008), with the vast majority of samples containing less than 45 ppb.[5] Therefore, significant public exposure to endothall via drinking water is not expected.

1997 PHG

The original PHG of 580 ppb (OEHHA, 1997) was based on a chronic toxicity study in which purebred beagle dogs (three/sex/group) were administered disodium endothall at 0, 100, 300, or 800 ppm (0, 2.5, 7.5 or 20 mg/kg-day, respectively) for two years in their diet (Keller, 1965). The highest dose was increased gradually to 2,000 ppm by the 22nd month. Increases in organ weight and organ-to-body weight ratio for the stomach and small intestine were observed in the intermediate- and high-dose groups and appeared to be dose-related. A NOAEL of 2.5 mg/kg-day was identified and calculation of the PHG incorporated a total UF of 30 (10 for intraspecies variability and 3 for interspecies extrapolation). The exposure parameters in the PHG calculation assumed a 70 kg adult body weight, water consumption rate of 2 L/day, and an RSC of 20 percent. There was insufficient evidence for the carcinogenicity of endothall, and cancer slope factors were not determined.

Recent Literature

A thorough examination of recent literature revealed no new toxicity studies since the publication of the original endothall PHG in 1997. However, OEHHA reviewed a 2005 U.S. EPA reregistration eligibility decision document for endothall (U.S. EPA, 2005) and located a multigenerational study by Trutter (1993). The study had been reviewed in the 1997 PHG document, but the document reported incorrect doses and did not describe a fetal birth weight endpoint (see below). From this study, a chronic reference dose of 7 µg/kg-day was derived (U.S. EPA, 2005). Trutter (1993) administered to Sprague-Dawley rats at 6 weeks of age the disodium salt of endothall (19.9%) in the diet (26/sex/dose) at 0, 30, 150, or 900 ppm for 2 successive generations (Trutter, 1993). The reported average doses across both generations were 0, 2, 10.2, or 68 mg/kg-day for males and 0, 2.3, 11.7, or 78.7 mg/kg-day for females, during the premating period. Doses were estimated to be 0, 1.8, 9.4, or 60 mg/kg-day for females during the gestation period, and 0, 3.1, 17.3, or 104.7 mg/kg-day during the lactation period.

[5]Data accessed with GeoTracker GAMA: http://geotracker.waterboards.ca.gov/gama/

There was no evidence of male or female reproductive toxicity in any generation. Decreased body weights were observed in parental rats and in the F_1 and F_2 pups at the highest dose on postnatal day (PND) 0 (Trutter, 1993). The percent reductions in pup body weight were comparable to body weight reductions seen in dams during gestation (6-9%) in the F_0 and F_1 generations. The observed dose-response was non-monotonic, and the effect was statistically significant on PND 0, but not on PND 4 or PND 7 (culling F_1 female pups to 4/litter on day 4 achieved statistical significance at the highest dose). U.S. EPA identified a developmental NOAEL of 9.4 mg/kg-day based on decreased pup body weight in the F_1 and F_2 generations. OEHHA did not select this dataset for PHG derivation because reduction in fetal birth weight was not the most sensitive toxicity endpoint, and the non-monotonic nature of the dataset complicated the analysis of the dose-response relationship.

Additionally, U.S. EPA (2005) identified a parental LOAEL of 2 mg/kg-day for males and 2.3 mg/kg-day for females based on lesions of the gastric epithelium observed in the Trutter (1993) study. Exposure to ≥2 mg/kg-day endothall in the diet appeared to induce proliferation of gastric foveolar epithelium in the stomach of F_1 animals (Trutter, 1993). However, there were no stomach examinations of control males, and only one control female was examined for stomach pathology. Furthermore, the low numbers of observed animals (0 to 3 animals/sex/dose) make it difficult to accurately assess the incidence of stomach alterations, and whether toxicity is incidental or compound-related. Due to the absence of acceptable control data, confidence in the histopathologic data is low and OEHHA does not consider these data adequate for PHG derivation.

PHG Derivation

After evaluating the available endothall toxicity studies, OEHHA is retaining the Keller (1965) study as the critical study. Because of the small sample size (3 dogs/sex/dose) and the complicating issue of the highest dose increasing incrementally over the course of two years, OEHHA determined that this dataset would not be amenable to BMD modeling. The NOAEL of 2.5 mg/kg-day for increased stomach and small intestine weight is retained as the POD, and a total UF of 100 is applied (10 for interspecies extrapolation and 10 for intraspecies variability).

In the 1997 PHG, an interspecies UF of 3 for pharmacodynamics was applied because it was assumed that toxicity results from the activity of the parent compound and that pharmacokinetics did not contribute to toxicity. However comparative data on the rates of excretion between rats and humans are not available. If, as expected, the rat excretes the parent compound at a faster rate than humans, a UF of 3 may be insufficient. Thus, the full interspecies UF of 10 is applied.

An examination of endothall metabolism in rats revealed that it was poorly absorbed, and that it was excreted predominantly as the parent compound in feces (>90%), urine (approximately 7%), or exhaled as carbon dioxide (approximately 3%). Biotransformation was not evident following oral administration of endothall (Soo et al.,

1967). Additional metabolic studies cited in a 2004 U.S. EPA toxicity summary also reported excretion of unchanged endothall administered to rats via intravenous injection or oral gavage (Hallifax, 1990a; Hallifax, 1990b; Bounds, 1997 as cited in U.S. EPA, 2004). Because it is anticipated that endothall is minimally absorbed and metabolized in humans, an intraspecies pharmacokinetic factor of √10 is sufficient to account for differences in excretion among members of the population. Thus, with the default intraspecies pharmacodynamics factor of √10, the total intraspecies variability factor is 10. Therefore, the ADD is:

$$\text{ADD} = \frac{\text{POD}}{\text{UF}} = \frac{2.5 \text{ mg/kg-day}}{100} = 0.025 \text{ mg/kg-day}$$

From the same study (Keller, 1965), U.S. EPA derived an oral reference dose of 0.02 mg/kg-day (the NOAEL was rounded from 2.5 to 2.0 mg/kg-day) using a total uncertainty factor of 100 (10 for intraspecies variability, 10 for interspecies extrapolation) (U.S. EPA, 1991).

The daily water intake rates adjusted for body weight using "consumers only" 95th percentile values accounts for high-end water consumers of all ages (OEHHA, 2012). The time-weighted average 95th percentile lifetime daily water consumption rate is 0.053 L/kg-day.

Endothall is not a volatile compound, and inhalation exposure to endothall in tap water is predicted to be negligible. A dermal penetration study (Johnson et al., 1990) cited by U.S. EPA (2004) suggested that endothall is poorly absorbed by the skin. In this study, [^{14}C]-endothall monohydrate as dilutions of the Hydrothal 191 Aquatic Algicide and Herbicide formulation was applied dermally to Sprague-Dawley rats (30/dose) at concentrations of 0.15, 0.75 and 1.5% spread over 24 cm^2 of skin area. These concentrations were reported as dermal dose levels of 0.0125 mg/cm^2, 0.0625 mg/cm^2, and 0.125 mg/cm^2, respectively. Absorption was measured by examining [^{14}C]-endothall equivalents in the urine, feces, skin site, and carcass. At 24 hours, systemic bioavailability of 3.9%, 2.2%, and 7.3% were reported at the 0.0125, 0.0625 and 0.125 mg/cm^2 dose levels, respectively. Urinary excretion accounted for 2.3% of the highest applied dose, whereas fecal excretion was <0.1% at all doses. The majority of endothall (55-82%) was washed from the application site. Therefore, exposure to endothall in water is estimated to occur primarily through oral ingestion.

