

TOXICOLOGICAL PROFILES FOR THREE ORGANIC ACIDS

Prepared for
Syngenta Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419-8300

Prepared by



2661 Riva Road, Bldg 500
Suite 520
Annapolis, MD 21401

November 16, 2007

CONTENTS

LIST OF FIGURES	iv
LIST OF TABLES	v
ACRONYMS AND ABBREVIATIONS	vi
1 INTRODUCTION	1-1
2 METHODS	2-1
2.1 LITERATURE SEARCH AND CRITICAL REVIEW	2-1
2.1.1 Human Health Toxicity Data Considered	2-1
2.1.2 Ecological Toxicity Data Considered.....	2-2
2.2 TOXICITY CRITERIA DEVELOPMENT	2-2
2.2.1 Human Health Toxicity Criteria.....	2-2
2.2.2 Ecological Toxicity Criteria	2-3
3 TOXICITY DATA REVIEW: BSA	3-1
3.1 HUMAN AND ANIMAL TOXICITY STUDIES.....	3-2
3.1.1 Carcinogenicity	3-2
3.1.2 Noncarcinogenic Toxicity.....	3-2
3.1.3 Toxicity Criteria	3-3
3.1.4 Discussion.....	3-3
3.2 ECOLOGICAL TOXICITY	3-4
4 TOXICITY DATA REVIEW: PCBSA	4-1
4.1 HUMAN AND ANIMAL TOXICITY STUDIES.....	4-1
4.1.1 Carcinogenicity	4-1
4.1.2 Noncarcinogenic Toxicity.....	4-2
4.1.3 Toxicity Criteria	4-2
4.1.4 Discussion.....	4-2
4.2 ECOLOGICAL TOXICITY	4-3
5 TOXICITY DATA REVIEW: PHTHALIC ACID	5-1
5.1 HUMAN AND ANIMAL TOXICITY STUDIES	5-2
5.1.1 Human Studies	5-2
5.1.2 Carcinogenicity	5-2
5.1.3 Noncarcinogenic Toxicity.....	5-2
5.1.4 Toxicity Criteria	5-4

5.2	DISCUSSION	5-5
5.3	ECOLOGICAL TOXICITY	5-6
6	SUMMARY OF FINDINGS	6-1
7	REFERENCES.....	7-1

LIST OF FIGURES

- Figure 3-1. Chemical Identification: BSA
Figure 3-2. Chemical Identification: pTSA
Figure 4-1. Chemical Identification: pCBSA
Figure 5-1. Chemical Identification: Phthalic Acid
Figure 5-2. Chemical Identification: Phthalic Anhydride

LIST OF TABLES

- Table 3-1. Human Health Toxicity Data for BSA and pTSA, by Test Category
- Table 3-2. Ecological Toxicity Data for BSA and pTSA
- Table 4-1. Human Health Toxicity Data for pCBSA, by Test Category
- Table 4-2. Ecological Toxicity Data for pCBSA Acid
- Table 5-1. Human Health Toxicity Data for Phthalic Acid and Phthalic Anhydride, by Test Category
- Table 5-2. Ecological Toxicity Data for Phthalic Acid

ACRONYMS AND ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
BMI	Black Mountain Industrial
BSA	benzenesulfonic acid
bw	body weight
Cal/EPA	California Environmental Protection Agency
DEHP	di-(2-ethylhexyl) phthalate
EC50	median effective concentration
ECOTOX	Ecotoxicology
HPV	High Production Volume
LC50	median lethal concentration
LD50	median lethal dose
LOAEL	lowest-observed-adverse-effects level
MBeP	monobenzyl phthalate
MBuP	monobutyl phthalate
MDEQ	Michigan Department of Environmental Quality
NCI	National Cancer Institute
NDEP	Nevada Department of Environmental Protection
NIH	National Institutes of Health
NLM	National Library of Medicine
NOAEL	no-observed-adverse-effects level
NOEC	no-observed-effect concentration
NOTOX	NOTOX Safety and Environmental Research BV
OEHHA	Office of Environmental Health Hazard Assessment
PAE	phthalic acid ester
pCBSA	p-chlorobenzenesulfonic acid
pTSA	p-toluenesulfonic acid
REL	reference exposure level
RfC	reference concentration

RfD	reference dose
RTECS	Registry of Toxic Effects of Chemical Substances
SRC	site related chemical
TOXNET	Toxicology Data Network
USEPA	U.S. Environmental Protection Agency

1 INTRODUCTION

This report summarizes human health and ecological toxicity information for three organic acids - benzenesulfonic acid (BSA), p-chlorobenzenesulfonic acid (pCBSA), and phthalic acid – and where possible, recommends toxicity values for use in assessing risks from environmental exposures. BSA, pCBSA, and phthalic acid have been identified as site related chemicals (SRCs) for the former Montrose and Stauffer facilities within the Black Mountain Industrial (BMI) Complex, in Henderson, Nevada, but no toxicological criteria have been developed for these chemicals by the U.S. Environmental Protection Agency (USEPA) or the Nevada Department of Environmental Protection (NDEP). This paper summarizes the available toxicity data, assesses its adequacy to support hazard criteria development, develops toxicological criteria that can be used in risk assessment, and calculates drinking water based concentration criteria that can be used in a screening-level evaluation of overall groundwater quality.

The remainder of this paper is organized into five principal sections. First we describe the methods used to conduct the evaluation, next we present toxicity profiles for each of the three organic acids, and finally, we present an overall summary of the findings.

2 METHODS

Our approach included identification and critical review of relevant literature and development of toxicity criteria and drinking water criteria using USEPA methodology.

2.1 LITERATURE SEARCH AND CRITICAL REVIEW

An extensive literature search was conducted using various online databases including the National Library of Medicine (NLM) and National Institutes of Health (NIH) PubMed, the Registry of Toxic Effects of Chemical Substances (RTECS), USEPA's Ecotoxicology (ECOTOX) database, and the U.S. Library of Medicine Toxicology Data Network (TOXNET).

Web-accessible library files from USEPA, the Agency for Toxic Substances and Disease Registry (ATSDR), and other state health agencies were also researched. Primary data sources were obtained and reviewed when feasible.

Because few toxicological data are available for the three organic acids, we supplemented our efforts to include searches for data on toxicological surrogates that are structurally similar and expected to behave similarly to the organic acid. Toxicological surrogates were identified for BSA and phthalic acid based on these considerations. The basis for these selections will be discussed in subsequent sections.

2.1.1 Human Health Toxicity Data Considered

We searched for human health effects data derived from epidemiological studies and from toxicity tests conducted in laboratory animals. We did not find sufficient epidemiological data to support criteria development, and therefore largely relied on animal studies as the basis for development of toxicity criteria for the three organic acids. Occupational exposure standards were however considered and presented, as available.

In reviewing the animal data, we considered the full range of available toxicity data. We evaluated key studies to assess overall quality and considered the strength and breadth of the overall database when determining the confidence in the database and toxicity criteria derived from it. For studies completed in animals, the most robust data set includes results from a battery of tests including acute and chronic studies and tests for specific endpoints including reproductive and developmental endpoints. Study design should incorporate known information regarding the absorption, distribution, metabolism, and excretion of a chemical, as well as any information that is known regarding the mechanism of toxicity. Studies also should include several doses relevant to toxicity to aid in complete characterization of the dose-response curve.

