OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Public Health Concentration

Chlorthal-dimethyl (DCPA) and its Degradates Monomethyl Tetrachloroterephthalic Acid (MTP) and Tetrachloroterephthalic Acid (TPA) in Groundwater

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

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Prepared by

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I. EXECUTIVE SUMMARY

This report describes the evaluation conducted by the Office of Environmental Health Hazard Assessment (OEHHA) on the toxicity of chlorthal-dimethyl (DCPA; dimethyl tetrachloroterephthalate; dacthal) and its degradates, monomethyl tetrachloro-terephthalic acid (MTP) and tetrachloroterephthalic acid (TPA). DCPA is the active ingredient of pre-emergent herbicide products such as Dacthal®, used for the control of annual grasses and certain broadleaved weeds affecting various fruit and vegetable crops and ornamental turf. Recently, both MTP and TPA were detected in groundwater by the Department of Pesticide Regulation (DPR) monitoring program. DPR compared the detected levels to the US Environmental Protection Agency (US EPA) lifetime Health Advisory Level of 70 ppb for DCPA. Since some of the detected levels were higher than 70 ppb and were determined by DPR to originate from legal uses of DCPA-containing herbicide products, DPR initiated the evaluation of DCPA, MTP, and TPA in groundwater by the subcommittee of the Pesticide Registration Evaluation Committee (PREC) pursuant to the California Pesticide Contamination Prevention Act (DPR, 2018a).

OEHHA, as a member of the PREC subcommittee, reviewed the toxicity studies in humans and animals to (1) evaluate DCPA, MTP, and TPA for the toxicity endpoints specified in the Act: carcinogenicity, mutagenicity, teratogenicity, or neurotoxicity, (2) develop public health concentrations (PHCs) in drinking water for DCPA and TPA, and (3) use the PHCs to determine the risks from potential exposures to these chemicals in the groundwater. PHC is the concentration of a chemical in drinking water that is not expected to pose a significant risk to health, when consumed over a lifetime, and is developed using approaches and methods of OEHHA's Public Health Goal Program.

OEHHA found that the DCPA toxicity database was sufficient for the toxicity evaluation. Based on the studies reviewed, DCPA is possibly carcinogenic, and is not mutagenic, teratogenic, or neurotoxic. The finding for carcinogenicity is an interim finding pending an analysis of the contribution of impurities to the cancer effects reported in the DCPA rodent studies. The toxicity database of MTP as the test compound consisted of only a 28-day study and one mutagenicity study; these were too limited to make findings. The toxicity database for TPA was also limited. While it had several short-term toxicology studies and data to support the finding that it is not mutagenic, there was only one study on teratogenicity, and no studies on neurotoxicity or lifetime carcinogenicity.

OEHHA derived PHCs for DCPA for non-cancer and cancer effects. We derived a PHC of 7 ppb for increased centrilobular hepatocytic swelling in the liver of male rats exposed to DCPA in diet for two years (Lucas et al., 1993). The PHC for cancer effect was 2 ppb for hepatocellular adenomas and carcinomas in male mice exposed to DCPA in diet for two years (Lucas and Killeen, 1988). Since the PHC based on cancer was lower than

the PHC derived from the non-cancer data, this PHC of 2 ppb was selected as the PHC for DCPA.

For TPA, the database was adequate to derive the PHC when considering the available short-term test data, the relative toxicity between DCPA and TPA, and with an application of an uncertainty factor to address the data gap. We developed a PHC of 2500 ppb for TPA based on two oral rat studies (Major, 1985; Goldenthal et al., 1977), one reported changes in red blood cells and soft stools following exposure to TPA and another with no effects at the doses tested. A PHC for MTP was not established because the database was too limited.

We compared the derived PHCs for DCPA and TPA to concentrations measured in groundwater. For DCPA, we used the reporting limit of 0.05 ppb as the concentration level, as there were no detections of DCPA over this level. This concentration is over 40-fold lower than the PHC of 2 ppb (or 2.5% of PHC). We applied the PHC for TPA to the sum of the highest detected levels of TPA and MTP for this risk assessment. This approach is supported by these factors: (1) the molecular structures and solubilities in water for TPA and MTP are similar, (2) MTP is a minor, intermediate degradate of DCPA, and the final degradate is TPA, and (3) MTP was only detected in groundwater samples with relatively high levels of TPA. The combined highest detected levels of TPA and MTP is 159 ppb and is more than 15-fold lower the PHC of 2500 ppb (or 6.4% of the PHC).

Overall, our evaluation shows that adverse health effects are not expected from lifetime exposure from drinking water to DCPA at the reporting limit, or to TPA and MTP at the detected levels reported by DPR.

II. INTRODUCTION

A. Background

Chlorthal-dimethyl (DCPA, dimethyl tetrachloroterephthalate) is the active ingredient of pre-emergent herbicide products such as Dacthal®, and was first registered in the US in 1958 (US EPA, 1998a). It is used for the control of annual grasses and certain broadleaved weeds affecting various fruit and vegetable crops and ornamental turf (DPR, 2018b). The mechanism of action of DCPA appears to be inhibition of normal cell division of root tips of a wide spectrum of plants.

The California Department of Pesticide Regulation (DPR) has detected two environmental degradates of DCPA: monomethyl tetrachloroterephthalate (MTP) and 2,3,5,6-tetrachloroterephthalaic acid (TPA or chlorthal) in groundwater (DPR, 2018 a, b). DPR determined that the presence of MTP and TPA in the well water samples was the result of legal uses of DCPA-containing herbicide products (DPR, 2018b). Furthermore, DPR determined that some of the detected levels exceeded the US Environmental Protection Agency (US EPA) lifetime Health Advisory Level (HAL) for drinking water of 70 ppb (US EPA, 2008 a, b) (see Section II.C.).

Pursuant to the California Pesticide Contamination Protection Act (PCPA), DPR initiated the evaluation of DCPA and its degradates (DPR, 2018a) by a subcommittee of the Pesticide Registration and Evaluation Committee (PREC), consisting of one member each from DPR, the Office of Environmental Health Hazard Assessment (OEHHA), and the State Water Resource Control Board (SWRCB). The subcommittee is tasked to make the finding whether or not “DCPA/MTP/TPA have polluted” or “threaten to pollute” the groundwater. “Pollute” is defined as a concentration “above a level that does not cause adverse health effects, accounting for an adequate margin of safety.” In addition, with respect to toxicity, the subcommittee was also to make a determination if exposure to the pesticide and degradates would cause carcinogenic, mutagenic, teratogenic, or neurotoxic adverse health effects.

OEHHA reviewed the toxicity studies in humans and animals to (1) evaluate DCPA, MTP, and TPA for the four toxicity endpoints specified in the Act, (2) develop public health concentrations (PHCs) in the drinking water for DCPA and TPA, and (3) use the PHCs to determine the health risk from potential exposures to these chemicals in the groundwater. PHC is the concentration of a chemical in drinking water that is not expected to pose a significant risk to health, when consumed over a lifetime. The PHCs in this report were developed using approaches and methods used in OEHHA’s Public Health Goal (PHG) Program.

B. Physical and Chemical Properties, Environmental Fate and Transport

DCPA is a phthalate herbicide. DCPA has a much lower solubility in water (0.5 parts per million, ppm) compared to its mono-acid and di-acid metabolites, MTP and TPA (Figure 1; Table 1). The water solubility for MTP and TPA were 3000 ppm (parts per million) and 5780 ppm, respectively (US EPA, 2014; PPDB, 2018). The three chemicals have similar partition coefficients (Log Kow) and have low volatility at 25ºC, as shown by the low vapor pressure values and Henry's law constants which are lower than a threshold value of $1x10^{-5}$ atmospheres per cubic meter per mole (atm-m^3/mole).

Figure 1. Metabolic pathway of DCPA

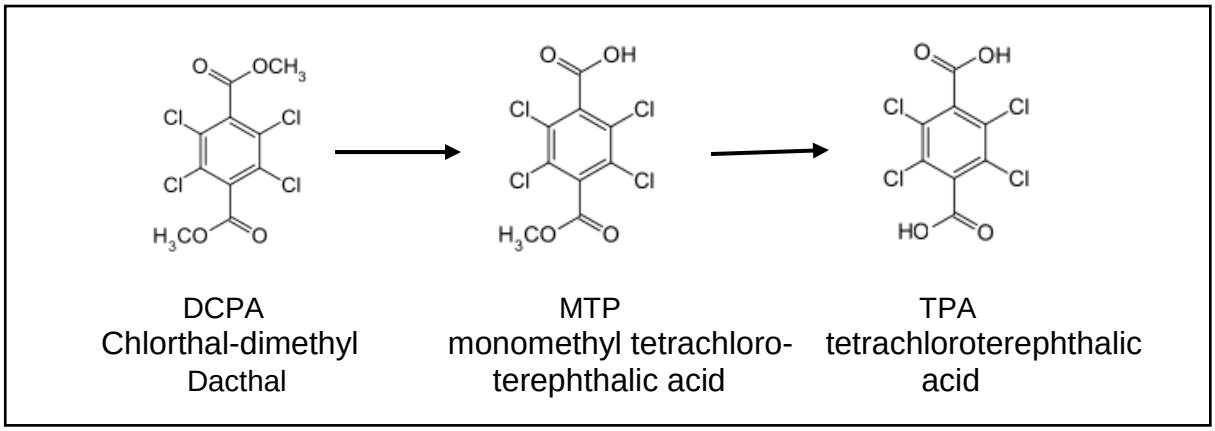

Table 1. Physical and chemical properties of DCPA, MTP, and TPA

Name and Properties	**DCPA[a]**	**MTP[a, b, c]**	**TPA[a, b, c]**
CAS	1861-32-1	887-54-7	2136-79-0
EPA Pesticide Chemical Code	078701	N/A	078702
DAC ID[d] or SDS ID[d]	DAC-893; SDS-893	DAC-1449	DAC-954; SDS-954 DAC-1209
Formula	$C_{10}H_6Cl_4O_4$	$C_9H_4Cl_4O_4$	$C_8H_2Cl_4O_4$
Molecular weight (g/mole)	331.99	317.94	303.93
Water Solubility (mg/L, ppm)	0.5 mg/L at 25°C	3,000 mg/L at 20ºC	5,780 mg/L at 20ºC
Log K_{ow}	4.19	(3.45)	(3.27)
Vapor Pressure (mm Hg)	2.5×10^{-6} at 25°C	(1.53×10^{-6})	(1.71×10^{-8})
Henry's Law Constant (atm-m^3/mole)	2.18×10^{-6}	(3.22×10^{-10})	(6.80×10^{-10})

[a] US EPA (2014)

[b] PPDB, Pesticide Properties Data Base (2018)

[c] Parenthetical numbers are modeled: US EPA (2018a), OPERA (OPEn (quantitative) structure-activity Relationship Application model)

[d] DPR (1994)

DCPA is not persistent or mobile in the environment. In surface soil, the field dissipation half-life is estimated to be 35 to 44 days in California (US EPA, 1998a). While it is stable to hydrolysis and photolysis, biodegradation is the primary dissipation process. Microbial degradation is enhanced by warmer temperature and increased soil water content with estimated half-lives of 18 to 37 days under aerobic conditions and 37 to 59 days under anaerobic conditions. Two major degradates identified are MTP and TPA. All of DCPA from aerobic and anaerobic metabolism in soil are transformed to TPA after 197 days with MTP as a minor intermediate metabolite with a half-life of 2.8 days (US EPA, 2014). Also, volatilization from soil is a major dissipation route for DCPA only under field conditions with high temperatures. It has been detected in the air at low concentrations in the most recent 2017 air monitoring network results (DPR, 2018c).

TPA is mobile, persistent, and can leach from any type of soil to surface water and groundwater. There is a potential for TPA to accumulate in groundwater over long periods of time under certain conditions, as has occurred in Washington State (WSDA, 2014).

DCPA, MTP, and TPA are monitored in California by DPR as part of DPR's Groundwater Protection Program, and they are included on its Groundwater Protection List (GWPL). In 2017, DPR conducted groundwater monitoring for DCPA, MTP and TPA in Monterey, San Luis Obispo, and Santa Barbara counties (DPR, 2018b). DPR did not detect DCPA in any of the well water samples tested at the reporting limit of 0.05 ppb. There was one trace detection of DCPA at 0.02 ppb, above the detection limit of 0.0063 ppb. In Monterey County, TPA was detected in 5 of 13 wells sampled, at concentrations ranging from 0.91 to 101 ppb. The two wells with the two highest concentrations of TPA (101 and 22.7 ppb) also contained MTP (0.073 and 0.13 ppb, respectively). TPA was also detected in 13 of 23 unique wells sampled in Santa Barbara and San Luis Obispo counties (0.121-159 ppb), and MTP (0063-0.101 ppb) was detected in 3 of 16 unique wells in Santa Barbara County.

C. Existing Drinking Water Standards

There is no published PHG or maximum contaminant level for DCPA, MTP, or TPA in California.

US EPA has developed short-term and lifetime drinking water advisory levels (2008 a, b) for DCPA. The lifetime HAL was based on non-cancer thyroid and liver toxicity from a two-year rat study (Lucas et al., 1993). The HAL assumed a 70 kilogram (kg) adult consuming 2 liters per day (L/day) of water (0.029 L/kg-day) and a relative source contribution (RSC) of 20%. The RSC of 20% was a default value because the data on relative contributions of food and air to total exposure was considered inadequate. US

EPA did not derive a HAL based on carcinogenicity because of the impurities in the feed, but concluded that the impurities, hexachlorobenzene (HCB) or dioxin/furans could not fully account for the carcinogenic response in the lifetime rat study. US EPA has not established lifetime HALs for MTP and TPA because of data limitations. Instead, US EPA stated that the HAL for DCPA is protective when applied to the sum of the parent and the degradate levels. As will be discussed in this report, OEHHA has determined that there is sufficient information to establish separate PHCs for DCPA and TPA.