The RSC is set to the default value of 0.20 because endothall is actively in use in California and specific information regarding source contribution (e.g., exposure to residue on food or soil) is not available.

The public health-protective concentration, C, is:

$$C = \frac{0.025 \text{ mg/kg-day} \times 0.20}{0.053 \text{ L/kg-day}} = 0.094 \text{ mg/L} = 94 \text{ μg/L or 94 ppb}$$

Thus, OEHHA is publishing a PHG for endothall of 94 ppb.

Endothall is not commonly found at high levels in California water systems, and wide-spread public exposure is not anticipated. Additionally, there are no new toxicity studies for this chemical. However, an update of risk assessment methodology to provide an improved estimation of water consumption by the general population and an update of the interspecies extrapolation factor have changed the 1997 PHG of 580 ppb to its current value of 94 ppb. U.S. EPA's MCLG for endothall is 100 ppb,[6] based on stomach and intestinal effects from the Keller study (listed as Pennwalt AgChem., 1965, in U.S. EPA's IRIS database; both studies have MRID No. 00101735[7]), using a total uncertainty factor of 100 for inter- and intraspecies differences, an RSC of 0.20, and a drinking water intake rate of 2 L/day .

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UPDATED PHG FOR HEXACHLOROCYCLOPENTADIENE

Hexachlorocyclopentadiene (HCCPD) is a chemical intermediate in the manufacture of chlorinated cyclodiene pesticides, such as endrin, dieldrin, and chlordane. Registration for all uses of endrin, dieldrin, and chlordane were cancelled in the U.S. in the 1980s. However, HCCPD is also used in the manufacture of flame retardants, nonflammable resins, plastics, ketones, esters, fluorocarbons, and dyes (HSDB, 2012). U.S. EPA's Toxics Release Inventory (TRI) reported that 474 pounds of HCCPD were released to air, 46 pounds were released to landfills, and 3 pounds were released to surface water in the U.S. in 2011.[8] Monitoring data from the past three years show that HCCPD has been detected in public water supply wells at various sites in California, but all levels were below 1 ppb, which is well below the state and federal MCL of 50 ppb (CDPH, 2008).[9] Therefore, public exposure to significant levels of HCCPD in California drinking water is not anticipated.

1999 PHG

In the 1999 HCCPD PHG, the health-protective drinking water concentration was derived from a subchronic oral toxicity study by Abdo et al. (1984), where B6C3F1 mice and F344 rats (10/sex/dose) were administered HCCPD in corn oil via oral gavage once daily, 5 days/week, for 13 weeks (OEHHA, 1999). Rats received doses of 0, 10, 19, 38, 75, or 150 mg/kg-day HCCPD, whereas mice received doses of 0, 19, 38, 75, 150, or 300 mg/kg-day HCCPD. In the highest-dose group, increased mortality and increased incidences of stomach and kidney lesions were observed in both species (Abdo et al., 1984). A NOAEL of 10 mg/kg-day in rats was selected as the POD, and a UF of 1,000 (10 for interspecies extrapolation, 10 for intraspecies variability, and 10 for the use of a subchronic study for lifetime exposure) was applied. The exposure parameters in the PHG calculation assumed a 70 kg adult body weight, an equivalent water consumption rate of 4 L_{eq}/day, and an RSC of 40 percent. Due to insufficient evidence of HCCPD-induced carcinogenicity, the compound was not considered to be carcinogenic and cancer slope factors were not determined. Additionally, HCCPD did not cause developmental toxicity in the available studies conducted with animals. However, there were no reproductive toxicity studies available.

Recent Literature

A thorough review of the current scientific literature on HCCPD did not identify any new critical studies that could be used to derive a PHG. However, there are a few reports that examine HCCPD and its potential to induce adverse health effects. One recent report describes case studies of two human subjects who developed fragile X-associated tremor/ataxia syndrome (FXTAS) earlier than the normal age of onset (Paul et al., 2010). Both individuals were carriers of the premutation of the fragile X mental

[8]Available online at: http://iaspub.epa.gov/triexplorer/tri_release.chemical.
[9]Data accessible online with GeoTracker GAMA: http://geotracker.waterboards.ca.gov/gama/

retardation 1 gene (FMR1), and both lived near a chemical plant that produced HCCPD from 1956 to 1977. Due to improper disposal practices, the chemical plant contaminated the air, surface water, and groundwater with HCCPD, and it was presumed that the individuals were chronically exposed. The authors reported that chronic exposure to particular environmental toxicants accelerated the onset of FXTAS in the FMR1 premutation carriers. However, there are no exposure data presented in this report, and it is unclear to what levels of HCCPD the individuals were exposed. More evidence is needed to establish a causative link between HCCPD exposure and early onset FXTAS in FMR1 premutation carriers.

Another recent study reported that male mice given tap water contaminated with a number of chemicals, from Nanjing, China, for 90 days displayed signs of reproductive toxicity, including a reduction in the percentage of elongated spermatids, alterations in germ cell composition, increased level of abnormal sperm, and histopathological abnormalities in the testes (Zhao et al., 2011). However, because HCCPD was one of 22 chemicals detected, the data are not adequate for an evaluation of the toxicity of HCCPD itself.

Boogaard et al. (1993) reported that male workers in a Dutch chemical plant (n = 73) exposed via inhalation to HCCPD and three other chlorinated hydrocarbons (allyl chloride, 1,3-dichloropropene, and epichlorohydrin) did not exhibit signs of liver or kidney toxicity. Despite the fact that HCCPD and allyl chloride levels sometimes exceeded the maximum allowable concentration levels in the Netherlands, the only significant change observed was increased urinary albumin levels in the exposed workers. However, the reported urinary albumin levels were within normal range and not correlated with employment duration (Boogaard et al., 1993).

PHG Derivation

After evaluating the available HCCPD toxicity studies, OEHHA is retaining the Abdo et al. (1984) study for PHG derivation. The incidences of stomach lesions and toxic nephrosis in rats and mice are summarized below in Tables 7-9.

Table 7. Incidence of stomach lesions in F344 rats exposed to HCCPD via oral gavage for 13 weeks (Abdo et al., 1984)

Endpoint	mg/kg-day					
	0	**10**	**19**	**38**	**75**	**150**
Males						
Epithelial hyperplasia	0/10[a]	0/10	0/10	5/10*	9/10*	8/9*
Focal inflammation	0/10	0/10	0/10	4/10	9/10*	8/9*
Ulceration	0/10	0/10	0/10	2/10	2/10	0/10 [sic]

Endpoint	mg/kg-day					
	0	10	19	38	75	150
Total lesions	0/10	0/10	0/10	5/10*	9/10*	8/9*
Females						
Epithelial hyperplasia	0/10	0/10	2/10	5/10*	9/10*	9/10*
Focal inflammation	0/10	0/10	2/10	2/10	9/10*	9/10*
Ulceration	0/10	0/10	0/10	0/10	0/10	0/10
Total lesions	0/10	0/10	2/10	5/10*	9/10*	9/10*

[a]Number of animals with lesions/number of animals examined
*Significantly different from control, p<0.05, calculated by OEHHA using Fisher's exact test

Table 8. Incidence of stomach lesions in B6C3F1 mice exposed to HCCPD via oral gavage for 13 weeks (Abdo et al., 1984)

Endpoint	mg/kg-day					
	0	19	38	75	150	300
Males						
Epithelial hyperplasia	0/10[a]	0/10	2/10	8/10*	9/10*	8/10*
Focal inflammation	0/10	0/10	2/10	7/10*	7/10*	10/10*
Ulceration	0/10	0/10	0/10	0/10	0/10	8/10*
Total lesions	0/10	0/10	2/10	8/10*	9/10*	10/10*
Females						
Epithelial hyperplasia	0/10	0/10	2/9	9/10*	10/10*	7/9*
Focal inflammation	0/10	0/10	2/9	6/10*	10/10*	9/9*
Ulceration	0/10	0/10	0/10	0/10	0/10	1/9
Total lesions	0/10	0/10	2/9	9/10*	10/10*	9/9*

