Public Health Goals

Carbofuran
Diquat
Endrin
Picloram
Thiobencarb
in Drinking Water

September 2016

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

Updated Public Health Goals for Chemicals in California Drinking Water

Carbofuran

Diquat

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Picloram

Thiobencarb

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Prepared by

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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.

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

In July 2014, responsibility for the state's drinking water regulatory program was transferred to SWRCB from the California Department of Public Health. References in this document to drinking water monitoring and regulation may cite either or both entities as appropriate.

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SUMMARY

This document presents public health goal (PHG) updates for carbofuran, diquat, endrin, picloram, and thiobencarb. 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.

Carbofuran is a highly toxic carbamate insecticide and nematocide. The previous PHG of 1.7 µg/L or 1.7 parts-per-billion (ppb) was developed by OEHHA in 2000 based on adverse male reproductive effects in a subchronic rat study (Pant et al., 1995) using the lowest-observed-adverse-effect level/no-observed-adverse-effect level (LOAEL/NOAEL) approach. This study is retained as the critical study, and the updated PHG of 0.7 ppb is derived using updated dermal and inhalation exposure estimates, updated water intake rates, and an updated intraspecies variability factor to account for sensitive individuals.

Diquat is a non-selective herbicide and crop desiccant that is currently used in California. A PHG of 15 ppb for diquat was developed by OEHHA in 2000 using a NOAEL of 0.22 mg/kg-day based on lens opacities and cataracts observed in rats fed diquat in the diet for two years (Colley et al., 1985). This study is retained as the critical study on which this PHG is based, and the updated PHG of 6 ppb is derived using benchmark dose (BMD) modeling, updated drinking water ingestion rates and an updated factor to account for variability within the human population.

Endrin is an obsolete organochlorine pesticide with all uses in the U.S. banned by 1991 (US EPA, 1992). The previous PHG (OEHHA, 1999, 2008) of 1.8 ppb was based on convulsions observed in a chronic feeding study in dogs (Jolley et al., 1969). This study is retained as the critical study on which the PHG calculation is based. The updated PHG of 0.3 ppb is derived by incorporating an updated intraspecies variability factor to account for sensitive individuals, an updated daily drinking water intake rate to account

for multi-route exposure, a revised relative source contribution (RSC) value, and updated dose-response analysis using BMD modeling.

Picloram is a broad spectrum herbicide that was widely used in California before its registration was terminated in 1988. A PHG of 500 ppb for picloram was developed by OEHHA in 1997 using a NOAEL of 7 mg/kg-day based on increased liver weight observed in dogs in a six-month feeding study (Dow, 1982). This study is retained as the critical study on which this PHG is based, and the updated PHG of 166 ppb is derived using BMD modeling, updated drinking water ingestion rates and relative source contribution, and an updated factor to account for variability within the human population.

Thiobencarb is an herbicide used to control many broadleaf weeds, grasses, and sedges in food crops such as rice. The previous PHG of 70 ppb was developed by OEHHA in 2000 based on the decreased body weight gain and reduced food consumption and food efficiency identified in a chronic feeding study in rats (Ashby et al., 1984). This study is retained as the critical study and the updated PHG of 42 ppb is derived by incorporating updated drinking water intake rates, dose-response modeling, and an updated factor to account for variability among individuals.

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	Previous PHG in ppb[a]	Updated PHG in ppb	CA MCL[b] in ppb	Endpoint[c]	Change(s)
Carbofuran	1.7 (OEHHA, 2000)	0.7	18	male reproductive effects	• Updated inhalation and dermal exposure estimates • Updated water intake rate • Updated intraspecies variability factor
Diquat	15 (OEHHA, 2000)	6	20	cataracts	• Updated dose-response modeling • Updated water intake rate • Updated intraspecies variability factor
Endrin	1.8 (OEHHA, 2008[d])	0.3	2	central nervous system effects	• Updated dose-response modeling • Updated inhalation and dermal exposure estimates • Updated water intake rate • Updated intraspecies variability factor • Updated relative source contribution
Picloram	500 (OEHHA, 1997)	166	500	increased liver weight	• Updated dose-response modeling • Updated water intake rate • Updated intraspecies variability factor • Updated relative source contribution
Thiobencarb	70 (OEHHA, 2000)	42	70	body weight reduction	• Updated dose-response modeling • 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.
[d]The original PHG for endrin was published in 1999 and updated in 2008.

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]	Previous PHG in ppb[b]	CA MCL[c] in ppb	Concentration Range of Detections[d] in ppb
Carbofuran	1563-66-2	1.7	18	ND[e]
Diquat	85-00-7	15	20	0.44 to 14
Endrin	72-20-8	1.8	2	ND[e]
Picloram	1918-02-1	500	500	0.0021 to 0.0036
Thiobencarb	28249-77-6	70	70	ND[e]

[a]CAS No.: Chemical Abstracts Service Registry Number
[b]ppb: parts per billion
[c]CA MCL: California Maximum Contaminant Level
[d]Based on monitoring data over the last three years for public 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]ND, not detected; information on detection limits for purposes of reporting can be found at: http://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/Labinfo.shtml.

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

The five chemicals presented in this document have not been shown to be carcinogenic; therefore, their respective PHGs are calculated using the equations discussed below 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 (US EPA) Benchmark Dose Software (BMDS) when appropriate. This software is publicly available (http://www.epa.gov/ncea/bmds/). The model can be used to determine the dose that corresponds to a pre-determined level of response (typically five percent) above the background or control group. This dose is known as the benchmark dose (BMD). In order to take into account the uncertainty of the data, the model also calculates the 95% lower confidence limit of the BMD and it is called the BMDL (L stands for lower confidence limit). For PHGs, the BMDL is used as the POD for the calculation of a health-protective drinking water concentration when the data are amenable to BMD modeling. 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 mg/kg-day) that can be consumed by humans for an entire lifetime without adverse effects. This is similar to the term "reference dose" used by the US EPA. To determine the ADD, the POD is divided by factors that account for uncertainties and variabilities in the risk assessment, such as differences between animals and humans, and differences among humans in response to 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 to account for interspecies and intraspecies uncertainty and variability (OEHHA, 2008).

This combined UF includes:

- A UF of 10 for interspecies extrapolation accounting for possible differences in the way laboratory animals and humans respond to the chemical, consisting of
    - $\sqrt{10}$ for pharmacodynamics; and
    - $\sqrt{10}$ for pharmacokinetics
- A UF of 30 for intraspecies variability, which accounts for some human subpopulations, such as children, pregnant women, and the elderly, possibly being more sensitive to the chemical than the general population. This UF consists of
    - $\sqrt{10}$ for pharmacodynamics; and
    - 10 for pharmacokinetics.

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

The ADD is calculated using the following equation:

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

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 (United States 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 A2 in Appendix II). 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). Health and Safety Code section 116365.2 requires OEHHA 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 can be inhaled by the person taking the shower. 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 some volatile chemicals from routes other than oral ingestion may be as large as or larger than exposure from ingestion

alone (McKone, 1987). To estimate inhalation and dermal exposures to chemicals in tap water, OEHHA uses the CalTOX 4.0 multimedia total exposure model developed for the California Department of Toxic Substances Control by the Lawrence Berkeley National Laboratory.[1] Details on model inputs used in calculating PHGs are described in Appendix II.

Relative Source Contribution

The relative source contribution (RSC) is the proportion of exposures to a chemical attributed to tap water (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. The RSC helps to ensure that the PHG identifies a level of a drinking water contaminant that would pose no significant health risk after taking into account exposures to the chemical from food, air pollution and other sources.

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 daily water intake of the chemical (DWI) and the relative amount of the chemical obtained from tap water (RSC):

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

For contaminants that only have non-cancer endpoints, including the five chemicals discussed in this document, the health-protective concentration, C, is the PHG.

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

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UPDATED PHG FOR CARBOFURAN

Carbofuran (2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate) is a highly toxic insecticide and nematocide that was banned in 2011 for use in the United States. It belongs to the carbamate class of pesticides and causes neurotoxicity in pest species via a rapid inhibition of cholinesterase (ChE), an enzyme that affects the transmission of signals in the nervous system. Prior to the cancelation of its registration, there were a number of products registered in California under the trade name Furadan containing carbofuran as the active ingredient.[2] The last product registered in California (Furadan 4F) expired in 2011. Use of carbofuran in California had been declining over the last decade; only 4 pounds were applied in 2010 and 1 pound in 2011.[3] Carbofuran has not been detected above its limit of detection of 5 ppb[4] in California drinking water supply wells in the last three years.[5] OEHHA last published a PHG of 1.7 µg/L or 1.7 ppb for carbofuran in 2000, about 10-fold lower than the CA MCL of 18 ppb and more than 20-fold lower than the federal MCL of 40 ppb. This was based on reproductive toxicity in male rats (Pant et al. 1995). Because of its canceled registration status and lack of detection in California drinking water in the past three years, public exposure to carbofuran from drinking water is not anticipated.

2000 PHG

The previous PHG of 1.7 ppb was based on a subchronic reproductive toxicity study with approximately five-week-old male Druckery rats (average body weight 80 g) (Pant et al., 1995). Carbofuran was administered by oral gavage at 0, 0.1, 0.2, 0.4, or 0.8 mg/kg, 5 days per week for 60 days. The NOAEL was determined to be 0.1 mg/kg based on decreases in body weight and various reproductive toxicity endpoints (including changes in selected reproductive organ weights, decreased sperm motility, significant changes in testicular enzymes, and morphological sperm abnormalities) at 0.2 mg/kg and above. Because the exposure regimen in the study was five days per week, the NOAEL was adjusted to reflect seven days of exposure (0.1 x 5/7), yielding an adjusted NOAEL of 0.07 mg/kg-day. An uncertainty factor of 300 was applied (10 for interspecies extrapolation, 10 for human variability, and 3 for extrapolation from a subchronic to chronic exposure), and default values for body weight (70 kg), water consumption rate (2 L/day), and RSC (0.2) were used to calculate the PHG of 1.7 ppb.

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[2] Output reporting for carbofuran, all products. Query retrieved on 10 June 2014, from http://apps.cdpr.ca.gov/cgi-bin/label/labq.pl?p_chem=106&activeonly=off.

[3] Summary of pesticide use report data, 2012, indexed by chemical from California Department of Pesticide Regulation. Accessed at: http://www.cdpr.ca.gov/docs/pur/purmain.htm.

[4] Information on detection limits for purposes of reporting can be found at: http://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/Labinfo.shtml.

[5] Data 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.

Carbofuran exerts its neurotoxic effects in insects by inhibiting ChE activity in the nervous system. The same effect can occur in humans, making ChE inhibition a relevant non-cancer endpoint to consider for PHG derivation. ChE inhibition was reported at low doses (0.25-0.54 mg/kg) in dog, rat, and human studies. However, ChE inhibition was not chosen as a critical endpoint for PHG derivation due to greater uncertainty in the interpretation of the studies and higher LOAELs than reported for reproductive toxicity. Carbofuran was also negative in two cancer bioassays in two species and thus cancer potency was not determined.

Recent Literature

There are a substantial number of reports in the open literature on carbofuran since the publication of the PHG in 2000. There have been no new pesticide registrant-submitted toxicity studies.

A number of recent animal studies have investigated the reproductive toxicity of carbofuran. Carbofuran-induced female reproductive toxicity, indicated by estrous cycle disruption and decreased number of healthy follicles, was noted in female mice exposed to doses as low as 1 mg/kg-day for 30 days (Baligar and Kaliwal 2002). Mice and rats showed signs of male reproductive toxicity including endocrine disruption and histological effects on reproductive organs following acute and subchronic exposures to carbofuran (Aziz et al., 2008; Elayan et al., 2013; Goad et al., 2004). Elayan et al. (2013) described a dose-dependent decrease in serum testosterone in male mice treated with 0.1 to 0.4 mg/kg-day carbofuran for 30 days, although reporting deficiencies (e.g., lack of statistical analysis and presentation of data in bar graphs only) limit the usefulness of the study for more in-depth evaluation. Only a single dose was used in the studies reported by Aziz et al. (2008) and Goad et al. (2004) (2 mg/kg-day and 1.5 mg/kg, respectively), thus, the data cannot be used for dose-response assessment. Chauhan et al. (2000) found that carbofuran at 1 or 2 mg/kg caused a dose-dependent increase in abnormal sperm in singly dosed male mice. Kobeasy et al. (2015) found drastic effects on male reproductive toxicity, including decreased fertility index, sperm abnormalities, and effects on male sex organ weights and serum testosterone levels in rats treated with 2.4 mg/kg-day (the only dose evaluated) for 70 days.

Only one study documented the effect of carbofuran on male reproductive toxicity in humans. In a short communication by Gallegos-Avila et al. (2010), semen analysis of two farmers with chronic occupational exposure to carbofuran and complaints of infertility showed high percentages of binucleated spermatozoa and multinucleated spermatids, as well as impaired sperm motility. One patient also had an abnormally low percentage of normal shaped sperm. Although this was a study of only two men, it provides support to the findings from animal studies indicating that carbofuran is a male reproductive toxicant. Overall, the male reproductive effects of carbofuran found in recent studies are consistent with those reported by Pant et al. (1995). Further studies would need to be conducted to determine the mechanisms involved in the reproductive toxicity of carbofuran.

Brkić et al. (2008) conducted a toxicity study with rats given carbofuran in the drinking water. In this study, male and female Wistar rats (five/sex/dose) were administered 0, 25, 100, or 400 ppm (mg/L) carbofuran in drinking water for 90 days. ChE levels were determined in red blood cells (RBC), serum, and brain. Animal body weight and food and water consumption were reported. Organs were weighed (liver, kidney, heart, spleen, brain, lungs, and adrenal glands) but only brain, liver and kidney were selected for further biochemical and histopathological analyses. All doses had significant effects on ChE activity but no other remarkable signs of toxicity were observed. At the lowest dose tested, female rats had significantly depressed RBC and brain ChE (34.9% and 16.3%, respectively), while males only had depressed RBC ChE (39.5%). The study authors reported histopathological examination of the liver and kidneys showed effects at 100 and 400 ppm carbofuran. Changes in the liver included fatty degeneration and necrosis, while changes in the kidneys included hydropic degeneration and proximal tubule dilation. These changes were considered insignificant by study authors with little explanation. There were not sufficient data presented to assess the extent of kidney and liver effects outside the interpretation presented in the paper. There were also no changes in absolute organ weights at any dose tested and no decreases in body weight gain in either sex. This study did not convert the doses from ppm to mg/kg-day, thus OEHHA used the European Food Safety Authority (EFSA) default value of 0.09 for converting the mg/L or ppm dose in a subchronic study to a mg/kg-day dose (EFSA, 2012),[6] multiplied by the relative water consumption reported in the publication for each dose group. The estimated doses used in the study were calculated as 0, 2.3, 7.9 and 29.7 mg/kg-day for males and 0, 2.2, 8.5 and 28.0 mg/kg-day for females. The data for ChE inhibition, presented graphically in the publication with no information on standard deviations or standard errors, were not amenable to BMD modeling. ChE inhibition in the brain was significant at the lowest dose tested in females, therefore an uncertainty factor of 10 would be applied to extrapolate from LOAEL to NOAEL. Using this default method, the estimated NOAEL is 0.23 mg/kg-day, a value higher than the NOAEL of 0.1 mg/kg-day identified for male reproductive toxicity in the critical study (Pant et al., 1995) used for the previous PHG.