2.1.2 Ecological Toxicity Data Considered

We searched for ecological toxicity data for both aquatic and terrestrial species. If no studies for terrestrial wildlife were available, studies conducted in laboratory animals (e.g., rats, mice, etc.) were reviewed. In these cases, oral exposure studies were considered most applicable for evaluating toxicity to ecological receptors. Studies on growth, reproduction, and survival were summarized if available, as these endpoints are most relevant to assessing ecological risks. Acute and chronic data were compiled and reviewed.

2.2 TOXICITY CRITERIA DEVELOPMENT

All literature and data were critically reviewed to assess data adequacy and relevancy for developing toxicological criteria. USEPA guidance was used to frame the toxicity data assessment and criteria development (e.g., USEPA 1989, 1991, 1993, 1994a, 2002, 2005a, 2005b).

2.2.1 Human Health Toxicity Criteria

Human health toxicity criteria are numerical values established to evaluate potential carcinogenic and noncarcinogenic health effects for humans. There was no quantitative information from which to develop carcinogenic toxicity criteria for any of the organic acids; therefore, only toxicity criteria for noncancer health effects are presented in this report.

The toxicity criteria for noncancer health effects are termed reference doses (RfDs) or reference concentrations (RfCs). The potential for noncancer health effects is evaluated by comparing an estimated daily dose for an exposure scenario with an oral RfD, or by comparing an estimated exposure concentration in air with an inhalation RfC. By definition, RfC and RfD toxicity values represent average daily exposure levels at which no adverse effects are expected to occur during chronic or subchronic exposures (USEPA 1989). RfDs and RfCs reflect the underlying assumption that systemic toxicity occurs as a result of processes that have a threshold (i.e., that a safe level of exposure exists and that toxic effects will not be observed until this level has been exceeded).

RfDs or RfCs are generally derived by identifying the no-observed-adverse-effects level (NOAEL) or lowest-observed-adverse-effects level (LOAEL) from an appropriate animal or epidemiological study. This dose or concentration is then divided by uncertainty factors to calculate an RfD or RfC. Uncertainty factors are applied to account for limitations of the underlying data and are intended to ensure that the toxicity value calculated based on the data will be unlikely to result in adverse health effects in exposed human populations. For example, an uncertainty factor of 10 may be used to account for interspecies differences or to address the potential that human subpopulations such as children or the elderly may have increased sensitivity to a chemical's adverse effects.

In the case that quantitative data were available, we developed a chronic RfD and RfC for each organic acid. We then calculated the chemical concentration in drinking water that would result in a daily dose equivalent to the RfD (i.e., The chronic oral RfD was used to estimate a drinking water criterion for each organic acid using standard default exposure factors and the following equation (USEPA 1991):

$$C = \frac{THI \times BW \times AT}{EF \times ED \times IR \times \left(\frac{1}{RfDo} \right)}$$

Where:

- C = Chemical concentration in drinking water (mg/L)
- THI = Target hazard index, 1.0
- BW = Body weight of adult, 70 kg
- AT = Averaging time, 10,950 days (365 days/year for 30 years)
- EF = Exposure frequency, 350 days/year
- ED = Exposure duration, 30 years
- IR = Ingestion rate, 2 L/day
- RfDo = Oral reference dose, mg/kg-day

2.2.2 Ecological Toxicity Criteria

We summarized ecological toxicity data as reported in the literature. Median lethal and effective concentrations (LC50 and EC50, respectively) and median lethal dosages (LD50) were compiled. Longer-term toxicity values such as LOAELs and NOAELs were also summarized. No ecological toxicity criteria were developed here because of the receptor-specific nature of ecological toxicity reference values. However, the reported toxicity values can be used to support development of receptor-specific toxicity reference values, as needed in site-specific risk assessments.

3 TOXICITY DATA REVIEW: BSA

BSA is a colorless crystalline solid that is stable in air and soluble in water, alcohol, and other solvents (Lewis 1997). Basic information on chemical identity is presented in Figure 3-1.

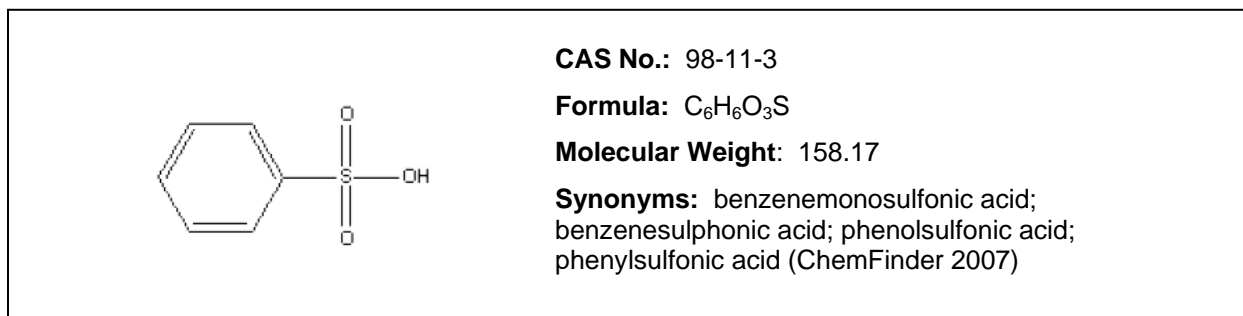


Figure 3-1. Chemical Identification: BSA.

Because few toxicity data were located for BSA, we also researched and summarized toxicological data for p-toluenesulfonic acid (pTSA), which is a well accepted toxicological surrogate for BSA (Denison 2004; Hernandez 2004; NOTOX 2004, 2007). Basic information on chemical identity for pTSA is presented in Figure 3-2.

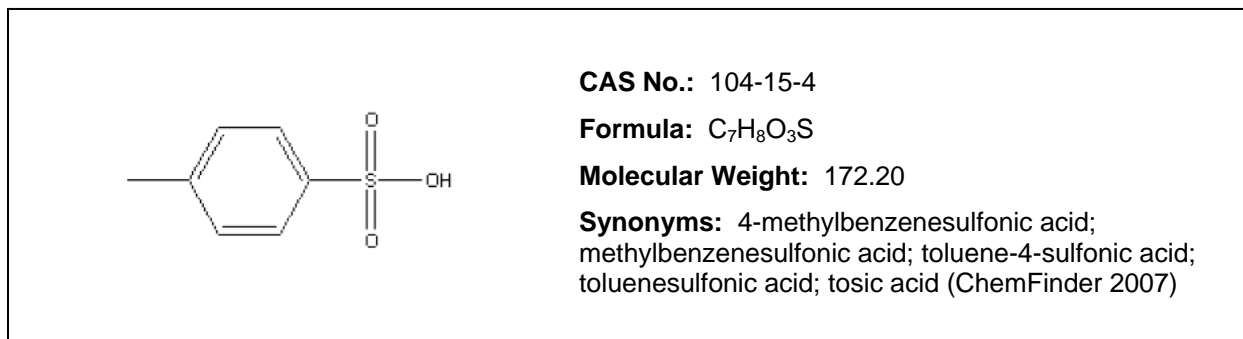


Figure 3-2. Chemical Identification: pTSA.

Compared to BSA, pTSA contains an extra methyl group para- to the sulfonic acid group. The extra methyl group exerts a weakly activating effect on the benzene ring, making it slightly more prone to electrophilic aromatic substitution. It also imparts an extra electron donating effect and resonance effect on the substance, both of which influence the acidity of the sulfonic group. These two effects work in opposing directions, and therefore, the overall acidity of the sulfonic group in pTSA is not expected to change significantly compared to that of BSA (NOTOX 2004, 2007).