[a]Number of animals with lesions/number of animals examined
*Significantly different from control, p<0.05, calculated by OEHHA using Fisher's exact test

Table 9. Incidence of toxic nephrosis in kidneys of F344 rats and B6C3F1 mice exposed to HCCPD via oral gavage for 13 weeks (Abdo et al., 1984)

Sex/Species	mg/kg-day					
	0	**10**	**19**	**38**	**75**	**150**
Male rats	0/10[a]	0/10	0/10	10/10*	9/10*	8/10*
Female rats	0/10	0/10	0/10	10/10*	10/10*	10/10*
Sex/Species	**mg/kg-day**					
	0	**19**	**38**	**75**	**150**	**300**
Male mice	0/10	0/10	0/10	0/10	0/10	0/10
Female mice	0/10	0/10	0/10	9/10*	10/10*	7/10*

[a]Number of animals affected/total number of animals examined
*Significantly different from control, $p<0.05$, calculated by OEHHA using Fisher's exact test

OEHHA reanalyzed the dose-response data in the Abdo et al. (1984) studies and estimated the POD using BMDS (Version 2.2, U.S. EPA). The BMD modeling results are summarized in Table 10 and details of the BMD analyses are presented in Appendix II.

Table 10. Benchmark dose modeling of endpoints in rats and mice following oral exposure to HCCPD for 13 weeks, data from Abdo et al. (1984)

Endpoint	Model[a]	BMD_{05} (mg/kg-day)	$BMDL_{05}$ (mg/kg-day)
Male Rats			
Epithelial hyperplasia (stomach)	Dichotomous-Hill	32.1	26.0
Focal inflammation (stomach)	Dichotomous-Hill	32.9	26.6
Total stomach lesions	Dichotomous-Hill	32.1	26.0
Toxic nephrosis (kidney)	Dichotomous-Hill	22.9	17.1
Female Rats			
Epithelial hyperplasia (stomach)	LogLogistic	10.7	**4.71**
Focal inflammation (stomach)	LogLogistic	13.9	6.45
Total stomach lesions	LogLogistic	10.7	**4.71**
Toxic nephrosis (kidney)	LogProbit	24.6	17.4

Male Mice			
Epithelial hyperplasia (stomach)	Dichotomous-Hill	30.1	17.3
Focal inflammation (stomach)	LogProbit	21.5	10.3
Total stomach lesions	LogLogistic	23.6	12.8
Female Mice			
Epithelial hyperplasia (stomach)	Dichotomous-Hill	34.5	19.3
Focal inflammation (stomach)	Multistage	17.3	7.41
Total stomach lesions	Multistage	21.7	8.50
Toxic nephrosis (kidney)	Dichotomous-Hill	47.2	33.5

[a]All models were run with default parameters.

Among the modeled datasets, epithelial hyperplasia and total lesions in the stomach of female rats have good model fit, give the lowest $BMDL_{05}$, and are considered the most sensitive endpoints. Therefore, the $BMDL_{05}$ of 4.71 mg/kg-day is selected as the POD. For ADD determination, a total UF of 3,000 is applied: 10 for interspecies extrapolation, 30 for intraspecies variability, √10 for subchronic to chronic exposure extrapolation, and √10 for data deficiency due to the absence of reproductive toxicity studies. An additional adjustment factor of 5/7 is included in the ADD calculation to account for discontinuous exposure (gavage was administered 5 days/7 days). Therefore, the ADD is:

$$\text{ADD} = \frac{\text{POD}}{\text{UF}} = \frac{4.71 \text{ mg/kg-day} \times 5/7}{3{,}000} = 0.0011 \text{ mg/kg-day}$$

In the original PHG, an RSC of 40 percent, instead of the default 20 percent, was used because it was anticipated that volatile chemicals are less likely to be found in food and soil (OEHHA, 1999). In the absence of specific source data, OEHHA is keeping the relative source contribution at 40 percent.

The inhalation and dermal exposure pathways for HCCPD are estimated with the CalTOX model. Details of the CalTOX model inputs and outputs are presented in Appendix I. The relative contributions of each pathway to the total exposure to HCCPD in tap water are presented in Table 11.

Table 11. CalTOX results for relative contributions of multiple routes of exposure to HCCPD in tap water for various life stages

Life Stage	Oral Ingestion (%)	Inhalation (%)	Dermal (%)
Fetus (Pregnancy)	29	16	55
Infant	51	0[a]	49
Child	23	21	56
Adult	28	13	59

[a]Infants are expected to be exposed to negligible levels of chemicals in tap water via inhalation (compared to other pathways) because they typically do not shower or flush toilets. These are the dominant inhalation exposure scenarios, therefore the inhalation pathway is excluded for infants.

It has been reported that the lung retention of inhaled HCCPD in rats ranged from 77 percent after 30 minutes of exposure to 95 percent after 120 minutes of exposure (Lawrence and Dorough, 1982). The authors argued that the change in lung retention was due to the animal better acclimating to its environment during prolonged exposures, and not the result of any chemical or physiological process. There are no data quantifying HCCPD lung retention and pulmonary absorption in humans, thus for this PHG, it is assumed that 95 percent of inhaled HCCPD is absorbed into the bloodstream. Liter equivalent (L_{eq}) values for inhalation and dermal exposure are calculated using life-stage-specific oral ingestion rates (OEHHA, 2012) and the relative contribution of the oral ingestion value. These values are presented in Table 12.

Table 12. Total liter equivalent values for multi-route exposure to HCCPD in tap water

Life Stage	Age range (years)	Oral Ingestion (L/kg-day)	Inhalation[a,b] (L_{eq}/kg-day)	Dermal[a] (L_{eq}/kg-day)	Total Exposure (L_{eq}/kg-day)
Fetus (Pregnancy)	N/A[c]	0.047[d]	0.025[d]	0.089[d]	0.161
Infant	0-2	0.196	0	0.188	0.384
Child	2-16	0.061	0.053	0.149	0.263
Adult	16-70	0.045	0.020	0.095	0.160
Time-weighted average over lifetime					0.189

[a]Inhalation and dermal exposure estimates are calculated using life-stage-specific oral ingestion rates (OEHHA, 2012) and the corresponding relative contribution of the oral ingestion values.
[b]L_{eq} for inhalation assumes 95% absorption in the lung (Lawrence and Dorough, 1982).
[c]Not applicable; a time period of 0.75 year is used to represent the fetus in calculating the time-weighted average total exposure over a lifetime of 70 years.
[d]The fetus is assumed to be exposed to the same dose as the pregnant mother, thus the liter equivalent values for the fetus are based on exposure parameters for the pregnant woman as shown in Table A1 of Appendix I.

Using the total multi-route exposure estimate of 0.189 L_{eq}/kg-day, a health protective concentration (C) for HCCPD in tap water that protects against non-carcinogenic adverse health effects is:

$$C = \frac{0.0011 \text{ mg/kg-day} \times 0.40}{0.189 \text{ L}_{eq}\text{/kg-day}} = 0.002 \text{ mg/L} = 2 \text{ µg/L or 2 ppb}$$

Thus OEHHA is publishing 2 ppb as the PHG for HCCPD. This value is 25-fold lower than the 50 ppb value calculated in the 1999 PHG. U.S. EPA's MCLG for HCCPD is 50 ppb, based on kidney and stomach effects in rats from the Abdo et al. (1984) study, an uncertainty factor of 1,000 (10 for interspecies extrapolation, 10 for intraspecies variability, √10 for use of a subchronic study to characterize lifetime exposure, and √10 for database deficiencies due to the absence of reproductive studies), an RSC of 0.20, and a drinking water rate of 2 L/day.[10] In the previous PHG, non-oral exposures (inhalation and dermal) were assumed to be equivalent to the default oral exposure of 2 L/day, resulting in a total water consumption rate of 4 L_{eq}/day. However, results from CalTOX modeling suggest that this assumption may lead to an underestimation of the total contribution of the non-oral pathways. The updated PHG value incorporates more sophisticated estimations of the POD and multi-route exposure estimations, updated water intake rates, and includes an updated intraspecies variability factor to protect sensitive populations.