Age-related sensitivity to the neurotoxicity and ChE inhibition of carbofuran was studied using adult and young rats in two studies by the same research group. McDaniel et al. (2007) exposed adult male Long-Evans rats (10/dose group) once to carbofuran at doses of 0, 0.1, 0.3, 0.5, 0.75, and 1.5 mg/kg by oral gavage. They reported significantly inhibited brain ChE at 0.1 mg/kg and RBC ChE inhibition and decreased motor activity at 0.3 mg/kg and above. The reported range of BMD_{10} values (the dose

[6] The ESFA default value was based on drinking water consumption and body weight data from eight NTP chronic studies in mice and rats in which the test substance was administered in drinking water. This conversion factor was chosen as it was similar to the consumption rate of 0.1 L/kg-day for rats reported by various other animal care and use committees. Furthermore, US EPA published reference water consumption values for rats based on an allometric relationship of water consumption to body weight for all species evaluated (US EPA, 1988). Because the species-specific correlation coefficient (r^2) calculated for the rat was low (0.24), the rat-specific allometric equation was not used. Thus, OEHHA has higher confidence in the EFSA conversion factor.

estimated to produce a 10 percent decrease in response compared to controls) was 0.04 – 0.09 mg/kg in the study. Moser et al. (2010) conducted a similar study on preweanling and adult rats (postnatal day (PND) 11 and PND 17, and adult males; 5-6 male rats/group/dose) exposed to a single gavage dose of 0, 0.1, 0.3, 0.6, or 1 mg/kg carbofuran and measured motor activity and ChE inhibition. While the pre-weanling rats were more susceptible to brain and RBC ChE inhibition than adults at the lowest dose, this did not result in measured changes in motor activity. At 0.1 mg/kg, PND 17 rats had approximately 50 percent depression of RBC ChE yet showed no reduction in motor activity, the indicator of ChE toxicity measured in the study (Moser et al., 2010). In comparison, at 0.1 mg/kg in adult rats, brain and RBC ChE depression were approximately 20 percent and motor activity was reduced, although the effect was not statistically significant (McDaniel et al., 2007). Moser et al. (2010) did not report findings for motor activity for the adult rats in their study. The BMD_{10} for brain ChE inhibition for adult, PND 17 and PND 11 rats were 0.067, 0.012 and 0.0046 mg/kg, respectively (Moser et al. 2010). However, the confidence intervals for the BMD_{10} were spread over several orders of magnitude, indicating there was considerable uncertainty in these estimates. Neither of these studies was chosen for PHG derivation because both studies consisted of single exposures and there are uncertainties in evaluating the endpoints reported. Motor activity and ChE activity were measured between 15 and 45 minutes post-dosing. Peak ChE depression occurred approximately 15 minutes post-dosing for RBC and 45 minutes post-dosing for brain, after which recovery occurred rapidly with full recovery by 24 hours (Moser et al., 2010).

Much of the recently published literature on carbofuran focused on organ-specific toxicity, mostly attributed to oxidative stress. Carbofuran has been shown to induce myocardial necrosis and inflammation after an acute 1.5 mg/kg intraperitoneal exposure in rats (Mori et al., 2010; Tonomura et al., 2009). An epidemiology study by Dayton et al. (2010) of over 22,000 female pesticide applicators or female spouses of pesticide applicators from Iowa and North Carolina found a statistically significant correlation between carbofuran use and non-fatal acute myocardial infarction in female applicators and female spouses of applicators (odds ratio=2.5, 95% confidence interval, 1.3-5.0). While another study failed to find a similar association in male farm workers (Mills et al., 2009), the findings of Dayton et al. (2010) imply that cardiac toxicity may be a relevant health effect in humans exposed to carbofuran.

Other recent animal studies investigated the association between carbofuran exposure and toxicity to the brain, intestines, kidneys, liver, and reproductive organs (Jaiswal et al., 2014; Mishra et al., 2012; Rai and Sharma, 2007; Kamboj et al., 2008; Gera et al., 2011; Kaur et al., 2012; Kaur and Sandhir, 2006; Baligar and Kaliwal, 2002; Cinar et al., 2015). Hadie et al. (2012) found significant toxic effects on the thyroid gland following exposure to 2.4 mg/kg carbofuran by oral gavage for 28 days. All of these studies were analyzed and ultimately not chosen for PHG derivation due to deficiencies in length of study (acute or less than 30 days), inadequate dosing regimen (single concentration exposures), and insufficiencies in study design and reporting.

Some recent studies suggest carbofuran may have genotoxic and carcinogenic potential. In previous risk assessments by both state and federal regulatory agencies, carbofuran has not been determined to be a carcinogen (DPR, 2006 and US EPA, 2006). However, several in vitro studies using human lymphocytes detected damage to DNA, likely mediated by oxidative stress, from carbofuran and carbofuran-containing pesticide mixtures (Das et al., 2007; Naravaneni and Jamil, 2005; Sharma and Sharma, 2012). Gbadegesin et al. (2014) conducted an in vivo genotoxicity study in male rats following administration of 0, 1, 2, 3, 4, or 5 mg/kg carbofuran by oral gavage three times per week, for five weeks. They found a dose-dependent increase in micronucleated polychromatic erythrocyte formation (statistically significant, $p<0.05$, at 1 mg/kg) in bone marrow cells. Chauhan et al. (2000) reported similar findings in acutely dosed mice. In the only human genotoxicity study, Želježić et al. (2007) showed a small (less than 4 percent) but statistically significant increase in mean tail length in the comet assay conducted on blood lymphocytes of carbofuran exposed workers.

There is also limited evidence of the potential carcinogenicity of carbofuran in human studies. An epidemiology study by McDuffie et al. (2001) found an increased odds ratio for developing non-Hodgkin lymphoma with carbamate pesticide exposure. However, the odds ratio for developing lymphoma from carbofuran exposure alone was not significantly higher. Another epidemiology study by Bonner et al. (2005) found an increased incidence of lung cancer in high versus low carbofuran exposed groups. However, this was not significant when compared to non-exposed controls. While these studies provide some evidence of genotoxicity and carcinogenicity, the two-year cancer bioassays conducted in two animal species were both negative (IRDC, 1979; IRDC, 1980) and there is not sufficient evidence of carcinogenicity from these new studies to support the use of a cancer endpoint for PHG derivation.

There are several studies documenting human occupational exposures, accidental exposures, and suicides/homicides involving carbofuran. Two recent articles in the open literature document carbofuran poisoning of farm workers, both from non-U.S. countries of origin. One farmer in Korea developed Steven-Johnson syndrome, an acute, life-threatening dermatosis (Lim et al., 2010), while 13 others in Turkey presented with a range of symptoms indicative of cholinergic poisoning (Satar et al., 2005). In all instances, the patients were treated with supportive care and eventually recovered. Occupational exposure to carbofuran is mostly by dermal exposure. Dermal absorption by human skin is relatively low (Gammon et al., 2011) and dermal exposure is moderately less toxic than by other exposure routes. There have been no recent incidences of occupational exposure reported in California to the Department of Pesticide Regulation's Pesticide Illness Surveillance Program, with the last reported exposure occurring in 2001.

PHG Derivation

After reviewing the available carbofuran toxicity studies, OEHHA is retaining the Pant et al. (1995) study for PHG derivation because it is the study with the most sensitive endpoint, showing multiple significant measurements of male reproductive toxicity at

doses lower than those showing adverse effects in other animal toxicity studies. A summary of the major study results is presented in Table 3. There was also a dose-dependent decrease in body weight from 0.2 to 0.8 mg/kg-day; however the data were presented graphically and not numerically. OEHHA estimated the body weights from the graphical representation and the body weights were approximately 14%, 28%, and 33% lower than the controls at 0.2, 0.4, and 0.8 mg/kd-day, respectively. However, because these were estimates from a graph, OEHHA determined these values were not appropriate for statistical analysis. The NOAEL from this study is determined to be 0.1 mg/kg-day due to various reproductive effects and reduced body weight observed at higher doses. Reproductive toxicity as a critical health effect is supported by recent open literature studies (discussed above) citing endocrine disruption and effects on sperm in rodents exposed to carbofuran (Chauhan et al., 2000; Elayan et al., 2013; Goad et al., 2004). In addition, pesticide registrant-submitted studies also support reproductive toxicity as the critical endpoint (reviewed in DPR, 2006). These include a one-year study in dogs citing testicular degeneration with a NOAEL of 0.6 mg/kg-day (Toxigenetics, 1983) and a study in rabbits showing negative effects on semen at doses of one tenth and one hundredth of the median lethal dose (LD_{50}) (Yousef et al., 1995). Yousef et al. (1996) also demonstrated inhibition of human sperm motility in vitro, further supporting the relevance of carbofuran reproductive toxicity in humans.

Table 3. Reproductive toxicity data for male rats exposed to carbofuran in a 60-day oral gavage study (Pant et al., 1995)

Endpoint	Dose (mg/kg-day)				
	0 n=10	**0.1 n=10**	**0.2 n=10**	**0.4 n=10**	**0.8 n=3**
Sperm motility (percent)	85.0 ± 3.6[a]	83.7 ± 4.4	63.7 ± 5.0*	51.2 ± 7.9*	36.6 ± 5.8*
Total epididymal sperm count (x 10^7)	9.0 ± 1.1	8.0 ± 1.6	5.0 ± 1.2*	4.0 ± 0.6*	3.0 ± 2.6*
Total sperm abnormalities (percent affected)	10.5 ± 3.4	10.8 ± 2.0	22.3 ± 2.1*	33.8 ± 2.0*	54.6 ± 1.0*
Absolute testis weight (g)	2.50 ± 0.25	2.50 ± 0.11	2.40 ± 0.16	2.40 ± 0.09	2.36 ± 0.10
Absolute epididymis weight (g)	0.81 ± 0.03	0.78 ± 0.08	0.50 ± 0.09*	0.49 ±0.08*	0.43 ± 0.24*
Absolute seminal vesicle weight (g)	0.18 ± 0.04	0.17 ± 0.05	0.09 ±0.04*	0.08 ±0.04*	0.05 ±0.01*

Absolute ventral prostate weight (g)	0.11 ± 0.03	0.11 ± 0.02	0.09 ± 0.01*	0.05 ±0.03*	0.03 ± 0.01*
Absolute coagulating glands weight (g)	0.05 ± 0.009	0.05 ± 0.006	0.02 ± 0.003*	0.02 ±0.009*	0.01 ± 0.014*

[a] All results are mean ± standard deviation.
*Significantly different from control, p<0.05, calculated by Pant et al. using Student's t-test.

OEHHA analyzed all of the endpoints shown in Table 3 using BMDS continuous models with a benchmark response of one standard deviation change from the control mean (BMDS Version 2.4, US EPA). Absolute organ weights were analyzed instead of relative organ to body weight ratio as reproductive organ weight is not necessarily related to body weight changes (Bailey et al., 2004). Furthermore, there is relatively low inter-animal variability with respect to male reproductive organ weight, such as testis weight, making absolute organ weight a better indicator of reproductive toxicity (US EPA, 1996).

Despite a clear dose-response relationship and in many cases statistical significance at doses of 0.2 mg/kg-day and above, the only endpoints with data amenable to BMD modeling were absolute testis weight and absolute seminal vesicle weight. Sperm motility, sperm count, sperm abnormalities, and the remaining absolute reproductive organ weights (with the exception of absolute ventral prostate weight) failed goodness of fit tests (p-values <0.05) for all BMDS models. There was a steep dose-response between the 0.1 and 0.2 mg/kg-day doses and a narrow dose range used in the study, characteristics that likely resulted in poor fit of data at the low dose range using the models available in US EPA's BMDS. Absolute ventral prostate weight failed the test for modeled variance. For the two endpoints that were successfully modeled by BMDS, the $BMDL_{1SD}$ for absolute testis weight was 0.5 mg/kg-day using the Power Model and for absolute seminal vesicle weight was 0.1 mg/kg-day using the Hill Model. The details of the BMD analysis for absolute seminal vesicle weight are presented in Figure A1 of Appendix I.

Because of poor BMDS model fitting for this dataset, OEHHA is using the NOAEL/LOAEL approach for the determination of the POD. Based on the data shown in Table 3, a NOAEL of 0.1 mg/kg-day and a LOAEL of 0.2 mg/kg-day are identified for male reproductive effects and 0.1 mg/kg-day is selected as the POD. A 5/7 adjustment is applied to the NOAEL to account for dosing occurring five out of seven days per week, resulting in an adjusted POD of 0.071 mg/kg-day. The ADD is calculated using a total UF of 1,000: 10 for interspecies extrapolation, 30 for intraspecies variability, and √10 for extrapolation from a subchronic study:

$$ADD = \frac{POD}{UF} = \frac{0.071\ mg/kg\text{-}day}{1{,}000} = 0.000071\ mg/kg\text{-}day$$

Inhalation and dermal exposures to carbofuran in tap water are calculated for various life stages using CalTOX modeling. Details on model inputs and outputs are presented in Appendix II. The relative contributions from each route to the overall exposure to carbofuran in tap water are presented in Table 4. 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 5).

Table 4. CalTOX results for relative contributions of multiple routes of exposure to carbofuran in tap water for various life stages

Life Stage	Oral Ingestion (%)	Inhalation (%)	Dermal (%)
Fetus[a] (Pregnancy)	65	32	2
Infant[b]	98	0	2
Child	54	43	2
Adult	69	29	2

[a]The fetus is assumed to have the same exposure as the pregnant mother.
[b]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 5. Total liter equivalent values for multi-route exposure to carbofuran 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]	0.023[d]	0.001[d]	0.071
Infant	0-2	0.196	0.000	0.004	0.200
Child	2-16	0.061	0.049	0.002	0.112
Adult	16-70	0.045	0.019	0.001	0.065
Time-weighted average over lifetime					0.079

[a]Inhalation and dermal estimates are calculated using the life-stage-specific oral ingestion rates (OEHHA, 2012) and relative contribution of the oral ingestion value.
[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.
[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 A3 of Appendix II.

The 2000 PHG applied a RSC of 0.2 because carbofuran was in active use at the time and it was assumed that exposures to residues on food and in the air would be greater than those from drinking water. The default RSC of 0.80 is applied in this update because carbofuran is no longer being used in California and exposure to residues on food or inhalation exposures from ambient air are not expected.

The public health-protective concentration, C, is:

$$C = \frac{0.000071 \text{ mg/kg-day} \times 0.80}{0.079 \text{ L}_{eq}\text{/kg-day}} = 0.0007 \text{ mg/L} = 0.7 \text{ µg/L or } 0.7 \text{ ppb}$$

Thus, OEHHA is setting an updated PHG of 0.7 ppb for carbofuran. The updated PHG incorporates an updated drinking water intake rate, updated inhalation and dermal exposure estimates, and a factor that accounts for differences in pharmacokinetic and pharmacodynamic variability within the human population.

