OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Public Health Protective Concentration

para-Chlorobenzene Sulfonic Acid in Drinking Water

February 2015

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

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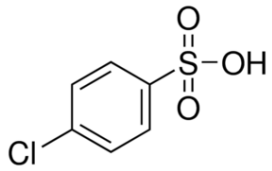

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SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) is identifying a public health protective concentration of 3 parts per million (ppm) for the chemical para-chlorobenzene sulfonic acid (pCBSA) in drinking water. pCBSA is a byproduct of the production of dichloro-diphenyl-trichloroethane (DDT) and is often found in soil at former DDT manufacturing sites. pCBSA is highly water soluble and has contaminated aquifers beneath these sites. A public health protective concentration is the maximum concentration of a contaminant in drinking water that can be consumed by humans with no expected adverse health effects.

The toxicological database for pCBSA is very sparse. There are only five studies: three genotoxicity studies, a screening-level teratology study, and a short-term (28 days) toxicity study. In addition to these data, OEHHA also considered information derived from structure-activity relationship analyses and results of high throughput assays of cells and cell components. There are no long-term toxicity or cancer studies or studies on effects in young animals for the chemical. These data gaps make the determination of a public health protective concentration particularly challenging.

The public health protective concentration is derived by first calculating an Acceptable Daily Dose (ADD) from toxicology data and uncertainty factors (UFs) to account for limitations in the database, variations in human response, and potential differences between animal and human responses to pCBSA. The ADD is defined as the estimated maximum daily dose that can be consumed by humans without toxic effect, and is similar in definition to the reference dose (RfD) used by the U.S. Environmental Protection Agency (US EPA). Second, the volume of drinking water consumed each day is taken into account, in order to determine the concentration of the chemical that can be consumed in water without exceeding the ADD.

The ADD for pCBSA was estimated using data from the 28-day toxicity study conducted by the American Biogenics Corporation (1985). In this key study, male rats gained less body weight as the dose of pCBSA was increased. A mathematical model was used to estimate the dose of pCBSA which would not be expected to cause a significant decrease in body weight gain. This dose is 797 milligrams per kilogram of body weight per day (mg/kg-day). OEHHA estimated an ADD and public health protective

concentrations for two exposure scenarios, acute (short-term) exposure, and chronic (lifetime) exposure.

For acute exposure, consideration is given to sensitive and susceptible populations consuming water over a short period of time. Infants can have greater sensitivity to a given dose of a chemical than adults, and also drink more water per kilogram of body weight than adults and so receive a higher dose of the chemical than adults drinking the same water (OEHHA, 2012). OEHHA applied a total UF of 1,000 to derive the acute ADD value of 0.80 mg/kg-day. The UF accounted for possible differences in the ways that laboratory animals and humans may be affected by pCBSA, variability in human susceptibility (including the greater potential sensitivity of infants) and the limited available toxicity data – for example, no studies were available on the effects of the chemical in developing and young animals. Assuming infants consume 0.237 liters of water per kilogram of body weight per day (L/kg-day) (OEHHA, 2012), and that all of the pCBSA consumed is from water, OEHHA derived a drinking water public health protective concentration of 3 milligrams per liter (mg/L), equivalent to 3 ppm.

For chronic exposure, OEHHA applied a total UF of 3,000 to estimate a chronic ADD of 0.27 mg/kg-day. The UF is larger than that used in the acute calculation since the period of exposure is for a lifetime and only a 28-day study is available for estimating the chronic (lifetime) ADD. Starting with the chronic ADD and applying the time-weighted average (over a lifetime) water consumption rate of 0.053 L/kg-day and an assumed 80% exposure of pCBSA from water to allow for pCBSA from other sources such as soil, OEHHA derived a drinking water concentration of 4 mg/L (equivalent to 4 ppm) that is protective of chronic exposures. Since the drinking water concentration derived for acute exposure is lower, the 3 ppm is selected as the public health protective concentration for pCBSA.