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UPDATED PHG FOR SILVEX (2,4,5-TP)

Silvex (2,4,5-TP; 2-(2,4,5-trichlorophenoxy)propionic acid) is a member of the phenoxy acid class of herbicides, which includes 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). These compounds were used primarily for mitigation of broadleaf weeds and later to control aquatic weeds along southern waterways. All registered uses for silvex were cancelled in 1985 due to contamination with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) as a by-product during production (HSDB, 2012; OEHHA, 2003). Silvex has not been detected in California public drinking water supply wells in the last three years.[11] The California MCL for silvex is 50 ppb (CDPH, 2008).

2003 PHG

The original PHG of 25 ppb (OEHHA, 2003) was based on a NOAEL of 0.9 mg/kg-day in a two-year feeding study conducted in beagle dogs (Mullison, 1966). Four dogs/sex/dose were exposed to KUROSAL® SL herbicide (potassium salt of silvex manufactured by Dow Chemical) in the diet at levels of 0, 56, 190, or 560 ppm. Changes in liver pathology were observed in males at 190 and 560 ppm and in females at 560 ppm. The NOAELs were identified as 56 ppm for males and 190 ppm for females, corresponding to 0.9 and 2.6 mg/kg-day, respectively. These liver changes were described in a later publication as "mild degeneration and necrosis of hepatocytes with slight fibroblastic proliferation" (Gehring and Betso, 1978). A UF of 1,000 (10 for interspecies extrapolation, 10 for intraspecies variability, and 10 for study deficiencies and data gaps) was applied. The original PHG included exposure assumptions of 70 kg adult body weight, an RSC of 80 percent, and a default water consumption rate of 2 L/day. There was insufficient evidence of silvex-induced carcinogenicity, thus the PHG was based on a non-cancer endpoint. Additionally, developmental toxicity studies were reviewed, and developmental effects were observed in mice and rats. However, deficiencies in study design and reporting precluded the use of these studies for PHG derivation.

Recent Literature

A survey of current scientific literature identified no new studies that would replace the Mullison (1966) study as the basis for the PHG derivation (OEHHA, 2003). The results of one large prospective study of breast cancer among farmer's wives (Engel et al., 2005) suggest that the use of this pesticide might be associated with an increased risk of breast cancer. Previous studies have not examined the relationship of silvex with breast cancer. While the finding in the Engel et al. study is of note, the authors caution that additional follow-up studies are needed for confirmation due to limitations in this study. As noted in the 2003 PHG, assessing the suggestive evidence of carcinogenicity in epidemiological studies of chlorophenoxy herbicides such as silvex has been

[11]Data accessible online with GeoTracker GAMA: http://geotracker.waterboards.ca.gov/gama/.

compromised by the presence of other compounds such as dioxin (OEHHA, 2003). Available animal studies are of low quality.

PHG Derivation

OEHHA is retaining the Mullison (1966) study as the critical toxicity study. The limited dose-response data reported precludes BMD modeling, thus the NOAEL of 0.9 mg/kg-day is used for PHG derivation. Using a total UF of 3,000 (30 for intraspecies variability, 10 for interspecies extrapolation, and 10 for study deficiencies and data gaps as described in the 2003 PHG), the ADD is calculated as:

$$\text{ADD} = \frac{\text{POD}}{\text{UF}} = \frac{0.9 \text{ mg/kg-day}}{3{,}000} = 0.0003 \text{ mg/kg-day}$$

Human exposure to silvex is assumed to occur primarily through domestic uses of tap water as the result of leaching from waste dump sites into groundwater (Gintautas et al., 1992). This route of exposure is also assumed to be the most probable due to the discontinuation of silvex production. Thus, an RSC of 80 percent was chosen to describe exposure to humans.

The inhalation and dermal exposure pathways for silvex are estimated with CalTOX modeling. Details of the CalTOX model inputs and outputs are presented in Appendix I. The relative contributions of each pathway to the total exposure to silvex in tap water are presented in Table 13.

Table 13. CalTOX results for relative contributions of multiple routes of exposure to silvex in tap water for various life stages

Life Stage	Oral Ingestion (%)	Inhalation (%)	Dermal (%)
Fetus (Pregnancy)	74	7	19
Infant	89	0[a]	11
Child	69	10	21
Adult	74	6	20

[a]Infants are expected to be exposed to negligible levels of chemicals in tap water via inhalation (compared to other pathways) because they typically do not shower or flush toilets. These are the dominant inhalation exposure scenarios, therefore the inhalation pathway is excluded for infants.

There are currently no animal or human data regarding the lung retention of inhaled silvex. Therefore, it is assumed that 100 percent of inhaled silvex is absorbed into the bloodstream. Liter equivalent (L_{eq}) values for inhalation and dermal exposure are calculated using life-stage-specific oral ingestion rates (OEHHA, 2012) and the relative contribution of the oral ingestion value. These values are presented in Table 14.

Table 14. Total liter equivalent values for multi-route exposure to silvex in tap water

Life Stage	Age range (years)	Oral Ingestion (L/kg-day)	Inhalation[a,b] (L_{eq}/kg-day)	Dermal[a] (L_{eq}/kg-day)	Total Exposure (L_{eq}/kg-day)
Fetus (Pregnancy)	N/A[c]	0.047[d]	0.004[d]	0.012[d]	0.063
Infant	0-2	0.196	0	0.024	0.220
Child	2-16	0.061	0.009	0.019	0.089
Adult	16-70	0.045	0.004	0.012	0.061
Time-weighted average over lifetime					0.072

[a]Inhalation and dermal exposure estimates are calculated using life-stage-specific oral ingestion rates (OEHHA, 2012) and the corresponding relative contribution of the oral ingestion values.
[b]L_{eq} for inhalation assumes 100% absorption in the lung.
[c]Not applicable; a time period of 0.75 year is used to represent the fetus in calculating the time-weighted average total exposure over a lifetime of 70 years.
[d]The fetus is assumed to be exposed to the same dose as the pregnant mother, thus the liter equivalent values for the fetus are based on exposure parameters for the pregnant woman as shown in Table A1 of Appendix I.

Using the multi-route exposure estimate of 0.072 L_{eq}/kg-day, the health-protective concentration is calculated as shown below.

$$C = \frac{0.0003 \text{ mg/kg-day} \times 0.80}{0.072 \text{ L/kg-day}} = 0.003 \text{ mg/L} = 3 \text{ } \mu\text{g/L or 3 ppb}$$

Thus the updated PHG is 3 pbb. U.S. EPA's MCLG for silvex is 50 ppb, based on liver effects in dogs from the Mullison (1966) study, an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for intraspecies variability), an RSC of 0.20, and a drinking water rate of 2 L/day.[12] The change in the PHG from 25 ppb to 3 ppb reflects a more accurately estimated drinking water consumption rate, more sophisticated multi-route exposure estimations, and an updated intraspecies variability factor to protect sensitive populations.