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UPDATED PHG FOR DIQUAT

Diquat (1,1'-ethylene-2,2'-dipyridylium dibromide) is a non-selective herbicide with widespread use in California, including as an aquatic and terrestrial herbicide as well as a crop desiccant. There are currently 52 products registered in California with diquat listed as an active ingredient.[7] In the most recent pesticide use report, the California Department of Pesticide Regulation (DPR) reported 88,834 pounds of diquat were used in 2012.[8] Of the total amount of diquat applied in 2012, roughly 45 percent was as a terrestrial herbicide on rights of way, 19 percent as a desiccant on alfalfa, 16 percent was for landscape maintenance, and 5 percent was used in water as an aquatic herbicide. The remaining was applied on a variety of ornamental and agricultural commodities. Diquat adsorbs strongly to soil, thus leaching from soil into ground water is not expected to occur. When used as an aquatic herbicide, diquat residues in the water decline rapidly to undetectable levels, with a half-life generally less than 48 hours (WHO, 2004).

In the last three years, there were nine detections of diquat, ranging from 0.44 to 14 ppb, in California public water supply wells tested,[9] none of which met or exceeded the previous PHG of 15 ppb or the California MCL of 20 ppb. One detection of 14 ppb returned to undetectable levels at the next monitoring, less than three months later. Therefore, widespread exposure of the public to this drinking water contaminant is not anticipated.

2000 PHG

The original PHG of 15 ppb for diquat was based on a chronic toxicity study of Sprague-Dawley rats (50/sex/dose) fed 0, 5, 15, 75, or 375 ppm diquat in the diet for 104 weeks (Colley et al., 1985). Eye examinations were conducted at 13, 26, 52, 78, and 104 weeks of exposure. At 104 weeks, cataracts and lens opacities were determined to be the most sensitive endpoints in the study and the chronic NOAEL was identified as 0.22 mg/kg-day (the combined average dose for males and females at 5 ppm). The PHG was calculated with the NOAEL of 0.22 mg/kg-day and a total uncertainty factor of 100 (10 for intraspecies extrapolation and 10 for potentially sensitive subpopulations). The exposure parameters in the calculation assumed an adult body weight of 70 kg, water consumption rate of 2 L/day, and an RSC of 20 percent to allow for exposure to diquat residues in food.

Teratology studies in three species suggested some evidence of developmental toxicity. In offspring of pregnant rabbits dosed by gavage on gestational days 7 to 19 and

[7] California Department of Pesticide Regulation output reporting for diquat dibromide, active chemicals only, accessed at: http://www.cdpr.ca.gov/docs/label/chemcode.htm.

[8] Summary of pesticide use report data, 2012, indexed by chemical from California Department of Pesticide Regulation. Accessed at: http://www.cdpr.ca.gov/docs/pur/purmain.htm.

[9] Data 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.

sacrificed on day 30, there was a slight but significant increase in delayed ossification at all doses tested (1, 3 and 10 mg/kg-day) (Hodge, 1989). Fetal malformations were increased at all doses, but statistically significant only at the low dose. The incidences for all malformations (expressed as affected litters/total litters) for control to high-dose groups were: 2/18, 8/15 ($p<0.01$), 4/20, and 5/13. In a mouse study with gavage doses of 0, 1, 2 or 4 mg/kg on gestation days 6 through 15, major malformations and skeletal anomalies were observed at 2 and 4 mg/kg-day (Palmer et al., 1978). However, the incidences were low and not statistically significant ($p>0.2$) compared to the control. In the rat, the developmental NOAEL was 12 mg/kg-day for delayed skeletal ossification (Wickramaratne, 1989). While there is some indication of developmental toxicity for diquat in experimental animals, the points of departure for developmental toxicity were higher than the 0.22 mg/kg-day used to derive the PHG based on cataracts in adult rats (Colley et al., 1985). Thus, the PHG was protective for developmental toxicity.

In two rat multigenerational reproductive toxicity studies, there were no direct effects on the rat reproductive system but a NOAEL was set in one study at 1.6 mg/kg-day for reduced male pup weight (Hodge, 1990; Fletcher et al., 1972). Diquat did not cause tumors in two cancer bioassays conducted with mice and rats fed diquat in the diet for two years (Colley et al., 1985; Ben-Dyke et al., 1975).

Recent Literature

There have been a number of peer-reviewed studies on diquat since the publication of the PHG in 2000 (OEHHA, 2000). Diquat cytotoxicity is known to be caused by redox cycling and the generation of reactive oxygen species in target tissues (Sandy et al., 1986). Because of this, diquat is used as a model compound to study redox cycling. A majority of the recent studies involving diquat are of this nature and not useful for characterizing the toxicology of diquat pesticide exposure. For example, Han et al. (2007) and Higuchi et al. (2011) exposed animals to a single dose of diquat to investigate changes in gene expression and iron metabolism in response to oxidative stress. These studies are not further evaluated in this update.

There are a few studies related to the toxicity of diquat when used as an herbicide, which focused on neurotoxicity, reproductive toxicity, and genotoxicity, as summarized below.

Diquat is structurally similar to paraquat, which has been linked to Parkinson's disease, a progressive neurodegenerative disorder characterized by loss of dopaminergic neurons in the substantia nigra (Tanner et al., 2011). While the causal link between paraquat and Parkinson's disease remains unclear (Miller, 2007), the ability of paraquat to cause neurotoxicity is less arguable. Diquat is generally thought to be less toxic than paraquat; however, there are concerns that potentially low-dose chronic exposures to diquat, such as might occur through drinking water, could have similar neurotoxic effects. A study by Karuppagounder et al. (2012) investigated the neurotoxicity of diquat. In this study, male mice (n=6) were given diquat (10 mg/kg) or water by intraperitoneal injection twice a week for six weeks and assessed for behavioral, neurochemical, and immunohistochemical changes related to neurotoxicity. The battery

of tests chosen was designed to assess specific components of Parkinson-like diseases. Based on their results, the authors concluded that diquat caused mild dopaminergic degeneration but only induced muscular rigidity without inducing other Parkinsonian motor symptoms. Diquat also did not induce dopamine depletion in the striatum (a hallmark of Parkinson's disorder), but did decrease the major dopamine metabolite, implying a decrease in dopamine turnover and mild generation of free radicals in the central nervous system. Results supported concerns for mild neurotoxic effects of diquat but these effects were not as severe as those associated with paraquat. Furthermore, guideline neurotoxicity studies in the rat failed to show delayed neuropathies (up to 150 mg/kg-day) or evidence of neurotoxicity in the functional observational battery or motor activity measurements (up to 38.5 mg/kg-day) (Horner, 1992a; Horner, 1992b).

In an in vitro study using preimplantation mouse embryos, Greenlee et al. (2004) found that diquat treatment significantly increased the percentage of apoptotic cells in the embryo (14.12 percent versus 10.26 percent in the control) without significantly affecting blastocyst formation or cell number per embryo. While a 4 percent increase in apoptosis alone is not necessarily indicative of a negative developmental outcome, defects in embryonic apoptosis may alter normal fetal development and may account for some of the fetal abnormalities observed in mice, rabbits and rats (OEHHA, 2000).

Another study, by Dimitrov et al. (2006), investigated the genotoxicity of various herbicide formulations including Reglone®, a commercial formulation of diquat, in plant and mouse bone marrow test systems. The authors found that Reglone® did not induce chromosomal aberrations but was positive for increased micronucleus frequency. The authors suggested that Reglone® may damage the mitotic apparatus leading to loss of chromosomes. As this study investigated effects of the commercial formulation, whether the active ingredient or inert ingredients caused the increase in micronuclei formation could not be determined. Furthermore, the U.S. Environmental Protection Agency (US EPA) and DPR have analyzed the genotoxicity database for diquat and found that while there was evidence of in vitro genotoxicity, there was no evidence of in vivo DNA damage and the two-year cancer bioassays in rats and mice were both negative (Colley et al., 1985; DPR, 1994; Hodge, 1991). OEHHA has reviewed the toxicological summaries for these studies and agrees with DPR and US EPA's assessment. Diquat was assigned the cancer classification of Group E, evidence of non-carcinogenicity in humans, by US EPA (US EPA, 1995).

In summary, a review of recent scientific literature did not identify any new toxicity studies that would replace Colley et al. (1985) as the critical study for PHG derivation. OEHHA reconsidered other studies presented in the original PHG but did not identify more sensitive endpoints or stronger data sets to replace the critical study previously selected. Of the three teratology studies described above (Hodge, 1989; Palmer et al., 1978; Wickramaratne, 1989), only the Hodge (1989) study had data amenable to BMD modeling. However, BMD modeling of these data resulted in a $BMDL_{05}$ of 2.7 mg/kg-day for delayed ossification, which is an order of magnitude higher than the POD of 0.22 mg/kg-day used in the 2000 PHG. In addition to cataracts, reduced weight gain and/or

kidney effects were observed in two rat multigenerational studies, two chronic dog studies, and a mouse chronic study. Cataracts were the most sensitive endpoint and occurred in toxicity studies in both rats (Colley et al., 1985) and dogs (Hopkins et al., 1990) at similar doses. The dog study is not chosen as the critical study due to greater uncertainty with the data set; there were fewer animals per dose group than in the rat study and an additional uncertainty factor would be needed to extrapolate from subchronic to lifetime exposure. However, the NOAEL of 0.5 mg/kg-day based on lens opacities observed in the dog study by Hopkins (1990) is supportive of the $BMDL_{05}$ of 0.45 mg/kg-day derived from cataracts observed in rats in the Colley et al. (1985) study.

PHG Derivation

After reviewing the available diquat toxicity studies, OEHHA is retaining the Colley et al. (1985) study for PHG derivation. The incidence of spontaneous cataracts in rats is very low (Taradach et al., 1981) and the cataracts observed in the Colley et al. (1985) study showed a clear dose-dependent increase in occurrence in both male and female rats (Table 6).

Table 6. Incidence of cataracts in Sprague-Dawley rats exposed to diquat dibromide in the diet for 104 weeks (Colley et al., 1985)

	Dose (mg/kg-day)[a]				
Males	**0**	**0.19**	**0.58**	**2.91**	**14.88**
Total Cataracts	0/22[†]*	0/16	1/22 (5%)	3/21** (14%)	24/24** (100%)
	Dose (mg/kg-day)[a]				
Females	**0**	**0.24**	**0.72**	**3.64**	**19.44**
Total Cataracts	0/20*	0/22	1/20 (5%)	3/20** (15%)	27/27** (100%)
	Dose (mg/kg-day)[b]				
Combined	**0**	**0.22**	**0.65**	**3.28**	**17.16**
Total Cataracts	0/42*	0/38	2/42 (5%)	6/41** (15%)	51/51** (100%)

[a] Doses converted from ppm to mg/kg-day by Colley et al. (1985)
[b] Average of male and female doses
[†] Number of animals affected/number of animals examined
* p<0.01 for trend (indicated at the control group, using Cochran-Armitage trend test)
** p<0.01 treated compared with the control (Fisher Exact test)

OEHHA reanalyzed the dose-response data in the Colley et al. (1985) study and estimated the POD using BMDS (Version 2.4, US EPA). For BMD modeling, the highest dose was not included because there was 100 percent incidence at this dose and there are three additional doses showing a good dose-response. Furthermore, removing the high dose gave a better fit to the model in the low-dose range which is more important for setting a PHG. A benchmark response of five percent results in a modeled BMD that corresponds very well to the dose resulting in the observed five

percent response in the study. The BMD modeling results are summarized in Table 7 and the details of the BMD analyses are presented in Figure A2 of Appendix I.

Table 7. Benchmark dose modeling of incidence of cataracts in rats exposed to diquat dibromide in the diet for 104 weeks (Colley et al., 1985)

Endpoint	Model[a]	BMD_{05} (mg/kg-day)	$BMDL_{05}$ (mg/kg-day)
Male Rats			
Total Cataracts	Gamma[b]	0.93	**0.45**
Female Rats			
Total Cataracts	Multistage[c]	1.1	0.54
Male + Female Rats			
Total Cataracts	Multistage[c]	1.0	0.60

[a] All models were run with default parameters and the highest dose excluded.
[b] The Gamma, Multistage, Weibull, and Quantal-Linear models produced the same results.
[c] The Multistage and Quantal-Linear models produced the same results.

The $BMDL_{05}$ of 0.45 mg/kg-day, derived from the Gamma model (Table 7) using male rat data, is selected as the POD because it is the lowest BMDL derived from a model that fit the data well (see Appendix I) for a robust endpoint (Table 6). This POD is supported by the NOAEL of 0.65 mg/kg-day (male and female combined) and the NOAEL of 0.58 mg/kg-day (male only). The ADD is calculated using a total UF of 300: 10 for interspecies extrapolation, and 30 to account for variability among humans, including sensitive individuals:

$$\text{ADD} = \frac{\text{POD}}{\text{UF}} = \frac{0.45 \text{ mg/kg-day}}{300} = 0.0015 \text{ mg/kg-day}$$

Diquat is non-volatile with a Henry's Law constant of $<6.3 \times 10^{-14}$ atm-m^3/mol at 20-25 ºC, thus inhalation exposure to diquat in tap water during showering and bathing is expected to be negligible. Dermal exposure is also not likely to be significant because dermal absorption of diquat is estimated to be very low, at 1 to 2 percent (OEHHA, 2000). For these reasons, oral ingestion of diquat in water and food is determined to be the main exposure route.

When diquat is applied directly to crops for weed control, it binds very effectively to the soil and very little residue is taken up into the edible part of the plant. However, when diquat is used as a desiccant on harvested crops, diquat residue is detectable in both the raw commodity and the processed products of some crops (WHO/FAO, 1995). Since diquat is currently used in California, the RSC is set at the default of 0.20 for the contribution of exposure from water, which allows for significant exposure to diquat from residues in food in the absence of data to indicate otherwise.

Using the time-weighted average of 95th percentile "consumers only" high-end water consumption rates of all age groups adjusted for body weight, 0.053 L/kg-day (OEHHA, 2012), the public health-protective concentration, C, is:

$$C = \frac{0.0015 \text{ mg/kg-day} \times 0.20}{0.053 \text{ L/kg-day}} = 0.006 \text{ mg/L} = 6 \text{ µg/L or 6 ppb}$$

Thus, OEHHA is setting an updated PHG of 6 ppb for diquat. The updated PHG incorporates a new dose-response analysis using BMD modeling, an updated drinking water intake rate, and an updated factor that accounts for pharmacokinetic and pharmacodynamic variability within the human population. The federal Maximum Contaminant Level Goal (MCLG) for diquat is 20 ppb, as is the federal MCL.