An evaluation and assessment report on BSA, submitted under the USEPA's High Production Volume (HPV) Chemical Challenge Program, adopted pTSA as a toxicological surrogate

(NOTOX 2004). In comments responding to the HPV test plan, USEPA and Environmental Defense agreed with the selection of pTSA as an analog for health and ecological effects endpoints (Denison 2004; Hernandez 2004).

Greim et al. (1994) compiled and compared toxicological endpoints for sulfonic acids. The evaluation concluded that sulfonic acids behave in a toxicologically similar manner, and further supports the use of pTSA as a toxicological surrogate for BSA.

Data for BSA and pTSA are summarized here and were considered in the development of toxicological criteria.

3.1 HUMAN AND ANIMAL TOXICITY STUDIES

Toxicity data for BSA and its toxicological surrogate pTSA are summarized in Table 3-1.

Overall, the toxicity data for BSA and pTSA are sparse. No studies evaluating the toxicity of BSA or pTSA in humans were identified.

3.1.1 Carcinogenicity

The available data were not adequate to fully assess the carcinogenicity of BSA or pTSA. The results of short-term *in vitro* tests do, however, provide evidence that BSA and pTSA are not genotoxic carcinogens. The ability for short-term bioassays, including *in vitro* tests for bacterial mutagenicity and chromosomal breakage in cultured mammalian cells, to detect genotoxic carcinogens is well established (Waters et al. 1993). Two such tests were available for BSA and pTSA; *Salmonella* Ames assays for BSA and pTSA, and an assay for chromosomal aberrations with pTSA, all yielded negative results. No data to assess carcinogenicity via nongenotoxic mechanisms were located.

3.1.2 Noncarcinogenic Toxicity

The available data for evaluating noncarcinogenic adverse effects of BSA and pTSA are also limited. BSA and pTSA are both strong acids that are expected to show local effects in the gastrointestinal tract (NOTOX 2004, 2007). Acute oral toxicity tests in rats reported LD50s of 1,100 and 1,410 mg/kg body weight (bw) for BSA and pTSA, respectively.

No repeated dose toxicity studies were available for BSA, but a subchronic repeated dose study was available for pTSA. In this study, Wistar rats were orally dosed with pTSA at 0, 4, 20, 100, and 500 mg/kg bw for 28 days. Though we could not obtain the original study for review, the secondary summary of this study (NOTOX 2007) reported that no signs of morbidity or mortality were present at the highest dose tested. A NOAEL of >500 mg/kg-day was

established for this study. The reliability of this study was not assessed by the authors in the secondary reference (NOTOX 2007).

No chronic toxicity studies for either BSA or pTSA were located in the available literature. Additionally, none of the available studies evaluate reproductive or developmental endpoints.

3.1.3 Toxicity Criteria

There is no quantitative information from which to develop a carcinogenic toxicity criterion or a noncancer RfC for BSA. One study on pTSA can be used to develop an oral RfD.

Using the available toxicity data, we recommend a chronic RfD for BSA of 0.5 mg/kg-day. The RfD is derived from the subchronic NOAEL for pTSA of 500 mg/kg-day. An uncertainty factor of 1,000 was applied to the NOAEL to obtain the chronic oral RfD (10 for interspecies extrapolation, 10 to protect sensitive subgroups of human population, and 10 to extrapolate from a subchronic study to the chronic exposure period of interest).

Using the equation and standard USEPA assumptions described earlier, the RfD of 0.5 mg/kg-day equates to a drinking water criterion for BSA of 18 mg/L.

3.1.4 Discussion

Overall, the confidence in the RfD and corresponding drinking water criterion is low, given the limited amount of data available for BSA and its surrogate. There are several important sources of uncertainty that limit our confidence in the values.

First, the reliance on data from a toxicological surrogate imparts some uncertainty on the derived RfD. Given what is known about the reactivity of the compounds and the similarities in chemical properties and acute toxicity, pTSA is believed to be an appropriate toxicological surrogate for BSA toxicity. The use of a surrogate, however, imparts some uncertainty on the evaluation.

Second, as mentioned previously, the available studies for BSA and pTSA do not provide a comprehensive data set from which to evaluate toxicity. Primary references were not available, and therefore the details and quality of the studies could not be verified. Only one subchronic toxicity study is available, and therefore, effects that would be anticipated to occur following chronic exposure required extrapolation to account for the different exposure period. Also, the NOAEL used as the basis for the RfD is unbounded, given no effect was observed at the highest dose administered. Therefore, the true threshold could be much higher, and the toxicity criterion derived from the unbounded NOAEL conservative.

In addition, a full suite of noncancer endpoints was not examined. Given the high polarity and water solubility of BSA and pTSA, the substances are expected to be rapidly excreted and

minimally absorbed into systemic circulation (NOTOX 2004, 2007). Some toxicity evaluations (NOTOX 2004, 2007) based decisions not to conduct further toxicity studies on these properties. The lack of direct data for these timeframes and endpoints remain as sources of uncertainty in the evaluation, however.

Considering all of these factors the confidence in the recommended RfD is rated as low. The value, however, is believed to provide a conservative estimate of toxicity.

3.2 ECOLOGICAL TOXICITY

Table 3-2 summarizes the available ecological toxicity data for BSA and pTSA. Overall, few data are available to characterize potential ecological toxicity.

Available results for aquatic organisms that are relevant for assessing ecological toxicity include EC50 and LC50 values for invertebrates and fish, respectively. No toxicity studies of BSA or pTSA in terrestrial wildlife species were identified. Measures of acute toxicity in laboratory rats dosed with BSA or pTSA via oral administration are available. Only a single longer-term (28 day repeated dose) study was identified. This NOTOX Safety and Environmental Research BV (NOTOX) (2007) study summarized above evaluated the toxicity of pTSA in rats, and established a NOAEL of >500 mg/kg-day.

Overall, based on the available data, BSA is expected to be relatively nontoxic to ecological receptors.

4 TOXICITY DATA REVIEW: PCBSA

pCBSA is a gray crystalline solid that is soluble in water (ChemicalLand21.com 2000). Basic information on chemical identity is presented in Figure 4-1.

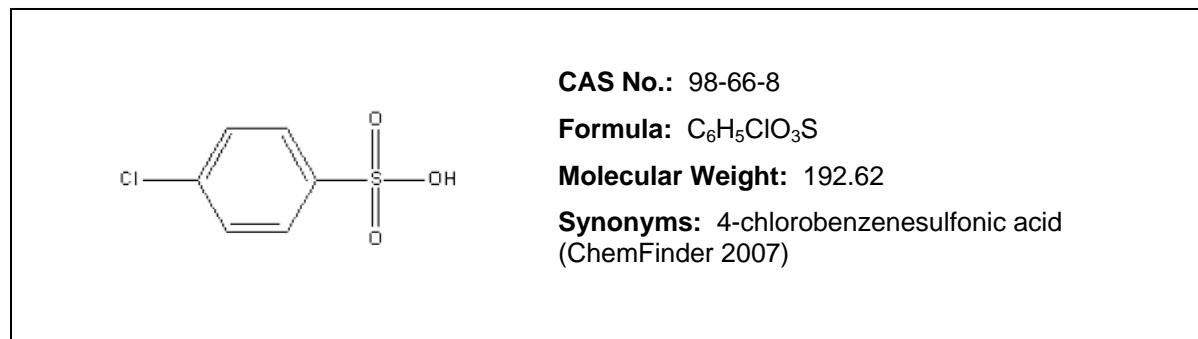


Figure 4-1. Chemical Identification: pCBSA.