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UPDATED PHG FOR TRICHLOROFLUOROMETHANE (FC-11)

Trichlorofluoromethane (FC-11) belongs to a group of chemicals called chlorofluorocarbon chemicals (CFCs) containing carbon, fluorine, and chlorine atoms. The most common commercial CFCs are marketed under the trade name Freon®. FC-11 was primarily used as a solvent, refrigerant, and aerosol propellant. The U.S. ceased production and importation of this chemical in 1996 due to its ability to cause significant stratospheric ozone depletion and contribute to global warming.

Currently, automobiles, refrigerators and freezers in many countries, including the U.S., are shredded after they are taken out of service. Up to 68 percent of the blowing agent (typically FC-11) is released into the atmosphere during the shredding process. The shredder waste is then deposited in landfills (Scheutz et al., 2007). Furthermore, liquid Freons® (Freons 11®, 12®, and 113®) are used as solvents in the clandestine manufacture of methamphetamine (OEHHA, 2003), and these chemicals may be left on the premises, illegally dumped in backyards, open spaces, ditches, or municipal sewer systems. FC-11 is very resistant to chemical and biological degradation and is likely to be a persistent contaminant if it reaches groundwater. Ongoing emissions of the banned FC-11 were observed in California's South Coast Air Basin in 2005 (Gentner et al., 2010), and high concentrations of FC-11 have been detected in groundwater at a contaminated industrial site (Shan et al., 2010). Monitoring data from the past three years show that FC-11 has been detected in various drinking water supply wells in California, but all detections were below California's MCL of 150 ppb, with the vast majority of water samples containing less than 5 ppb FC-11.[13] Therefore, significant public exposure to FC-11 is not anticipated in California.

1997 PHG

OEHHA's 1997 PHG of 0.7 mg/L (700 ppb) for FC-11 was based on a subchronic inhalation study in dogs (Jenkins et al., 1970). The LOAEL for liver effects and changes in blood chemistry was identified as 1,008 ppm (1,802 mg/kg-day). The PHG calculation included exposure assumptions of a 70 kg adult body weight, an equivalent water consumption rate of 25.86 L_{eq}/day, and an RSC of 40 percent. A UF of 3,000 (10 for interspecies extrapolation, 10 for intraspecies variability, 10 for extrapolation from a subchronic study to lifetime exposure, and 3 for extrapolation from a LOAEL to a NOAEL) was applied. There was insufficient evidence of carcinogenicity, thus the PHG was based on non-cancer endpoints. Additionally, a developmental toxicity study in which a mixture of FC-11 and FC-12 (10:90) administered to rats and rabbits during gestation was reviewed and developmental toxicity was not observed. No studies examining developmental/reproductive toxicity of FC-11 alone were identified.

[13]Data are accessible onlined with GeoTracker GAMA: http://geotracker.waterboards.ca.gov/gama/

Recent Literature

A review of the current scientific literature on FC-11 has not identified any new toxicity studies that could be used in deriving a PHG. However, the National Cancer Institute's (NCI, 1978) bioassays of FC-11 for carcinogenicity in Osborne-Mendel rats and B6C3F1 mice of both sexes were re-evaluated. Animals (50/species/sex/dose) were administered FC-11 via oral gavage (doses shown in Table 15) 5 days/week for 78 weeks. Two control groups, 20 animals/sex/group, received either corn oil (vehicle controls) or no treatment (untreated controls). A statistically significant positive association between increased dosage and accelerated mortality was observed in male and female rats and female mice (Table 15). In rats, the decline in survival was observed in treated groups during the first year of the study. Compound-related deaths were noted as early as week 4 in high-dose female rats, increasing gradually in both sexes and at both doses as the study progressed. Early high mortality in both sexes of rats precluded meaningful analyses of late-developing tumors. Chronic murine pneumonia was reported in 88 to 100 percent of the rats and appeared to be a factor in early mortality. However, elevated incidences of pleuritis and pericarditis were also observed, primarily in the dosed groups. The reported pericarditis may be indicative of more extensive cardiac toxicity. Exposure to high concentrations of CFCs has been associated with cardiac arrhythmias and sudden death due to myocardial sensitization to endogenous catecholamines (Lessard et al., 1977a, 1977b; OEHHA, 2003). Survival of mice was adequate for meaningful statistical analyses of tumor incidence. NCI concluded that, under the conditions of this bioassay, FC-11 was not carcinogenic to B6C3F1 mice.

Table 15. Mortality data for rats at 52 weeks and mice at 75-78 weeks (NCI, 1978).

Sex/Species	Mortality			
Female rats	Control		mg/kg-day[a]	
	Untreated	Vehicle	384	769
	0/20[b]	3/20	19/50	33/50*
Male rats	Control		mg/kg-day[a]	
	Untreated	Vehicle	349	698
	6/20	0/20	30/50*	35/50*
Female mice	Control		mg/kg-day[a]	
	Untreated	Vehicle	1401	2804
	3/20	2/20	13/50	18/50*
Male mice	Control		mg/kg-day[a]	
	Untreated	Vehicle	1401	2804
	7/20	5/20	9/50	21/50

[a]A time-weighted average dose was derived with the following adjustment: dose x 5 days/7 days
[b]Number of animals affected/number of animals in exposure group
*Significantly different from vehicle control, $p<0.05$, calculated by OEHHA using Fisher's exact test

PHG Derivation

After re-evaluation of the NCI bioassays (NCI, 1978), OEHHA determined that the Jenkins et al. (1970) inhalation study is not the optimal study on which to base the FC-11 PHG, for several key reasons. Humans may be more susceptible to FC-11 toxicity via inhalation than dogs. Inhalation studies in humans show adverse health effects (significant acute reduction of ventilatory lung capacity, bradycardia, and increased variability in heart rate) in subjects exposed to FC-11 concentrations between 16 and 150 mg/m^3 for 15, 45 or 60 seconds (WHO, 1990). These exposure levels are significantly lower than the LOAEL of 5,746 mg/m^3 (1,008 ppm) reported in the Jenkins et al. (1970) subchronic dog study. Similar cardiotoxic findings (higher mean pulse rate, arrhythmias) and other toxic effects have been reported in workers occupationally exposed to CFCs (Sabik et al., 2009). Furthermore, the NCI (1978) oral exposure study is chronic in duration and shows effects of greater severity at FC-11 levels many-fold lower than in the Jenkins et al. (1970) study. For these reasons, the NCI cancer bioassay findings of premature mortality in rodents are being used in the revision of the FC-11 PHG.

After evaluating the NCI (1978) data, OEHHA determined that this dataset would not be amenable to BMD modeling for several reasons: the observed response levels are well above the applied benchmark response level of 5%; male rats and female mice exhibited similar levels of response to both doses, which limits the information about the dose-response below the lowest dose; the doses are only two-fold apart, and although the data can be modeled, the resulting dose-response curve contains high uncertainty in the low-dose region (U.S. EPA, 2012). OEHHA identified a chronic oral LOAEL of 488 mg/kg-day, based on premature mortality in male rats in the NCI studies (NCI, 1978). This was converted to 349 mg/kg-day based on extrapolation from a 5-day/week exposure to a 7-day/week exposure, and this value is used for PHG derivation. By week 52, 60 percent of the animals at this dose level (30/50) had died. This LOAEL for mortality is much lower than the LOAEL of 1,802 mg/kg-day from the inhalation study (Jenkins et al., 1970) used to derive the original FC-11 PHG (OEHHA, 1997).