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UPDATED PHG FOR ENDRIN

Endrin is an obsolete organochlorine cyclodiene pesticide (US EPA, 1992). It was used to control insects, rodents, and birds from the 1950s until its registration was voluntarily canceled in the 1980s due to its toxicity (ATSDR, 1996). Endrin has low water solubility and low volatility at ambient temperature. It is lipophilic and bioaccumulates in the food chain (US EPA, 1980). It is persistent in soils and sediments with a half-life longer than 10 years. Endrin is one of the persistent organic pollutants (POPs) outlawed world-wide by the Stockholm Convention in 2001. It has not been used in California for over 20 years.[10] Endrin has not been detected in California public drinking water supply wells at levels above 0.1 ppb, the detection limit for purposes of reporting (DLR), in the last three years.[11] Therefore, public exposure to endrin via drinking water is not expected. In 1997, Endrin was added to California's Proposition 65 list as a chemical known to cause reproductive toxicity, based on its developmental toxicity.[12] The federal and California MCL for endrin is 2 ppb.[13]

1999 PHG and 2008 PHG Update

The original PHG of 1.8 ppb (OEHHA, 1999) was based on a chronic toxicity study in which three beagle dogs/sex/dose were fed endrin at 0, 0.1, 0.5, 1.0, 2.0, or 4.0 ppm in the diet for two years (Jolley et al., 1969). Additional groups of four dogs/sex/dose were fed 0, 1.0, or 4.0 ppm endrin in the diet. Two dogs of each sex from the 0, 1.0, and 4.0 ppm groups were sacrificed at six and twelve months. Female and male dogs in the two highest dose groups were observed with convulsive seizures. The authors attributed the convulsions with brain edema and hemorrhages to the two-year exposure to endrin. Dogs receiving 2.0 or 4.0 ppm had slightly increased relative liver weight and cytoplasmic pigmentation and vacuolization of hepatic cells. A NOAEL of 1.0 ppm was identified and, based on a standard food intake factor of 2.5 percent body weight/day for dogs, US EPA (2002) estimated that this was equivalent to 0.025 mg/kg-day.

Calculation of the PHG incorporated a total UF of 100, including 10 for intraspecies variability and 10 for interspecies extrapolation (OEHHA, 1999). The exposure parameters in the PHG calculation assumed a 70 kg adult body weight, a drinking water intake rate of 2 L/day, and an RSC of 20 percent.

There was inadequate evidence to assess the potential carcinogenicity of endrin for humans (US EPA, 1992), thus the PHG was based on non-cancer endpoints. Developmental toxicity studies were reviewed in the PHG (OEHHA, 1999). Altered locomotor activity levels indicating neurotoxic effects in dams were observed in

[10]Summary of pesticide use report data, indexed by chemical from California Department of Pesticide Regulation. Accessed at: http://www.cdpr.ca.gov/docs/pur/purmain.htm.
[11]Data accessed with GeoTracker GAMA: http://geotracker.waterboards.ca.gov/gama/.
[12]Proposition 65 listing is based on the US EPA (1992) Drinking Water Criteria Document summarizing a major finding of developmental neurotoxicity in three species. Accessed at: http://oehha.ca.gov/prop65/pdf/abpkg5rb.pdf.
[13]Accessed at: http://www.waterboards.gov/drinking-water/certlic/drinkingwater/MCLsandPHGs.shtml

hamsters and mice but less clearly in rats, and various types of abnormal bone formation were reported in all three species (US EPA, 1980, 1992). Other reported developmental toxicity effects included embryolethality, morphological malformations, growth deficits and changes in behavior. However, the developmental toxicity endpoint, in terms of doses applied in the studies, was not as sensitive as the neurotoxicity and hepatotoxicity endpoints used for PHG derivation.

The 2008 endrin PHG update did not find any new toxicity data justifying any changes to the original 1999 PHG (OEHHA, 2008).

Recent Literature

A thorough examination of recent literature has not revealed any new toxicological or epidemiological studies for endrin alone since the publication of the original PHG in 1999 and the update in 2008. All the new publications have evaluated endrin as one component within a mixture of organochlorine pesticides (OCPs) or POPs. There are no new studies reporting the detection of endrin in environmental or biomonitoring samples in California, which reduces concerns for endrin exposure in this state. The exposure to endrin world-wide is also declining, as reflected in a number of studies examining levels of endrin in human breast milk, serum, or other human tissues or fluids (Bedi et al., 2013; Boada et al., 2012; Kanazawa et al., 2012; Luzardo et al., 2009, 2013; Meza-Montenegro et al., 2013).

Two cases of endrin poisoning in humans were reported in Japan from 2003 to 2006; however, symptoms and endrin levels were not provided (Kudo et al., 2010). In case reports of poisoning by endosulfan and other organochlorine pesticides during an 8-year period (1999-2007) in India, one case of endrin poisoning with an unremarkable course was identified and the patient survived (Moses and Peter, 2010). One publication reported symptoms related to endrin or OCP exposures among migrant agricultural pesticide workers in Oman (Esechie et al., 2012).

Furthermore, the levels of endrin in serum samples in the U.S. population measured in the National Health and Nutrition Examination Survey (NHANES) have declined substantially over the years, again demonstrating a reduction in exposure to endrin in the U.S. (Patterson et al., 2010). In the most recently reported NHANES annual subsets from 2001 to 2010, endrin levels in serum samples from adults and children in the U.S. at the 50th percentile were below the average detection limit of about 7.8 ng/g lipid (CDC, 2013; Patterson et al., 2009).

Among seven head and neck cancer patients from rural Oklahoma, one 76-year-old Caucasian woman had an endrin level of 38.6 ng/g of adipose tissue while all five non-cancer control individuals living in the same area did not have endrin levels above the study's detection limit of 10 ng/g (Govett et al., 2011). Three U.S. studies also reported negative findings for endrin in human blood and tissues. Endrin was not detected in serum samples of 50 patients with Parkinson's disease, 20 patients with Alzheimer's disease, and 43 control subjects (Richardson et al., 2009). Endrin and one of its major

metabolites, endrin aldehyde, were not detected in serum or subcutaneous, visceral, retroperitoneal, and pelvic fat compartments measured in six male and one female surgery patients (Yu et al., 2011). Endrin was not detected in 225 occipital lobe brain samples of Japanese-American male participants in the Honolulu-Asia Aging Study (Ross et al., 2012).

In a case-control study in Egypt, investigators found a correlation between elevated OCPs in newborns and lactating mothers, and altered bleeding tendencies, hematologic indices, and perturbed cytokine immunosuppression responses in the infants (Schaalan et al., 2012). The study measured elevated levels of OCPs (including endrin) in maternal milk and infant serum in 180 OCP-exposed breast-fed newborns and their OCP-exposed lactating mothers, compared with a control group of 180 non-OCP-exposed newborns and their lactating mothers. The authors discussed the possibility of OCP-induced liver toxicity causing hemolysis in the exposed infants, suggesting that the disturbed hematologic profiles might be caused by endrin-induced liver toxicity. As in most of the new studies, the effect of endrin alone was not analyzed.

Evidence for an effect of endrin on the thyroid is suggestive, but not conclusive, in two human studies. In a birth cohort study of prenatal OCP exposure and thyroid-stimulating hormone (TSH) status in 220 newborn boys from southern Spain, 75 of the 220 placentas analyzed had detectable endrin levels (Freire et al., 2011). Higher endrin levels in placentas were associated with a greater than two-fold odds ratio of having TSH cord blood levels at or greater than the 80^{th} percentile. In a population-based survey study for relationships of long-term OCP exposures and thyroid function in 193 children younger than 15 years old in Brazil, correlations were not found between the low detectable endrin levels in serum and changing levels of free thyroxine (T4) and TSH, independent of gender and age (Freire et al., 2012). On the other hand, this study showed a consistent and significant increasing linear trend in total triiodothyronine (T3) with OCP exposures, including endrin, as indicated by serum concentrations.

Kinter and Pritchard (2011) reviewed the alteration of cell membrane permeability pathways by various OCPs, including endrin and its major metabolites such as endrin ketone and endrin aldehyde. Endrin and its metabolites inhibit GABA activation of chloride channels, which is one of the mechanisms leading to the neurotoxicity of endrin. Allen et al. (2013) examined the structural components contributing to the toxicity of dieldrin, a stereoisomer of endrin, in cultured dopaminergic cells (Allen et al., 2013). The study found that dieldrin is more cytotoxic than endrin and the structural difference between dieldrin and endrin, i.e., the position and orientation of the epoxide and methylene bridge, largely influenced the toxicity of these chemicals (Allen et al., 2013). In another in vitro study, endrin promoted adipocyte differentiation with lipid accumulation, likely through glucocorticoid receptor activation, in the murine 3T3-L1 preadipocyte cell line (Sargis et al., 2010).

PHG Derivation

After evaluating the available endrin toxicity studies, OEHHA is retaining the Jolley et al. (1969) study as the critical study. In this study, dietary intake of endrin resulted in dose-related increased incidences of convulsions with central nervous system (CNS) damage and, to a lesser degree of severity, liver cytoplasmic effects (Table 8).

Table 8. Adverse effects in dogs following dietary exposure to endrin (Jolley et al., 1969)

Reported Dose (ppm)	Liver Effects[a,b]		Central Nervous System (CNS) Effect[a,b]
	Pigmentation	Pigmentation and Vacuolization	Convulsions
0.0	0/5 (p<0.0001[c])	1/5 (p<0.0001[c])	0/6
0.1	0/5	0/5	0/6
0.5	0/5	1/5	0/6
1.0	0/5	0/5	0/6
2.0	4/5 (p=0.02[d])	5/5 (p=0.02[d])	1/6 (17%)
4.0	5/5 (p=0.003[d])	5/5 (p=0.02[d])	3/7[d,e] (43%)

[a]Number of dogs affected/number of dogs examined (both sexes)
[b]Although three dogs/sex/group were exposed to endrin, one male dog from each dose group was retained for a separate reproduction study.
[c]BMDS trend test
[d]Significantly different from control, p<0.05, determined by Fisher's exact test
[e]One male from the early sacrifice group had convulsions at 10 months, thus was added to this treatment group. One other male dog, sacrificed at 26 months, had convulsions during month 5 and a female dog, sacrificed at 27 moths, had convulsions at 12, 21, and 23 months.

The authors (Jolley et al., 1969) reported that one female and two male dogs receiving 4.0 ppm endrin in the diet and one female dog receiving 2.0 ppm endrin in the diet had convulsions at various time points during the experiment up to 27 months. The endrin-induced CNS effects included petechial hemorrhages scattered throughout the brain, diffuse cerebral edema, and edema in the pituitary gland in the female dog in the 4.0 ppm group. One male dog in the 4.0 ppm group exhibited internal hydrocephalus, atrophy of the optic nerves, and a decrease in the thickness of the cerebral cortex, degeneration in the ganglion cells of the cerebral cortex and nuclei in the medulla oblongata, and degenerative changes in the Purkinje cells of the cerebellum with clumping of the cytoplasm and fading away of the cell.

In all female dogs that received 2.0 or 4.0 ppm endrin in the diet up to 24 months, liver cells were slightly enlarged with vacuoles in various sizes. One male dog in the 2.0 ppm group exhibited only pigment and no vacuolization of the hepatic cells. In all dogs fed the two highest doses of endrin, dark brown pigment granules were observed in the cytoplasm of the hepatic cells and the pigment was diffuse throughout the liver.

The authors (Jolley et al., 1969) considered 4.0 ppm and 2.0 ppm as adverse-effect levels based on liver pathology and convulsions. The authors also concluded that 1.0 ppm was a no-effect level for male and female dogs fed endrin in the diet for two years. The authors attributed the effects to "the content of endrin in their diet." Furthermore, convulsions have been reported in other endrin studies in humans and several laboratory animal species (ATSDR, 1996). This neurotoxicity endpoint is being selected as the critical endpoint for PHG derivation.

The study report (Jolley et al., 1969) provided body weights and food consumption rates at the beginning and end of the endrin treatment. Using the actual food consumption data to convert the dose from ppm to mg/kg-day is more accurate than performing the dose conversion based on a standard food intake factor of 2.5 percent body weight/day to approximate consumption, as was done previously. Thus, the average food intake and dose conversion are calculated as shown in Table 9. Since the average food intake rates between males and females differ by less than ten percent, intake rates for both sexes are combined.

Table 9. OEHHA conversion of endrin dose in dogs, data from (Jolley et al., 1969)

Reported Dose (ppm)	Average Food Intake rate[a,b,c] (g/kg-day)	Converted Endrin Dose[d] (mg/kg-day)
0.0	34.76	0.0000
0.1	31.93	0.0032
0.5	34.93	0.0175
1.0	35.36	0.0354
2.0	35.01	0.0700
4.0	33.43	0.1337

[a]average food consumption for all dogs in the dose group (g/kg-day) = {[∑initial food intake rate (kg/kg-day) + ∑final food intake rate (kg/kg-day)] / [2 x number of dogs in the dose group]} x 1,000 g/kg
[b]initial food intake rate (kg/kg-day) = [initial food intake weight (kg/week) / 7 (day/week)] / initial body weight (kg)
[c]final food intake rate (kg/kg-day) = [final food intake weight (kg/week) / 7 (day/week)] / final body weight (kg)
[d]converted endrin dose (mg/kg-day) = average food intake rate (g/kg-day) x 0.001 kg/g x reported dose of endrin (ppm or mg/kg)

The converted doses are then applied to BMD modeling of the incidence data for convulsions. The LogProbit model is chosen as the best fitting model and its resulting $BMDL_{05}$ of 0.022 mg/kg-day is the POD for PHG derivation (Table 10). It is noted that this POD is lower than the NOAEL of 1 ppm (equivalent to 0.035 mg/kg-day as shown in Table 9) determined by Jolley et al. (1969). Because there were only 6 or 7 dogs in each dose group, the study has lower statistical power and less sensitivity to detect an effect. This can result in a higher NOAEL as well as larger confidence limits in the BMD model and a lower BMDL.

Table 10. Benchmark dose modeling results for convulsions observed in dogs exposed to endrin in the diet, data from Jolley et al. (1969)

Model Name	AIC	p-value[a]	BMD_{05} (mg/kg-day)	$BMDL_{05}$[b] (mg/kg-day)	Scaled Residual[c]
Gamma	19.33	0.992	0.051	0.012	-0.321
Logistic	20.11	0.912	0.060	0.031	0.806
LogLogistic	19.37	0.991	0.050	0.012	-0.344
LogProbit	**19.22**	**0.996**	**0.051**	**0.022**	**-0.284**
Multistage	19.49	0.984	0.050	0.012	-0.376
Probit	19.81	0.948	0.057	0.029	0.691
Weibull	19.44	0.987	0.050	0.012	-0.365
Quantal-Linear	19.27	0.920	0.019	0.009	-0.546

[a] p-values ≥ 0.05 indicate the model adequately fits the data.
[b] The BMDL is the lower limit of the 95% confidence interval of the BMD resulting in the benchmark response.
[c] Scaled residual for the dose group near the BMD; this provides a measurement of how close the modeled response is to the actual data point. A scaled residual greater than the absolute value of 2.0 indicates poor fit to the data point.

As shown in Table 10, all eight BMD models exhibit acceptable ranges of scaled residual (absolute value ≤2) and corresponding goodness of fit (p-value >0.05). The BMD values for all the models in Table 10 except the Quantal-Linear model are close (between 0.05 and 0.06), with most of the variation in the BMDLs resulting from broader or narrower confidence limits for the various models. The LogProbit model has the lowest Akaike's Information Criterion (AIC) which is the primary criterion for selecting between models when all other selection criteria are met. The LogProbit model also has the lowest scaled residual value for the dose group nearest the BMD and the highest goodness of fit p-value, indicating that this model is the best fit in the low dose area of interest (as confirmed by visual inspection of the fitted curve shown in Figure A2 in Appendix I).