III. TOXICITY PROFILE

The toxicity of DCPA and its two degradates have been reviewed in the US EPA Registration Eligibility Document (RED; US EPA, 1998a), Drinking Water Health Advisory (US EPA, 2008a), Health Effects Support Document (US EPA, 2008b), Regulatory Determination Support Document (US EPA, 2014), and in DPR's Toxicology Summary (DPR, 1994[1]). OEHHA included these reviews in our analysis and focused on the subchronic and chronic toxicity studies to develop the PHCs, as the PHC assumes lifetime exposure to the chemical in drinking water. No additional animal or human toxicity studies of these chemicals were available in the published literature.

The database for DCPA is sufficient, while it is incomplete for MTP, and limited for TPA. All of the subchronic and chronic toxicity studies were conducted by the oral route with the exception of one subchronic dermal study with DCPA. Note that in some studies, the same dose could be designated as NOEL (No-Observed-Effect-Level) or NOAEL (No-Observed-Adverse-Effect Level). For simplicity, the term NOAEL is used to represent both terms in this report. It should be noted that the benchmark dose (BMD), instead of the NOAEL, is the preferred value to determine the significance of reported effects to determine the points of departure (POD) in the PHC derivation, as explained in Section IV.

A. Pharmacokinetics and Metabolism of DCPA

The oral absorption of DCPA appeared to be dose dependent. Data from five rat studies using 14C-DCPA (1 or 1000 milligram per kilogram of bodyweight per day [mg/kg-day]) showed the chemical was relatively well absorbed (79% of administered dose) by gavage at low dose (1 mg/kg-day), but poorly absorbed (8% of dose) at high dose (1000 mg/kg-day) (summarized in US EPA, 1998a). The full reports were not

[1] DPR has indicated that the 1994 Toxicology Summary is the most recent version (Personal communication with DPR on August 1, 2018). A 2005 90-day study with DCPA in rats (Moxon, 2005) has not been reviewed by DPR.

available for OEHHA to review. Skinner and Stallard (1963) conducted both a single oral dose (100 or 1000 mg/kg, 3/group) and 2-year dietary (10,000 ppm, 1 male and 1 female) metabolism studies in dogs. Both studies showed low absorption, as the majority of the administered dose was excreted unchanged in the feces. The 2-year dog study reported the distribution of trace levels of TPA and MTP in the kidney and liver, and DCPA and MTP in the adipose tissue. These levels in the organs could be due to the last dosing. The presence of residues in the adipose tissue could suggest storage; however, the levels were very low and reported as <1 ppm of DCPA and <2 ppm of MTP.

After DCPA exposure, MTP was the major metabolite detected in urine, with TPA as a minor metabolite, but both were at very low levels. In the single-dose dog study, only 2% of the dose was recovered as MTP and <1% was TPA in the urine (Skinner and Stallard, 1963). In a human study, male volunteers (3/per group) received a single oral dose of 25 mg or 50 mg pure DCPA. Only 4 to 11% of the dose was excreted in the urine as MTP, and <1% as TPA, over a 3-day period following exposure (Tusing, 1963). No DCPA was measured in the urine. US EPA (2008b) suggested that the mammalian metabolism of DCPA is likely via hydrolysis by nonspecific esterases, with MTP as an intermediate and TPA as the final metabolite. This pathway is the same as that described for environmental degradation of DCPA (Section II.B.).

There is no available disposition study with animals given MTP. A dog metabolism study with TPA (the disodium salt of DAC-954) showed that 80-90% was eliminated in the feces, and the remainder unchanged in urine. No further breakdown product was noted (Skinner and Stallard, 1963).

B. Toxicity of DCPA

1. Acute Toxicity

A summary of the acute toxicity profile with DCPA is presented in Appendix IA. The acute toxicity studies are short-term with high doses, with toxicity characterized by the lethal concentration (LC_{50}) or lethal dose (LD_{50}) that caused death in 50 percent of the tested animals. In general, DCPA has low acute oral, dermal and inhalation toxicity, and is a mild eye and skin irritant. It has not been shown to be a skin sensitizer.

2. Subchronic Toxicity

A summary of the available subchronic toxicity studies for DCPA is presented in Appendix IB. Only those relevant for derivation of the PHC are mentioned below.

In a 90-day dietary rat study, treatment-related effects were found in liver, lung, and kidney (Lucas and Benz, 1991). A summary of the results are presented in Appendix II.

The lowest NOAEL was 50 mg/kg-day for centrilobular hepatocellular hypertrophy (males and females) and increased relative liver weight (females only) at 100 mg/kg-day. Treatment-related increase in accumulation of foamy macrophage in the alveolar space of lung was also found at $\geq$ 100 mg/kg-day in males, and the corresponding increase in white foci in the lung was observed at 1000 mg/kg-day in both sexes in the 60-day satellite study. Increased kidney weight and increase in regenerative epithelium, epithelium hyperplasia, and tubular hypertrophy were observed in the kidney at an administered dose of $\geq$ 150 mg/kg-day in males. In the thyroids, follicular cell hypertrophy in both sexes were observed at a dose of 1000 mg/kg-day.

In a 28-day subchronic dietary study in rats, the liver was also the target organ showing a dose-related increase in absolute and relative liver weight along with centrilobular hepatocyte hypertrophy (Lucas and Killeen, 1990). These effects were observed at the lowest dose tested at 215 and 228 mg/kg-day for males and females, respectively.

In a 90-day mouse dietary study, there were no effects other than minimal centrilobular hepatocyte enlargement in the liver at 1235 mg/kg-day in males, and 1049 mg/kg-day in female mice (Ford, 1986). The NOAELs were 406 and 517 mg/kg-day for males and females, respectively.

3. Chronic and Lifetime Toxicity

There are four chronic/lifetime animal bioassays of sufficient quality[2] for evaluating the chronic toxicity and carcinogenic potential of DCPA, including both sexes in mice and rats (Lucas and Killeen, 1988; Lucas et al., 1993). We also reviewed a two-year chronic toxicity dog study (Hazelton and Dieterich, 1963) but a two-year study duration is too short to examine lifetime effects in that species.

Chronic Mouse Studies

CD-1 mice (60/dose/sex plus an additional 10/dose/sex for each interim sacrifice at 23, 56 and 76 weeks) were fed technical DCPA (96.7% purity) in the diet for two years at concentrations of 0, 100, 1000, 3500, or 7500 ppm (0, 12, 123, 435 or 930 mg/kg-day for males; 0, 15, 150, 510 or 1141 mg/kg-day for females) (Lucas and Killeen, 1988). The reported impurities include 0.04% HCB as well as other impurities. Doses of HCB were estimated at 0.005, 0.05, 0.17, or 0.37 mg/kg-day for males and 0.006, 0.06, 0.20, or 0.46 mg/kg-day for females (calculated by OEHHA). No treatment related mortality was observed in males or females. Effects from treatment with DCPA were limited to the liver (Tables 2 and 3). There were increased relative liver weight at interim (female)

[2] A two-year dietary study in rats completed in 1963 (Paynter and Kundzin) was not considered as most of the animals were suffering from a respiratory infection and were on antibiotics during the course of the study.

and terminal sacrifices for both sexes at the highest dose. Liver enzymes (glutamic-pyruvic transaminase and sorbitol dehydrogenase, SDH) were also significantly elevated in females at week 76 (interim sacrifice) at 150 mg/kg-day and above, but only SDH was significantly increased at the terminal sacrifice (104 weeks) at the highest dose (Table 3). Liver enzymes were not significantly elevated in males at both interim and terminal sacrifices. The NOAELs for non-cancer effects were 435 mg/kg-day in males and 150 mg/kg-day in females.

For carcinogenicity, males showed a significant dose-response trend for increased combined liver tumors, but had a high control incidence (19/48) (Table 2). The female control incidence was low (2/39). A dose-related trend for combined liver tumors was observed in females and was statistically significant by pair-wise comparison only at the highest dose group.

Table 2. Non-neoplastic and neoplastic effects of DCPA in male mice in a two-year dietary study (Lucas and Killeen, 1988)

Male Mice	**DCPA Dose (mg/kg-day)**				
	0	**12**	**123**	**435**	**930**
	Relative liver weight (as percent body weight)[a]				
Week 53	4.9	6.0	5.3	5.3	6.0
Week 105/6	6.5	6.7	6.6	6.5	9.0*
	Glutamic-Pyruvic Transaminase (GTP, ALT) mU/ml				
Week 76	49	52	55	65	55
Week 102	63	85	57	68	87
	Sorbitol Dehydrogenase (SDH) mU/ml				
Week 76	34	36	35	52	43
Week 102	53	56	58	55	65
	Incidence of Liver Tumors[b]				
Hepatocellular adenoma	14/48	16/48	13/50	9/48	22/54
Hepatocellular carcinoma	6/48	6/48	9/50	8/48	11/54
Combined liver tumors[a]	19/48**	18/48	20/50	17/48	29/54

[a] Statistical significance by Cochran-Armitage test for trend (indicated on control group), and Fisher Exact test (quantal data) or Williams' test (continuous data) for pair-wise comparison (indicated on significant dose group when compared to control) with * $p<0.05$, ** $p<0.01$.

[b] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals alive at the time of first occurrence of tumor (reported in study addendum 5).

Table 3. Non-neoplastic and neoplastic effects of DCPA in female mice in a two-year dietary study (Lucas and Killeen, 1988)

Female Mice	DCPA Dose (mg/kg-day)				
	0	15	150	510	1141
	Relative liver weight (as percent body weight)[a]				
Week 53	5.1	5.0	5.5	6.4*	6.3*
Week 105/6	5.1	5.0	5.0	5.5	6.3*
	Glutamic-Pyruvic Transaminase (GTP, ALT) mU/ml[a]				
Week 76	24	20	55**	57**	41**
Week 102	33	28	51	31	54
	Sorbitol Dehydrogenase (SDH) mU/ml[a]				
Week 76	19	15	35*	47**	37**
Week 102	22	23	40	27	47**
	Incidence of Liver Tumors[a,b]				
Hepatocellular adenoma	2/39**	0/37	2/39	3/39	8/36*
Hepatocellular carcinoma	0/39	1/37	0/39	1/39	1/36
Combined liver tumors	2/39**	1/37	2/39	4/39	9/36*

[a] Statistical significance by Cochran-Armitage test for trend (indicated on control group), and Fisher Exact test (quantal data) or Williams' test (continuous data) for pair-wise comparison (indicated on significant dose group when compared to control) with * $p<0.05$, ** $p<0.01$.

[b] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals alive at the time of first occurrence of tumor (reported in study addendum 5).

Chronic Rat Studies

Sprague Dawley rats (60/sex/group, plus additional 10/sex/group terminated for evaluation after one year) were fed DCPA (97.7% purity) in the diet at target concentrations of 0, 1, 10, 50, 500, or 1000 mg/kg-day for two years (Lucas et al., 1993)[3]. Actual doses consumed were close to target concentrations. The technical DCPA contained up to 0.13% HCB as an impurity, equivalent to 0.0013, 0.013, 0.065, 0.65, or 1.3 mg HCB/kg-day for the respective DCPA doses (calculated by OEHHA). Survival in high-dose males was reduced, with 73% in the high-dose group died versus 52% in the control group before the termination of the study at 104 weeks. At 85 weeks, mortality was 45% in the high dose group versus 20% in the controls. At the time of appearance of the first thyroid adenoma (week 65), mortality was not different between the control and treatment groups. DCPA had no significant effect on survival in females.

[3] Lucas et al., 1993 is the same study as Powell, et al., 1993, as cited in the US EPA chlorthal-dimethyl documents.

Animals of both sexes in the two highest dose groups showed clinical signs of poor health, including decreased body-weight gain of greater than 10%. The maximum tolerated dose (MTD) was exceeded in the high dose groups. Target organs for non-cancer effects were liver, thyroid, lung, kidney, and eyes (Table 4 and Table 5).

In both sexes, liver effects included increases in both the incidence and severity of centrilobular hepatocytic swelling, increased eosinophilic foci, and increased relative liver weights at the higher dose groups (Table 4 and Table 5).

Non-neoplastic thyroid effects at study termination included basophilic clumped colloid (total of minimal and slight/mild severity), follicular cell hyperplasia and hypertrophy, and minor thyroid hormone disruption, as discussed below (Table 4 and Table 5). The interim sacrifice thyroid hormone data are shown in Appendix III. There were dose-dependent and statistically significant decreases in thyroxine (T4) hormone levels at the higher dose groups in both sexes (at ≥ 10 mg/kg-day for males, and ≥ 50 mg/kg-day for females) at all of the time points measured (52, 83, and 104 weeks). There was a trend for decreasing triiodothyronine (T3) in males at 52 weeks, which was statistically significant in the high dose group. There were no effects on T3 in males at the later sampling times and no effects in females at any time point. There was a dose dependent increase in thyroid-stimulating hormone (TSH) at 52 weeks in males and females, but neither was statistically significant. There were no effects on TSH at 83 weeks in males or females. At study termination, TSH in all dose groups for males were greater than control, but the effect lacked dose dependency and was only statistically significant at 500 mg/kg-day. There was a dose dependent trend for females for elevated TSH at 104 weeks as well, but there was no significance by pair-wise comparison.

There was a dose-related increase in the incidence and severity of focal accumulation of foamy-appearing macrophages and thickening of the alveolar walls in the lungs in males and females. Other findings in the lungs included cholesterol clefts, fibrosis, pigment deposition, and pneumonitis. There was also a statistically significant increase in relative kidney weight in males at 50 mg/kg-day and higher, and an increase in bilateral retinal atrophy in females only at 10, 500 and 1000 mg/kg-day (Table 5).