It is of note that the U.S. EPA (1992) oral reference dose (RfD) of 0.3 mg/kg-day was also based on increased premature mortality in the NCI (1978) animal cancer bioassays. U.S. EPA applied a total uncertainty factor of 1,000 (10 for LOAEL-to-NOAEL extrapolation, 10 for interspecies extrapolation, and 10 for sensitive human subpopulations). OEHHA is applying a combined UF of 3,000 (10 for LOAEL-to-NOAEL extrapolation, 10 for interspecies extrapolation, and 30 for intraspecies variability). The ADD is calculated as:

$$\text{ADD} = \frac{\text{POD}}{\text{UF}} = \frac{\text{349 mg/kg-day}}{\text{3,000}} = \text{0.116 mg/kg-day}$$

The 1997 FC-11 PHG used a drinking water RSC of 40 percent to account for exposure scenarios besides the use of contaminated tap water, such as inhalation of ambient air. In this update, a maximum RSC of 80 percent is used because background exposures

from sources other than contaminated drinking water are expected to be negligible since FC-11 production was banned in 1996. Inhalation and dermal exposures to FC-11 during household uses of tap water are calculated for individual life stages using CalTOX. The relative contributions of exposures through these routes are presented in Table 16 and details of CalTOX modeling inputs and outputs are included in Appendix I.

Table 16. CalTOX results for relative contributions of multiple routes of exposure to FC-11 in tap water for various life stages

Life Stage	Oral Ingestion (%)	Inhalation (%)	Dermal (%)
Fetus (Pregnancy)	54	37	9
Infant	92	0[a]	8
Child	43	48	9
Adult	57	33	10

[a]Infants are expected to be exposed to negligible levels of chemicals in tap water via inhalation (compared to other pathways) because they typically do not shower or flush toilets. These are the dominant inhalation exposure scenarios, therefore the inhalation pathway is excluded for infants.

Lung absorption of inhaled FC-11 appears to be relatively low. One study reported the lung absorption of FC-11 in three human subjects to range from 13.5-21.9 percent, with a mean value of 18.2 percent (Angerer et al.,1985). Another study with four human subjects reported a range of 19.8-26.6 percent, with a mean value of 23.0 percent (Morgan et al., 1972). OEHHA determined that 23 percent is the best estimate of human lung absorption of FC-11, and this is factored in when calculating the overall exposure to FC-11 in tap water. Liter equivalent (L_{eq}) values for inhalation and dermal exposure are calculated using life-stage-specific oral ingestion rates (OEHHA, 2012) and the relative contribution of the oral ingestion value.

Table 17. Total liter equivalent values for multi-route exposure to FC-11 in tap water

Life Stage	Age range (years)	Oral Ingestion (L/kg-day)	Inhalation[a,b] (L_{eq}/kg-day)	Dermal[a] (L_{eq}/kg-day)	Total Exposure (L_{eq}/kg-day)
Fetus (Pregnancy)	N/A[c]	0.047[d]	0.007[d]	0.008[d]	0.062
Infant	0-2	0.196	0	0.017	0.213
Child	2-16	0.061	0.016	0.013	0.090
Adult	16-70	0.045	0.006	0.008	0.059
Time-weighted average over lifetime					0.070

[a]Inhalation and dermal exposure estimates are calculated using life-stage-specific oral ingestion rates (OEHHA, 2012) and the corresponding relative contribution of the oral ingestion values.
[b]L_{eq} for inhalation assumes 23% absorption in the lung
[c]Not applicable; a time period of 0.75 year is used to represent the fetus in calculating the time-weighted average total exposure over a lifetime of 70 years.
[d]The fetus is assumed to be exposed to the same dose as the pregnant mother, thus the liter equivalent values for the fetus are based on exposure parameters for the pregnant woman as shown in Table A1 of Appendix I.

The health-protective concentration would then be calculated as follows:

$$C = \frac{0.116 \text{ mg/kg-day} \times 0.80}{0.070 \text{ } L_{eq}/\text{kg-day}} = 1.3 \text{ mg/L} = 1300 \text{ µg/L or } 1300 \text{ ppb}$$

The revised PHG is 1.3 mg/L (ppm) or 1300 ppb, which is nearly 2-fold larger than the previously published PHG of 700 ppb (OEHHA, 1997). The difference results from OEHHA's use of the NCI oral exposure studies (NCI, 1978), updated drinking water intake rates, changes in exposure parameters and assumptions (RSC and multi-route exposure considerations) and an adjustment of the intraspecies variability factor to protect sensitive populations, all of which constitute a stronger scientific basis for the revised PHG. Additionally, in the 1997 PHG document, an equivalent daily water intake of 25.86 L_{eq}/day for a 70 kg individual was applied. When normalized to body weight, this value (0.37 L_{eq}/kg-day) is approximately 5 times larger than the current DWI of 0.07 L_{eq}/kg-day. Thus, application of the new DWI estimates an overall lower daily exposure to FC-11, and subsequently results in a larger PHG.

There is currently no U.S. EPA MCL or MCLG for FC-11.[14]

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[14] A list of US EPA MCLs and MCLGs is available online at http://water.epa.gov/drink/contaminants/index.cfm#List

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APPENDIX I. CalTOX Modeling

This appendix describes the multi-route exposure assessment of chlorobenzene, hexachlorocyclopentadiene, silvex, and trichlorofluoromethane in drinking water using CalTOX modeling. In addition to oral ingestion, exposure to chemical contaminants in tap water can occur via inhalation or dermal contact while performing common household activities, such as bathing, showering, and flushing toilets. OEHHA applies the CalTOX model (available at http://energy.lbl.gov/ied/era/caltox/index.html) to assess these exposures and calculate the relative contribution of each exposure pathway to the total daily exposure to these contaminants in tap water.

Exposure Pathways Included in CalTOX Modeling:

- All inhalation exposures indoor active
- All inhalation exposures indoor resting
- Inhalation exposure in shower/bath
- Use of contaminated water as tap water
- Ingestion of tap water
- Dermal exposure during shower/bath

Table A1 provides OEHHA-derived human exposure parameters for various life stages that are applied during CalTOX exposure modeling of contaminants in drinking water (OEHHA, 2012).

Table A1. OEHHA-derived 95th percentile exposure parameters for various life stages used for CalTOX modeling

Life Stage	Age Range (years)	Drinking Rate (L/kg-day)	Inhalation rate (m^3/kg-hr)	Body Surface Area (m^2/kg)	Reference
Fetus (Pregnancy)	N/A[a]	0.047[b]	0.015[b]	0.029[b]	OEHHA (2012)
Infant	0-2	0.196	0[c]	0.059	
Child	2-16	0.061	0.031	0.045	
Adult	16-70	0.045	0.012	0.029	

[a]Not applicable

[b]Fetuses are assumed to be exposed to the same dose as the pregnant mothers, thus drinking and inhalation rates for the pregnant woman are used for the fetus. The adult body surface area parameter is used for pregnant women.

[c]Infants are expected to be exposed to negligible levels of chemicals in tap water via inhalation (compared to other pathways) because they typically do not shower or flush toilets. These are the dominant inhalation exposure scenarios, therefore the inhalation pathway is excluded for infants.

CalTOX estimates the relative contributions of oral ingestion, inhalation, and dermal exposure to total exposure to contaminants in water based on the input parameters in Table A1 and the exposure pathways selected for inclusion. Liter equivalents (L_{eq}) for inhalation and dermal exposure are calculated for each life stage using the age-specific drinking water ingestion rate and relative contribution of the oral ingestion value.

Examples of CalTOX outputs are presented below. For the sake of brevity, only the results using adult exposure parameters are included in this document.