To calculate the ADD, a total UF of 1,000 is applied, including 10 for interspecies extrapolation and 100 for intraspecies variability as listed in Appendix 1. The rationale for using a higher UF for toxicodynamics is because of the neurotoxic effects, i.e., convulsions with brain edema and hemorrhages, observed in the exposed dogs. Children are considered more sensitive to neurotoxicants and the additional factor of 3 is applied to protect this sensitive sub-population. Therefore, the ADD is:

$$\text{ADD} = \frac{\text{POD}}{\text{UF}} = \frac{0.022 \text{ mg/kg-day}}{1{,}000} = 0.000022 \text{ mg/kg-day}.$$

Exposure to endrin in drinking water is expected to occur primarily through oral ingestion based on its chemical and physical characteristics. Inhalation and dermal exposures to endrin during household uses of tap water, such as bathing and

showering, are estimated with CalTOX 4.0. Details of the CalTOX model inputs and outputs are presented in Table A4 in Appendix II. The relative contributions of each pathway to the total exposure to endrin in tap water are presented in Table 11.

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

Life Stage	Oral Ingestion (%)	Inhalation (%)	Dermal (%)
Fetus[a] (Pregnancy)	92.1	2.7	5.2
Infant	97.3	0[b]	2.7
Child	89.7	4.2	6.1
Adult	92.3	2.2	5.5

[a]The fetus is assumed to have the same exposure as the pregnant mother.
[b]Infant exposure to endrin in tap water via inhalation is anticipated to be negligible, 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.

Liter equivalent (L_{eq}) values for inhalation and dermal exposures are calculated using life-stage-specific oral ingestion levels (OEHHA, 2012) and the relative contribution of the oral ingestion values. These values are presented in Table 12. Since endrin is listed under Proposition 65 for its developmental toxicity, OEHHA pays special attention to the fetus and compares the calculated fetal exposures of all three major routes of exposure through the pregnant mother with the adult exposures listed in Tables 11 and 12. Considering the potential developmental toxicity of endrin, it is worth noting that the fetus-only daily drinking water intake (DWI) of 0.050 L_{eq}/kg-day is fairly close to the lifetime average DWI of 0.057 L_{eq}/kg-day for the general population as shown in Table 12.

Table 12. Total liter equivalent values for multi-route exposure to endrin 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]	0.000684[d]	0.002683[d]	0.050
Infant	0-2	0.196	0	0.005458	0.201
Child	2-16	0.061	0.001434	0.004163	0.067
Adult	16-70	0.045	0.000547	0.002683	0.048
Time-weighted average over lifetime					0.057

[a]Inhalation and dermal estimates are calculated using the life-stage-specific oral ingestion rates (OEHHA, 2012) and relative contribution of the oral ingestion value.
[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.
[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 A4 of Appendix II.

Since endrin has not been used in California for over 20 years, exposures from residue on food and from air pollution are considered not likely. Endrin is not on the US EPA's hazardous air pollutant (HAP) list and not on the California Air Resources Board's toxic air contaminant (TAC) list. Endrin has not been on the US EPA's Toxics Release Inventory (TRI) lists, both federally[14] and for California[15], since 1995 and hazardous waste treatment facilities or dump sites are not required to report endrin releases. Even though endrin bioconcentrates in aquatic organisms, it is not very soluble in water and is not on the list to be reported by the SWRCB fish monitoring programs. Human exposure to endrin in drinking water is assumed to occur primarily through domestic uses of tap water contaminated by endrin either leaching from waste dump sites into groundwater or as any residue possibly remaining in the drinking water. Therefore, the RSC of 0.80, instead of the 0.20 value in the previous PHG, is now used in the PHG calculation.

The PHG, using the $BMDL_{05}$ as POD, can be calculated as:

$$C = \frac{0.000022 \text{ mg/kg-day} \times 0.80}{0.057 \text{ L}_{eq}\text{/kg-day}} = 0.0003 \text{ mg/L} = 0.3 \text{ µg/L or } 0.3 \text{ ppb}$$

OEHHA is revising the existing endrin PHG of 1.8 ppb to 0.3 ppb using updated dose-response modeling, an updated intraspecies variability factor, an updated multi-route exposure estimate, and an updated RSC.

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UPDATED PHG FOR PICLORAM

Picloram (4-amino-3,5,6-trichloropicolinic acid) is a water-soluble chemical that was widely used as a broad spectrum herbicide for the control of broad-leaf weeds and woody plants. It was used alone or in combination with 2,4-dichlorophenoxyacetic acid (2,4-D) against deep-rooted perennials on non-crop land and in combination with 2,4-D or 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) for brush control (Worthing and Walker, 1987). Picloram does not bind strongly with soil particles and is not degraded rapidly in the environment, allowing it to be highly mobile and persistent. The average half-life in soil is 90 days but the persistence of picloram in soil has been estimated to range from one month to 116 years (Fryer et al., 1971; Hance 1979). Picloram has been detected in over 43 states and above the federal MCL of 500 ppb in 136 water systems or 0.41 percent of the U.S. systems analyzed (US EPA, 2009). In California public drinking water supplies, there were three detections of picloram ranging from 0.0021 to 0.0036 ppb in the last three years.[16] In addition, picloram has not been registered for use in California since 1988.[17] However, the DPR Pesticide Use Database reports that approximately 93 pounds of picloram were used in California in 2012, presumably from pre-existing supplies.[18]

1997 PHG

The PHG of 500 ppb developed for picloram in 1997 was based on increased liver weight observed in dogs (Dow, 1982). In this study, picloram was fed in the diet to three-month-old beagle dogs (six dogs/sex/dose) at doses of 0, 7, 35 or 175 mg/kg-day for six months. In both male and female groups there were treatment-related increases in absolute and relative liver weights, decreased body weights and body weight gain, decreased food consumption, and changes in liver enzymes, all observed at the highest dose of 175 mg/kg-day. The increased liver weights were not associated with histopathological changes. Treatment-related increases in absolute liver weight were noted at the intermediate dose of 35 mg/kg-day in male dogs only. No compound-related effects were detected in female dogs at 35 mg/kg-day and in male or female dogs at 7 mg/kg-day. Using the NOAEL of 7 mg/kg-day, a relative source contribution of 20 percent, an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability), a 70 kg adult body weight, and a drinking water consumption rate of 2 L/day, a PHG of 500 ppb for picloram was derived (OEHHA, 1997). There was insufficient evidence for the carcinogenicity of picloram, thus the PHG was based on a non-carcinogenic endpoint. Additionally, reproductive and developmental toxicity studies were reviewed but deficiencies in study design and the lower sensitivity of these

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

[17] Accessed at: http://www.cdpr.ca.gov/docs/label/prodnam.htm.

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endpoints, compared to liver toxicity, precluded the use of these studies for PHG derivation.

Recent Literature

Various databases were searched to determine if there were any studies since 1997 that would provide a more appropriate health endpoint for the development of a new PHG for picloram. Very few new studies were found in the literature. They include a toxicity study evaluating testicular effects in male rats and a follow-up study that investigated potential male-mediated developmental effects in offspring using the same male rats (Oakes et al., 2002a,b); an epidemiological study evaluating the relationship between parental occupational exposures to pesticides and risk of childhood leukemia (Monge et al., 2007); and two in vitro studies evaluating the effects on oxidative functions of mitochondria (Oakes and Pollak, 1999) and the potential neurotoxicity of picloram (Reddy et al., 2011).

The study by Oakes et al. (2002a) described testicular effects (decrease in testicular weight, shrunken tubules with germ cell depletion) only in the high-dose male rats gavaged 5 days a week for 9 weeks with Tordon™ 75-D, a commercial formulation containing 300 g/L 2,4-D and 75 g/L picloram. The treatment groups consisted of water, 0.125 ml/kg, 0.25 ml/kg, and 0.5 ml/kg of Tordon™ 75-D. Thus the corresponding dose equivalents for 2,4-D and picloram were 37.5 and 9.38 mg/kg-day for the low dose, 75 and 18.8 mg/kg-day for the mid dose, and 150 and 37.5 mg/kg-day for the high dose, respectively. The NOAEL was 18.8 mg/kg-day for picloram (and 75 mg/kg-day for 2,4-D). Because a mixture of two herbicides was used in this study and the NOAEL for picloram was higher than that of the original critical study, this study is not appropriate for PHG derivation.

In Oakes et al. (2002b), the authors evaluated potential male-mediated developmental effects using the same animals treated in the first study (Oakes et al., 2002a). Male-mediated developmental effects can originate from transmission of chemicals from the father to the conceptus via seminal fluid, and/or paternal preconception exposures that result in transmissible genetic changes. No developmental effects (e.g., birth defects or other adverse reproductive outcomes) were observed in the offspring of untreated female rats mated with Tordon™ 75-D-treated male rats.

A population-based case-control study by Monge et al. (2007) evaluated the association between parental occupational exposures to several pesticides and the risk of leukemia in the offspring. Parents of 300 children with leukemia and 579 children in the control group were interviewed with a list of questions including preselected confounders and history of pesticide exposures. For those who worked in farming or agriculture, additional questions such as the frequency of exposure, length of exposure, and protective practices were asked. Monitoring data were not available, so the interview data were combined with application rates from an external database to develop an exposure assessment model. The authors suggested there was an exposure-response gradient for children with leukemia from fathers exposed to picloram. For picloram, an odds ratio (OR) of 2.8 (95% confidence interval (CI) = 0.9-8.1) was reported for total

leukemia in children (N=8) from fathers exposed during the first trimester compared to children from fathers not exposed to picloram. Lower ORs were reported for children (N=11) from fathers exposed a year prior to conception (OR = 1.3; 95% CI = 0.6-2.9) and during the first year of life (N=10, OR = 1.3; 95% CI = 0.6-2.8) as compared to children from non-exposed fathers. Although the authors suggest an association between picloram exposure and childhood leukemia exists, the small study size and the relative exposure data are not sufficient for considering in the PHG calculation.

There is limited evidence for the genotoxicity of picloram, and picloram has not been determined to be a carcinogen by the International Agency for Research on Cancer (IARC) and US EPA, and is not on California's Proposition 65 list as a carcinogen.

In in vitro studies, picloram was not associated with causing mitochondrial damage in rat liver cells, but was reported to be toxic to neuroblastoma cells and primary neurons from C57BL/6 mice. Oakes and Pollak (1999) reported that 25 microliters of a combination of 169.7 µM 2,4-D and 38.8 µM picloram did not affect the rat liver mitochondria. However, Reddy et al. (2011) reported that a 5 mM concentration of picloram did cause a statistically significant decrease in total RNA content and cell viability in mouse neuroblastoma (N2a) cells compared to untreated cells. In addition, 5 mM picloram caused decreased neuronal branching and degeneration of primary neurons from C57BL/6 mice (Reddy et al., 2011).

Results from ToxCast (US EPA, 2015) indicate that picloram affected the following molecules in vitro: aryl hydrocarbon receptor (AHR), a transcription factor that has been shown to regulate xenobiotic-metabolizing enzymes such as cytochromes P450; pregnane X receptor (PXR), a nuclear receptor that is also involved in regulating cytochrome P450 activity; serine protease inhibitor PAI-1, which is involved in inflammatory reactions during vascular injury; caspase-10, which is involved in apoptosis; nuclear factor erythroid 2 (NF-E2)-related factor 2 (*Nrf2*), which is involved in anti-oxidant response; and thrombomodulin, an endothelial cell receptor that is involved in coagulation.

PHG Derivation

OEHHA re-evaluated a two-year rat study (Dow, 1986) that was not considered for PHG derivation previously (OEHHA, 1997). In this study, male and female Fischer 344 rats (50 rats/sex/dose) were given picloram in the diet at 0, 20, 60, or 200 mg/kg-day for two years. Hepatocellular swelling accompanied by altered tinctorial properties were observed in liver lobules in the middle and high dose treatment groups. Increased liver weights were seen in the high dose group though no statistically significant differences were observed. US EPA considered this study when developing the chronic oral reference dose (RfD) for picloram and identified a NOAEL of 20 mg/kg-day but did not select it as the principal study. Instead, the RfD was based on a NOEL of 7 mg/kg-day identified from the Dow (1982) dog study. The liver is the target organ in both the rat (Dow, 1986) and the dog (Dow, 1982). OEHHA conducted BMD modeling on the dog and rat data and found the dog to be the more sensitive species. Thus, OEHHA is

retaining the Dow (1982) dog study as the critical study for PHG derivation. The liver weight data from the Dow (1982) study are shown in Table 13.

For BMD modeling, continuous models were run using the dog data (Table 13) with default parameters and a benchmark response (BMR) of one standard deviation (SD) from the control mean, which is typically used when there are no data to indicate what level of response is biologically significant (US EPA, 2012). The $BMDL_{1SD}$ of 11 mg/kg-day based on the increase in relative liver weight (defined as a ratio of liver weight relative to body weight) in males is selected as the POD. BMD modeling was also conducted with the absolute liver weight data presented in Table 13, and yielded a $BMDL_{1SD}$ of 4.7 mg/kg-day. Although the $BMDL_{1SD}$ for absolute liver weight is lower than that for relative liver weight, the $BMDL_{1SD}$ for absolute liver weight is not selected as the POD because relative liver weight accounts for the body weight of individual animals and gives a better indication of a treatment-related change in organ weight. Due to the difference in average weights between the males and females at some dose levels, the liver weight data for the males and females were not combined for the BMD modeling. Better model fit and lower BMDLs were achieved with the data from the males than from the females, thus only the results for the relative liver weight in males, which were selected for POD consideration, are presented in Table 14 and Figure A4 of Appendix I.

Table 13. Absolute and relative liver weights at necropsy of dogs fed picloram in the diet for 6 months[a] (data from Dow, 1982)[b]

Dose (mg/kg-day)	Absolute Liver Weight (g)		Relative Liver Weight (g/100 g body weight)	
	Mean	Standard Deviation	Mean	Standard Deviation
Males				
0	286.5	36.6	2.6	0.4
7	298.1	40.1	2.4	0.2
35	360.4*	37.8	3.0	0.2
175	371.2*	48.0	3.7*	0.4
Females				
0	269.6	57.3	2.5	0.2
7	291.6[c]	40.0	2.7[c]	0.2
35	288.5	47.7	2.6	0.2
175	352.7*	18.4	3.8*	0.2

[a] 186-187 days for males, 188-189 days for females
[b] N=6 for all groups except as noted
[c] N=5
* Statistically significant difference from corresponding control group mean ($p \leq 0.05$)

Table 14. BMD modeling for increased relative liver weight in male dogs following dietary exposure to picloram for 6 months, data from Dow (1982)

Model	AIC	p-value[a]	BMD_{1SD}[b,c] (mg/kg-day)	$BMDL_{1SD}$[b,c] (mg/kg-day)	Scaled Residual[e]
Exponential2	-23.4	0.04	57	44	1.7
Exponential3	-23.4	0.04	57	44	1.7
Exponential4	**-24.1**	**0.06**	**21**	**11**	**0.4**
Exponential5	-24.2	N/A	33	15	0.0[d]
Hill	-24.2	N/A	33	15	0.0[d]
Linear	-24.0	0.06	49	36	1.5
Polynomial2	-24.0	0.06	49	36	1.5
Polynomial3	-24.0	0.06	49	36	1.5
Power	-24.0	0.06	49	36	1.5

[a] p-values ≥ 0.05 indicate the model adequately fits the data.
[b] For continuous data, the benchmark response is one standard deviation from the control mean, resulting in BMD_{1SD} and $BMDL_{1SD}$.
[c] The BMDL is the lower limit of the 95% confidence interval of the BMD resulting in the benchmark response.
[d] Actual value is in the 10^{-8} to 10^{-9} range.
[e] Scaled residual for the dose group near the BMD; this provides a measurement of how close the modeled response is to the actual data point. A scaled residual greater than the absolute value of 2.0 indicates poor fit to the data point.