No toxicological surrogates were identified for pCBSA. The Michigan Department of Environmental Quality (MDEQ) reviewed the structural analog 4-chlorobenzenesulfonate (chlorfenson) in their toxicological assessment of pCBSA (MDEQ 2006). MDEQ concluded that the analog is less water soluble and significantly more toxic than pCBSA. This structural analog was therefore not considered in our review here.

4.1 HUMAN AND ANIMAL TOXICITY STUDIES

Toxicity data for pCBSA are summarized in Table 4-1.

Overall, the toxicity data for pCBSA are sparse. No studies evaluating the toxicity of pCBSA in humans were identified.

4.1.1 Carcinogenicity

The available data were not adequate to fully assess the carcinogenicity of pCBSA. The results of short-term *in vitro* tests however, provide evidence that pCBSA is not a genotoxic carcinogen. The ability for short-term bioassays, including *in vitro* tests for bacterial mutagenicity and chromosomal breakage in cultured mammalian cells, to detect genotoxic carcinogens is well established (Waters et al. 1993). Negative results for three such tests for genotoxicity conducted in bacteria, mice, and rats, provide evidence that pCBSA is not a genotoxic carcinogen. No data to assess carcinogenicity via nongenotoxic mechanisms were located.

4.1.2 Noncarcinogenic Toxicity

The available data for evaluating noncarcinogenic effects of pCBSA is limited.

No acute toxicity data were identified for pCBSA. In a subchronic duration study, rats were dosed at 0, 10, 50, 1,000, and 2,000 mg/kg via oral gavage for 28 days (MDEQ 2006). Decreased bw, salivation, gasping, and irregular breathing were found in males in the 1,000 and 2,000 mg/kg dose groups. Because it was not apparent that the observed effects were related to treatment, the study established a NOAEL for male rats of 1,000 mg/kg-day. No effects were found in female rats in the highest dose group, and a NOAEL of 2,000 mg/kg-day was reported for female rats (MDEQ 2006). We could not obtain the primary reference so the test methods and interpretation could not be critically reviewed.

A teratogenicity screen conducted in rats administered "high" doses of pCBSA on days 7 and 16 of pregnancy, found no dose-related effects for the number of live births or offspring newborn weight (MDEQ 2006). No information on the doses administered, or method of dosing were provided. Therefore, the utility of this study in assessing dose-response is severely limited.

4.1.3 Toxicity Criteria

There is no quantitative information from which to develop a carcinogenic toxicity criterion or a noncancer RfC for BSA. The repeat dosing study in rats reported by MDEQ (2006), and described above, can be used to derive an RfD. This study also was used by MDEQ and the California Environmental Protection Agency (Cal/EPA) to develop a toxicity criterion to support development of drinking water standards for pCBSA.

Using the available toxicity data, we recommend a chronic RfD for pCBSA of 1 mg/kg-day. This RfD is derived from the NOAEL for male rats of 1,000 mg/kg-day. An uncertainty factor of 1,000 is applied to the NOAEL to obtain the RfD (10 for interspecies variability, 10 to protect sensitive subgroups of human population, and 10 for extrapolation from a subchronic study to a chronic exposure). This RfD is the same as that identified by MDEQ and Cal/EPA.

Using the equation and standard USEPA assumptions described earlier, the RfD of 1 mg/kg-day equates to a drinking water criterion for pCBSA of 37 mg/L.

4.1.4 Discussion

There is substantial uncertainty associated with the RfD and corresponding drinking water criterion recommended here. The available studies do not provide comprehensive information from which to evaluate toxicity. Only a single 28 day repeated dose study yielded results from which an RfD could be derived. The primary reference for this study was not available, so the study methods and interpretation could not be critically reviewed. The study duration was

subchronic, and therefore, effects that would be anticipated to occur following chronic exposure required extrapolation to account for the different exposure period. Due to its high water solubility, pCBSA is likely to be rapidly excreted in urine and is unlikely to accumulate in the body (MDEQ 2006); however, the lack of a chronic study remains a source of uncertainty in the assessment.

It is unclear whether the effects measured in male rats at 1,000 and 2,000 mg/kg-day in the subchronic study were caused by pCBSA or were related to some other factor. It is possible that the NOAEL from this study could be much higher than that used here to derive the RfD. Therefore, the established toxicity criterion may be conservative.

Considering all of these factors, the confidence in this RfD is rated as low. The value, however, is believed to provide a conservative estimate of toxicity.

4.2 ECOLOGICAL TOXICITY

Table 4-2 summarizes the available ecological toxicity data for pCBSA. Overall, few data are available to characterize potential ecological toxicity.

Acute toxicity data (LC50s) are available for *Daphnia magna*, though not for other aquatic species. No toxicity studies of pCBSA in terrestrial wildlife species were found. A limited number of studies in laboratory rats are available, and only a single repeated dose study with complete description of the doses tested was identified. The study established a NOAEL of 1000 mg/kg-day. However, the toxicological endpoints in this study have little relevance to assessing ecological toxicity. NOAELs for ecologically relevant endpoints are likely much higher.

Overall, based on the available data, pCBSA is expected to be relatively nontoxic to ecological receptors.

5 TOXICITY DATA REVIEW: PHTHALIC ACID

Phthalic acid is a colorless crystalline solid that is soluble in alcohol and sparingly soluble in water (Lewis 1997). Basic information on chemical identity is presented in Figure 5-1.

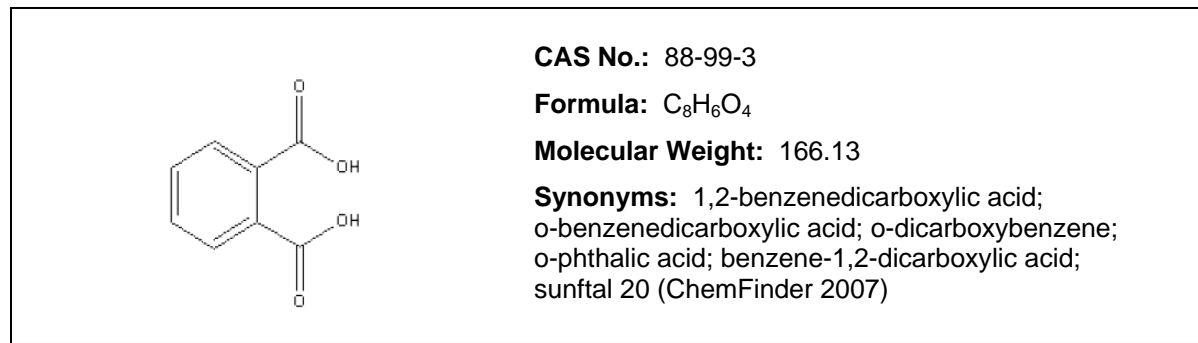


Figure 5-1. Chemical Identification: Phthalic Acid.

Because few toxicity data were located for phthalic acid, we also researched and summarized toxicological data for phthalic anhydride, which we have selected as a toxicological surrogate for phthalic acid. Phthalic anhydride is the anhydrous form of phthalic acid, and is readily hydrolyzed to the acid form when in contact with water. Therefore, it is assumed that the absorbed form of phthalic anhydride would be phthalic acid. This assumption is supported by the findings of Pfuffli (1986). Pfuffli (1986) reported that inhalation exposure to phthalic anhydride resulted in associated concentrations of phthalic acid in human urine.