Table A2. Chlorobenzene CalTOX output, adult exposure scenario

PATHWAYS	**Air (gases & particles)**	**Surface soil**	**Root-zone soil**	**Ground water**	**Surface water**	**Totals**	**%**
INHALATION	2.58E-263	0.00E+00	0.00E+00	2.59E+00	0.00E+00	2.59E+00	**31.51**
INGESTION:							
Water				4.37E+00	0.00E+00	4.37E+00	53.14
Exposed produce	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Unexposed produce			0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Meat	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Milk	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Eggs	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Fish					0.00E+00	0.00E+00	0.00
Soil		0.00E+00	0.00E+00			0.00E+00	0.00
Total ingestion	0.00 E+00	0.00 E+00	0.00 E+00	4.37 E+00	0.00 E+00	4.37 E+00	**53.14**
DERMAL UPTAKE		0.00E+00	0.00E+00	1.26E+00	0.00E+00	1.26E+00	**15.34**
Dose SUM	2.58E-263	0.00E+00	0.00E+00	8.22E+00	0.00E+00	8.22E+00	**100.0**

Table A3. Hexachlorocyclopentadiene CalTOX output, adult exposure scenario

PATHWAYS	Air (gases & particles)	Surface soil	Root-zone soil	Ground water	Surface water	Totals	%
INHALATION	1.07E-264	0.00E+00	0.00E+00	2.06E+00	0.00E+00	2.06E+00	**13.27**
INGESTION:							
Water				4.37E+00	0.00E+00	4.37E+00	28.09
Exposed produce	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Unexposed produce			0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Meat	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Milk	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Eggs	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Fish					0.00E+00	0.00E+00	0.00
Soil		0.00E+00	0.00E+00			0.00E+00	0.00
Total ingestion	0.00 E+00	0.00 E+00	0.00 E+00	4.37 E+00	0.00 E+00	4.37 E+00	**28.09**
DERMAL UPTAKE		0.00E+00	0.00E+00	9.13E+00	0.00E+00	9.13E+00	**58.65**
Dose SUM	1.07E-264	0.00E+00	0.00E+00	1.56E+01	0.00E+00	1.56E+01	**100.0**

Table A4. Silvex CalTOX output, adult exposure scenario

PATHWAYS	Air (gases & particles)	Surface soil	Root-zone soil	Ground water	Surface water	Totals	%
INHALATION	2.06E-264	0.00E+00	0.00E+00	3.33E-01	0.00E+00	3.33E-01	**5.68**
INGESTION:							
Water				4.37E+00	0.00E+00	4.37E+00	74.57
Exposed produce	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Unexposed produce			0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Meat	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Milk	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Eggs	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Fish					0.00E+00	0.00E+00	0.00
Soil		0.00E+00	0.00E+00			0.00E+00	0.00
Total ingestion	0.00 E+00	0.00 E+00	0.00 E+00	4.37 E+00	0.00 E+00	4.37 E+00	**74.57**
DERMAL UPTAKE		0.00E+00	0.00E+00	1.16E+00	0.00E+00	1.16E+00	**19.76**
Dose SUM	2.06E-264	0.00E+00	0.00E+00	5.86E+00	0.00E+00	5.86E+00	**100.0**

Table A5. Trichlorofluoromethane CalTOX output, adult exposure scenario

PATHWAYS	Air (gases & particles)	Surface soil	Root-zone soil	Ground water	Surface water	Totals	%
INHALATION	1.95E-262	0.00E+00	0.00E+00	2.51E+00	0.00E+00	2.51E+00	**32.83**
INGESTION:							
Water				4.37E+00	0.00E+00	4.37E+00	57.19
Exposed produce	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Unexposed produce			0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Meat	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Milk	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Eggs	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Fish					0.00E+00	0.00E+00	0.00
Soil		0.00E+00	0.00E+00			0.00E+00	0.00
Total ingestion	0.00 E+00	0.00 E+00	0.00 E+00	4.37 E+00	0.00 E+00	4.37 E+00	**57.19**
DERMAL UPTAKE		0.00E+00	0.00E+00	7.62E-01	0.00E+00	7.62E-01	**9.97**
Dose SUM	1.95E-262	0.00E+00	0.00E+00	7.64E+00	0.00E+00	7.64E+00	**100.0**

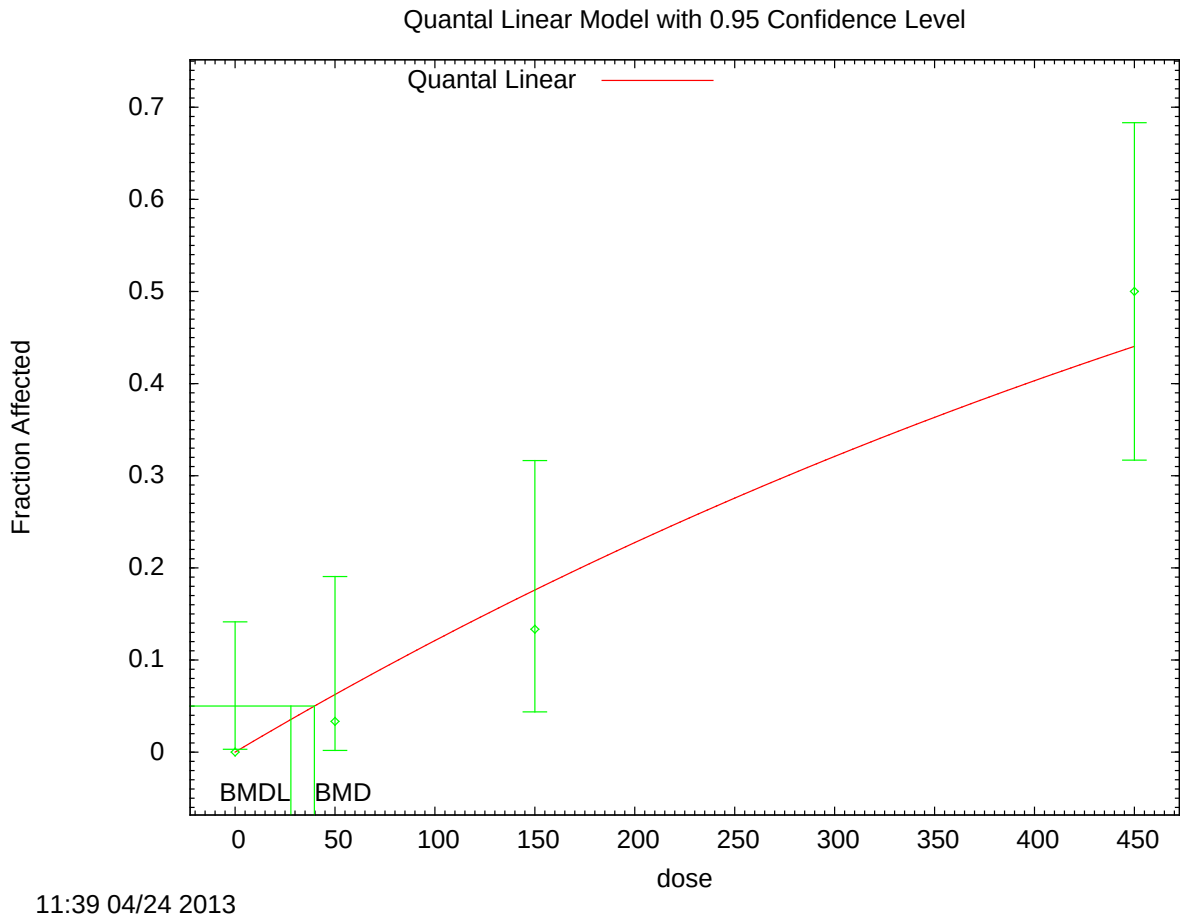
References

OEHHA (2012). Air toxics hot spots program risk assessment guidelines: technical support document for exposure assessment and stochastic analysis. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.