Thus, using the POD of 11 mg/kg-day for liver toxicity in male dogs derived from the Dow (1982) study, the ADD is calculated as follows:

$$\text{ADD} = \frac{\text{POD}}{\text{UF}} = \frac{11 \text{ mg/kg-day}}{1{,}000} = 0.011 \text{ mg/kg-day}$$

A total UF of 1,000 is applied: 30 for human variability, 10 for interspecies extrapolation, and a factor of √10 for subchronic to chronic exposure. The default factor for subchronic to chronic exposure extrapolation is 10, however, the mild liver effects observed in rats exposed for two years in the Dow (1986) study suggest that the liver effects observed in dogs (Dow, 1982) are unlikely to worsen over time. Thus, a factor of 10 is not necessary for the subchronic to chronic exposure extrapolation.

An RSC value of 0.20 was used in the 1997 risk assessment. Because picloram is no longer in use and exposures from ambient air or food would be considered minimal, an RSC value of 0.80 is used for the current PHG calculation.

Since the publication of the picloram PHG in 1997, OEHHA has adopted new drinking water intake values. The time-weighted lifetime average drinking water consumption rate of 0.053 L/kg-day, based on lifestage-specific water consumption rates, is used for the general population (OEHHA, 2012). Dermal and inhalation exposures to picloram from drinking water are not a concern due to its low volatility and low dermal absorption

(Budavari, 1989; Nolan et al., 1984). The health-protective concentration, C, is calculated as follows:

$$C = \frac{0.011 \text{ mg/kg-day} \times 0.80}{0.053 \text{ L/kg-day}} = 0.166 \text{ mg/L or } 166 \text{ ppb}$$

Thus, OEHHA is setting an updated PHG of 166 ppb for picloram. This PHG incorporates an updated dose-response modeling, an updated drinking water intake rate, and an updated uncertainty factors to account for variability within the human population.

US EPA last revised its RfD for picloram in 1992; an RfD of 0.07 mg/kg-day was developed by using the NOAEL of 7 mg/kg-day from the Dow (1982) study and an uncertainty factor of 100 (US EPA, 1992a). The federal MCL and MCLG, and the California MCL[19] are at the same value of 500 ppb and are based on the same six-month dog feeding study (US EPA, 1992b).

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[19] Accessed at: http://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/Chemicalcontaminants.shtml

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UPDATED PHG FOR THIOBENCARB

Thiobencarb is a pre-emergent and early post-emergent systemic thiocarbamate herbicide used to control many broadleaf weeds, grasses, and sedges in rice fields. Thiobencarb is currently registered for use in California, and DPR reported 277,342 pounds of thiobencarb applied to fields for agricultural use in 2012.[20] Thiobencarb can be associated with a taste problem (i.e., organoleptic property) in the drinking water primarily from surface water contamination and runoff from treated rice fields into the Sacramento River. Recently, methods of application have changed to reduce the incidental contamination outside of the rice fields (DWWSP, 2011). Thiobencarb has not been detected at concentrations above its detection limit[21] in public water supply wells across California for the past three years.[22] California's primary Maximum Contaminant Level (MCL) for thiobencarb is 70 ppb (based on protection of public health), with an enforceable secondary MCL of 1 ppb (based on taste and odor concerns). There is no federal MCLG or MCL for thiobencarb.

2000 PHG

The original PHG of 70 ppb (OEHHA, 2000) was based on a combined chronic toxicity and carcinogenicity feeding study in rats (100 rats/sex/group) administered thiobencarb (95.3 percent purity) at 0, 20, 100 or 500 ppm (0, 1, 5 and 25 mg/kg-day, respectively) for 108 weeks (Ashby et al*.,* 1984). There was no increase in tumor rates in both sexes. Systemic toxicity was observed as decreased body weight gain, reduced food consumption and food efficiency in both sexes at 5 mg/kg-day and higher. There was also an increase in blood urea nitrogen at 5 and 25 mg/kg-day in both male and female rats and increases in the packed red blood cell counts, red blood cell volumes, and hemoglobin concentration. The NOAEL identified in this study was 1 mg/kg-day for systemic toxicity, and the calculation of the PHG incorporated a total uncertainty factor of 100 (10 for interspecies extrapolation and 10 for intraspecies variability). The exposure parameters in the PHG calculation assumed a 70 kg adult body weight, water consumption rate of 2 L/day, and a relative source contribution of 20 percent. There was no evidence of carcinogenicity at the dose levels tested. After reviewing the available reproductive and developmental toxicity studies, OEHHA determined that reproductive effects were not observed and developmental effects observed were not statistically significant; thus these endpoints were not considered in the PHG derivation.

[20] Summary of pesticide use report data, 2012, indexed by chemical from California Department of Pesticide Regulation. Accessed at: http://www.cdpr.ca.gov/docs/pur/purmain.htm.
[21] The thiobencarb detection limit for purposes of reporting is 1 ppb, accessed at: http://www.swrcb.ca.gov/drinking_water/certlic/drinkingwater/Chemicalcontaminants.shtml
[22] Data 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.

Recent Literature

A thorough examination of recent literature revealed no new toxicity studies since the publication of the original thiobencarb PHG (OEHHA, 2000). However, OEHHA reviewed a document presenting the evaluation of toxicology studies by the European Food Safety Authority (EFSA). EFSA (2013) outlines nine genotoxicity studies and four of them are not cited in the original PHG document. These four additional genotoxicity studies are all unpublished and unavailable for review. According to EFSA (2013), thiobencarb tested positive in three of these studies (i.e., in vitro mammalian cell gene mutation assay with S9, in vivo micronucleus assay, and in vivo unscheduled DNA synthesis assay). While the positive studies add to the genotoxicity potential of thiobencarb, these results do not support a change in the determination of the carcinogenic potential of thiobencarb based on whole animal testing.

PHG Derivation

After evaluating the available toxicity studies for thiobencarb, OEHHA is retaining the Ashby et al. (1984) study for PHG derivation. In this combined chronic toxicity and carcinogenicity study, Fisher 344 rats (100 rats/sex/group) were administered 0, 20, 100, or 500 ppm technical Bolero® (95.3 percent thiobencarb) in the diet for 108 weeks (Ashby et al., 1984). Animals in the chronic toxicity phase of the study were sacrificed after 104 weeks and animals in the oncogenicity phase were sacrificed after 108 weeks. Group mean body weights were very similar for both sexes of rats at the start of the study (106-109 g for males and 96-98 g for females). However, there was a statistically significant treatment-related reduction in body weight gain in rats over the course of the study.

To examine whether the decrease in body weight gain was due to reduced food consumption, OEHHA normalized the consumption rate from the Ashby et al. (1984) study to the bodyweight (g/g body weight/week) to provide an indicator for the animals' appetite or willingness to eat (Figures 1 and 2). The normalized food consumption rate changes over time as the animal goes through various life stages. For any particular time point, the rates should be comparable among treatment groups if there is no treatment-related effect on food consumption. This was the case for this dataset as shown in Figures 1 and 2. Thus, OEHHA determined that the weight reduction was related to the systemic toxicity of thiobencarb and is retaining this as the critical health endpoint for the derivation of the point of departure (POD) for PHG calculation. Data for female rats are used for benchmark dose (BMD) modeling because they exhibited a greater reduction in body weight than the male rats and thus may be more sensitive to the toxicity of thiobencarb. This data set is presented in Table 15.

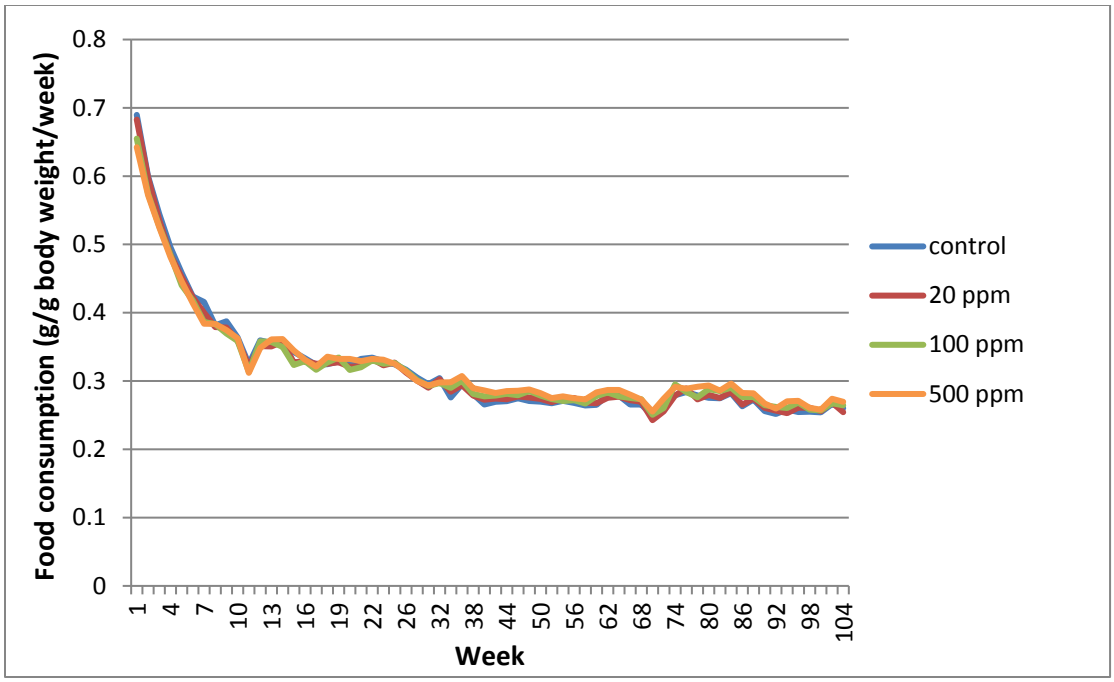

Figure 1. Relationship between body weight, food consumption, and exposure duration in male rats exposed to thiobencarb (data from Ashby et al., 1984). Food consumption is normalized to bodyweight.

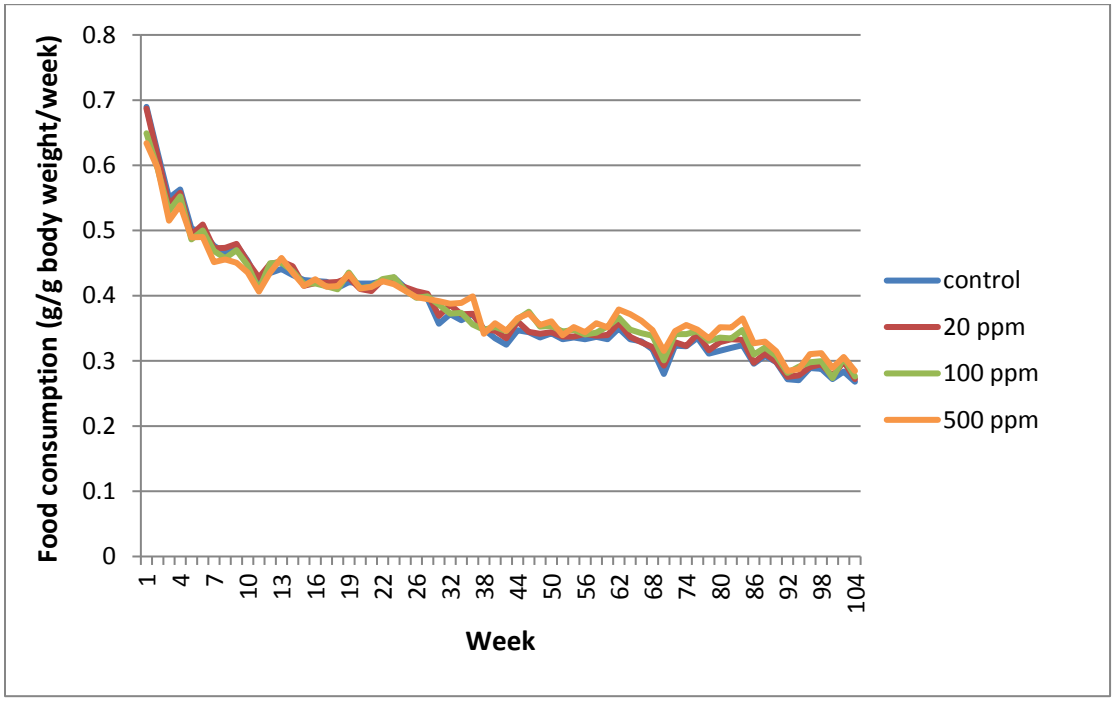

Figure 2. Relationship between body weight, food consumption, and exposure duration in female rats exposed to thiobencarb (data from Ashby et al., 1984). Food consumption is normalized to bodyweight.

Table 15. Decrease in mean body weight for female F344 rats at 104 weeks (Ashby et al., 1984)

Dose (mg/kg-day)[a]	Number of Animals	Mean Body Weight (g)	SD[b] (g)	Percent Difference in Mean Body Weight
0	46	332	30	0
1.0	52	327	32	1.5
5.4	50	297[c]	25	10.5
26	54	281[c]	26	15.4

[a] Group mean values for achieved dose determined by Ashby et al. (1984)
[b] SD: standard deviation
[c] Significantly different from control, p<0.01, determined by OEHHA using one-way ANOVA followed by Tukey pairwise comparison

BMD modeling was conducted with continuous models using the following parameters:

- Constant variance or modeled variance
- Benchmark response (BMR) set at 10 percent decrease from the control mean (0.1 Rel. Dev.) or one standard deviation (SD) from the control mean

Of the continuous BMD models run, Exponential Model 4 provides the best fit for the terminal body weight data and the lowest BMDL values, 2.4 and 3.2 mg/kg-day, as the potential PODs (Table 16). The BMD modeling output for this analysis is presented in Figure A5 of Appendix I. BMD modeling of the male rat data was also conducted for comparison. The BMDLs are 5.8 mg/kg-day (BMR of 1 SD) and 4.7 mg/kg-day (BMR of 0.1 Rel. Dev.) (modeling outputs not shown).