Data for phthalic anhydride are presented only for those pathways, endpoints, and study durations for which there are no or minimal data on phthalic acid. Basic information on chemical identity for phthalic anhydride is presented in Figure 5-2.

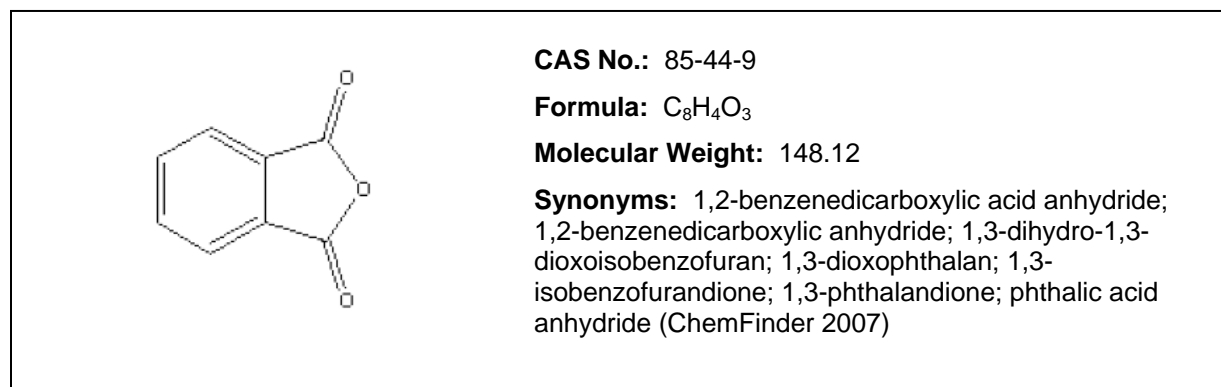


Figure 5-2. Chemical Identification: Phthalate Anhydride.

5.1 HUMAN AND ANIMAL TOXICITY STUDIES

Toxicity data for phthalic acid and its toxicological surrogate phthalic anhydride are summarized in Table 5-1.

5.1.1 Human Studies

Phthalic acid is a metabolite of various phthalic acid esters (PAEs) in humans and other mammals. The toxicokinetics of phthalic acid are only understood insofar as they are a metabolite of various PAEs. In the case of dietary exposure to di-(2-ethylhexyl) phthalate (DEHP), phthalic acid is formed as a secondary metabolite associated with hydrolysis of the mono-ester derivative (mono-ethylhexylphthalate) (ATSDR 2002). Phthalic acid is also a metabolite of diethyl phthalate and di-n-butyl phthalate (ATSDR 1995, 2001). Current evidence does not indicate further metabolism of phthalic acid in the mammalian system. Phthalic acid has been detected in human blood and urine, and is used as a biomarker of exposure to PAEs from both dietary sources and internal exposure from medical equipment (e.g., in dialysis patients).

In general, human occupational studies have included exposure to PAEs, as well as to both phthalic acid and phthalic anhydride, thus making it difficult to identify effects specific to phthalic acid. Inhalation exposures of workers to phthalic anhydride have been associated with conjunctivitis, rhinitis, rhinoconjunctivitis, asthma, and chronic bronchitis (OEHHA 2000). All of these potential adverse effects occur at the point of entry to the body and may not represent systemic effects associated with absorbed doses.

5.1.2 Carcinogenicity

No carcinogenicity studies have been published for phthalic acid. However, the National Cancer Institute (NCI) conducted two chronic dietary studies, in mice and rats, to evaluate phthalic anhydride for potential carcinogenicity. The NCI study concluded no evidence for carcinogenicity in mice or rats (NCI 1979).

5.1.3 Noncarcinogenic Toxicity

There are limited animal data available for phthalic acid. Table 5-1 provides a summary of available animal data that may be relevant to human health. Where little or no toxicity data were available for phthalic acid, toxicity data are provided for the identified surrogate, phthalic anhydride. Because acute data are available for phthalic acid, several acute studies available for phthalic anhydride are not included in Table 5-1. Acute toxicity data summarized in the RTECS database for phthalic anhydride have substantially lower LD50 values for oral exposure (ranging from 800 to 1,530 mg/kg for various mammals) than the LD50 of 2,530 mg/kg for oral

exposure to phthalic acid in the mouse (RTECS 2007a,b). The limited acute toxicity data suggest that phthalic anhydride is likely to be more acutely toxic to mammals than phthalic acid.

While PAEs have been found to be teratogenic and to have other reproductive effects in rodents, there are limited toxicological data for their metabolite, phthalic acid. Existing evidence suggests that the major active metabolites of PAEs are mono-esters, such as monobutyl phthalate (MBuP) and monobenzyl phthalate (MBeP). These active metabolites have been shown to act as teratogens (ATSDR 1995). Phthalic acid, on the other hand, has not been shown to be teratogenic in rodents at the relatively high dose of 1,763 mg/kg-day (Ema et al. 1997).

The most sensitive endpoint for PAE toxicity appears to be male reproductive toxicity (ATSDR 2002). For this reason, several PAE metabolites have been investigated for male reproductive effects. In the majority of cases, investigations have focused on the mono-esters and other intermediate metabolites. One male reproductive study of phthalic acid was identified and reviewed. The dominant lethality and spermhead abnormality study in rats found that phthalic acid has the potential to be a gene mutagen; however, the route of administration was intraperitoneal injection and the exposure duration was acute (1 day or 5 days) (Jha et al. 1998). Due to the nature of the study (both route of administration and exposure duration), the results cannot be used to estimate toxicity criteria that are relevant for environmental exposures. Other mutagenicity assays conducted for phthalic acid have not found it to be a potential gene mutagen (Phillips et al. 1982, NTP 2007, Agarwal et al. 1985).

Acute toxicity data are available for phthalic acid; however, these data are not relevant to subchronic or chronic exposures of interest here. No subchronic or chronic exposure studies of phthalic acid were located. One subchronic study of phthalic acid in rats was identified in the RTECS database; however, we were unable to obtain the primary study for evaluation. Critical effects identified in the RTECS database were changes in blood serum composition. Such effects may or may not be associated with clinical toxicity.

There are several chronic toxicity studies for the identified surrogate, phthalic anhydride. Two chronic dietary studies, in mice and rats, were conducted by the NCI to evaluate phthalic anhydride for potential carcinogenicity. These studies provide the most relevant toxicological data for human exposure under environmental conditions and were used by USEPA to develop an oral RfD (USEPA 2007a).

Phthalic anhydride was also implicated as a potential male reproductive toxin in rats at an inhalation dose of 0.2 mg/m³ in a small study conducted in 1970 (Protsenko 1970). In their chronic toxicity summary for phthalic anhydride, the Cal/EPA Office of Environmental Health Hazard Assessment (OEHHA) concluded that this result had not been verified or further explored in more recent toxicological or epidemiological studies. The small sample size of six per group further weakened their confidence in the result (OEHHA 2000). Neither USEPA nor

OEHHA used this inhalation study in the development of toxicity criteria. It is worth noting that rodents appear to be much more sensitive to male reproductive toxicity endpoints than other test animals, including nonhuman primates, when exposed to the parent compounds (PAEs) (ATSDR 2002).