LIST OF ABBREVIATIONS AND KEY TERMS

ADD	acceptable daily dose It is an estimate representing the maximum daily dose (in milligrams per kilogram of body weight per day, mg/kg-day) that can be consumed by humans for an entire lifetime with no expected adverse health effects. This is similar to the term “reference dose” used by U.S. EPA.
ANOVA	analysis of variance A collection of statistical methods to analyze the average measured values between groups.
BMD	benchmark dose A dose determined by the benchmark dose modeling, which considers the shape of the entire dose-response curve and a predetermined change in the response rate as an adverse effect.
BMDL	95% lower confidence limit on the BMD. This dose accounts for the uncertainty in the BMD because of variance in the data and fitness of the data by the model equation. It is generally used as the point of departure, the dose which would not cause the adverse effect.
$BMDL_{1SD}$	The 95% lower confidence limit on the BMD when the benchmark response is based on the standard deviation (1SD) of the control mean.
C	public health protective concentration Following determination of ADD, a health-protective concentration (C, in milligrams/liter, mg/L, or ppm) in drinking water can be derived by dividing the ADD by the estimated intake of the chemical via drinking water as well as other relevant exposure routes such as inhalation and dermal contact.
C_{acute}	water concentration for acute exposure
$C_{chronic}$	water concentration for chronic exposure
DDT	dichloro-diphenyl-trichloroethane
DTSC	Department of Toxic Substances Control, California Environmental Protection Agency
HTP	high throughput assay
L/kg-day	liters (of water) per kilogram of body weight per day

MDEQ	Michigan Department of Environmental Quality
mg/kg	milligrams (of chemical) per kilogram of body weight
mg/kg-day	milligrams (of chemical) per kilogram of body weight per day
mg/L	milligrams (of chemical) per liter
NOAEL	no-observed-adverse-effect level
OEHHA	Office of Environmental Health Hazard Assessment, California Environmental Protection Agency
pCBSA	para-chlorobenzene sulfonic acid
ppm	parts per million
POD	point of departure POD is the dose of a chemical (in units of milligrams per kilogram of body weight per day [mg/kg-day]) derived from an animal or human study that is used as a starting point for calculating ADD.
QSAR	quantitative structure activity relationship
RSC	relative source contribution The proportion of exposures to a chemical attributed to tap water (including inhalation and dermal exposures, e.g., during showering), as part of total exposure from all sources (including food and air pollution).
RfD	reference dose An estimate of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of adverse health effects during a lifetime.
UF	uncertainty factor A factor used in risk assessment to account for various unknowns due to limitation in the toxicology or exposure database as well as our understanding of certain biological processes.
UF_A	interspecies uncertainty factor An uncertainty factor to account for toxicokinetic and toxicodynamic differences between humans and test animals. The default UF for interspecies extrapolation is 10.

UF_H	intraspecies uncertainty factor An uncertainty factor to account for toxicokinetic and toxicodynamic differences within the human population. It is often used to protect infants, children, and pregnant women. The default UF for intraspecies variability is 30.
U.S. EPA	United States Environmental Protection Agency

INTRODUCTION

Background

The Office of Environmental Health Hazard Assessment (OEHHA) has determined a public health protective concentration of 3 parts per million (ppm) for para-chlorobenzene sulfonic acid (pCBSA) in drinking water. This report describes the toxicity database evaluated and the approaches used to derive the concentration.

pCBSA is an environmental chemical contaminant generated as a byproduct of dichloro-diphenyl-trichloroethane (DDT) manufacturing (Lim, 1972). In California, DDT was produced from 1947 to 1982 at the Montrose Chemical Company plant in Los Angeles. Years of DDT production released pCBSA into the environment and contaminated the groundwater at the former plant site (the Montrose Chemical Corp Superfund site) as well as at the neighboring land (Del Amo Superfund site). Other sites of pCBSA contamination across the country include the Stringfellow Acid Pits in California, the Basic Management Incorporated Complex in Nevada, and the Velsicol Superfund site in Michigan.

Physical Properties and Environmental Fate and Transport

pCBSA is an organic compound with a molecular weight of 192.62 and a CAS registry number of 98-66-8. It is a strong acid and has negligible vapor pressure because it is highly water soluble and resistant to both degradation in water and adsorption to soil. Using structure activity relationship analysis, the Department of Toxic Substances Control (DTSC, 1997) determined that pCBSA would not bioaccumulate in animal tissues and assigned a bioconcentration factor of one to the chemical.

TOXICITY DATABASE

The toxicological database for pCBSA is very sparse. The evaluation of potential human effects of pCBSA is determined mainly from five U.S. Environmental Protection Agency (U.S. EPA)-commissioned studies (CH2M Hill, 1994; reviewed in Michigan Department of Environmental Quality, MDEQ, 2006). The studies are summarized in this section:

- *In vitro* Genotoxicity (Ames) assays (Pharmakon Research International 1985a).
- *In vitro* Genotoxicity (L5178Y $TK^{+/-}$ mouse lymphoma cell) assay (Pharmakon Research International 1986).
- *In vivo* Genotoxicity (Bone Marrow Cytogenics) assay (Pharmakon Research International 1985b).
- Teratology Screening Study (Chernoff and Rosen, 1985).
- 28-day Toxicity Study (American Biogenics Corp., 1985).