Table 16. Results of benchmark dose modeling of mean body weight for female rats at 104 weeks (Ashby et al., 1984) using Exponential Model 4

BMR[a] 1 SD[b]		BMRF[c] 10 percent (0.1 Rel. Dev.)	
BMD[d]	BMDL[e]	BMD	BMDL
3.7	2.4	4.8	**3.2**

[a] BMR: benchmark response
[b] SD: standard deviation
[c] BMRF: benchmark response factor, set as 10 percent change from the control mean, or 0.1 relative deviation
[d] BMD: benchmark dose
[e] BMDL: lower 95 percent confidence limit of the benchmark dose

The preferred approach for selecting a BMR for continuous data is to determine a level of change in the endpoint that is biologically significant, such as a 10 percent reduction in body weight (US EPA, 2012). As shown in Table 15, there was a 10.5 percent decrease in mean body weight that was statistically significant (p<0.01) at 5.4 mg/kg-day. The POD is expected to be at or below this experimental dose. Thus, OEHHA is selecting the $BMDL_{10}$ value of 3.2 mg/kg-day as the POD for this endpoint. The BMD

and BMDL corresponding to one SD from the control mean are also listed for comparison purposes.

In this update, a total uncertainty factor (UF) of 300 is applied: 10 for interspecies extrapolation, and 30 for intraspecies variability. The ADD is calculated using the $BMDL_{10}$ of 3.2 mg/kg-day for the decrease in terminal body weight in the female rats derived from the Ashby et al. (1984) study:

$$ADD = \frac{POD}{UF} = \frac{3.2 \text{ mg/kg-day}}{300} = 0.011 \text{ mg/kg-day}$$

OEHHA developed distribution profiles of "consumer-only" daily water intake rates, adjusted for body weight, for various age groups (OEHHA, 2012). The time-weighted average of the 95th percentile values of all age groups was then calculated to estimate a lifetime water consumption rate of 0.053 L/kg-day.

Thiobencarb has a low dermal absorption factor (1.3 percent, as calculated with equations extracted from CalTOX[23]; see Appendix III) and a very small Henry's Law constant of 2.67 x 10^{-7} atm-m^3/mole (OEHHA, 2000). Thus, exposure to thiobencarb through the dermal and inhalation routes during bathing and showering is not expected to be significant and is not included in this assessment.

Thiobencarb is currently used in California, and specific information regarding source contribution (e.g., exposure to residue in food or soil) is not available. In the absence of data to indicate otherwise, the 20 percent default relative source contribution (RSC) value is used for the contribution of exposure from water, which allows for exposure to thiobencarb from other sources, such as residues in food.

The public health-protective concentration, C, is:

$$C = \frac{0.011 \text{ mg/kg-day} \times 0.20}{0.053 \text{ L/kg-day}} = 0.042 \text{ mg/L} = 42 \text{ µg/L or } 42 \text{ ppb}$$

Therefore, the updated PHG for thiobencarb is 42 ppb.

Thiobencarb has not recently been found at levels above its secondary MCL of 1 ppb in California public water systems. Also, there are no new toxicity studies for this chemical other than the four additional genotoxicity studies described above. In the absence of substance-related tumor or developmental effects, the risk associated from the exposure to thiobencarb in drinking water is based on the female rat body weight reduction in the chronic toxicity study by Ashby et al. (1984). The risk assessment methodology incorporated in this update includes a more sophisticated estimation of

[23] A multimedia total exposure model available at http://energy.lbl.gov/ied/era/caltox/index.html

POD, an updated estimate of water consumption by the general population, and an updated intraspecies variability factor.

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APPENDIX I. BMD Modeling

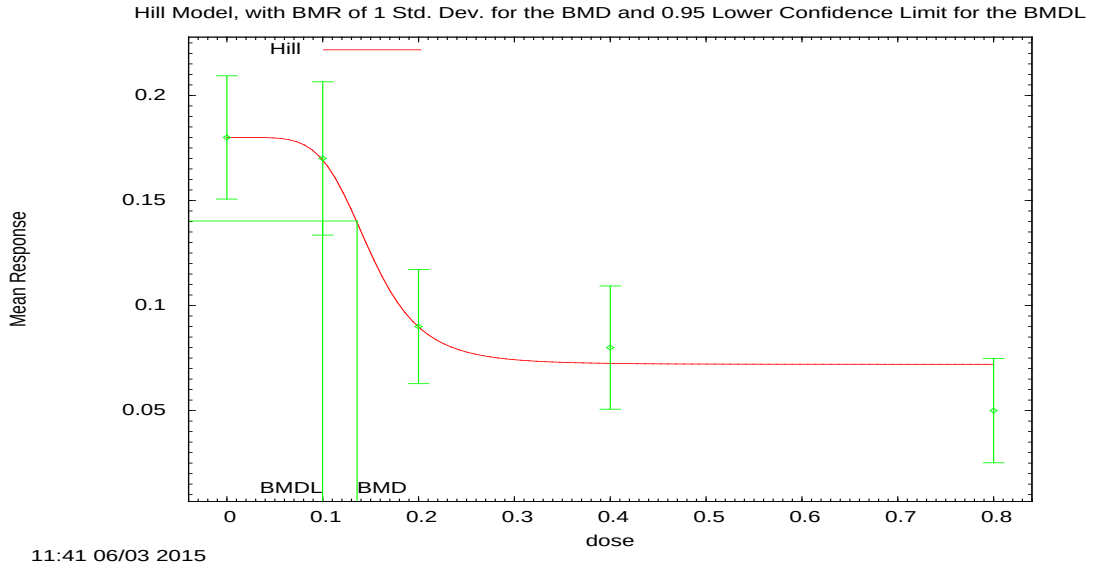
This appendix provides the BMD modeling ouput for carbofuran, endrin, picloram, and thiobencarb, for which data were amenable to dose-response modeling. All models were run with default parameters and a benchmark response of 1 standard deviation or a relative deviation of 10 percent above the control mean. Model selection criteria when 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. When using BMD modeling, the BMDL, which is the lower limit of the 95 percent confidence interval of the BMD resulting in the benchmark response, is selected as the POD. The model selected to derive the POD is presented here.

Table A1. BMD modeling of absolute seminal vesicle weight in male rats exposed to carbofuran in a 60-day oral gavage study (Pant et al., 1995)

Model[a]	Goodness of Fit		BMD_{1SD}	$BMDL_{1SD}$
	p-value[a]	AIC		
Exponential (M2) Exponential (M3)[b]	0.0389	-220.68	0.119	0.0799
Exponential (M4)	0.0227	-219.48	0.0978	0.0584
Exponential (M5)	0.251	-223.74	0.145	0.101
Hill	**0.258**	**-223.77**	**0.136**	**0.0998**
Power[c] Polynomial 4°[d] Polynomial 3°[e] Polynomial 2°[f] Linear	0.00243	-214.67	0.241	0.181

[a] p-values ≥ 0.05 indicate the model adequately fits the data.

Figure A1. Hill model output for carbofuran – decreased absolute seminal vesicle weight from Pant et al. (1995)




```
 ***************************************************************************
        Hill Model. (Version: 2.17;  Date: 01/28/2013)
        Input Data File: U:/PETB/Water Toxicology Section/PHGS/Carbofuran/EK
BMDS/hil_abs sem ves wt_Opt.(d)
        Gnuplot Plotting File:  U:/PETB/Water Toxicology Section/PHGS/Carbofuran/EK
BMDS/hil_abs sem ves wt_Opt.plt
                                                Mon Jul 13 09:31:31 2015
 ***************************************************************************

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

                  Default Initial Parameter Values
                          alpha =   0.00175955
                            rho =            0   Specified
                      intercept =         0.18
                              v =        -0.13
                              n =      8.63721
```

k = 0.16875

Asymptotic Correlation Matrix of Parameter Estimates

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

	alpha	intercept	v	n	k
alpha	1	4.7e-007	-5e-007	2.5e-007	3.4e-007
intercept	4.7e-007	1	-0.75	-0.54	-0.54
v	-5e-007	-0.75	1	0.63	0.12
n	2.5e-007	-0.54	0.63	1	0.29
k	3.4e-007	-0.54	0.12	0.29	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.0016019	0.000345474	0.00092478	0.00227901
intercept	0.180258	0.012628	0.155508	0.205009
v	-0.107817	0.0177659	-0.142637	-0.072996
n	5.51895	3.00796	-0.376541	11.4144
k	0.14944	0.0272122	0.0961056	0.202775

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	0.18	0.18	0.041	0.04	-0.0204
0.1	10	0.17	0.17	0.051	0.04	0.0262
0.2	10	0.09	0.0904	0.038	0.04	-0.0338
0.4	10	0.08	0.0729	0.041	0.04	0.56
0.8	3	0.05	0.0725	0.01	0.04	-0.972

Model Descriptions for likelihoods calculated

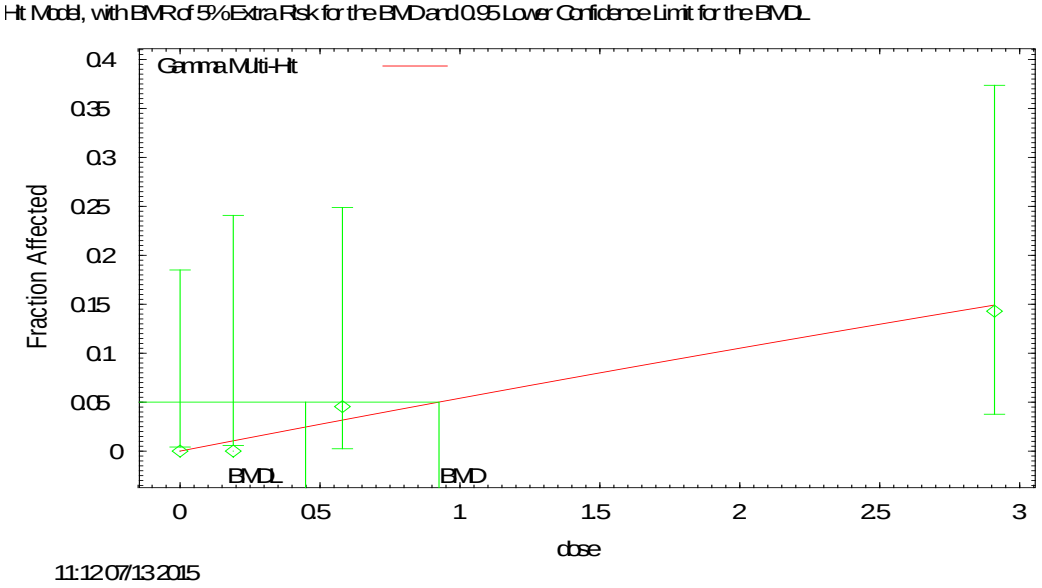
Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

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

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

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

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

                       Likelihoods of Interest

              Model      Log(likelihood)   # Param's      AIC
               A1          117.525657            6    -223.051315
               A2          121.375570           10    -222.751141
               A3          117.525657            6    -223.051315
           fitted          116.886210            5    -223.772421
                R           97.881305            2    -191.762611

                     Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                      Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              46.9885          8          <.0001
   Test 2              7.69983          4          0.1032
   Test 3              7.69983          4          0.1032
   Test 4              1.27889          1          0.2581

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

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

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

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

        Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =       0.135831

            BMDL =     0.0998193
```

Figure A2. Gamma model output for diquat – cataracts in male rats from Colley et al. (1969)




```
 ======================================================================
        Gamma Model. (Version: 2.16;  Date: 2/28/2013)
        Input Data File: K:/PETB/PHG Reviews/Diquat/gam_diquat_male_104
nohidose_diquat104mfopt.(d)
        Gnuplot Plotting File:  K:/PETB/PHG Reviews/Diquat/gam_diquat_male_104
nohidose_diquat104mfopt.plt
                                              Fri Mar 28 10:41:04 2014
 ======================================================================

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

   The form of the probability function is:

   P[response]= background+(1-background)*CumGamma[slope*dose,power],
   where CumGamma(.) is the cummulative Gamma distribution function


   Dependent variable = Effect
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial (and Specified) Parameter Values
                     Background =    0.0416667
                          Slope =     0.127233
                          Power =          1.3
```

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

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Slope	0.0554507	0.027748	0.00106558	0.109836
Power	1	NA		

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	-12.6804	4			
Fitted model	-12.9126	1	0.464399	3	0.9266
Reduced model	-15.9322	1	6.50356	3	0.08952

AIC: 27.8252

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	22	0.000
0.1900	0.0105	0.168	0.000	16	-0.412
0.5800	0.0316	0.696	1.000	22	0.370
2.9100	0.1490	3.129	3.000	21	-0.079

Chi^2 = 0.31 d.f. = 3 P-value = 0.9577

Benchmark Dose Computation

Specified effect = 0.05

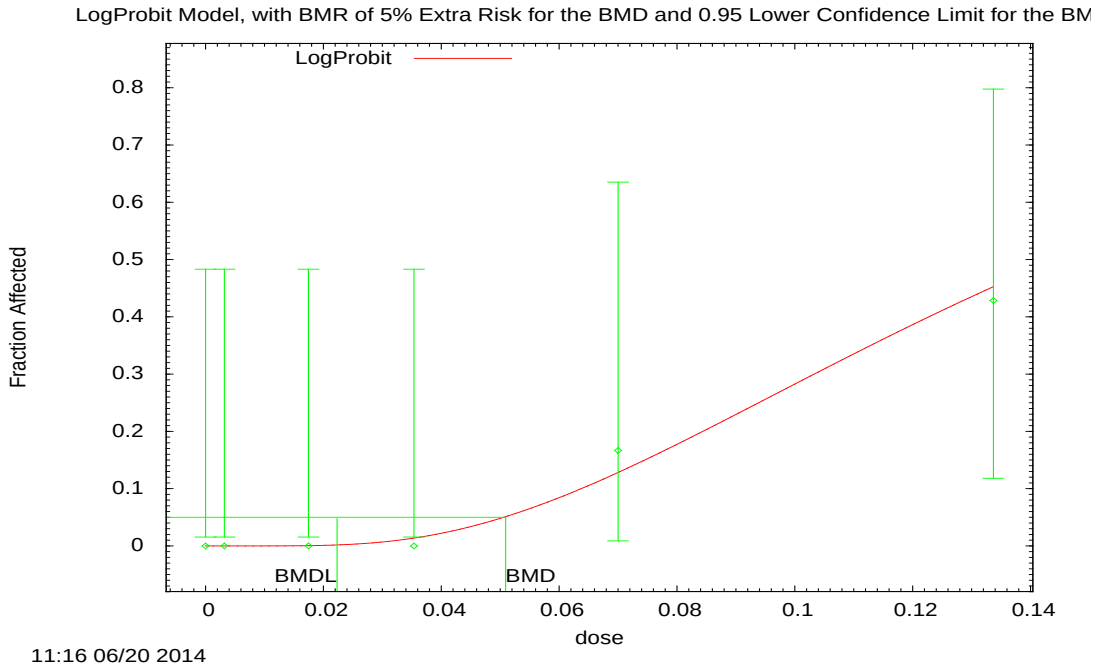
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.925025

BMDL = 0.448268

Figure A3. LogProbit model output for endrin – convulsions in male and female dogs from Jolley et al. (1969)