The NOAELs for non-cancer effects in this study were 1 mg/kg-day for males (centrilobular hepatocytic swelling and thyroid follicular cell hyperplasia and hypertrophy) and 10 mg/kg-day for females (centrilobular hepatocytic swelling, thyroid follicular cell hyperplasia, and retinal atrophy). OEHHA also conducted dose-response modeling of the significant effects in this study (see Section IV.A.1, Table 10).

Table 4. Non-neoplastic effects of DCPA in male rats from a two-year dietary study (Lucas et al., 1993)

Male Rats	**DCPA Dose (mg/kg-day)**					
	0	**1**	**10**	**50**	**500**	**1000**
Liver Histopathology						
# examined	60	59	56	54	57	59
Centrilobular hepatocytic swelling	3	6	23**	41**	53**	55**
Focus/Foci, eosinophilic	6	10	13	21**	20**	17*
Liver – Other Effects						
# examined (except as noted)	10	10	10	10	10	10
Relative liver weight (g/100 g body weight)	2.391 (0.381) n=8	2.414 (0.479)	2.577 (0.371)	3.045 (0.707)	3.702** (1.078)	3.698** (0.974)
Thyroid Histopathology						
# examined	60	59	56	54	57	58
Basophilic clumped colloid	21	14	30*	35**	45**	49**
Follicular cell hyperplasia, diffuse	9	4	21**	25**	40**	45**
Follicular cell hypertrophy	6	7	19**	30**	40**	45**
Thyroid – Other effects						
# examined	10	10	10	10	10	10
T3 (ng/dL)	74.24 (25.76)	84.70 (26.08)	78.64 (25.55)	79.19 (19.02)	72.99 (18.72)	72.81 (15.22)
T4 (µg/dL)	2.39 (1.13)	2.70 (0.86)	1.84 (1.03)	1.08** (0.80)	0.39** (0.45)	0.23** (0.40)
TSH (ng/ml)	1.492 (0.742)	2.001 (0.601)	2.877 (2.170)	2.051 (0.787)	2.899** (1.193)	2.167 (1.127)
Relative thyroid+ parathyroid weight (mg/100g body weight)	6.92 (2.40)	7.83 (3.01)	6.74 (1.17)	7.51 (1.52)	7.19 (1.53)	9.29 (2.11)
Relative thyroid+ parathyroid weight (mg/g brain weight)	20.09 (5.36)	22.86 (4.39)	19.44 (2.82)	20.48 (3.59)	19.54 (1.09)	25.02* (4.69)

Table 4 (continued). Non-neoplastic effects of DCPA in male rats from a two-year dietary study (Lucas et al., 1993)

Male Rats	**DCPA Dose (mg/kg-day)**					
	1	**10**	**50**	**500**	**1000**	
Lung						
# examined	60	59	56	54	57	59
Accumulation of foamy macrophage	11	10	18	24**	54**	59**
Thickening, alveolar walls	8	8	20**	26**	50**	58**
Cholesterol Cleft(s)	1	3	6	13**	44**	52**
Fibrosis, polarized light	1	2	11**	10**	40**	47**
Pigment deposition	0	1	1	4*	9**	12**
Pneumonitis, granulomatous, focal	2	1	1	4	13**	22**
Pneumonitis, interstitial, focal	10	4	11	16	43**	51**
Kidney						
# examined	60	59	56	54	57	59
Chronic nephropathy	59	53	54	53	57	58
Relative kidney weight (g/100 g body weight)	0.682 (0.110) n=10	0.780 (0.437) n=10	0.780 (0.257) n=10	1.098* (0.495) n=10	1.203** (0.525) n=10	1.039* (0.395) n=10

Continuous data were expressed as means and standard deviations (in parentheses). Statistically significant by Bartlett's test (continuous data) or by Fisher Exact test (quantal data) for pair-wise comparison (indicated on significant dose group when compared to control) with * $p<0.05$, ** $p<0.01$.

Table 5. Non-neoplastic effects of DCPA in female rats from a two-year dietary study (Lucas et al., 1993)

Female Rats	**DCPA Dose (mg/kg-day)**					
	0	**1**	**10**	**50**	**500**	**1000**
Liver Histopathology						
# examined	58	59	57	58	60	58
Centrilobular hepatocytic swelling	0	0	3	36**	54**	56**
Focus/Foci, eosinophilic	4	7	11	14	18**	24**
Liver – Other Effects						
# examined (except as noted)	10	10	10	10	10	10
Relative liver weight (g/100 g body weight)	2.508 (0.567)	2.287 (0.316)	2.666 (0.744) n=9	2.606 (0.473)	3.421** (0.879)	4.019** (0.489)
Thyroid Histopathology						
# examined	58	59	57	58	59	58
Basophilic clumped colloid	4	4	7	20**	50**	50**
Follicular cell hyperplasia, diffuse	4	3	2	18**	49**	49**
Follicular cell hypertrophy	4	3	1	12	37**	48**
Thyroid- Other Effects						
# examined	10	10	10	10	10	10
T3 (ng/dL)	117.12 (12.62)	106.44 (26.12)	100.31 (16.11)	103.36 (26.30)	107.09 (16.07)	109.69 (21.84)
T4 (µg/dL)	2.58 (0.55)	1.80 (0.97)	1.87 (0.65)	1.17** (0.81)	0.48** (0.48)	0.38** (0.42)
TSH (ng/ml)	1.213 (0.358)	1.198 (0.353)	1.345 (0.738)	1.519 (0.566)	1.679 (0.739)	2.178 (1.304)
Relative thyroid+parathyroid weight (mg/100g body weight)	6.73 (1.58)	8.22 (2.02)	10.21** (1.98)	8.65 (1.48)	8.43 (1.93)	9.34** (2.87)
Relative thyroid +parathyroid weight (mg/g brain weight)	13.38 (2.12)	18.77** (3.63)	20.29** (3.75)	19.83** (3.39)	16.08 (3.91)	15.53 (6.13)

Table 5 (continued). Non-neoplastic effects of DCPA in female rats from a two-year dietary study (Lucas et al., 1993)

Female Rats	**DCPA Dose (mg/kg-day)**					
	0	**1**	**10**	**50**	**500**	**1000**
Lung						
# examined	58	59	57	58	60	58
Accumulation of foamy macrophage	7	10	11	13	56**	58**
Thickening, alveolar walls	9	12	9	14	52**	58**
Cholesterol Cleft(s)	5	3	4	5	52**	52**
Fibrosis, polarized light	3	0	3	5	43**	47**
Pigment deposition	0	0	2	3	8**	10**
Pneumonitis, granulomatous, focal	1	0	2	2	20**	22**
Pneumonitis, interstitial, focal	3	8	15**	10*	50**	56**
Kidney						
# examined	58	59	57	58	60	58
Chronic nephropathy	42	47	47	53	53	53
Relative kidney weight (g/100 g body weight)	0.665 (0.203) n=10	0.646 (0.160) n=10	0.806 (0.361) n=10	0.670 (0.199) n=10	0.936 (0.305) n=10	0.933 (0.140) n=10
Eyes						
# examined	58	59	57	58	60	58
Retinal atrophy, total bilateral	0	2	4	5*	11**	11**

Continuous data were expressed as means and standard deviations (in parentheses). Statistically significant by Bartlett's test (continuous data) or by Fisher Exact test (quantal data) for pair-wise comparison (indicated on significant dose group when compared to control) with * $p<0.05$, ** $p<0.01$.

For carcinogenicity, there were no increases in liver hepatocellular adenomas, liver hepatocellular carcinomas, or combined hepatocellular adenomas or carcinomas in male rats fed DCPA (Table 6). There was a statistically significant dose-related trend for thyroid follicular cell adenomas and combined thyroid follicular cell tumors (although no increase in carcinomas alone) in the males. Follicular cell adenomas were statistically significant at the three highest dose groups and combined follicular cell tumors were statistically significant at 50 and 500 mg/kg-day.

Female rats fed DCPA had a significant dose-related increase in liver hepatocellular adenomas and combined hepatocellular tumors, with statistically significant incidents at the two high dose groups (Table 6). In females, both thyroid follicular cell carcinomas and combined follicular cell tumors were significant by trend and by pair-wise comparison at the high dose group.

Table 6. Effective tumor incidences in the thyroid and liver in the two-year rat study with DCPA (Lucas et al., 1993).

Tumor type and incidence[a]	**DCPA Dose (mg/kg-day)**					
	0	**1**	**10**	**50**	**500**	**1000**
Male Rats						
Hepatocellular adenoma (wk 95)[b]	1/41	1/33	0/36	0/33	0/32	1/22
Hepatocellular carcinoma (wk 84)	3/48	0/44	2/44	1/44	2/39	0/35
Combined liver tumors	4/48	1/44	2/44	1/44	2/39	1/35
Follicular cell adenoma[c] (wk 65)	1/59**	2/58	2/54	8/50**	10/54**	7/54*
Follicular cell carcinoma (wk 98)	1/39	1/28	1/34	0/30	0/31	0/20
Combined thyroid tumors	2/59*	3/58	3/54	8/50*	10/54**	7/54
Female Rats						
Hepatocellular adenoma (wk 69)	0/57**	0/58	1/54	1/56	4/60	7/52**
Hepatocellular carcinoma (wk 96)	0/37	0/40	1/34	0/35	3/43	3/41
Hepatocholangeocarcinoma (wk 106)	0/29	0/31	0/32	0/30	0/32	2/36
Combined liver tumors	0/57**	0/58	2/54	1/56	7/60**	11/52**
Follicular cell adenoma (wk 68)	1/57	1/58	2/54	4/47	1/60	4/54
Follicular cell carcinoma (wk 84)	0/50**	0/52	1/45	0/49	1/50	4/46*
Combined thyroid tumors	1/57**	1/58	3/54	4/56	2/60	7/54*

[a] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals alive at the time of first occurrence of tumor (calculated by OEHHA).
[b] Week (wk) of first occurrence of tumor.
[c] Statistical significance by Cochran-Armitage test for trend (indicated on control group) or Fisher Exact test for pair-wise comparison (indicated on significant dose group when compared to control) with * $p<0.05$, ** $p<0.01$.

Chronic Dog Study

Beagles (4/sex/dose) were fed a diet containing DCPA (Dacthal-T, purity not stated) at 0, 100, 1000 or 10,000 ppm, (male: 0, 2.6, 17.7 or 199 mg/kg-day; female: 0, 3, 20.7 or 238 mg/kg-day) for two years, with interim sacrifices at 1 year (Hazelton and Dieterich, 1963). No significant effects were observed in this study. OEHHA did not establish a NOAEL because of study deficiencies (small number of animals in each dose group per sex, poor study design, and limited histopathological examination) and reporting of the study.

4. Genotoxicity

OEHHA reviewed the genotoxicity studies of DCPA cited in the US EPA (US EPA, 1998) and DPR (DPR, 1994) reviews (Table 7). All of the guideline studies were reported as negative by US EPA (1998) and DPR (1994). However, some of these studies, while showing negative results, were not considered acceptable by DPR. A possible adverse effect (post-implantation loss) was noted for a dominant lethal assay where male Sprague Dawley rats were given a single oral gavage dose at 0, 3, 31.6 or 316 mg/kg-day and mated with females (Kouri et. al., 1977; DPR 1994). This study was considered to be unacceptable by DPR due to inadequate number of pregnant females per group, and inadequate high dose with no evidence of the MTD.

Table 7. Genotoxicity profile of DCPA

Assay type and end point	Test systems	Results		Reference[a, b]
		-S9	+S9	
***in vitro* Gene Mutation**				
Bacterial cells	*S. typhimurium* multiple strains at 0, 667 to 10,000 µg/plate ± S9 activation	(-)	(-)	b(A)
Bacterial cells	*S. typhimurium* multiple strains at 0, 1 to 333.3 µg/plate ± S9 activation	(-)	(-)	b(UA)
Bacterial cells	*S. typhimurium* TA1978, TA1538 differential inhibition of repair deficient and repair competent strain at 0, 2 to 20 µg/plate ± S9 activation	(-)	(-)	a(UA), b(UA)
Mammalian cells	Mouse lymphoma/L5178Y TK forward mutation at 0, 7.5 to 100 µg/mL without, and 0, 15 to 200 µg/mL with S9 activation	(-)	(-)	a(A), b(A)
***in vitro* Chromosomal Damage**				
Chromosomal aberration	Chinese hamster ovary at 0 to 1000 µg/mL ± S9 activation	(-)	(-)	a(A), b(A)
Sister chromatid exchange	Chinese hamster ovary at 0 to 300 µg/mL	(-)	(-)	a(A), b(A)
***in vivo* Chromosomal Damage**				
Chromosomal aberration	Sprague Dawley rat at 0 to 316 mg/kg	(-)		b(UA)
Dominant lethal assay	Sprague Dawley rat single gavage at 0 to 316 mg/kg-day	Post-implantation loss at 31.6 mg/kg-day		a(A), b(UA) Kouri et. al., 1977
***in vitro and in vivo* DNA Damage**				
in vitro UDS	Rat primary hepatocytes at 0 to 1000 µg/mL	(-)		a(A), b(A)

[a] US EPA (1998a)

[b] DPR (1994)

Abbreviations: A: acceptable under FIFRA guideline; UA: unacceptable under FIFRA guideline; S9: rat liver fraction of metabolic activation; UDS: unscheduled DNA synthesis and repair; (-): negative

5. Reproductive and Developmental Toxicity

Reproductive Toxicity

Sprague Dawley rats (35/sex/group) were given DCPA (purity of 96.4% and 97.6%) in the diet at doses of 0, 1000, 5000 or 20,000 ppm (males [F0-F1]: 0, 45, 233 or 952, and females [F0-F1]: 0, 63, 319, 1273 mg/kg-day) for two generations (Lucas et al., 1990). The doses for the dams at the low and mid-dose groups of the F2 generation were reduced to 200 and 500 ppm, respectively, on lactation day 0 to ensure a no-effect dose for post-weaning body weight for the F2b litter. For the F0, F1, or F2 parental animals, the treatment-related effects included reduced body weight (≥ 5000 ppm for F2 (both sexes), and increased histopathological lesions in the kidney, lung, liver, thyroid, and thymus. The most effected was the thymus (male) and lungs (female) at 1000 ppm; other organs were affected at higher doses. Thus, the parental NOAEL is <1000 ppm (i.e., <45 mg/kg-day) for histological lesions. Most of the histological findings in the lung, liver, and thyroid were similar to those observed in the chronic rat study with an experimentally determined NOAEL of 1 mg/kg-day (Lucas et al., 1993).