DTSC (2014) conducted a literature search that did not identify new *in vivo* toxicity data on pCBSA published since the 1999 DTSC record of decision identifying a provisional health standard to be used in reinjected groundwater of 25 milligrams per liter (mg/L). DTSC did identify results from high-throughput testing assays from a U.S. EPA database. pCBSA was tested in 25 high-throughput toxicogenomic assays and did not show any effect in the gene and protein activity tested. OEHHA also performed a search in January 2015 of regulatory and open-literature databases and also did not identify any additional toxicity information useful for deriving a public health protective concentration. OEHHA also conducted a structure-activity relationship analysis to assess the carcinogenic potential of pCBSA.

Genotoxicity

There are two *in vitro* gene mutation assays in the scientific literature. There were no increases in mutation frequency, with or without the addition of rat liver metabolic activation, in both the L5178Y $TK^{+/-}$ mouse lymphoma cell (Pharmakon Research International, 1986) and the Ames assay with five *Salmonella* strains (TA 1535, 1537, 1538, 98, and 100) exposed to various concentrations of pCBSA (Pharmakon Research International, 1985a).

In an *in vivo* bone marrow cytogenetic assay, male Sprague-Dawley rats (6 per time period) were given a single dose of 2000 milligrams per kilogram of body weight (mg/kg) pCBSA by gavage (Pharmakon Research International, 1985b). There were no significant increases in incidence of metaphase chromosomal aberrations or number of

cells with aberrations in bone marrow sampled at 6, 12, or 24 hours post dose. Some animals had diarrhea at 6 hour (3 of 6 males) and 12 hour (2 of 6 males) observation periods. This was not observed in the vehicle controls.

Carcinogenicity

No two-year animal cancer bioassay has been conducted for pCBSA. OEHHA carried out Quantitative Structure Activity Relationship (QSAR) modeling to investigate the carcinogenicity potential of pCBSA using both VEGA (http://www.vega-qsar.eu/) and Lazar (http://lazar.in-silico.de/predict). A more complete description of the programs and methods can be found in OEHHA's document on the evidence of the carcinogenicity of dibenzanthracenes (OEHHA, 2014a). Prediction results for pCBSA were inconsistent using either modeling programs. With VEGA, the CESAR carcinogenicity model predicted non-carcinogenicity for pCBSA while the Benigni-Bossa carcinogenicity model predicted carcinogenicity (see Appendix 1 A, B). In both assessments, the results for the compound were out of the model applicability domain, indicating the predictions were unreliable. Similarly conflicting results were also found using Lazar (see Appendix 1 C). Based on the conflicting and uncertain QSAR predictions coupled with negative but sparse genotoxicity data, and lack of direct *in vivo* carcinogenicity evidence OEHHA concluded that there is inadequate evidence for judging the carcinogenicity of pCBSA.

Developmental Toxicity

In a teratology screening study, pregnant female CD rats (25 per group) were treated by gavage with 0, 1000, or 2000 milligrams per kilogram of body weight per day (mg/kg-day) pCBSA from gestational days 7 to 16 (Chernoff and Rosen, 1985). Dams were allowed to give birth and litters were analyzed on postnatal days 1 and 3. Dams that did not give birth were sacrificed on postnatal day 3 and examined for implantation sites. The protocol for this study included limited observations and only two dose groups, and the study was not conducted according to Office of Prevention, Pesticides and Toxic Substances (OPPTS) guidelines (U.S. EPA, 1998). Results indicated there was no significant effect of treatment on reproduction or developmental effects measured (maternal weight gain, litter size, pup weight) at any dose tested. However, this study did not include observations, functional deficits, or analysis of fetal malformations or abnormalities. Thus, this study did not adequately investigate the teratogenic potential of pCBSA.

28-Day Toxicity

This is the only study of pCBSA with repeated exposure *in vivo*, using multiple doses, conducted in both sexes, with adequate reporting, and sufficient pathological examination (American Biogenics Corp., 1985). The results from this study have been the basis for reference levels by multiple agencies.

In this study, male and female Sprague-Dawley rats (10/sex/dose group) were dosed by gavage at 0, 10, 50, 500, 1000, or 2000 mg/kg-day for 31 or 32 days. For the purpose of this document, this study will be referred to as the 28-day rat toxicity study to retain consistency with previous documents that cite this study for determining reference levels (DTSC, 1997; MDEQ, 2006). Animals were closely monitored for signs of toxicity, and body weights and food consumption were recorded weekly throughout the study. At the study termination, blood samples were analyzed for hematology and clinical chemistry parameters, ophthalmological examinations were conducted, organs were weighed, and tissues were subjected to histopathological examination.