5.1.4 Toxicity Criteria

Based upon the negative results of the NCI carcinogenicity study for phthalic anhydride, phthalic acid is not suspected of being a carcinogen; therefore, only toxicity criteria for noncancer health effects are presented in this report.

Oral Reference Dose

No established toxicity criteria were found for phthalic acid. USEPA has established an oral reference dose of 2 mg/kg-day for phthalic anhydride based upon the 1979 carcinogenicity study by NCI. The RfD is based upon the LOAEL of 1,562 mg/kg-day. An uncertainty factor of 1,000 was applied to the LOAEL to obtain the RfD (10 for interspecies extrapolation, 10 to protect sensitive subgroups of human population, and 10 to extrapolate from a LOAEL). The critical effects in this study were lung and kidney histopathology (USEPA 2007a). USEPA rates their confidence in the RfD for phthalic anhydride as medium since the NCI study was a well-designed long-term feeding study in two species, but there is a lack of reproductive toxicity data. Phthalic anhydride is considered an appropriate surrogate for absorbed doses of phthalic acid; therefore, we recommend an RfD of 2 mg/kg-day for phthalic acid.

Using the equation and standard USEPA assumptions described earlier, the RfD of 2 mg/kg-day equates to a drinking water criterion for phthalic acid of 73 mg/L.

Inhalation Reference Dose

USEPA has not established inhalation toxicity criteria for either phthalic acid or phthalic anhydride (USEPA 2007a). Cal/EPA OEHHA has developed a noncancer chronic reference exposure level (REL) for phthalic anhydride of 20 $\mu\text{g}/\text{m}^3$. This value is based upon a LOAEL of 2.3 mg/ m^3 for respiratory effects observed in study of 23 occupationally-exposed workers (Nielsen et al. 1988, 1991). An uncertainty factor of 100 was applied to the LOAEL (10 for extrapolation from a LOAEL to a NOAEL, and 10 for intraspecies variation) to obtain the REL of 0.02 mg/ m^3 (20 $\mu\text{g}/\text{m}^3$) (OEHHA 2000). The REL is analogous to an inhalation RfC.

The REL was developed from an occupational exposure study. Uncertainties in the LOAEL determined by the study included estimating actual individual exposure and variability in exposure concentration, the potential low exposures of the group considered as controls, potential confounding by exposure to other chemicals, and the lack of observation of a NOAEL. OEHHA identified the lack of reproductive and developmental toxicity studies as an additional

source of uncertainty (OEHHA 2000). It is recommended that the REL of 20 $\mu\text{g}/\text{m}^3$ for phthalic anhydride be used as an inhalation RfC for phthalic acid.

5.2 DISCUSSION

The limited available toxicological evidence suggests that phthalic acid does not share the toxicity of its parent compounds, the PAEs. Based upon expected rapid hydrolysis of phthalic anhydride to phthalic acid in the body combined with the greater reactivity and acute toxicity of phthalic anhydride compared with phthalic acid, phthalic anhydride is considered an appropriate toxicological surrogate for phthalic acid for the ingestion pathway. This assumption is supported by the finding that the LOAEL for phthalic acid from a dietary reproductive study in which rats were exposed for 10 days is similar to the LOAEL for phthalic anhydride from a dietary study in which mice were exposed for 2 years. The LOAEL for phthalic acid for reproductive effects in the rat was 1,763 mg/kg-day, and the chronic LOAEL for phthalic anhydride for histopathological signs of toxicity in the mouse was 1,562 mg/kg-day. The similarity of these results provides further indication that the toxicity of absorbed doses of phthalic acid and phthalic anhydride are likely to be similar in nature and magnitude.

For the inhalation pathway, the use of phthalic anhydride as a toxicological surrogate involves greater uncertainty, since observed toxic effects of phthalic anhydride on the human respiratory system may reflect the different reactivity of phthalic anhydride at the point of entry to the body and not systemic effects associated with an absorbed dose. Thus, the toxic effects exhibited by inhaled phthalic anhydride may not be exhibited by inhaled phthalic acid.

The potential for male reproductive toxicity at high doses is a source of uncertainty for both phthalic anhydride and phthalic acid, although indications from related chemicals (PAEs) are that these effects may be specific to rodents. Despite the uncertainties associated with limited toxicological data, use of the oral RfD and inhalation REL as toxicity criteria for phthalic acid to estimate human health risk are likely to overestimate potential risk. The oral RfD of 2 mg/kg-day and the REL of 20 $\mu\text{g}/\text{m}^3$ are conservative values that include multiple uncertainty factors designed to provide protection even to sensitive subgroups of the human population.

Given the substantial number of well designed studies evaluating a variety of toxicity endpoints for phthalic anhydride, and the adequacy of this surrogate for phthalic acid, the confidence in the RfD is rated as medium. The confidence in the RfC is rated as low due to the large number of uncertainties surrounding the occupational study from which the value is derived. The values, however, are believed to provide conservative estimates of toxicity.

5.3 ECOLOGICAL TOXICITY

Table 5-2 summarizes the available ecological toxicity data for phthalic acid and phthalic anhydride.

Several LC50s and no-observed-effect concentrations (NOECs) are available for aquatic species. No toxicity studies of phthalic acid or phthalic anhydride in terrestrial wildlife species were found. An LD50 for rats, as well the LOAELs and NOAELs described above for reproductive endpoints in rodents, are regarded as the most appropriate from which to evaluate potential toxicity in terrestrial wildlife.

Overall, based on the available data, phthalic acid is expected to be relatively nontoxic to ecological receptors.

6 SUMMARY OF FINDINGS

This report summarized human health and ecological toxicity information for BSA, pCBSA, and phthalic acid, which have been identified as SRCs for the former Montrose and Stauffer facilities within the BMI Complex in Henderson, Nevada. Human health toxicological criteria and drinking water concentration criteria were developed for each of these compounds using the available data for the SRC or its established surrogate. Ecological toxicity data were summarized and can be used to support the development of receptor-specific toxicity reference values as needed in any subsequent risk assessments. Overall, these organic acids are expected to be relatively nontoxic to ecological receptors.

The human health toxicity criteria and corresponding drinking water concentration criteria are summarized in below.

Site Related Chemical	RfC ($\mu\text{g}/\text{m}^3$)	Oral RfD (mg/kg-day)	Drinking Water Criterion (mg/L)
BSA	--	0.5	18
pCBSA	--	1	37
Phthalic acid	20	2	73

Overall, few data were available to support the development of these values and as a result there is uncertainty associated with the RfDs and corresponding drinking water criteria recommended here. However, modifying factors were applied to the relevant toxicity criteria identified in our literature search and critical review to account for this uncertainty. Therefore, the calculated toxicity criteria and drinking water concentration are believed to represent conservative estimates of protective exposure level concentrations.