No effects on reproductive performance (mating and fertility indices and gestation length) were observed for both generations. However, there was increased mean stillborn index in all litter at 20,000 ppm (1273 mg/kg-day). The only treatment-related effect on the pups was decreased mean body weight at day 1 in F1a and F1b at 5000 ppm (319 mg/kg-day) and higher, and the decreased mean live litter size at day 1 of F2a at 20,000 ppm (952 mg/kg-day). The NOAEL for reproductive toxicity is 1000 ppm (63 mg/kg-day).

Developmental Toxicity

There were no developmental effects at doses without maternal toxicity in two rabbit and one rat studies. Two developmental toxicity studies of DCPA were conducted with pregnant New Zealand White rabbits treated by gavage at doses of 0, 500, 1000, or 1500 mg/kg-day on gestation days 6 through 19, and at doses of 0, 125, 250 or 500 mg/kg-day on gestation days 7 through 19 (Chun, 1989 in US EPA 1998a; and Schroeder, 1988). Maternal deaths and adverse clinical signs were reported at all doses in the first study, and none in the second study with lower doses. US EPA and DPR established a maternal NOAEL of 250 mg/kg-day based on maternal death from the first study. DPR also established a developmental NOAEL at 250 mg/kg-day for increased resorptions in does that died at $\underline{\geq}$ 500 mg/kg-day.

In a third developmental toxicity study, DCPA was administered by gavage at doses of 0, 500, 1000 or 2000 mg/kg-day to pregnant Sprague Dawley rats (25/group) on days 6 through 15 of gestation (Ford, 1986). There was no adverse effect noted in this study. The maternal NOAEL was established at 1000 mg/kg-day due to decrease weight gain

by 20 percent on days 9 through 12 of gestation at 2000 mg/kg-day, and developmental NOAEL was > 2000 mg/kg-day, the highest dose tested (DPR, 1994).

6. Neurotoxicity/Endocrine Disruption

A neurotoxicity study was not required when data were submitted for the registration of DCPA (DPR, 1994). US EPA (2008b) reported some dose-related signs of nervous system effects (i.e., ataxia, decreased motor activity, and poor righting reflex) in New Zealand White rabbits in the developmental toxicity study of DCPA after exposure to lethal doses $\geq$ 500 mg/kg-day (Chun et.al., 1989 in US EPA, 1998a). It is likely that these effects were due to the animals in moribund condition. These nervous system effects were not reported in another developmental study using rabbits at doses below 500 mg/kg-day (Schroder, 1988, cited in DPR, 1994).

There was one additional registrant submitted study that specifically addressed neurotoxicity. In this study, Sprague Dawley rats (12/sex/group) were given DCPA at 0, 100, 300, or 1000 mg/kg-day in the diet for 90 days (Moxon, 2005). The report stated that the HCB content was 0.002%. Cage-side observation was made once a week. On week 12, neurotoxicity was tested using a functional observation battery (FOB) which included landing foot splay, muscle weakness (fore and hind limb grip strength) and sensory perception (time to tail-flick), and motor activity using activity counts. DCPA treatment did not cause any effect on FOB tests or motor activity.

US EPA reviewed the results of the Endocrine Disruptor Screening Program (EDSP) Tier 1 assay for DCPA (US EPA, 2015). US EPA did not report any conclusive evidence of DCPA interacting with the estrogen or androgen pathways. However, DCPA was active in 6 of 20 assays in the steroid hormone target family in ToxCast®, including assays for estrogen and androgen receptors[4]. DCPA also demonstrated a potential for interaction with the thyroid hormone pathways in the absence of overt or systemic toxicity in the EDSP Tier 1 male and female pubertal assays in adult animals, and in the chronic rat bioassay (Lucas et al., 1993) (see Section III.B.3). US EPA (2015) recommended special thyroid assays be performed in pregnant animals, fetuses, postnatal animals, and adult animals be submitted for review.

7. Human Studies

Male volunteer subjects (3/dose) given a single 25 mg or 50 mg oral dose in capsule did not report any complaints (Tusing, 1963). There were no effects in the blood (hematology and biochemistry panels) or urine analyses. These doses corresponded to 0.36 or 0.71 mg/kg assuming individual's bodyweight of 70 kg. There were no long-

[4] http://actor.epa.gov/dashboard/#chemical/1861-32-1

term, reproductive or developmental exposure studies or data regarding potential carcinogenicity of DCPA in humans (US EPA, 2008a).

There were no cases of eye irritation reported or other findings from the occupational health surveillance amongst workers engaged in DCPA production (DPR, 1994). This surveillance study specifically addressed observation on eye effects from over exposure during operation of the production plant. There are seven reported incidences[5] associated with occupational exposures of field workers and pesticide applicators submitted by physicians through the California Pesticide Illness Surveillance Program (PISP) from 1997-2015. The most commonly reported symptoms were nausea, dizziness and headaches.

C. Toxicity of MTP

The MTP database consists of only one mammalian toxicity study, a 28-day single dose dietary study in rats treated at approximately 1% dietary concentration (860 mg/kg-day) (Hazelton, 1961). In this study, three groups of male Sprague Dawley rats (10/group) were fed treated diet containing either MTP, TPA or DCPA for 28 days. The control group was fed an untreated diet. There were no adverse effects reported and no signs of toxicity from exposure to DCPA, MTP, or TPA based on clinical signs, changes in body weights, liver and kidney weights, and from gross and histological examination of tissues.

There were only limited genotoxicity data -an *in vitro* gene mutation assay where MTP was tested in in *Salmonella typhimurium* (TA1535, TA1537, TA98, TA100) and one strain of *Escherichia coli,* both in the presence and absence of S9 activation (rat liver enzyme extract) (Callander, 2005). MTP at all concentrations tested (100-5000 µg/plate) did not induce any significant increases in the numbers of revertant colonies in both bacterial systems.

D. Toxicity of TPA

The TPA toxicology database is limited but included more studies than that for MTP (Table 8). There are three short-term oral toxicity studies: a 30-day oral gavage study (Major, 1985), a reproductive toxicity study (Mizens et al., 1985), and a 90-day feeding study (Goldenthal et. al., 1977). The available subchronic studies with TPA did not report any adverse effects. As with DCPA, TPA also showed no developmental toxicity at the doses tested, but it has only been tested in the rats. Generally, developmental toxicity studies are conducted in both rodent and non-rodent species.

[5] Data accessed through the California Pesticide Illness Query (CalPIQ) database at https://apps.cdpr.ca.gov/calpiq/

Table 8. Toxicity profile of TPA

Duration Route Species	Dose/test system	Result[a, b]	Reference[a, b]
Subchronic Toxicity			
Subchronic 90-days/diet/ Sprague Dawley rats	0, 50, 500, 1000, 10,000 ppm; (0, 2.5, 25, 50 or 500 mg/kg-day)	NOAEL ≥ 500 mg/kg-day; LOAEL not determined; no adverse effect	a, b Goldenthal et al., 1977
Subchronic 30-days/gavage/ Sprague Dawley rats	0, 100, 500, 2000 mg/kg-day	NOAEL: 500 mg/kg-day; LOAEL: 2000 mg/kg-day for soft stools and hematology effects	a, b Major, 1985
Developmental Toxicity			
Gestation days 6–15/gavage/ Sprague Dawley rats	0, 625, 1250 or 2500 mg/kg-day	Maternal NOAEL[a]: 1250 mg/kg-day; LOAEL: 2500 mg/kg-day for ↓ body weight gain and food consumption	a, b, c, Mizens et al., 1985
		Maternal NOAEL[b]: 625 mg/kg-day; LOAEL: 1250 mg/kg-day for excess salvation Developmental NOAEL > 2500 mg/kg-day	
Genotoxicity			
Test System	**Dose**	**Result**	**Reference**
In vitro Gene Mutation	0, 50 to 1500 µg/plate	(-) *Salmonella* ±S9 activation	a, b(A)
In vitro Gene Mutation	0, 100 to 2000 µg/plate	(-) CHO/HGPRT ±S9 activation	a, b(A)
In vitro Chromosomal Damage	0, 200 to 2000 µg/mL	(-) SCE/Chinese Hamster Ovary ±S9 activation	a, b(A)
In vitro Unscheduled DNA synthesis	0, 20 to 6000 µg/well	(-) no ↑ in unscheduled DNA synthesis	a, b(A)
In vivo Chromosome aberration/micronucleus	(M): 0, 1000 to 10,000 mg/kg (F): 0, 500 to 5000 mg/kg	(-) mouse female clastogenicity (+/-) mouse male ↑ micronucleated poly-chromatic erythrocytes and bone marrow toxicity both sexes	a, b(A)

[a] US EPA (1998a) [b] DPR (1994) [c] US EPA (2008a)

Abbreviations: A: acceptable under FIFRA guideline, CHO=Chinese hamster ovary, HGPRT: hypoxanthine-guanine phosphoribosyltransferase, SCE=sister chromatid exchange.

Subchronic Toxicity

In the 90-day study, Sprague Dawley rats (15/sex/group) were dosed with TPA at 0, 50, 500, 1000 or 10,000 ppm in the diet (i.e., approximately: 0, 2.5, 25, 50 or 500 mg/kg-day) (Goldenthal et. al., 1977). There were no significant changes in clinical observations, histopathology, hematology and organ weights. Occasional soft stools were seen in controls and high dose animals. A non-significant decrease in thyroid to body weight ratio was observed at the highest dose tested. The NOAEL for this study was 500 mg/kg-day.

As a follow up to augment the findings of this 90-days study, a 30-days gavage study with TPA was performed using Sprague Dawley rats (10/sex/group) at doses of 0, 100, 500 or 2000 mg/kg-day (Major, 1985). There were not treatment-related mortalities or changes in organ weights. Gross and histological evaluations of the organs at the highest dose and selected tissues at the lower doses did not reveal any abnormalities. The NOAEL was 500 mg/kg-day based on soft stools found in both sexes as well as occult blood in the urine and increases in hemoglobin and hematocrit in males at 2000 mg/kg-day.

While the database of toxicity studies for TPA is limited, comparison of the 90-day studies in DCPA (Lucas and Benz, 1991) and TPA (Goldenthal et al., 1977) demonstrate that TPA is much less toxic to the liver and thyroid than the parent compound (Table 9; Appendix II).

Developmental Toxicity

There was no evidence of developmental toxicity with TPA up to 2500 mg/kg-day, based on a rat gavage study (Mizens et al., 1985). The maternal NOAEL of 1250 mg/kg-day was based on decrease in bodyweight gain and food consumption at 2500 mg/kg-day (US EPA, 1998a). DPR (1994) assigned a lower maternal NOAEL of 625 mg/kg-day for excess salvation at 1250 mg/kg-day.

There are no reproductive toxicity studies for TPA (US EPA, 2008a).

Genotoxicity

The available studies showed that TPA is not mutagenic (Table 8). However, an *in vivo* mouse micronucleus assay with TPA did show a weak response at the highest dose (Siou, 1985 in US EPA, 2008b).

Table 9. Comparison of toxicity endpoints in rats after 90-day exposure to either DCPA or TPA.

Effects	**DCPA** (Lucas and Benz, 1991)	**TPA** (Goldenthal et al., 1977)
Liver weights	increases in liver weights were observed at 150 mg/kg-day in males and 50 mg/kg-day in females	no increases up to the highest dose tested in either sex (500 mg/kg-day)
Centrilobular hepatocyte hypertrophy	increased incidences in male rats at ≥100 mg/kg-day and for female rats at 150 and 1000 mg/kg-day	None, up to 500 mg/kg-day in both sexes
Thyroid weight	(Increased in the 104 week study at 1000 mg/kg-day, significant only in females; Lucas et al., 1993)	Decreased, but not statistically significant in both sexes
Follicular cell hypertrophy	0/15 at 150 mg/kg-day (males and females) 13/15 (males) and 11/15 (females) at 1000 mg/kg-day	None, up 500 mg/kg-day in both sexes

IV. HAZARD IDENTIFICATION AND DOSE-RESPONSE ASSESSMENT

The determinations of critical studies, critical toxicity endpoints, and PODs are discussed in this section. The POD is the critical dose level of a chemical from a study in animals or humans that is used for risk assessment as a starting point for the calculation of the acceptable daily dose (ADD). The POD is typically determined by fitting a dose-response model to the toxicity data using US EPA's Benchmark Dose Software (BMDS) (US EPA, 2018b). OEHHA selects the 95% lower confidence limit (L) of the benchmark dose (BMD), or the BMDL, as the POD. The $BMDL_{05}$ is the BMDL with the response level set at 5% for quantal data and the $BMDL_{1SD}$ is the BMDL with the response set at 1 standard deviation for continuous data. When data are not amenable to BMD modeling, OEHHA uses the traditional NOAEL/LOAEL (lowest-observed adverse effect level) approach in identifying a POD.

A. DCPA

1. Non-Cancer Effects

OEHHA selected the chronic rat study (Lucas et al., 1993) as the most sensitive study to evaluate chronic DCPA exposure. The rat study had more significant effects and a lower NOAEL (1 mg/kg-day for males) than the chronic mouse study (150 mg/kg-day for

females; Lucas and Killeen, 1988). The rat study was also selected by US EPA for their lifetime HAL of 70 ppb (US EPA, 2008a, b).