There was no early mortality reported for the study. Females were generally unaffected by treatment at all doses. The no-observed-adverse-effect level (NOAEL) for females in this study was 2000 mg/kg-day.

Table 1. Results of male toxicity endpoints from 28-day rat toxicity study (American Biogenics Corp., 1985).

Effects	Dose mg/kg-day[a]					
	0	10	50	500	1000	2000
Adrenal Weight (left) (g)	0.0375± 0.0042	0.0313± 0.0062	0.0336± 0.0048 N=9[a]	0.0252± 0.003*	0.0323± 0.0086	0.0320± 0.0044
Adrenal Organ/body Weight Ratio	0.0105± 0.0014	0.0088± 0.0020	0.0090± 0.0016 N=9[a]	0.0072± 0.0009*	0.0092± 0.0022	0.0093± 0.0014
Final Fasted Body Weight (g)	360.511± 25.976	357.437± 28.070	374.856± 20.127	349.908± 29.583	349.168± 34.291	344.753± 34.654
Body Weight Gain (g)**	165± 20.9	170± 21.3	176± 9.8	160± 14.9	153± 19.6	150± 29.2
Clinical Signs-Salivation, gasping***	0/10	0/10	0/10	0/10	0/10	1/10
Irregular Breathing***	0/10	0/10	0/10	0/10	0/10	2/10
Crusty Eyes	0/10	0/10	1/10	1/10	1/10	1/10
Misaligned Incisor	0/10	0/10	1/10	1/10	2/10	1/10

[a]Total animal per group=10, except noted. * p<0.01 relative to control **significant by ANOVA p<0.05 and trend test p<0.001 *** significant by trend test p<0.05

Males, however, showed some evidence of toxicity with multiple endpoints (see Table 1). Males dosed with 500 mg/kg-day had a statistically significant decrease in left

adrenal weight, both absolute weight and the organ weight relative to body weight ratio. This change was not significant at higher doses and thus showed no dose-response relationship. There was also a trend for dose-dependent decrease in final fasted body weight, although not statistically significant. The decrease in average body weight gain in males was statistically significant by analysis of variance (ANOVA) ($p<0.05$) with positive test for trend ($p<0.001$) but was not significant by pairwise comparison of individual treatment groups with the controls. While there was no significant change in the group total average or daily food consumption, examination of the individual data showed that the decrease in body weight gain in the 2000 mg/kg-day group was due to two animals that were most affected by the treatment. One male had clinical signs of toxicity including irregular breathing, while another male also displayed signs of salivation and gasping. The finding of reduced body weight gain was associated with these clinical observations of toxicity and was thus considered biologically significant.

Furthermore, while there was a low incidence of crusty eyes and misaligned incisors in male rats dosed at 50 mg/kg-day and above, there was a lack of dose response for these observations and they were of limited toxicological relevance. Therefore, based on decreasing body weight gain and clinical signs of toxicity observed in the male rats at 2000 mg/kg-day, the NOAEL for this study was 1000 mg/kg-day, the next lower dose tested.

PUBLIC HEALTH PROTECTIVE CONCENTRATION FOR pCBSA

Existing Drinking Water Reference Levels

In 1994, DTSC reviewed the U.S. EPA-commissioned studies of pCBSA and calculated a provisional reference dose (RfD) and an acceptable drinking water concentration. The RfD was based on a NOAEL of 1000 mg/kg-day from the results of the 28-day rat toxicity study (American Biogenics Corporation, 1985). Using the NOAEL of 1000 mg/kg-day and applying an uncertainty factor of 1000 (10-fold for extrapolation from short-term exposure to long-term exposure; 10-fold extrapolation from animal data to humans; and 10-fold to account for sensitive human populations), the RfD was determined to be 1 mg/kg-day. Applying a daily consumption of 2 L water per day and a 70 kg body weight, DTSC calculated a safe drinking water concentration of 35 mg/L, which could be consumed by humans with no likely adverse effects. In 1997, OEHHA reviewed the 1994 DTSC determination and the toxicity studies identified, and at that time agreed with the DTSC determination.

In January 2006, the Remediation and Redevelopment Division of the Michigan Department of Environmental Quality (MDEQ, 2006) also conducted a toxicological risk assessment on pCBSA based on the toxicity studies for pCBSA as well as its structural analogue, 4-chlorophenyl ester of 4-chlorobenzenfulfonate (chlorofenson). Data from this structural analogue was used to support the determination that pCBSA is not likely to be a carcinogen. The assessment also noted that the analogue was significantly more toxic. Based on their generic drinking water criteria and an RfD of 1 mg/kg-day (in agreement with DTSC and the 1997 OEHHA review), MDEQ developed a residential drinking water criterion of 7.3 ppm. Differences between this value and those derived by DTSC are attributed to addition of a 20% relative source contribution (RSC) in the MDEQ evaluation. The RSC is the proportion of pCBSA exposure that is estimated to come from drinking water. In the MDEQ evaluation they applied a default value for their program of 0.2 or 20%.