Appendix II. BMD Modeling

This appendix provides the BMD modeling outputs for the two chemicals, chlorobenzene and hexachlorocyclopentadiene, for which data were amenable to dose-response modeling. All models were run with default parameters and a benchmark response of 5 percent for dichotomous data and one standard deviation above the control mean for continuous data. The model selected to derive the POD for each chemical is presented here. Model selection criteria (comparing outputs of different models for the same endpoint/dataset) were: the lowest Akaike's information criterion (AIC), goodness of fit p-value ≥ 0.05, scaled residual ≤ the absolute value of 2, and visual inspection of the dose-response curve.

Figure A1. Quantal-linear model output for chlorobenzene – renal tubular dilation with eosinophilic material in F_0 male rats from Nair et al. (1987)



```
 ================================================================
        Quantal Linear Model using Weibull Model (Version: 2.15;  Date: 10/28/2009)
        Input Data File: C:/Users/cbanks/Documents/Modeling
Data/Chlorobenzene/qln_Nair 1987 F0 tubular dilation_Qln-BMR05.(d)
        Gnuplot Plotting File:  C:/Users/cbanks/Documents/Modeling
Data/Chlorobenzene/qln_Nair 1987 F0 tubular dilation_Qln-BMR05.plt
                                            Wed Apr 24 11:39:25 2013
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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


   Dependent variable = Effect
   Independent variable = Dose

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial (and Specified) Parameter Values
                     Background =      0.03125
                          Slope =   0.00146977
                          Power =            1   Specified


           Asymptotic Correlation Matrix of Parameter Estimates

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

                  Slope

     Slope            1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0              NA
          Slope       0.00129328      0.000292341         0.000720307
0.00186626

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

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-36.959	4			
Fitted model	-37.6345	1	1.35098	3	0.7171
Reduced model	-54.0673	1	34.2167	3	<.0001

AIC: 77.269

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	30	0.000
50.0000	0.0626	1.879	1.000	30	-0.662
150.0000	0.1763	5.290	4.000	30	-0.618
450.0000	0.4412	13.236	15.000	30	0.649

Chi^2 = 1.24 d.f. = 3 P-value = 0.7432

Benchmark Dose Computation

Specified effect = 0.05

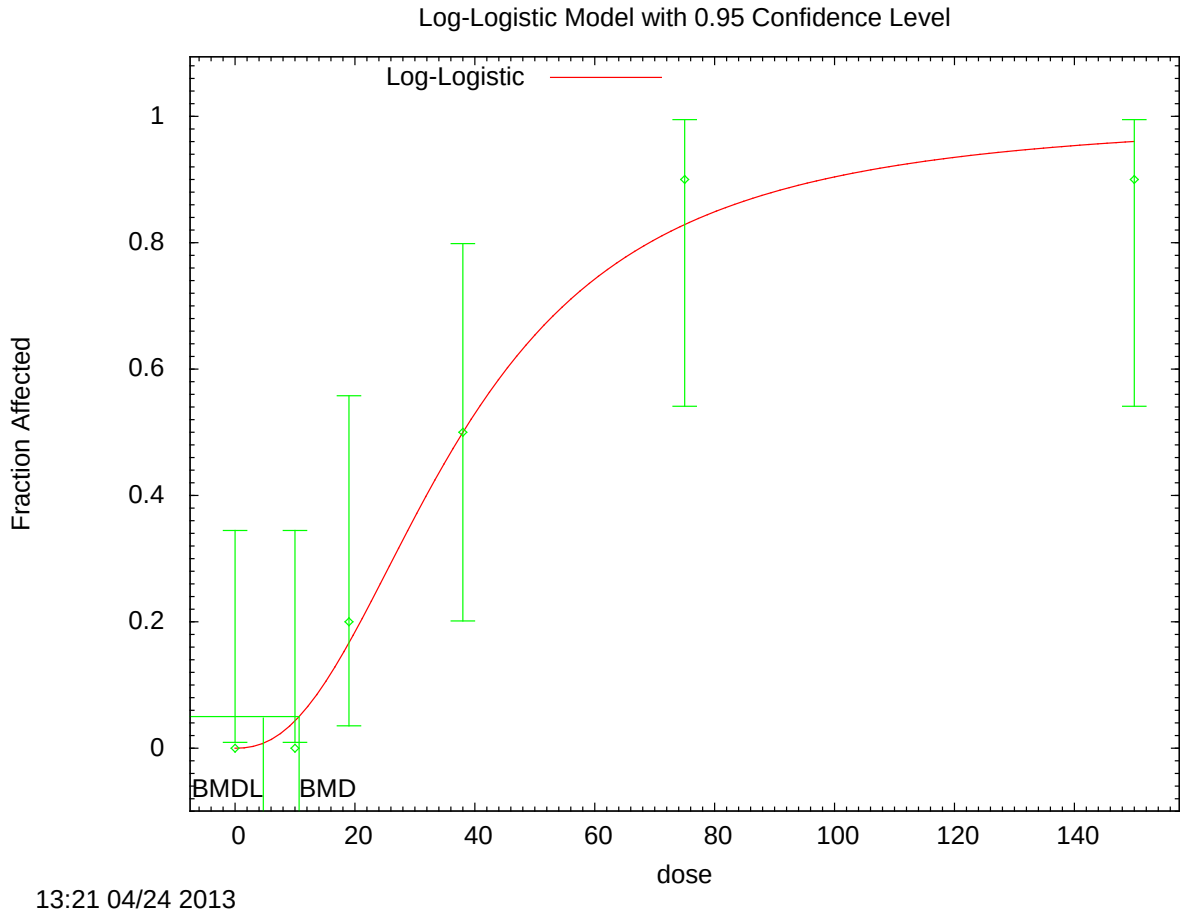
Risk Type = Extra risk

Confidence level = 0.95

BMD = 39.6613

BMDL = 27.9182

Figure A2. LogLogistic model output for hexachlorocyclopentadiene – total stomach lesions in female rats from Abdo et al. (1984)




```
 ================================================================
        Logistic Model. (Version: 2.13; Date: 10/28/2009)
        Input Data File: C:\Users\cbanks\Documents\Modeling
Data\Hexachlorocyclopentadiene\lnl_female rat stomach epithelial hyperplasia_Lnl-
BMR05-Restrict.(d)
        Gnuplot Plotting File: C:\Users\cbanks\Documents\Modeling
Data\Hexachlorocyclopentadiene\lnl_female rat stomach epithelial hyperplasia_Lnl-
BMR05-Restrict.plt
                                        Wed Apr 24 13:21:19 2013
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
```

```
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial Parameter Values
                    background =            0
                     intercept =     -7.54216
                         slope =      2.06858


           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 )

              intercept        slope

 intercept            1        -0.98

     slope        -0.98            1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0            *                *                   *
      intercept         -8.44236            *                *                   *
          slope          2.32123            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -18.4372         6
   Fitted model         -19.4604         2       2.04658      4          0.7272
  Reduced model         -40.7516         1       44.6289      5         <.0001

           AIC:          42.9209


                                Goodness  of  Fit
                                                              Scaled
```

Dose	Est._Prob.	Expected	Observed	Size	Residual
0.0000	0.0000	0.000	0.000	10	0.000
10.0000	0.0432	0.432	0.000	10	-0.672
19.0000	0.1669	1.669	2.000	10	0.281
38.0000	0.5003	5.003	5.000	10	-0.002
75.0000	0.8291	8.291	9.000	10	0.595
150.0000	0.9604	9.604	9.000	10	-0.979

Chi^2 = 1.84 d.f. = 4 P-value = 0.7644

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 10.6817

BMDL = 4.71425

Appendix III. Default Uncertainty Factors for PHG Derivation

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

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

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

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

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

References

OEHHA (2008). Air toxics hot spots risk assessment guidelines: technical support document for the derivation of noncancer reference exposure levels. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.