To determine the POD for non-cancer effects, OEHHA conducted BMD model analysis for all endpoints that were statically significant by pair-wise comparison for male (Table 4) and female (Table 5) rats. BMD modeling results for candidate critical PODs (BMDLs less than the study NOAEL) with good visual model fit and significant p values (model selection as recommended by the BMDS wizard) are presented in Table 10.

OEHHA chose the lowest $BMDL_{05}$ of 0.54 mg/kg-day for centrilobular hepatocytic swelling in the male rats from Lucas et al. (1993) as the POD. The $BMDL_{05}$ is lower than the NOAEL for this endpoint at 1 mg/kg-day (Table 5). The BMD output for male rat centrilobular hepatocytic swelling is in Appendix IV. The next highest $BMDL_{05}$ values were 0.58 mg/kg-day for basophilic clumped colloid in the thyroid of males, and 0.60 mg/kg-day for eosinophilic foci in the liver of female rats. Endpoints with $BMDL_{05}$ values higher than 1 mg/kg-day are not shown in Table 10; the exception is centrilobular hepatocytic swelling for female rats which is included for comparison with the male rats.

Table 10. Comparison of benchmark doses for non-cancer endpoints in the two-year rat study with DCPA (Lucas et al., 1993).

Endpoint Description	**Best fit BMD Model**	**$BMDL_{05}$[a] (mg/kg-day)**
Male Rat		
Centrilobular hepatocytic swelling	Hill	**0.54**
Basophillic clumped colloid	Hill	0.58
Follicular cell hypertrophy	Hill	0.75
Thickening alveolar walls	LogProbit	0.85
Female Rat		
Centrilobular hepatocytic swelling	Hill	5.6
Focus/Foci, eosinophilic	Hill	0.60
Retinal atrophy	Hill	0.79

[a] The $BMDL_{05}$ is the BMDL with the response level set at 5% response.

2. Cancer Effects

OEHHA conducted a weight of evidence (WOE) analysis of carcinogenicity for DCPA, in considering whether to calculate a cancer PHC for the compound. As outlined above, liver tumors were observed with a dose related trend in male mice, and by dose related trend and at the high dose in female mice (Lucas and Killeen, 1988). Thyroid tumors

were seen in both sexes of rats and liver tumors were seen in female rats (Lucas et al., 1993). This analysis considered these results from the cancer bioassays in rodents, genotoxicity data, and US EPA's guidelines regarding evaluation of thyroid tumors in rat.

US EPA has classified DCPA as a group C, possible human carcinogen (US EPA, 1998a). It should be noted that US EPA has indicated that DCPA has not been evaluated using the current cancer risk assessment guidelines (US EPA, 2008a, b). While tumors were observed in the chronic rodent bioassays, there are limited data on the mode of action (MOA) for the tumorigenic effects of DCPA. Klopman et al. (1996) found that DCPA could react with 4-nitrobenzyl-pyridine, and thus suggested the possibility that the alkylating potential of DCPA could account for the carcinogenic response observed in the animal studies.

With respect to thyroid tumors in the chronic rat studies, for some chemicals it has been determined that thyroid tumor formation in the rat occurs via a process that is likely not relevant for human exposure (US EPA, 1998b). The MOA is a disruption in thyroid-pituitary hormone balance (e.g., caused by increased catabolism of thyroid hormone by the liver), which leads to chronic reduction in circulating T3 and T4 thyroid hormones and an increase in TSH, which in turn leads to increases in the size and number of thyroid follicular cells, increased thyroid gland weight and finally tumors of the thyroid. According to the US EPA science policy on assessing thyroid follicular cell tumors, data on five lines of evidence are required to support this mode of action (US EPA, 1998b). These are:

(1) Increases in follicular cell size and number (hyperplasia and hypertrophy),

(2) Changes in thyroid and pituitary hormones,

(3) Knowledge of where the chemical affects thyroid functioning,

(4) Correlations between doses producing thyroid effects and cancer, and

(5) Reversibility of effects when chemical dosing ceases.

US EPA also identifies three additional types of information as desirable for supporting the MOA (US EPA, 1998b). These are knowledge of progression of lesions over time, chemical structure-activity relationships, and various other investigations (e.g., initiation-promotion studies). When experimental animal data support this MOA of tumorigenesis, a non-linear approach to determining cancer potency for the chemical is recommended. However, in the absence of sufficient data, the default assumption is that a chemical that produces thyroid tumors in the rat is relevant for human exposure and warrants a traditional linear cancer potency derivation.

With DCPA, there is evidence supporting the criteria (1) and (4) above. Thyroid follicular cell hypertrophy occurred in the 90-day rat studies at the highest dose tested (1000 mg/kg-day; Lucas and Benz, 1991; Appendix II), as well as at lower doses in the chronic toxicity study (10 and 50 mg/kg-day, Table 4 and 5) for males and females, respectively; Lucas et al., 1993). There is a correlation between the doses causing thyroid effects and tumors. Significant pre-neoplastic effects such as hyperplasia and hypertrophy were observed at lower doses (≥ 10 mg/kg-day in males and ≥ 50 mg/kg-day in females; Tables 4 and 5) than those for thyroid tumors (≥ 50 mg/kg-day in males and 1000 mg/kg-day in females, Table 6).

There is also evidence for criterion (2). Thyroid hormone levels were moderately affected by DCPA treatment in the two-year dietary rat study (Lucas et al., 1993; Tables 4 and 5; Appendix III). There were clear, dose-dependent decreases in T4 levels at weeks 52, 83, and 104 in both males and females. There were also dose-dependent increases in TSH levels in males and females at the 52-week time point, and in females at 104 weeks, although the effect lacked statistical significance.

However, there is no evidence for criteria (3) and (5). There is no information on where DCPA is directly affecting thyroid function and the toxicity studies for DCPA did not address reversibility of the effect on thyroid upon cessation of treatment. Thus, we concluded that the data are inadequate to support a thyroid hormone disruption MOA for the thyroid tumors.

The presence of HCB in the technical formulation raises some uncertainty if tumors formed in the liver of mice and rats are relevant to DCPA carcinogenicity. This is discussed in more detail below (Section IV.A.3. Impurities).

3. Impurities

Technical grade DCPA contains various impurities that could contribute toward the toxic effects observed in the rodent studies. With limited time to conduct the risk assessment, OEHHA explored only the contribution of HCB. A full analysis of HCB and other impurities is needed to definitely rule out their contribution to the DCPA toxicity reported.

In subchronic and chronic rodent studies conducted with only HCB, the most sensitive effects were hepatotoxicity and developmental toxicity (reviewed in OEHHA, 2003). For non-cancer liver effects, female rats appeared to be more sensitive than male rats to HCB, and no toxicity were reported for the thyroid or the eyes. This profile is different than that for DCPA where male rats were more sensitive than the female to liver effects (hepatocytic swelling and incidence of eosinophilic foci), and toxicity to other organs occurred at similarly low doses. Thus, the non-cancer toxicity of DCPA in the two-year rat study (Lucas et al., 1993) is unlikely to be attributed to the presence of HCB alone.

As for cancer effects, HCB is a liver carcinogen in rodents. It has been classified by US EPA as a probable human carcinogen (a B2 carcinogen) and is on California's Proposition 65 list. US EPA calculated a human oral cancer slope factor of 1.6 $(mg/kg\text{-}day)^{-1}$ for HCB based on the hepatocellular carcinomas in female Sprague Dawley rats in a two-year dietary study (Erturk et al., 1986) at incidences of 0/52, 36/56, and 48/55 at 0, 4-5, and 8-9.5 mg/kg-day, respectively (OEHHA, 2003). Male incidences were 0/54, 3/52, and 4/56 at the same respective dose groups. Similar to DCPA (Table 6), HCB caused higher liver tumor incidences in female compared to male rats.

OEHHA estimated the relative contribution of HCB to total liver tumor incidences reported in rodents after exposure to DCPA technical formulation containing HCB. The approach involved deriving a potency, or cancer slope factor (CSF) using the multistage cancer model in BMDS for liver tumor incidence data from studies conducted with HCB alone for each species. The CSF was then used to extrapolate the hypothetical tumor incidence for the amount of HCB in the DCPA formulation.

Of the animal cancer bioassays for HCB in rats, Erturk et al. (1986) in particular was chosen because of its similarities in the protocol to the chronic rat study for DCPA. Specifically it was a two year chronic dietary study in the same strain of rat (Sprague Dawley) of sufficient quality and study design. The CSFs calculated for liver carcinomas in male and female rats exposed to HCB alone from Erturk et al. (1986) were 0.017 $(mg/kg\text{-}day)^{-1}$ and 0.28 $(mg/kg\text{-}day)^{-1}$, respectively. The predicted tumor response estimated from the CSF due to HCB (1.3 mg/kg-day) in the highest dose of the DCPA technical formulation was 36% for female rats and 2% for male rats. Actual tumor responses in the chronic rat studies (for hepatocellular adenomas and carcinomas) were 21% for females and 3% for males. Thus it is possible that the liver tumors in the chronic rat study (Lucas et al., 1993) could have arisen from exposure to HCB in the technical DCPA formulation. Thyroid follicular cell tumors did not occur in the HCB study so thyroid follicular cell tumors in the chronic rat studies was unlikely due to HCB as an impurity (OEHHA, 2003).

OEHHA also calculated a hypothetical tumor response for hepatocellular adenomas and carcinomas in the mouse. To estimate the tumor response, OEHHA used liver cell tumor incidences from a chronic study of dietary HCB in outbred Swiss mice (Cabral et al., 1979). This study was chosen as it was the only mouse study reported for HCB. It was a lifetime dietary study of sufficient quality, and similar protocol to Lucas and Killeen (1988) for mice exposed to DCPA. The doses used in the study were 0, 6, 12, and 24 mg/kg-day and liver tumor incidences were 0/47, 0/30, 3/29, and 7/44 for males and 0/49, 0/30, 3/30, and 14/41 for females. The CSFs calculated from male and female mice exposed to HCB alone from this study were 0.011 $(mg/kg\text{-}day)^{-1}$ and 0.018 $(mg/kg\text{-}day)^{-1}$, respectively. The predicted tumor response estimated from the CSFs due to HCB at the highest doses in the DCPA mouse studies were less than 1% for

both sexes at 0.37 mg/kg-day (males) or 0.46 mg/kg-day (females). Actual liver tumors in the Lucas and Killeen (1988) study (corrected for the high incidences in the control animals) were higher than predicted, at 14% for males and 20% for females. Thus, OEHHA concluded that HCB contamination might have been a significant contributor to liver tumor formation in the DCPA rat study with 1.3 mg HCB/kg-day, but not in the mouse study with lower levels of HCB exposure (i.e., 0.46 HCB mg/kg-day for female, and 0.37 mg HCB mg/kg-day for males) in a less sensitive species. This finding was considered in the selection of tumor types for the cancer potency derivation.

4. Cancer Potency Derivation

Based on the WOE analysis, we determined that there was enough evidence for the carcinogenic potential of DCPA that a cancer potency should be derived for liver tumors in mice and thyroid tumors in rats. OEHHA omitted hepatocellular adenomas and carcinomas in female rats from the cancer dose-response analysis due to the possible contribution of HCB to tumor development in the liver. No other tumor types were excluded from the analysis.

We used the linearized multistage model (Appendix V) to derive a cancer potency estimate for each of the four animal cancer studies from Tables 2 and 3 (Lucas and Killeen, 1988) and Table 6 (Lucas et al., 1993) for both sexes of mice and rats. Resulting animal cancer potency factors or CSFs are presented in Table 11.

Human cancer potency was estimated by an interspecies scaling procedure (Appendix V). The default human body weight was 70 kg. The average body weights calculated for male and female Sprague Dawley rats from Lucas et al. (1993) were 0.664 kg and 0.390 kg, respectively. The average body weights calculated for male and female CD-1 mice from Lucas and Killeen (1998) were 0.0442 kg and 0.0347 kg, respectively. The human cancer slope factors derived using these body weights and the animal CSFs calculated using BMD are summarized in Table 11. Note that these estimates were derived only for the purpose of developing a PHC for the compound. As already mentioned, a more thorough evaluation of the role of impurities is needed for a definitive determination of the cancer potency of DCPA by itself.

Liver hepatocellular tumors in the mouse studies yielded higher human equivalent cancer potencies than thyroid follicular cell tumors in the rat studies. The combined liver tumor in male mice showed the highest potency and the BMD analysis is shown in Appendix VI. Thus, the highest human equivalent CSF estimate of 3.2×10^{-3} $(mg/kg\text{-}day)^{-1}$ was chosen for calculating a screening level PHC for DCPA. This estimate is higher than the human equivalent CSF calculated by US EPA (1998a) of 1.48×10^{-3} $(mg/kg\text{-}day)^{-1}$ for DCPA, based on liver and thyroid tumors from the chronic rat study (Powell et al., 1993; cited in this document as Lucas et al., 1993).

Table 11. BMD results and CSFs for tumors from the two-year chronic mouse (Lucas and Killeen, 1988) and rat studies (Lucas et al., 1993) with DCPA

Tumor type	Sex	Species	BMD (mg/kg-day)	$BMDL_{05}$ (mg/kg-day)	Animal CSF $(mg/kg\text{-}day)^{-1}$	Human equivalent CSF $(mg/kg\text{-}day)^{-1}$
Combined hepatocellular adenomas and carcinomas	M	Mouse	207	98	$5.1X10^{-4}$	$3.2X10^{-3}$
Combined hepatocellular adenomas and carcinomas	F	Mouse	295	156	$3.2x10^{-4}$	$2.1x10^{-3}$
Combined thyroid follicular cell adenomas and carcinomas	M	Rat	424	215	$2.3x10^{-4}$	$7.4x10^{-4}$
Combined thyroid follicular cell adenomas and carcinomas	F	Rat	691	332	$1.5x10^{-4}$	$5.5x10^{-4}$

Abbreviations: M: male; F: female; BMD: benchmark dose; BMDL05: lower 95% confidence limit of the BMD; CSF: cancer slope factor.