In a 2014 memo, DTSC also calculated a risk-based concentration using the exposure factors from U.S. EPA guidelines and an RfD of 1 mg/kg-day. The ‘child-specific risk-based concentration’ was determined to be 20 mg/L. Included in this memo was a Pubchem bioassay search citing results of high throughput (HTP) assays, mostly conducted as part of the U.S. EPA’s Tox21 project. pCBSA was tested in 25 HTP toxicogenomic assays and did not show any effect in the gene and protein activity tested. OEHHA has also reviewed this data and is in agreement with the DTSC conclusion.

Point of Departure

Since the DTSC and OEHHA reviews in the 1990s, risk assessment approaches have advanced with a better understanding of sensitivity of early-life exposures to toxic chemicals, new data on differences in tap water intake rates between infants and adults, and new dose-response modeling methodology. U.S. EPA has developed the Benchmark Dose (BMD) software to estimate the point of departure (POD) for the determination of exposure risk. BMD modeling provides a more quantitative approach to deriving a POD versus the traditional NOAEL approach. Using these new approaches, OEHHA in this report has calculated public health protective drinking water concentrations for pCBSA.

There were three *in vivo* studies available for POD determination. Both the *in vivo* cytogenetic study (Pharmakon Research International, 1985b) and teratology study (Chernoff and Rosen, 1985) had few doses and observations and were not adequate to assess acute or chronic toxicity. As before, OEHHA chose the 28-day rat toxicity study as the key study because it included measurements of clinical chemistry, hematology and pathology and was overall a well-conducted study. Results of the study indicated that pCBSA was not overtly toxic. Clinical observations including salivation, gasping, and irregular breathing were only observed in the highest dose tested and at low incidences. As noted above, male body weight gain significantly decreased with increasing dose (ANOVA $p<0.05$; trend test, $p<0.001$). The dose-response data for this endpoint was appropriate for BMD modeling. OEHHA chose this health effect as the critical endpoint and estimated the POD using BMD Software (Version 2.5, U.S. EPA; Davis et al., 2011). A benchmark response of one standard deviation (1SD) and the exponential M2 model were chosen based on the highest goodness of fit p value (0.145) and lowest Akaike's Information Criterion (AIC) value, consistent with standard methodology. The resulting doses, BMD_{1SD} and $BMDL_{1SD}$ (95% lower confidence limit on the BMD_{1SD}), were 1,374 and 797 mg/kg-day, respectively. The $BMDL_{1SD}$ is similar to but lower than the stated NOAEL of 1,000 mg/kg-day and was used for the determination of the public health protective concentration of pCBSA. Details of the BMD analysis are presented in Appendix 2.

The public health protective concentration is derived by first calculating an Acceptable Daily Dose (ADD) from the POD. The ADD is defined as the estimated maximum daily dose that can be consumed by humans without toxic effect, and is similar in definition to the RfD used by U.S. EPA. Second, drinking water consumption is taken into account, in order to determine the concentration of chemical that can be consumed in water without exceeding the ADD. OEHHA estimated an ADD and public health protective concentration for two exposure scenarios, acute short term exposure, and chronic, lifetime exposure.

Acute Exposure

For acute exposure, consideration is given sensitive and susceptible populations consuming water over a short period of time. Infants can have greater sensitivity to a given dose of chemical than adults, and also drink more water on a body-weight basis than adults and so receive a higher dose of chemical than adults drinking the same water (OEHHA, 2012).

OEHHA calculated an acute public health protective drinking water concentration (C_{acute}) for pCBSA based on the POD of 797 mg/kg-day, an uncertainty factor (UF), an estimated high-end tap water consumption rate, and an estimate of the RSC.

The approach and UF used in developing the C_{acute} are the same as those used to develop the Public Health Goals for drinking water (OEHHA, 2014b). They are:

1. An interspecies UF (UF_A) extrapolating from animal to human of 10,
2. An intraspecies UF (UF_H) to account for human variability of 30, and
3. A database deficiency factor for limited toxicity data, including insufficient neurotoxicity and developmental and reproductive toxicity data, of 3. There are no toxicological studies available on effects of pCBSA in developing or young animals.