```
=====================================================================
        Probit Model. (Version: 3.3;  Date: 2/28/2013)
        Input Data File: C:/Users/ywang/Desktop/BMDS250/Data/lnp_Patty edit
convulsion 2 yr data_Opt.(d)
        Gnuplot Plotting File:  C:/Users/ywang/Desktop/BMDS250/Data/lnp_Patty edit
convulsion 2 yr data_Opt.plt
                                                Fri Dec 19 14:31:44 2014
 =====================================================================
 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function

   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 (and Specified) Parameter Values
background = 0
intercept = 1.87539
slope = 1

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

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	3.04024	2.08189	-1.04019	7.12067
slope	1.57355	0.883117	-0.15733	3.30443

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	-7.48372	6			
Fitted model	-7.61361	2	0.259767	4	0.9923
Reduced model	-12.674	1	10.3806	5	0.06514

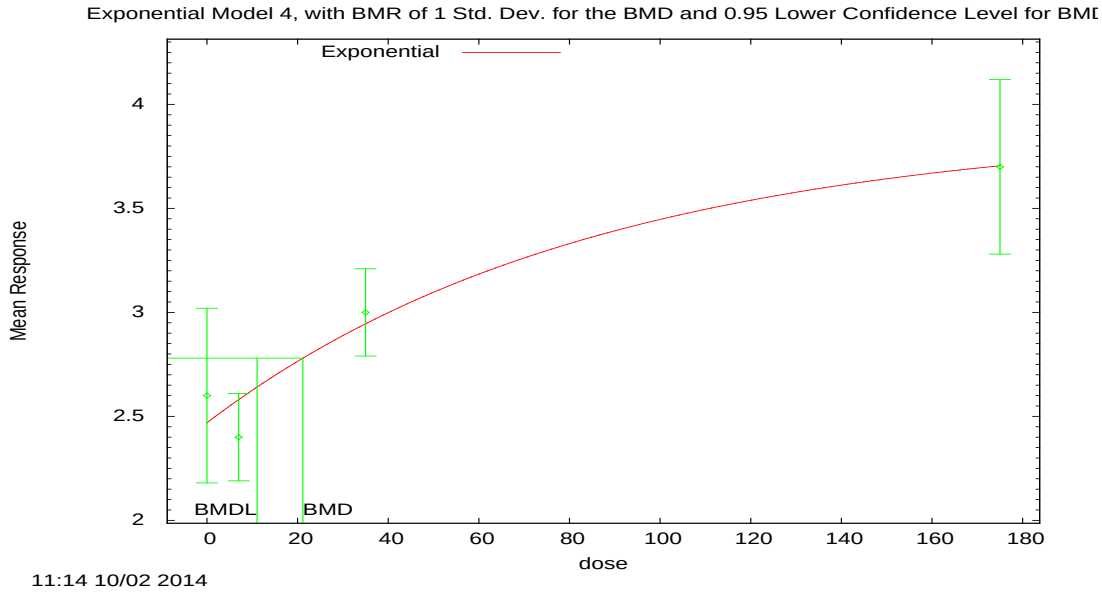
AIC: 19.2272

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	6	0.000
0.0032	0.0000	0.000	0.000	6	-0.000
0.0175	0.0004	0.003	0.000	6	-0.051
0.0354	0.0132	0.079	0.000	6	-0.284

```
    0.0700     0.1263         0.758     1.000           6        0.298
    0.1337     0.4499         3.149     3.000           7       -0.113

 Chi^2 = 0.18      d.f. = 4        P-value = 0.9960


   Benchmark Dose Computation

Specified effect =           0.05

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0509247

            BMDL =       0.022323
```

Figure A4. Exponential Model 4 output for picloram – increased relative liver weight in male dogs from Dow (1982)




```
==========================================================================
        Exponential Model. (Version: 1.9;  Date: 01/29/2013)
        Input Data File: K:/PETB/PHG Reviews/Picloram/EK BMDS/exp_male rel liver
wt_liver wt 1 SD.(d)
        Gnuplot Plotting File:
                                                Tue Apr 28 16:40:36 2015
 ==========================================================================
 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

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

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

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

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

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4
lnalpha	-2.48491
rho(S)	0
a	2.28
b	0.012523
c	1.70395
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	-2.33804
rho	0
a	2.46933
b	0.0116613
c	1.57506
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	6	2.6	0.4
7	6	2.4	0.2
35	6	3	0.2
175	6	3.7	0.4

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	2.469	0.3107	1.03
7	2.581	0.3107	-1.424
35	2.945	0.3107	0.4321
175	3.705	0.3107	-0.0381

Other models for which likelihoods are calculated:

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

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

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

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

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	17.81888	5	-25.63776
A2	20.4966	8	-24.9932
A3	17.81888	5	-25.63776
R	1.296378	2	1.407244
4	16.05653	4	-24.11306

Additive constant for all log-likelihoods = -22.05. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

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

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	38.4	6	< 0.0001
Test 2	5.355	3	0.1475
Test 3	5.355	3	0.1475
Test 6a	3.525	1	0.06046

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

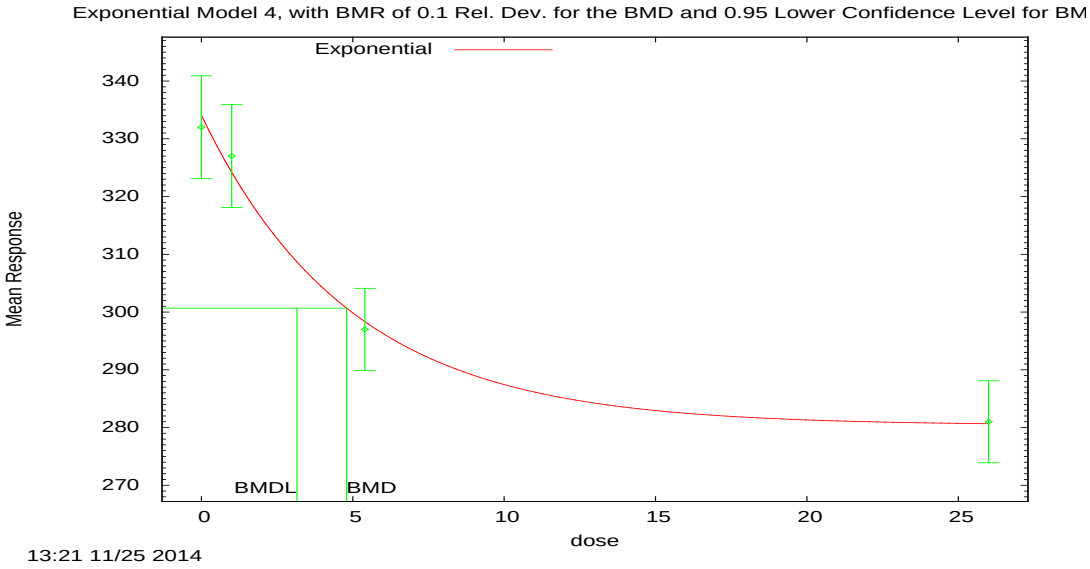
The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

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

The p-value for Test 6a is less than .1. Model 4 may not adequately describe the data; you may want to consider another model.

```
Benchmark Dose Computations:

  Specified Effect = 1.000000

         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      21.1725

              BMDL =      11.0716
```

Figure A5. Exponential Model 4 output for thiobencarb – decreased body weight in female rats from Ashby et al. (1984)




```
 ================================================================
        Exponential Model. (Version: 1.9;  Date: 01/29/2013)
        Input Data File: U:/PETB/Water Toxicology Section/PHGS/Thiobencarb/-Ashby
1984-Bodyweight-ExpCV-10RD-4d.(d)
        Gnuplot Plotting File:
                                                Tue Nov 25 13:21:50 2014
 ================================================================
 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

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

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

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


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

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 500
```

```
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

               Initial Parameter Values

               Variable          Model 4
               --------          --------
                 lnalpha            6.6695
                     rho(S)                0
                       a              348.6
                       b          0.0744804
                       c           0.767697
                       d                  1

  (S) = Specified

                 Parameter Estimates

                Variable          Model 4
                --------          -------
                 lnalpha           6.67387
                     rho                 0
                       a           334.083
                       b          0.202986
                       c          0.839293
                       d                 1

        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0     46          332           30
      1     52          327           32
    5.4     50          297           25
     26     54          281           26

             Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         334.1        28.13          -0.5022
      1         324.2        28.13           0.7127
    5.4         298.3        28.13          -0.3354
     26         280.7        28.13          0.08687



Other models for which likelihoods are calculated:

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

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

  Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)
  Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-774.6199	5	1559.24
A2	-772.5342	8	1561.068
A3	-774.6199	5	1559.24
R	-820.1455	2	1644.291
4	-775.061	4	1558.122

Additive constant for all log-likelihoods = -185.6. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

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

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	95.22	6	< 0.0001
Test 2	4.171	3	0.2435
Test 3	4.171	3	0.2435
Test 6a	0.8821	1	0.3476

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

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

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

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

Benchmark Dose Computations:

Specified Effect = 0.100000

Risk Type = Relative deviation

Confidence Level = 0.950000

BMD = 4.79601

BMDL = 3.15634

APPENDIX II. CalTOX Modeling

This appendix describes the multi-route exposure assessment of carbofuran and endrin 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 A2 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 A2. 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 A2 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 for carbofuran and endrin are presented below. For the sake of brevity, only the results using adult exposure parameters are included in this document.

Table A3. Carbofuran CalTOX output, adult exposure scenario

PATHWAYS	**Air (gases & particles)**	**Surface soil**	**Root-zone soil**	**Ground water**	**Surface water**	**Totals**	**%**
INHALATION	8.1E-263	0.00E+00	0.00E+00	1.35E-03	0.00E+00	1.35E-03	**28.53**
INGESTION:							
Water				3.27E-03	0.00E+00	3.27E-03	69.03
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	3.27E-03	0.00 E+00	3.27E-03	**69.03**
DERMAL UPTAKE		0.00E+00	0.00E+00	1.16E-04	0.00E+00	1.16E-04	**2.44**
Dose SUM	8.1E-263	0.00E+00	0.00E+00	4.74E-03	0.00E+00	4.74E-03	**100.0**

Table A4. Endrin CalTOX output, adult exposure scenario

PATHWAYS	Air (gases & particles)	Surface soil	Root-zone soil	Ground water	Surface water	Totals	%
INHALATION	2.77E-265	0.00E+00	0.00E+00	1.30E-02	0.00E+00	1.30E-02	**2.24**
INGESTION:							
Water				5.33E-01	0.00E+00	5.33E-01	92.25
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	5.33 E-01	0.00 E+00	5.33 E-01	**92.25**
DERMAL UPTAKE		0.00E+00	0.00E+00	3.18E-02	0.00E+00	3.18E-02	**5.50**
Dose SUM	2.77E-265	0.00E+00	0.00E+00	5.78E-01	0.00E+00	5.78E-01	**100.0**

APPENDIX III. Calculation of Dermal Absorption Factor for Thiobencarb

The amount of thiobencarb that can be taken up through the skin during normal household uses of tap water, such as bathing and showering, is calculated with equations extracted from CalTOX 4.0. CalTOX 4.0 is a multimedia, multiple pathway exposure model developed for the California Department of Toxic Substances Control by Lawrence Berkeley National Laboratory (available at http://energy.lbl.gov/ied/era/caltox/index.html).

The relationship between exposure time and diffusion lag time is calculated:

$[t_{lag} \times 2] / ET_{sb}$

Where: t_{lag} = diffusion lag time in skin (chemical specific, unitless)
ET_{sb} = exposure time, in shower or bath (0.27 h, default)

$t_{lag} = [\delta_{skin} \times Km] / [6 \times K_p^w]$

Where: δ_{skin} = skin thickness (0.0025 cm, default)
Km = skin-water partition coefficient (chemical specific, unitless)
K_p^w = steady-state skin permeability coefficient (chemical specific, cm/h)
= 0.0136 cm/h (Ref. Jones (2004, Table A6.1, p. 76)

$Km = 0.64 + [0.25 \times (Kow)^{0.8}]$

Where:
Kow = 2630.27 (or anti-log of log Kow = 3.23, Ref. Jones (2004, Table A6.1, p. 76) or see: Ceesay (2002))

Km = $0.64 + [0.25 \times (2630)^{0.8}] = 136.8$

t_{lag} = $[\delta_{skin} \times Km] / [6 \times K_p^w] = [0.0025 \text{ cm} \times 136.8] / [6 \times 0.0136 \text{ cm/h}] =$
= 4.191 h

$[t_{lag} \times 2] / ET_{sb}$ = $[4.191 \text{ h} \times 2] / 0.27 \text{ h} =$ **31.04**

When the exposure time (ET_{sb}) is less than the diffusion lag time in skin (t_{lag}), i.e., exposure time << diffusion lag time, or $[t_{lag} \times 2] / ET_{sb} > 3$:

Uptake$_{dermal}$ = $C_{tap\_water} \times ([\delta_{skin} \times Km] / 2) \times fs \times CF \times SA_b \times (ET_{sb} / [t_{lag} \times 2]) \times [1$ event/day]

Where:

C_{tap_water} = 100 ppm (or 100 mg/L); as long as the chemical concentration in tap water is low (well below the saturation concentration in water), input value of C_{tap_water} does not affect the calculation of relative contributions from the multi-route exposure; therefore, 100 ppm is the recommended adopted low value.

fs = 0.80 unitless or fraction of skin in contact of water during showering or bathing

CF = 10 L/cm-m^2; conversion factor for dermal uptake calculation

SA_b = 0.059 m^2/kg surface area, normalized to body weight (for infant 0<2 yr; OEHHA, 2012)

= 100 mg/L x ([0.0025 cm x 136.8] /2) x 0.80 x 10 L/ cm-m^2 x 0.059 m^2/kg x (0.27 h / 4.191 h x 2) x 1/day

$Uptake_{dermal}$ = **0.259 mg/kg-day** (based on C_{tap_water} = 100 ppm)

Relative Contribution from Dermal (%) is calculated as follows:

Relative Contribution from Dermal (%)

= $Uptake_{dermal}$ / [$Intake_{oral}$ + $Intake_{inh}$ + $Uptake_{dermal}$] x 100%

Thiobencarb is not a volatile, therefore:

Relative Contribution from Dermal (%)

= $Uptake_{dermal}$ / [$Intake_{oral}$ + $Uptake_{dermal}$] x 100%

Where: $Intake_{oral}$ = C_{tap_water} x Ifl

Ifl = 0.196 L/kg-day (water ingestion rate for infant 0<2 yr; OEHHA, 2012)

$Intake_{oral}$ = 100 mg/L x 0.196 L/kg-day

= 19.6 mg/kg-day

Relative Contribution from Dermal (%)

= 0.259 mg/kg-d / [19.6 mg/kg-d + 0.259 mg/kg-day] x 100%

= **1.3 %**

References

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APPENDIX IV. Default Uncertainty Factors for PHG Derivation

This appendix describes the default uncertainty factors OEHHA generally uses to calculate the Acceptable Daily Dose when deriving PHGs. When scientific evidence is compelling, these defaults are supplanted by alternative factors or modeled results. Table A5 below is adapted from OEHHA's "Technical Support Document for the Development of Noncancer Reference Exposure Levels" (OEHHA, 2008).

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

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

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