B. MTP and TPA

The toxicity database for MTP is inadequate for the derivation of a PHC for the compound. The toxicity database for TPA, while limited, can be used to derive the PHC for TPA, and can be applied as well as for MTP, when supplemented with information from DCPA studies to determine relative toxicity (Table 9).

For the derivation of PHC for TPA based on non-cancer effects, OEHHA selected the NOAEL of 500 mg/kg-day as the critical POD. The NOAEL was based on no effect observed in the highest dose tested in the 90-day dietary study (Goldenthal et al., 1977) and the soft stools and hematological effects reported at 2000 mg/kg-day in the 30-day gavage study (Major, 1985). This NOAEL was also lower than the dose of 860 mg/kg-day, the only dose used in the MTP study where no effects were noted (Hazelton, 1961).

C. Toxicity Determinations

OEHHA made the following findings for DCPA, MTP, and TPA for the specific endpoints as specified under the PCPA. OEHHA found that the DCPA toxicity database was

sufficient for the toxicity evaluation. Based on the studies reviewed, DCPA is possibly carcinogenic (Tables 2, 3, and 6), and is not mutagenic (Table 7), teratogenic (US EPA, 1998), or neurotoxic (Moxon, 2005). The finding for carcinogenicity is an interim finding pending an analysis of the contribution of impurities to the cancer effects reported in the DCPA rodent studies. The toxicity database of MTP is too limited with one mutagenicity study and no studies for the other endpoints to make findings (Section III.C.). TPA has sufficient data only for the finding that it is not mutagenic (Table 8); there was only one study on teratogenicity, and no studies on neurotoxicity or lifetime carcinogenicity (Section III.D.).

V. PUBLIC HEALTH CONCENTRATION DETERMINATION

A. General Approaches

OEHHA develops the PHCs using the general approach of the PHG program for exposure to chemicals in drinking water for a lifetime. For non-cancer and cancer effects, the derivation of a PHC starts with the PODs derived from the animal or human studies. This dose is converted to an acceptable daily dose (ADD), which is then back calculated to an acceptable level in drinking water.

1. Acceptable Daily Dose

An ADD is the estimated maximum average daily dose of a chemical (in mg/kg-day) that can be consumed by a human for an entire lifetime without adverse effects. To determine the ADD, the POD is adjusted by factors to account for uncertainties in the risk assessment, such as differences between animals and humans (interspecies extrapolation), and differences among humans in response to a chemical exposure (intraspecies variation, including sensitive subgroups). This combined factor is referred to as the total uncertainty factor (UF).

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

It includes:

- 10 for interspecies extrapolation consisting of
  $\sqrt{10}$ for pharmacodynamics and $\sqrt{10}$ for pharmacokinetics.
- 30 for intraspecies variability consisting of
  $\sqrt{10}$ for pharmacodynamics and 10 for pharmacokinetics.

A detailed discussion of these factors is presented in Appendix VII. Additional adjustments may be included depending on the limitations of the database.

An ADD is calculated using the following equation:

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

2. Drinking Water Concentration

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

The daily water intake 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 equivalent of the amount of tap water one would have to drink to account for the exposure to a chemical in tap water through oral, inhalation, and dermal routes. For oral intake rates, the PHG program uses age-specific water ingestion estimates (OEHHA, 2012) derived from a nationwide survey of food and beverage intake from approximately 20,000 people (US Department of Agriculture's Continuing Survey of Food Intake of Individuals 1994-1996, 1998 dataset). These age-specific intake rates are normalized to body weight and expressed as L/kg-day. To estimate inhalation and dermal exposures to chemicals in tap water, OEHHA uses equations extracted from the CalTOX 4.0 multimedia total exposure model developed for the California Department of Toxic Substances Control by Lawrence Berkeley National Laboratory (Appendix VIII). They provided % contribution value from each exposure route.

The PHC calculation also includes consideration of the RSC - the proportion of exposures to a chemical attributed to tap water, as part of total exposure from all sources (including food and air). The RSC values typically range from 20 to 80% (expressed as 0.2 to 0.8 in the equation), and are estimated based on available exposure information.

B. DCPA

1. Non-Cancer Effects

For non-cancer effects, OEHHA used the $BMDL_{05}$ of 0.54 mg/kg-day for centrilobular hepatic swelling from the chronic rat study (Lucas et al., 1993) as the POD to estimate the ADD. A total UF of 300 was applied.

$$\text{DCPA ADD} = \frac{0.54 \text{ mg/kg-day}}{300} = 0.0018 \text{ mg/kg-day}$$

A default RSC value of 0.2 was applied because there are other potential sources of DCPA, such as the diet and in air. The DWI for all exposure pathways was calculated as 0.055 L/kg-day (Appendix IX).

The PHC (in milligrams/liter, mg/L or in microgram/liter, µg/L) for non-cancer effects is derived by the following equation:

$$\text{PHC} = \frac{\text{ADD x RSC}}{\text{DWI}}$$

$$\text{DCPA PHC} = \frac{0.0018 \text{ mg/kg-day} \times 0.2}{0.055 \text{ L/kg-day}} = 0.0065 \text{ mg/L}$$

$$= 6.5 \text{ µg/L or } \textbf{7 ppb} \text{ (rounded)}$$

While it is OEHHA's opinion that the non-caner effects in the liver in the critical study were not likely due to the presence of HCB, OEHHA also calculated a PHC based on the thyroid effects in the male rat for comparison. The $BMDL_{05}$ for follicular cell hyperplasia was 0.75 mg/kg-day and using the same method used for the liver effect, OEHHA calculated a PHC of 9 ppb. Thus, the PHC using either endpoint is similar, but OEHHA recommends the lower PHC of 7 ppb for liver effects of DCPA.

2. Cancer Effects

The human equivalent cancer potency of 3.2×10^{-3} $(\text{mg/kg-day})^{-1}$ calculated from combined hepatocellular adenomas and carcinomas in male mice from the chronic mouse bioassay (Lucas and Killeen, 1988) was chosen to calculate the PHC for cancer effects of DCPA.

Following the determination of the potency, the drinking water PHC for cancer effects is derived by incorporating age sensitivity factors (ASFs) to account for increased susceptibility during early-in-life exposures (OEHHA, 2009) to the drinking water intake

of the chemical (Table 12). ASFs for each life stage are multiplied by the fractional duration of each life stage and the daily water intake (DWI, in L/kg-day) to yield the ASF-adjusted exposure for each life stage. The sum of these life stage exposures is the total exposure. Additional details on this approach are provided in Appendix V.

Table 12. Parameters for total lifetime drinking water lifetime exposure

Life Stage	Age Sensitivity Factor (ASF)[a]	Fractional Duration[b]	Daily Water Intake (DWI, L/kg-day)[c]	Life Stage adjusted DWI (L/kg-day)[d]
3rd trimester Fetus	10	0.25/70	0.049	0.0018
Infant (0-2 yr)	10	2/70	0.200	0.057
Child (2-16 yr)	3	14/70	0.064	0.039
Adult (16-70 yr)	1	54/70	0.047	0.036
Total Lifetime DWI				0.134

[a] Age sensitivity factors for different life stages adopted by OEHHA (2009)
[b] An average lifetime of 70 years is assumed for the general population
[c] DWI calculations are in Appendix IX
[d] Life stage adjusted DWI= ASF x Fractional Duration x DWI

Total Lifetime DWI = $\sum$ (ASF x Fractional Duration x DWI) for each life stage

The PHC is calculated for the *de minimis* risk of one in one million ($1x10^{-6}$):

$$PHC = \frac{10^{-6}}{\text{Total Lifetime DWI x Human cancer potency}}$$

$$PHC = \frac{10^{-6}}{0.134 \text{ L/kg-day} \times 0.0032 (\text{mg/kg-day})^{-1}}$$

$$= \frac{10^{-6}}{0.00043 \text{ L/mg}} = 0.0023 \text{ mg/L} = 2 \text{ µg/L or } \textbf{2 ppb} \text{ (rounded)}$$

Thus, for lifetime exposure to DCPA in water, OEHHA recommends the lower PHC value of 2 ppb derived from the cancer potency be used for DCPA exposure evaluation.

C. MTP and TPA

OEHHA decided to derive a PHC value for TPA based on its non-cancer toxicity, and to apply this PHC to the sum of MTP and TPA concentrations. Our rationale in supporting this approach includes:

- MTP and TPA both have free carboxylic acid functional group(s), and are structurally similar except TPA has an additional free carboxyl functional group than MTP. The additional free acid on TPA increases its solubility in water and longer half-life in soil.
- MTP is a minor, intermediate metabolite of DCPA, and the final degradate is TPA.
- TPA was the predominate degradate detected in groundwater. The available groundwater samples indicate that MTP is only detected in samples with relatively high levels of TPA (greater than 22.7 ppb), and the highest levels measured for MTP and TPA were 0.13 ppb and 159 ppb, respectively.

For the non-cancer effects of TPA, OEHHA used the NOAEL of 500 mg/kg-day as the POD to estimate the ADD. The NOAEL was based on no effect from the 90-day TPA dietary study (Goldenthal et al., 1977) and soft stools at 2000 mg/kg-day in the 30-day TPA gavage study (Major, 1985). This was also lower than the dose of 860 mg/kg-day, the only dose used in the MTP study where no effects were noted (Hazelton, 1961). A total UF of 3000 was applied. It included the default inter- and intra-species UF of 300, and an additional UF of 10 for the limited toxicity database.

$$\text{TPA ADD} = \frac{500 \text{ mg/kg-day}}{3000} = 0.167 \text{ mg/kg-day}$$

An RSC value of 0.8 was applied because drinking water is expected to be the predominant source of TPA (and MTP) exposure as only very low levels of the degradates have been detected on vegetation from soil treated with DCPA (CDFA, 1989). The DWI for all exposure pathways was calculated as 0.054 L/kg-day (Appendix IX). The PHC based on non-cancer effects is:

$$\text{TPA PHC} = \frac{0.167 \text{ mg/kg-day} \times 0.8}{0.054 \text{ L/kg-day}} = 2.47 \text{ mg/L}$$

$$= 2470 \text{ µg/L or } \textbf{2500 ppb} \text{ (rounded)}$$

D. Comparison of PHCs with Existing Advisory Levels

A comparison of the US EPA and OEHHA calculations for the HAL and PHCs are presented in Table 13.

Table 13. Factors in the derivation of lifetime drinking water levels for DCPA and degradates

Chemical and *Agency*	**POD mg/kg-day**	**Uncertainty factors**				**RSC**	**DWI**	**PHC**
		Inter-species	**Intra-species**	**Data gap**	**Total**		**L/kg-day**	**ppb**
DCPA								
OEHHA	[3.2x10-3 (mg/kg-day)$^{-1}$ cancer potency]						0.13	2[a]
	0.54	10	30		300	0.2	0.055	7
US EPA	1[b]	10	10		100	0.2	0.029[c]	70 (HAL)
TPA								
OEHHA	500	10	30	10[d]	3000	0.8	0.054	2500

[a] PHC derived from the human equivalent cancer potency of 3.2x10^{-3} (mg/kg-day)$^{-1}$ calculated from liver tumors in male mice (Lucas and Killeen, 1988), ASFs incorporated into the DWI, and a 1x10^{-6} cancer risk.
[b] US EPA POD derived from the NOAEL of 1 mg/kg-day from the chronic rat study with DCPA (Lucas et al., 1993; cited as ISK Biotech Corp., 1993 in US EPA, 2008a).
[c] Drinking water rate of 2 L/day and 70 kg body weight.
[d] UF for the limited toxicity database.
Abbreviations: DWI=drinking water intake, POD= point of departure, RSC=Relative Source Contribution, HAL=health advisory level.

VI. RISK CHARACTERIZATION

To quantify the margin of safety, OEHHA used a percent-of-reference-dose (% PHC) approach:

$$\% \text{ PHC} = \frac{\text{Detected level in ppb} \times 100\%}{\text{PHC in ppb}}$$

When the % PHC is < 100%, human exposure to the detected levels in the drinking water would not be expected to cause adverse health effects.

OEHHA compared the reporting limit of DCPA (0.05 ppb) as the detected level with the lower PHC value of 2 ppb for 1x10^{-6} cancer risk. This value is over 40-fold lower than the PHC of 2 ppb (or 2.5% of PHC) based on cancer effects. For MTP and TPA, OEHHA compared the sum of the highest detected levels (0.13 ppb for MTP, and 159 ppb for TPA) with the PHC of 2500 for TPA. The combined highest detected levels of TPA and MTP (159 ppb, rounded) is more than 15-fold lower the PHC of 2500 ppb (or 6.4% of the PHC). These comparisons showed that the detected levels are much lower than their respective PHCs (Table 14).

Table 14. Comparison of DCPA and the sum of TPA and MTP levels to the PHCs

Chemicals	Margin of Safety		
	Detected levels (ppb)	**PHC (ppb)**	**% PHC (Target <100%)[a]**
DCPA	0.05 (reporting limit)	2	2.5%
TPA and MTP	159[b]	2500	6.4%

[a] Target for no adverse effect expected from lifetime exposure to the detected level in the drinking water.
[b] Detected level of 0.13 ppb MTP converted to molecular weight equivalent of TPA is 0.12 ppb. The sum of MTP and TPA is 159.12 ppb, rounded off to 159 ppb.

The margin of safety values (as % PHC) potentially overstate health risk because of the assumptions and approaches used in the toxicity and exposure assessments. In the derivation of the PHCs for DCPA, OEHHA only explored the contribution of one impurity, HCB, to the liver effects observed in the rodent toxicity studies. There were other impurities which could have similar toxic effects as those of DCPA. The use of the reporting limit for detected level of DCPA in the groundwater may also be a source of overestimation because DCPA has a history of no detection and individuals are likely to have different water sources, instead of DCPA-contaminated groundwater only, over a lifetime. The margin of exposure for TPA and MTP, based on highest detected levels, were likely to overstate health risk because of the likelihood of multiple water sources and these chemicals were below the detection limits in the majority of the collected groundwater samples.