The combined UF applied was rounded to 1,000. Using the $BMDL_{1SD}$ of 797 mg/kg-day and UF of 1,000, OEHHA calculated an ADD of 0.797 mg/kg-day for acute exposure.

The acute ADD, the 95th percentile water intake of 0.237 liters per kilogram of body weight per day (L/kg-day) for an infant 0-6 months old (OEHHA, 2012), and a RSC of 1 to reflect 100% exposure from contaminated drinking-water sources, is used to calculate the C_{acute}, using the following equation:

$$C_{acute} = ADD \times RSC / \text{water intake rate}$$

$$= 0.797 \text{ mg/kg-day} \times 1.0 / 0.237 \text{ L/kg-day}$$

$$= 3 \text{ mg/L or } 3 \text{ ppm}$$

The 95th percentile water intake rate for an infant (< six months old) of 0.237 L/kg-day was chosen to represent the high-end water consumption rate (OEHHA, 2012). This is because infants have a relatively high daily water intake rate, on a body-weight basis. Furthermore, infants are generally considered to be more susceptible to chemical toxicity than adults. This approach would also be protective of the breast-fed infant (upper 95th percentile milk consumption of approximately 0.17 L/kg-day during the first 6 months of life) assuming this water soluble chemical, once ingested, does not bioaccumulate and is widely distributed in the mother.

The RSC is assumed to be one, as infants are not likely to be exposed to other environmental media contaminated with pCBSA.

Using the approach and parameters described above, OEHHA determined a drinking water level of 3 ppm for acute exposure.

Chronic Exposure

OEHHA used the same BMD modeling result and POD described for C_{acute} to calculate the water concentration for chronic exposure ($C_{chronic}$). However, the total uncertainty factor was increased from 1,000 to 3,000:

1. An interspecies UF (UF_A) extrapolating from animal to human of 10,
2. An intraspecies UF (UF_H) to account for human variability of 30, and
3. A duration extrapolation (from subchronic to chronic exposure) UF of 10.

A duration UF was applied to account for using a study that had exposure duration less than 8% of the lifetime of the test animal to estimate chronic toxicity. Because a 10-fold UF was added to account for duration of exposure, OEHHA determined that this was sufficient to also account for database deficiency (e.g., no long-term toxicity studies).

Thus the total UF applied for chronic exposure was 3,000. Based on the study $BMDL_{1SD}$ of 797 mg/kg-day, and UF of 3,000, the chronic ADD was calculated as 0.266 mg/kg-day.

Using the chronic ADD, lifetime average "consumers only" water consumption rates of 0.053 L/kg-day (i.e., 95th percentile of time-weighted average values and adjusted for body weight) (OEHHA, 2012), and a RSC of 0.8, the $C_{chronic}$ was calculated using the following equation:

$C_{chronic}$ = chronic ADD × RSC / water intake rate

= 0.266 mg/kg-day × 0.8 / 0.053 L/kg-day

= 4 mg/L or 4 ppm

The time-weighted average of 95th percentile "consumers only" high-end water consumption rates of all age groups adjusted for body weight, 0.053 L/kg-day (OEHHA, 2012), was used to estimate the water consumption rate for chronic exposure. A RSC is assumed to be 80 percent (0.8) to allow for potential exposure to pCBSA from other sources, such as soil, over a lifetime.

Using the approach and parameters described above, OEHHA determined a drinking water level of 4 ppm for chronic exposure. For health protection, OEHHA recommends the lower value of 3 mg/L as the public health protective concentrations for pCBSA.

Uncertainty Analysis

Overall the data available to assess the toxicity of pCBSA are limited. The limited studies commissioned by U.S. EPA in the 1980s are still the main source of information from which to assess potential human health hazards. Review of new data from high-throughput assays yielded little new information on pCBSA bioactivity, and evaluation of carcinogenicity through QSAR modeling yielded conflicting predictions and was deemed unreliable. While the 28-day rat toxicity study is sufficient to assess short-term exposures to pCBSA, there is uncertainty with regards to long-term exposure and potential for carcinogenicity. OEHHA believes a two-year cancer bioassay in test animals is needed to better assess chronic toxicity and carcinogenicity of pCBSA. More thorough developmental toxicity testing would also address the potential sensitivity of infants and children.

CONCLUSION

The present analysis calculated a public health protective concentration of pCBSA in drinking water of 3 mg/L (3 ppm). While the determination is based on a very limited toxicity database, it incorporates the current dose-response methodology and up-to-date water consumption rate estimates used by OEHHA for the PHG program and uncertainty factors to account for sparse data. It also accounts for short-term exposure to infants who may be more sensitive and who consume more water on a body-weight basis than adults.