7 REFERENCES

- Agarwal, D.K., W.H. Lawrence, L.J. Ninuz, and J. Autian. 1985. Mutagenicity evaluation of phthalic acid esters and metabolites in *Salmonella typhimurium* cultures. *J. Toxicol. Environ. Health.* 16(1):61-9.
- American Biogenics Corporation. 1985. Final report for American Biogenics Corporation study 410-2298: Twenty-eight day oral (gavage) toxicity study in albino rats using A-100. American Biogenics Corporation. (not seen, as cited in MDEQ 2006).
- ATSDR. 1995. Toxicological profile for diethyl phthalate. www.atsdr.cdc.gov/toxpro2.html. Accessed on July 12, 2007. Agency for Toxic Substances and Disease Registry, Department of Health and Human Services.
- ATSDR. 2001. Toxicological profile for di-*n*-butyl phthalate. www.atsdr.cdc.gov/toxpro2.html. Accessed on July 12, 2007. Agency for Toxic Substances and Disease Registry, Department of Health and Human Services.
- ATSDR. 2002. Toxicological profile for di(2-ethylhexyl)phthalate. www.atsdr.cdc.gov/toxpro2.html. Accessed on July 12, 2007. Agency for Toxic Substances and Disease Registry, Department of Health and Human Services.
- ChemFinder. 2007. ChemFinder.Com Database & Internet Searching home page. <http://chemfinder.cambridgesoft.com/>. Accessed on July 12, 2007. CambridgeSoft Corporation, Cambridge, MA.
- ChemicalLand21.com. 2000. 4-chlorobenzenesulfonic acid. www.chemicalland21.com. Accessed on November 2, 2007. Arokor Holdings Inc.
- Chernoff, N., and M. Rosen. 1985. Study of teratogenic potential of Na parachlorobenzene sulfonic acid. Health Effects Research Laboratory Developmental Biology Division. Research Triangle Park, N.C. (not seen, as cited in MDEQ 2006).
- Denison, R. 2004. Personal communication (email to opt.ncic@epa.gov, hpv.chemrtk@epa.gov, boswell.karen@epa.gov, chem..rtk@epa.gov, MTC@mchsi.com, and William.smock@verizon.net, dated February 17, 2004, regarding Environmental Defense comments on Benzene Sulfonic Acid (CAS# 98-11-3)). U.S. Environmental Protection Agency, Washington, DC.
- Dowden, B.F., and H.J. Bennett. 1965. Toxicity of selected chemicals to certain animals. *J. Water Pollut. Control Fed.* 37(9):1308-1316.

Ema, M., E. Miyawaki, A. Harazono, and K. Kawashima. 1997. Developmental toxicity evaluation of phthalic acid, one of the metabolites of phthalic acid esters, in rats. *Toxicology Letters*. 93:109-115.

Graham, B.E., and M.H. Kuizenga. 1945. Toxicity studies on benzyl benzoate and related benzyl compounds. *J. Pharmacol Exp Ther* 84:358-362. (not seen, as cited in RTECS 2007c).

Greim, H., J. Ahlers, R. Bias, B. Broecker, H. Hollander, H.P. Gelbke, H.J. Klimisch, I. Mangelsdorf, A. Paetz, N. Schong, G. Stropp, R. Vogel, C. Weber, K. Ziegler-Skylakakis, and E. Bayer. 1994. Toxicity and ecotoxicity of sulfonic acids: structure activity relationship. *Chemosphere*. 28(12): 2203-2236.

Hernandez, O. 2004. Personal communication (letter to W. Smock, Aromatic Sulfonic Acids Association, Washington, DC, dated February 26, 2004, regarding the transmittal of EPA's comment on the robust summaries and test plan for Benzenesulfonic Acid posted on the ChemRTK HPV Challenge Program Web site). U.S. Environmental Protection Agency.

Hoechst, A.G. 1981. Akute toxisitaet von p-toluolsulfonsaeure loesung an Goldorfen. Bericht 197/81. (not seen, as cited in NOTOX 2004).

Hoechst, A.G. 1988a. p-toluolsulfonsaeure: Pruefung der akuten oralen toxisitaet an der wistar-ratte. Bericht 88.1563, 1988. (not seen, as cited in NOTOX 2004, 2007).

Hoechst, A.G. 1988b. EXT 8804 p-toluenesulfonic acid: reverse mutation assay in vitro ames test. Bericht 88.0892, 1988. (not seen, as cited in NOTOX 2004, 2007).

Hoechst, A.G. 1988c. p-toluolsulfonsaeure: chromosome aberrations in vitro in V79 chinese hamster cells, Report No. 88.1940. 1988. (not seen, as cited in NOTOX 2004, 2007).

Hoechst, A.G. 1990. Internal report No. 900037 in IUCLID dataset toluene-4-sulfonic acid (CAS No. 104-15-5) on IUCLID CD-ROM, 2000 (not seen, as cited in NOTOX 2004, 2007).

Jha, A.M., A.C. Singh, and M. Bharti. 1998. Germ cell mutagenicity of phthalic acid in mice. *Mutation Res*. 422:207-212.

Lewis, R.J. 1997. *Hawley's condensed chemical dictionary*. Thirteenth Edition. John Wiley & Sons. New York.

MDEQ. 2006. Toxicological assessment for Part 201 criteria/213 RBSL development, para-chlorobenzoic acid, CAS #98-66-8. January 2006. Michigan Department of Environmental Quality, Remediation and Redevelopment Division, MI.

Merck. 1976. *The Merck index*. 9th ed. Merck & Co., Inc., Rahway, NJ. 959 pp. (not seen, as cited in NTP 2006).

- NCI. 1979. Bioassay of phthalic anhydride for possible carcinogenicity, TR-159. <http://ntp.niehs.nih.gov>. Accessed on May 24, 2007. National Cancer Institute, National Toxicology Program, Department of Health and Human Services. (not seen, as cited in USEPA 2007a).
- Nielsen, J., H. Welinder, A. Schutz, and S. Skerfving. 1988. Specific serum antibodies against phthalic anhydride in occupationally exposed subjects. *J Allergy Clin. Immunol.* 82:126-133. (not seen, as cited in OEHHA 2000).
- Nielsen, J., I. Bensryd, H. Almquist, M. Dahlqvist, H. Welinder, R. Alexandersson, and S. Skerfving. 1991. Serum IgE and lung function in workers exposed to phthalic anhydride. *Int. Arch. Occup. Environ. Health.* 63:199-204. (not seen, as cited in OEHHA 2000).
- Nishiuchi, Y. 1980. Toxicity of formulated pesticides to fresh water organisms. LXXIV. *The Aquiculture /Suisan Zoshoku.* 28(2):107-112 (JPN). (not seen, as cited in USEPA 2007b).
- NOTOX. 2004. HPV assessment report on benzenesulfonic Acid, CAS No. 98-11-3. Submitted on behalf of the Aromatic Sulfonic Acids Association, Washington, DC. NOTOX Safety and Environmental Research BV. May 10.
- NOTOX. 2007. HPV assessment report on p-toluenesulfonic acid, CAS No. 104-15-4. Submitted on behalf of the p-Toluenesulfonic Acid Coalition, Washington DC. NOTOX Safety and Environmental Research BV. June.
- NTP. 2006. CAS Registry Number: 88-99-3. <http://ntp.niehs.nih.gov/index.cfm?objectid=E883EF77-BDB5-82F8-F7570577D5465009>. Accessed on July 24, 2007. Last updated on April 3, 2006. National Toxicology Program: Department of Health and Human Services, Research Triangle Park, NC.
- NTP. 2007. Testing status of agents at NTP, phthalic acid, CAS No. 88-99-3. <http://ntp.niehs.nih.gov>. Accessed on May 24, 2007. National Toxicology Program, Department of Health and Human Services.
- OEHHA. 2000. Chronic toxicity summary, phthalic anhydride, determination of noncancer chronic reference exposure levels B \ batch 2A, December. www.oehha.ca.gov/air/chronic_rels/pdf/85449.pdf. Accessed on August 1, 2007. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment.
- Pfuffli, P. 1986. Phthalic acid excretion as an indicator of exposure to phthalic anhydride in the work atmosphere. *Int. Arch. Occup. Environ. Health.* 58 (3):209-216.