Overall, our evaluation showed that adverse health effects are not expected from lifetime exposure in the drinking water to DCPA at the reporting limit, or to TPA and MTP at the detected levels reported by DPR.

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APPENDIX IA: ACUTE TOXICITY PROFILE FOR DCPA.

Study Type	Species	Result[a] LC_{50} or LC_{50}	Toxicity Category[b]	Reference
Acute oral	Rat	>5,000 mg/kg	IV	a
	Spartan rat	>12,500 mg/kg	IV	c
	Beagle dog	>10,000 mg/kg	IV	c
Acute dermal	Rabbit	>2,000 mg/kg	III	a
	Rabbit	>10,000 mg/kg	IV	c
Acute inhalation	Rat	4.48 mg/L	III	a
		Effects		
Eye irritation	Rabbit	Mild irritation	III	a
Dermal irritation	Rabbit	Mild irritation	IV	a, c
Skin sensitization	Guinea pig	Not sensitizer	N/A	a

[a] US EPA (1998a). LC_{50} or LC_{50} is concentration or dose which causes death to 50% of the test animals.

[b] US EPA Toxicity Categories, 40 CFR 156.62. Categories are from I (highest toxicity) to IV (lowest toxicity). Accessed in: https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/fs_PC-021901_1-Feb-97.pdf

[c] Wazeter et al., 1974 in US EPA, 2008a.

APPENDIX IB: SUBCHRONIC TOXICITY PROFILE FOR DCPA.

Species/Route/ Duration	Dose (mg/kg-day)	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Reference
Sprague Dawley rats/diet/90-days	(M/F) 0, 10, 50, 100, 150, 1000	50	(M/F) 100 ↑ centrilobular hepatocellular hypertrophy (M,F) and ↑ relative liver weight (F)	a, b Lucas and Benz, 1991
Sprague Dawley rats/diet/60-days	(M/F) 0, 1000	NE	(M/F): 1000 ↑white foci in lung	a, b Lucas and Benz, 1991
Sprague Dawley rats/diet/28-days	(M): 0, 215, 860 or 1720 (F): 0, 228, 890 or 1760	NE	(M): 215 (F): 228 ↑ absolute and relative liver weights and centrilobular hepatocellular hypertrophy.	c Lucas and Killeen, 1990
CD-1 mice/diet/ 90-days	(M): 0, 100, 199, 406, 1235 (F): 0, 233, 517, 1049, 2198	(M): 406; (F): 517	(M): 1235 (F): 1049 minimal histopathological effects on liver	a Ford, 1986
Sprague Dawley rats/dermal/ 21-days	0, 100, 300, 1000	>1000	No dermal irritation, no adverse effect at HDT	a Lucas et. al., 1989

[a] US EPA (1998a)

[b] DPR (1994)

[c] US EPA (2008a)

Abbreviations: M: male, F: female, NOAEL: no observed effect level, LOAEL: lowest observed effect level, NE: NOEL not established, HDT: highest dose tested.

APPENDIX II: COMPARISON OF THE 90-DAY DCPA AND TPA RAT STUDIES.

Lucas and Benz, 1991 90-day dietary study of DCPA

Male Rats						
Dose (mg/kg-day)	**0**	**10**	**50**	**100**	**150**	**1000**
Liver						
# examined	15	15	15	15	15	15
Centrilobular hepatocyte hypertrophy	0	0	0	7**	13**	14**
Liver absolute organ wt (g)	23.063	23.873	24.185	24.873	24.892	28.168**
Liver organ wt (g)/100 g BW	3.709	3.851	3.907	3.975	4.193**	4.809**
Thyroid						
# examined	15	15	15	15	15	15
Clumped colloid	0	0	0	0	0	13
Cystic follicles	0	0	0	0	0	6
Follicular cell hypertrophy	0	0	0	0	0	13
Female Rats						
Dose (mg/kg-day)	**0**	**10**	**50**	**100**	**150**	**1000**
Liver						
# examined	14	15	15	15	14	14
Centrilobular hepatocyte hypertrophy	0	0	0	3	12**	14**
Liver absolute organ wt (g)	9.654	10.503	11.402**	10.993*	10.893*	11.749**
Liver organ wt (g)/100 g BW	3.221	3.502	3.733**	3.661**	3.739**	4.299**
Thyroid						
# examined	15	15	15	15	15	15
Clumped colloid	0	0	0	0	0	1
Cystic follicles	0	0	0	0	0	0
Follicular cell hypertrophy	0	0	0	0	0	11

Data presented as means or incidences. Statistically significant by Bartlett's test (continuous data) or by Fisher Exact test (quantal data) for pair-wise comparison (indicated on significant dose group when compared to control) with * $p<0.05$, ** $p<0.01$, as reported in the original study. Abbreviations: wt: weight, BW=body weight, g=grams

Goldenthal et al., 1977 90-day dietary study of TPA

Male Rats					
Dose (mg/kg-day)	**0**	**2.5**	**25**	**50**	**500**
Liver					
# examined	15	15	15	15	15
Perivascular lymphocytic foci	3	N/A	N/A	N/A	1 (very slight)
Microgranuloma	0	N/A	N/A	N/A	0
Liver absolute organ wt (g)	18.27	16.04	17.22	15.6	17.52
Liver organ wt (g)/100 g BW	3.52	3.16	3.19	3.32	3.34
Thyroid					
# examined	15	15	15	15	15
Ultimobranchial rest	4	N/A	N/A	N/A	1
Parathyroid hyperplasia	0	N/A	N/A	N/A	1 (slight)
Thyroid absolute organ wt (g)	0.04	0.035	0.03	0.025	0.029
Thyroidorgan wt/100 g BW	0.78	0.69	0.56	0.53	0.55
Female Rats					
Dose (mg/kg-day)	**0**	**2.5**	**25**	**50**	**500**
Liver					
# examined	15	15	15	15	15
Perivascular lymphocytic foci	4 (very slight)	N/A	N/A	N/A	1 (very slight)
Microgranuloma	0	N/A	N/A	N/A	1 (slight)
Liver absolute organ wt (g)	10.31	10	9.3	10.41	10.83
Liver organ wt (g)/100 g BW	3.34	3.21	3.01	3.36	3.35
Thyroid					
# examined	15	15	15	15	15
Ultimobranchial rest	1	N/A	N/A	N/A	2
Parathyroid hyperplasia	0	N/A	N/A	N/A	0
Thyroid absolute organ wt (g)	0.032	0.028	0.025	0.025	0.022
Thyroid organ wt (g)/100 g BW	1.05	0.92	0.81	0.80	0.67

Data presented as means or incidences.
Abbreviations: wt: weight, BW=body weight, g=gram

APPENDIX III. THYROID HORMONE LEVELS IN RATS EXPOSED TO DCPA IN THE DIET AT THE INTERIM SACRIFICES IN THE CHRONIC RAT STUDY (LUCAS ET AL., 1993).

Male Rats						
Dose (mg/kg-day)	**0**	**1**	**10**	**50**	**500**	**1000**
52 week interim measurements n=10						
T3 (ng/dL)	83.73 (12.51)	82.44 (13.90)	83.86 (14.39)	72.98 (11.98)	70.43 (12.77)	65.90** (11.41)
T4 (µg/dL)	3.68 (0.98)	3.82 (0.92)	2.62** (0.69)	1.69** (0.92)	1.10** (0.50)	0.77** (0.39)
TSH (ng/ml)	1.52 (0.53)	1.59 (0.67)	1.89 (0.76)	1.97 (1.30)	2.12 (0.78)	2.46 (1.03)
83 week interim measurements n=10						
T3 (ng/dL)	83.26 (16.32)	95.12 (20.03)	87.24 (22.82)	86.53 (16.9)	87.71 (20.35)	78.27 (13.49)
T4 (µg/dL)	2.79 (0.50)	2.79 (0.97)	1.74** (0.69)	1.24** (0.59)	0.53** (0.34)	0.44** (0.35)
TSH (ng/ml)	2.125 (0.910)	2.479 (0.871)	2.314 (0.838)	2.463 (1.239)	2.629 (2.069)	1.962 (0.518)
Female Rats						
Dose (mg/kg-day)	**0**	**1**	**10**	**50**	**500**	**1000**
52 week interim measurements n=10						
T3 (ng/dL)	114.74 (18.44)	114.92 (19.31)	117.77 (15.81)	105.13 (17.87)	113.54 (17.51)	114.71 (21.92)
T4 (µg/dL)	2.54 (0.57)	2.40 (0.64)	2.35 (0.86)	1.32** (0.72)	0.89** (0.41)	0.58** (0.33)
TSH (ng/ml)	1.28 (0.44)	1.32 (0.46)	1.22 (0.43)	1.45 (0.37)	1.51 (0.39)	1.70 (0.31)
83 week interim measurements n=10						
T3 (ng/dL)	92.60 (26.34)	105.82 (24.93)	89.92 (27.52)	96.66 (16.94)	105.06 (18.20)	98.08 (30.23)
T4 (µg/dL)	1.82 (0.77)	2.25 (0.74)	1.60 (0.41)	1.13 (0.65)	0.71* (1.00)	0.28** (0.17)
TSH (ng/ml)	1.332 (0.403)	1.392 (0.523)	1.261 (0.675)	1.458 (0.665)	1.786 (0.628)	1.518 (0.894)

All data presented as means (standard deviations). Statistically significant by Bartlett's test (continuous data) or by Fisher Exact test (quantal data) for pair-wise comparison (indicated on significant dose group when compared to control) with * $p<0.05$, ** $p<0.01$, as reported in the original study. Abbreviations: T3= triiodothyronine; T4= thyroxine; TSH=thyroid-stimulating hormone.

APPENDIX IV. BENCHMARK DOSE ANALYSIS OF NON-CANCER LIVER EFFECT IN MALE RATS AFTER EXPOSURE TO DCPA

Summary of BMD Modeling Results for centrilobular hepatocytic swelling in male rats (Lucas et al., 1993).

Model[a]	Goodness of fit		BMD_{5Pct} (mg/kg-day)	$BMDL_{5Pct}$ (mg/kg-day)
	p-value	AIC		
Gamma	0	328.69	11.8	9.08
Dichotomous-Hill	**0.984**	**264.32**	**0.969**	**0.535**
Logistic	0	346.99	30.6	24.8
LogLogistic	0.0426	267.07	1.11	0.779
Probit	0	352.25	35.4	29.9
LogProbit	0.307	265.77	0.458	0.174
Weibull Multistage 3° Multistage 2° Quantal-Linear	0	328.69	11.8	9.08

[a] Selected model in bold; scaled residuals for selected model for doses 0, 1, 10, 50, 500, and 1000 mg/kg-day were -0.03, 0.05, -0.03, 0, 0.12, -0.11, respectively.

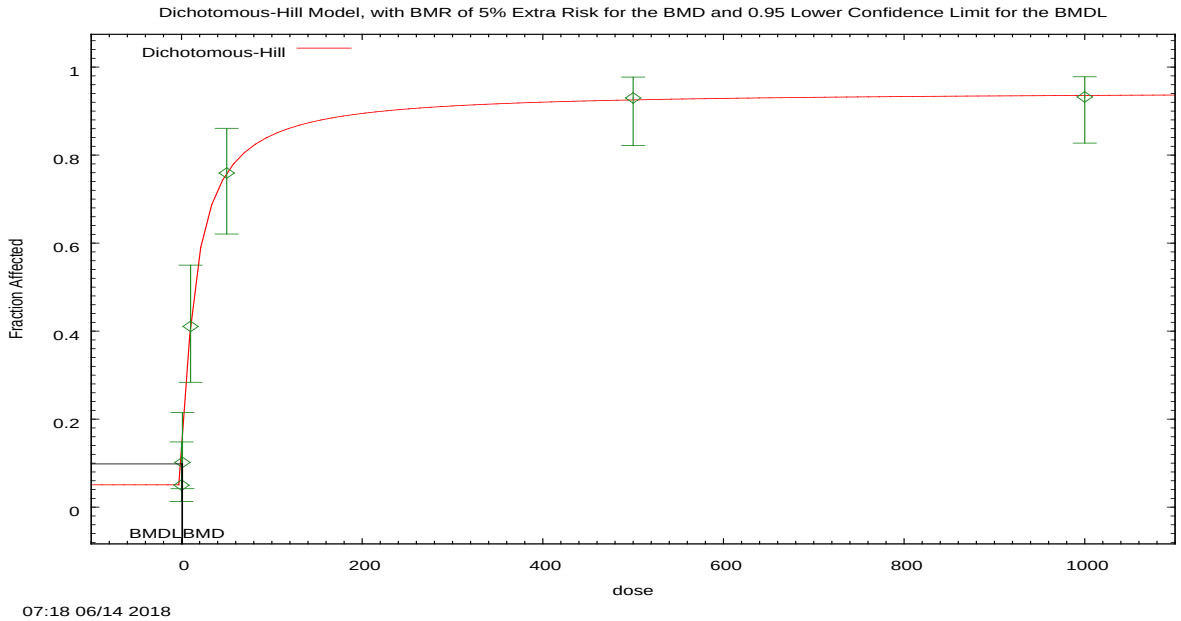

Figure IV-1. Plot of incidence rate by dose with fitted curve for Dichotomous-Hill model for centrilobular hepatocytic swelling in the male rat; dose shown in mg/kg-day.

Dichotomous Hill Model. (Version: 1.3; Date: 02/28/2013)

The form of the probability function is: P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.