The public health protective concentration is based on a single, well-conducted 28-day toxicity study in rats. Additional toxicity studies, including a developmental toxicity study, and an oral two-year chronic toxicity / cancer bioassay, would provide a more reliable basis for deriving a public health protective water concentration for pCBSA.

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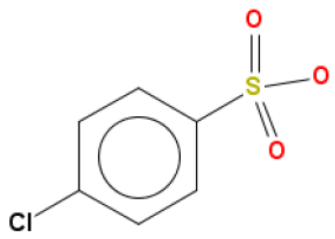
APPENDIX 1 QSAR CARCINOGENICITY RESULTS FOR PCBSA

A – CAESAR Carcinogenicity Prediction

1. Prediction Summary

Prediction for compound 1 (Molecule 1)



Prediction: Reliability:

Model assessment: Prediction is NON-Carcinogen, but the result may be not reliable. Careful check of the information given in the following section should be done, paying particular attention to the following issues:
- similar molecules found in the training set have experimental values that disagree with the predicted value
- accuracy of prediction for similar molecules found in the training set is not adequate
- a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments
- predicted value disagrees with experimental values of training set compounds laying in the same neuron
One or more fragments possibly related to carcinogenic activity were found: Halogenated benzene

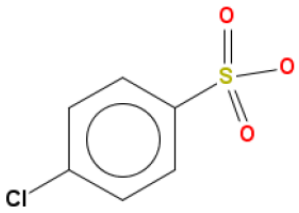
Compound: 1
Compound SMILES: O=S(=O)(O)c1ccc(cc1)Cl
Experimental value: -
Prediction: NON-Carcinogen
Carcinogen: 0.36
NON-Carcinogen: 0.64
Structural Alerts: Halogenated benzene
Reliability: Compound is out of model Applicability Domain
Remarks for the prediction:
none

B – Benigni-Bossa Carcinogenicity Prediction

VEGA Benigni-Bossa Carcinogenicity (TOXTREE) (version 1.0.0-DEV) page 5

1. Prediction Summary

Prediction for compound 1 (Molecule 1)



Prediction: Reliability:

Model assessment: Prediction is Carcinogenic, but the result may be not reliable. Careful check of the information given in the following section should be done, paying particular attention to the following issues:
- only moderately similar compounds with known experimental value in the training set have been found
- similar molecules found in the training set have experimental values that disagree with the predicted value
- accuracy of prediction for similar molecules found in the training set is not optimal
One or more fragments related to mutagen activity were found:
SA31a

Compound: 1
Compound SMILES: O=S(=O)(O)c1ccc(cc1)Cl
Experimental value: -
Prediction: Carcinogenic
Structural Alerts: SA31a
Reliability: Compound is out of model Applicability Domain
Remarks for the prediction:
none

C- Lazar Toxicity Predictions

Lazar Toxicity Predictions

Prediction Validation

User: guest

This is an experimental version based on OpenTox services. Please report problems and feature requests to our issue tracker.

New prediction

O=S(=O)(O)c1ccc(Cl)cc1

	DSSTox Carcinogenic Potency DBS MultiCellCall: non-carcinogen (Confidence : 0.105) Details	DSSTox Carcinogenic Potency DBS Rat: carcinogen (Confidence : 0.0556) Details	DSSTox Carcinogenic Potency DBS SingleCellCall: non-carcinogen (Confidence : 0.119) Details	DSSTox ISSCAN v3a Canc: carcinogen (Confidence : 0.0687) Details	DSSTox Carcinogenic Potency DBS Hamster: non-carcinogen (Confidence : 0.084) Details	DSSTox Carcinogenic Potency DBS Mouse: non-carcinogen (Confidence : 0.227) Details

APPENDIX 2 MALE RAT BODY WEIGHT GAIN BENCHMARK DOSE MODELING

Table A1. Model predictions for male body weight gain in 28 day rat toxicity study.

Model[a]	Goodness of fit		BMD_{1SD}	$BMDL_{1SD}$
	p-value	AIC		
Exponential (M2)	**0.145**	**421.85**	**1374**	**797**
Exponential (M3)	0.0773	423.85	1377	797
Exponential (M4)	0.0798	423.78	1295	508
Exponential (M5)	0.0419	425.36	1106	479
Hill	0.0429	425.32	1112	error[b]
Power[c] Polynomial 5°[d] Polynomial 4°[e] Polynomial 3°[f] Polynomial 2°[g] Linear	0.142	421.90	1404	842

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0352), selected model in bold; scaled residuals for selected model for doses 0, 10, 50, 500, 1000, and 2000 were -0.837, 0.1263, 1.336, -0.528, -0.6127, and 0.552, respectively.
[b] BMD or BMDL computation failed for this model.
[c] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[d] For the Polynomial 5° model, the b5, b4, and b3 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 5° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[e] For the Polynomial 4° model, the b4 and b3 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 4° model, the b4, b3, and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.

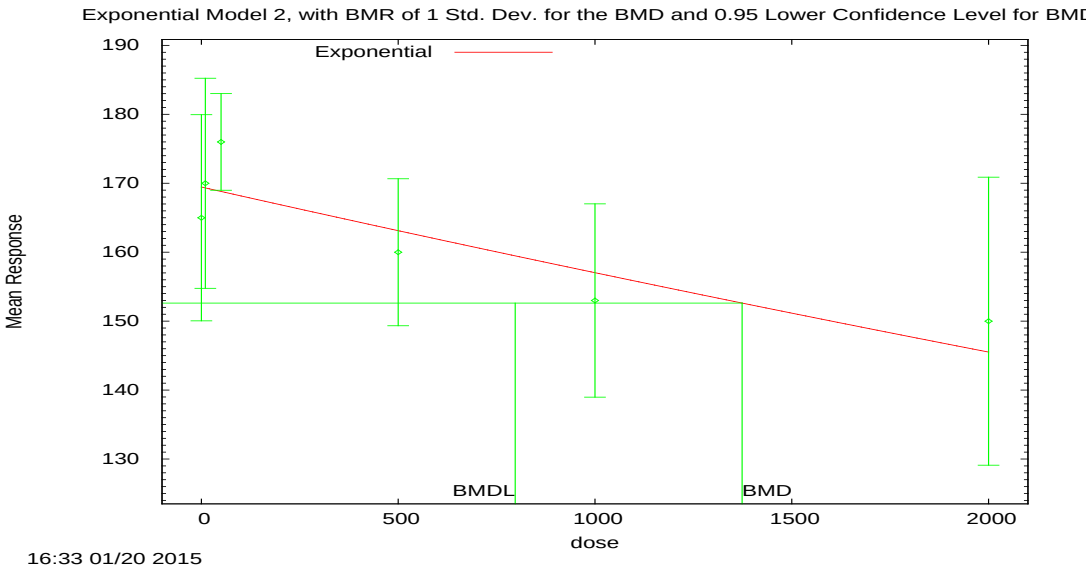


Figure 1. Plot of mean response by dose, with fitted curve for selected model; dose shown in mg/kg-day.

Exponential Model. (Version: 1.9; Date: 01/29/2013)

The form of the response function is: Y[dose] = a * exp(sign * b * dose)

A modeled variance is fit

Benchmark Dose Computation.

BMR = 1 Estimated standard deviations from control

BMD = 1373.73

$BMDL_{1SD}$ at the 95% confidence level = 797.32

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	34.1559	48.5868
rho	-5.55457	-8.40714
a	169.455	155.644
b	0.0000761556	0.000068268
c	0	0
d	1	1

Table of Data and Estimated Values of Interest

Dose	N	Observed Mean	Estimated Mean	Observed Standard Deviation	Estimated Standard Deviation	Scaled Residual
0	10	165	169.5	20.9	16.83	-0.837
10	10	170	169.3	21.3	16.87	0.1263
50	10	176	168.8	9.8	17.01	1.336
500	10	160	163.1	14.9	18.71	-0.528
1000	10	153	157	19.6	20.8	-0.6127
2000	10	150	145.5	29.2	25.7	0.552

Tests of Interest

Test	-2*log (Likelihood Ratio)	Test df	p-value
Test 1	24.2	10	0.007093
Test 2	11.97	5	0.03516
Test 3	4.701	4	0.3193
Test 4	6.836	4	0.1448

Description of tests, taken from BMDS 2.5.0 user manual (Davis et al., 2011).
http://www.epa.gov/ncea/bmds/documentation/BMDS250_manual.pdf

Test 1 - Tests the null hypothesis that responses and variances do not differ among dose levels. A p-value less than 0.05 is considered significant and indicates that the data is suitable for dose-response modeling.

Test 2 - Tests the null hypothesis that variances are homogeneous. A p-value greater than 0.1 is associated with the statement that a constant variance assumption is suitable for the dose-response modeling.

Test 3 - Tests the null hypothesis that the variances are adequately modeled. A p-value greater than 0.1 is associated with the statement that the modeled variance appears to be suitable for the dose-response modeling.

Test 4 - Tests the null hypothesis that the model for the mean fits the data. A p-value greater than 0.1 is associated with a statement that the Fitted Model appears to be suitable for dose-response modeling.