BMR = 5% Extra risk

BMD = 0.969422

BMDL at the 95% confidence level = 0.535449

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
v	0.945133	1
g	0.0537266	0.05
intercept	-2.8485E+00	-3.7807E+00
slope	1.06971	1

Analysis of Deviance Table

Model	Log(likelihood)	# Parameters	Deviance	Test degree of freedom	p-value
Full model	-128.14	6			
Fitted model	-128.16	4	0.03143	2	0.98
Reduced model	-238.72	1	221.15	5	<.0001

AIC: = 264.315

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Residual
0	0.0508	3.047	3	60	-0.03
1	0.0998	5.886	6	59	0.05
10	0.4128	23.119	23	56	-0.03
50	0.759	40.986	41	54	0
500	0.9256	52.756	53	57	0.12
1000	0.9357	55.206	55	59	-0.11

Chi^2 = 0.03 d.f = 2 P-value = 0.9844

APPENDIX V. LINEARIZED MULTISTAGE MODEL, CANCER POTENCY, AND AGE SENSITIVITY FACTOR DERIVATION

The lifetime probability of a tumor at a specific site given exposure to the chemical at dose d is modeled using the multistage polynomial model:

$$p(d) = \beta_0 + (1 - \beta_0)(1 - \exp[-(\beta_1 d + \beta_2 d^2 + \ldots + \beta j d^j)])$$

where the background probability of tumor, β_0, is between 0 and 1 and the coefficients β_i, i = 1…j, are positive. The β_i are parameters of the model, which are taken to be constants and are estimated from the data. The parameter β_0 provides the basis for estimating the background lifetime probability of the tumor.

The multistage polynomial model defines the probability of dying with a tumor at a single site. To derive a measure of the cancer response to a chemical (per mg/kg-day), the dose associated with a 5% increased risk of developing a tumor was calculated and the lower bound for this dose was estimated using the multistage polynomial model for cancer in US Environmental Protection Agency's (US EPA) Benchmark Dose Software (BMDS)[6]. The ratio of the 5% risk level to that lower bound on dose is known as the "animal cancer slope factor (CSF_{animal})," or the "animal cancer potency."

Human cancer potency is estimated by an interspecies scaling procedure. Dose in units of mg per kg body weight scaled to the three-quarters power is assumed to produce the same degree of effect in different species in the absence of information indicating otherwise. Thus, for each of the endpoints used in this report to calculate cancer potency, scaling to the estimated human potency (CSF_{human}) is achieved by multiplying the animal potency (CSF_{animal}) by the ratio of human to animal body weights (bw_{human}/bw_{animal}) raised to the one-fourth power when CSF_{animal} is expressed in units $(mg/kg\text{-}day)^{-1}$:

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

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

[6] US EPA Benchmark Dose Software (BMDS) Version 2.6.0.1 (Build 88, 6/25/2015). National Center for Environmental Assessment. Available from: http://www.epa.gov/bmds

cancer risk through the inhalation route. If only an inhalation cancer potency is available, then it will be applied to all routes when determining the PHC.

Accounting for Increased Susceptibility during Early-in-Life Exposures

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

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

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

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

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

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

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

Where:

R	=	default risk level of one in one million, or 10^{-6}
CSF_{oral}	=	oral cancer potency in $(mg/kg\text{-}day)^{-1}$
CSF_{inh}	=	inhalation cancer potency, in $(mg/kg\text{-}day)^{-1}$
$\sum_j$	=	sum of contributions at each age range

ASF_i	=	age sensitivity factors for the 3rd trimester + infants, children, and adults
d_j	=	duration of exposure for the 3rd trimester + infant, child, and adult life stages
$DWI^{inh/oral}_j$	=	equivalent water exposure values for each age range.

APPENDIX VI. BENCHMARK DOSE ANALYSIS OF LIVER TUMORS IN MALE MICE AFTER EXPOSURE TO DCPA

Summary of BMD Modeling Results for hepatocellular adenomas and carcinomas in male mice (Lucas and Killeen, 1988).

Model[a]	Goodness of fit		BMD_{5Pct} (mg/kg-day)	$BMDL_{5Pct}$ (mg/kg-day)
	p-value	AIC		
Three	0.915	336.74	526	114
Two	0.832	337.10	406	109
One	**0.632**	**337.96**	**207**	**98.1**

[a] Selected model in bold; scaled residuals for selected model for doses 0, 12, 123, 435, and 930 mg/kg-day were 0.36, 0.04, 0.15, -1.13, 0.54, respectively.

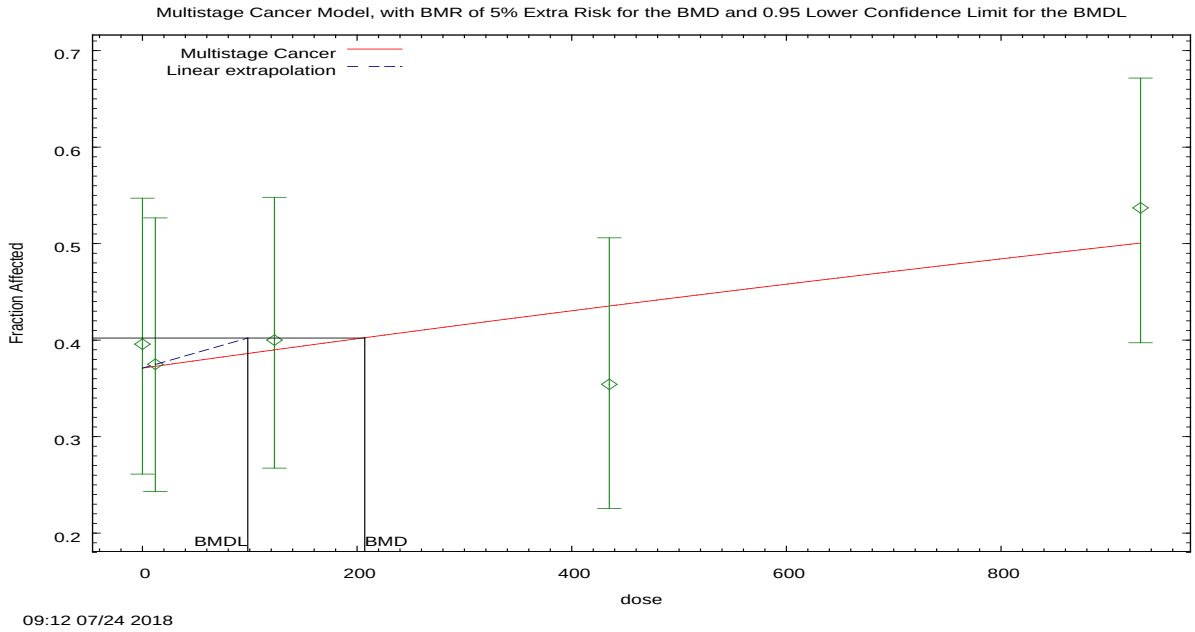

Figure VI-1. Plot of incidence rate by dose with fitted curve for Multistage-Cancer 1° model for liver tumors in male mice; dose shown in mg/kg-day.

Multistage Model. (Version: 3.4; Date: 05/02/2014)
The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]
The parameter betas are restricted to be positive

Benchmark Dose Computation.
BMR = 5% Extra risk
BMD = 207.125

BMDL at the 95% confidence level = 98.1471
BMDU at the 95% confidence level = 511499000000
Taken together, (98.1471, 511499000000) is a 90% two-sided confidence interval for the BMD
Multistage Cancer Slope Factor = 0.000509439

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.370648	0.367078
Beta(1)	0.000247644	0.000270009

Analysis of Deviance Table

Model	Log(likelihood)	# Parameters	Deviance	Test degree of freedom	p-value
Full model	-166.11	5			
Fitted model	-166.98	2	1.7466	3	0.63
Reduced model	-168.33	1	4.43684	4	0.35

AIC: = 337.963

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Residual
0	0.3706	17.791	19	48	0.36
12	0.3725	17.881	18	48	0.04
123	0.3895	19.476	20	50	0.15
435	0.4349	20.876	17	48	-1.13
930	0.5001	27.006	29	54	0.54

Chi^2 = 1.72 d.f = 3 P-value = 0.6318

APPENDIX VII. DEFAULT UNCERTAINTY FACTORS FOR PHC DERIVATION

The table describes the default uncertainty factors OEHHA generally uses to calculate the Acceptable Daily Dose (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)[a]		
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

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

APPENDIX VIII. DETERMINATION OF MULTI-ROUTE EXPOSURES

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

For PHG development, exposures to chemicals in tap water over a lifetime (70 years) are considered. Exposure estimates differ across life stages (fetus, infant, child, and adult) due to physiological and activity pattern changes. CalTOX equations are used to calculate how much each route (oral, inhalation, and dermal) contributes to total daily exposure to a contaminant in tap water. The relative contributions of the different routes are then used to estimate a daily drinking water intake equivalent (DWI, in L_{eq}/kg-day) of multiroute exposure to tap water for each life stage. The lifetime daily multi-route intake rate of tap water in L_{eq}/kg-day is the time-weighted average of these life-stage specific tap water intake rates.[8] The liter equivalent (L_{eq}/kg-day) value represents the equivalent of how much water a person would have to drink to account for exposures via ingestion, inhalation and dermal uptake. Table VIII.1 shows the descriptions and values of parameters applied in the exposure equations. Tables VIII.2 and VIII.3 show life-stage specific exposure parameter values.

Table VIII.1. Descriptions and Values of Model Defaults, Chemical-Specific and Exposure-Specific Parameters

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

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

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

Symbol	Parameter	Value	Unit	Source
C_{air}	chemical concentration in indoor air	-	mg/m^3	calculated
C_{bath_air}	chemical concentration in bathroom air	-	mg/m^3	calculated

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

Symbol	Parameter	Value	Unit	Source
t_{lag}	diffusion lag time in skin	chemical specific	hr	calculated
K_m	skin-water partition coefficient	chemical specific	unitless	literature
K_p^w	steady-state skin permeability coefficient	chemical specific	cm/hr	literature
MW	molecular weight	chemical specific	g/mole	literature
K_{ow}	octanol/water partition coefficient	chemical specific	unitless	literature

[a] As long as the chemical concentration in tap water is low (well below the saturation concentration in water), the input value of C_{tap_water} does not affect the calculation of relative contributions from the multi-route exposures and 100 ppm is an arbitrarily assigned low value.
[b] See Table 2 for life-stage specific values.
[c] See Table 3 for life-stage specific values.

Table VIII.2. OEHHA Calculated Exposure Parameters (OEHHA, 2012[9])

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

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

[9] OEHHA (2012). Air Toxics Hot Spots Program Risk Assessment Guidelines: Technical Support Document for Exposure Assessment and Stochastic Analysis. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, California.

Table VIII.3. CalTOX Model Default Exposure Durations

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

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

Oral Intake: Ingestion of Tap Water

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

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

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

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

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

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

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

and

[10] Abbreviations and symbols used in equations are defined in Table 1.

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

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

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

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

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

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

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

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

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

$\mathbf{Uptake_{dermal}} =$

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

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

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

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

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

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

Chemicals with MW < 280 g/mole:

$$\mathbf{K_p^w} = \frac{\mathbf{1}}{(\mathbf{MW})^{\mathbf{0.6}}} \times \frac{\mathbf{2.4 \times 10^{-6} + 3 \times 10^{-5} \times (K_{ow})^{0.8}}}{\delta_{\mathbf{skin}}}$$

Chemicals with MW ≥ 280 g/mole:

$$\mathbf{K_p^w} = \mathbf{0.0019} \times (\mathbf{K_{ow}})^{\mathbf{0.71}} \times \mathbf{10}^{(\mathbf{-0.0061 \times MW})}$$

Chemicals with calculated K_p^w > 1:

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

K_m is calculated using this equation:

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

Relative Contributions from Each Route of Exposure

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

Relative Contribution from Oral Ingestion (%)

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

Relative Contribution from Inhalation[12] (%)

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

Relative Contribution from Dermal Uptake (%)

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

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

APPENDIX IX. DAILY WATER INTAKE EQUIVALENT CALCULATIONS

This appendix shows the % contribution from each route (ingestion, inhalation, and dermal) in tap water from CalTOX equations (Appendix VIII), and lifetime DWI calculation.

DCPA

Groups	Ingestion %	Inhalation %	Dermal %	Total
FETUS	95.42286887	0.834889148	3.742241979	100
INFANT	98.12265331	0	1.877346686	100
CHILD	94.24927137	1.33156648	4.419162148	100
ADULT	95.39517662	0.69739382	3.907429557	100

Groups		Tap Water Exposure Level (L_{eq}/kg-day)			
	Fractional Duration (of 70 year lifespan)	Ingestion	Inhalation**	Dermal	Total
FETUS	0.75	0.047	0.00020561	0.001843	0.049049
INFANT	2	0.196	0	0.00375	0.19975
CHILD	14	0.061	0.000430908	0.00286	0.064291
ADULT	54	0.045	0.000164488	0.001843	0.047008
	Time-weighted average over lifetime DWI				**0.055354**

**assumes 50% absorption via inhalation

TPA

Groups	Ingestion %	Inhalation %	Dermal %	Total
FETUS	98.89671067	3.53068E-09	1.103289326	100
INFANT	99.45868993	0	0.541310067	100
CHILD	98.68375787	5.68893E-09	1.316242129	100
ADULT	98.84824036	2.94863E-09	1.151759641	100

Groups		Tap Water Exposure Level (L_{eq}/kg-day)			
	Fractional Duration (of 70 year lifespan)	Ingestion	Inhalation**	Dermal	Total
FETUS	0.75	0.047	8.38966E-13	0.000524	0.047524
INFANT	2	0.196	0	0.001067	0.197067
CHILD	14	0.061	1.75827E-12	0.000814	0.061814
ADULT	54	0.045	6.71173E-13	0.000524	0.045524
	Time-weighted average over lifetime DWI				**0.053621**

**assumes 50% absorption via inhalation