Pharmakon Research International Inc. 1985a. Ames salmonella/microsome plate test (EPA/OECD). Ph 301-EPA-001-85, 4 chlorobenzene sulfonic acid. Lot E-2663. Pharmakon Research International Inc., Waverly, PA. (not seen, as cited in MDEQ 2006).

Pharmakon Research International Inc. 1985b. L5178Y mouse lymphoma cell TK +/- forward mutation assay. Ph 313-EPA-001-85, 4 chlorobenzene sulfonic acid. Lot E-2663. Pharmakon Research International Inc., Waverly, PA. (not seen, as cited in MDEQ 2006).

Pharmakon Research International Inc. 1985c. In vivo bone marrow cytogenetics rate metaphase analysis. Ph 313-EPA-001-85, 4 chlorobenzene sulfonic acid. Lot E-2663. Pharmakon Research International Inc., Waverly, PA. (not seen, as cited in MDEQ 2006).

Phillips, B.J., T.E. James, and S.D. Gangolli. 1982. Genotoxicity studies of di(2-ethylhexyl)phthalate and its metabolites in CHO cells. *Mutation Res.* 102(3):297-304.

Product Investigations Inc. 1992. Initial submission: primary skin irritation of para toluene sulfonic acid in humans with cover letter dated 080792. TSCATS Document Number: TSCATS/450151. Entry date: January 2003. Abstract only.

Protsenko, E.I. 1970. Effect of phthalic anhydride on gonads. *Gig. Sanit.* 35:127-130. [in Russian]. (not seen, as cited in OEHHA 2000).

RTECS. 2007a. Registry of Toxic Effects of Chemical Substances database: Phthalic acid, RTECS Number TH9625000 (Cas No. 88-99-3). <http://ccinfoweb.ccohs.ca/rtecs/search.html>. Accessed on August 3, 2007. Canadian Centre for Occupational Health and Safety.

RTECS. 2007b. Registry of Toxic Effects of Chemical Substances database: Phthalic anhydride, RTECS Number TI3150000 (CAS No. 85-44-9). <http://ccinfoweb.ccohs.ca/rtecs/search.html>. Accessed on August 3, 2007. Canadian Centre for Occupational Health and Safety.

RTECS. 2007c. Registry of Toxic Effects of Chemical Substances database: Benzenesulfonic acid, RTECS Number DB4200000 (Cas No. 98-11-3). <http://ccinfoweb.ccohs.ca/rtecs/search.html>. Accessed on August 3, 2007. Canadian Centre for Occupational Health and Safety.

Schafer, E.W. 1972. The acute oral toxicity of 369 pesticidal, pharmaceutical, and other chemicals to wild birds. *Toxicol. and Appl. Pharmacol.* 21(3):315-330.

Schafer, E.W., R.B. Brunton, E.C. Schafer, and G. Chavez. 1982. Effects of 77 chemicals on reproduction in male and female coturnix quail. *Ecotoxicol. Environ. Saf.* 6:149-156.

Smythe, H.F., C.P. Carpenter, C.S. Weil, U.C. Pozzani, and J.A. Stiegel. 1962. *American Ind. Hygiene Association Journal.* 23: 95-107. (not seen, as cited in NOTOX 2004, 2007).

Streufert, J.M. 1977. Some effects of two phthalic acid esters on the life cycle of the midge (*Chironomus plumosus*). M.S.Thesis, Univ.of Missouri, Columbia, MO. (not seen, as cited in USEPA 2007b).

Tsuji, S., Y. Tonogai, Y. Ito, and S. Kanoh. 1986. The influence of rearing temperatures on the toxicity of various environmental pollutants for killifish (*Oryzias latipes*). *J.Hyg.Chem. (Eisei Kagaku)*. 32(1):46-53 (JPN) (ENG ABS). (not seen, as cited in USEPA 2007b).

USEPA. 1988. Petition to delist phthalic anhydride. Internal memorandum from L.M. Randecker to R. Kent. U.S. Environmental Protection Agency, Chemical Review and Evaluation Branch, Health and Environmental Review Division, Office of Pesticides and Toxic Substances, Washington, DC. (not seen, as cited in USEPA 1994b).

USEPA. 1989. Risk assessment guidance for Superfund: volume 1, human health evaluation manual, part 1, interim final. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response, Washington, DC. December.

USEPA. 1991. Risk assessment guidance for Superfund: volume 1, human health evaluation manual, part B, development of risk-based preliminary remediation goals, interim. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response, Washington, DC. December.

USEPA. 1993. Reference dose (RfD): description and use in health risk assessments. Available at: www.epa.gov/iris/rfd.htm. Last updated on January 25, 2007. U.S. Environmental Protection Agency.

USEPA. 1994a. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F. Available at: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993>. U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Washington, DC. October.

USEPA. 1994b. OPPT chemical fact sheets. (Phthalic anhydride) fact sheet: support document. (CAS No. 85-44-9). EPA 749-F-95-016a. Available at: www.epa.gov/chemfact/phtha-sd.txt. U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC.

USEPA. 2002. A review of the reference dose and reference concentration processes. Final Report. EPA/630/P-02/002F. Available at: www.epa.gov/iris/RFD_FINAL%5b1%5d.pdf. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. December.

USEPA. 2005a. Guidelines for carcinogen risk assessment. EPA/630/P-03/001F. Available at: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283>. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. March.

USEPA. 2005b. Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. EPA/630/R-03/003F. Available at: www.epa.gov/IRIS/children032505.pdf. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. March

USEPA. 2007a. Integrated Risk Information System. Available at: www.epa.gov/iris/subst/0308.htm. Accessed on May 23, 2007. U.S. Environmental Protection Agency.

USEPA. 2007b. ECOTOX Database. Available at: <http://cfpub.epa.gov/ecotox/>. Accessed on July 24, 2007. Last updated on July 31, 2007. U.S. Environmental Protection Agency, Duluth, MN.

Waters, M.D., H.F. Stack, M.A. Jackson, and B.A. Bridges. 1993. Hazard identification: efficiency of short-term tests in identifying germ cell mutagens and putative nongenotoxic carcinogens. *Environ. Health Perspect Suppl.* 101 (Suppl 3): 61-72.

Zeiger, E., B. Anderson, S. Haworth, T. Lawlor, K. Mortelmans. 1988. Salmonella mutagenicity tests: IV. Results from the testing of 300 chemicals. *Environ. Mol. Mutagen.* 11(Suppl. 12): 1-158. (not seen, as cited in NOTOX 2004, 2007).

1967. *Gigiena I Sanitariya.* 32(8): 12. (not seen, as cited in RTECS 2007a).

1992. *J. American College of Toxicol.* 1(Part B): 711. (not seen, as cited in RTECS 2007a).

Table 3-1. Human Health Toxicity Data for Benzenesulfonic Acid and p-Toluenesulfonic Acid, by Test Category.

Chemical of Interest	Test Organism	Endpoint	Test Effects ^a	Measure	Result	Study Detail	Primary Reference	Secondary Reference
Genotoxicity								
BSA	Bacteria (<i>Salmonella typhimurium</i>)	Genotoxicity	<i>in vitro</i> mutation	Positive/Negative	Negative	Ames test. Cell type: <i>Salmonella typhimurium</i> TA97, TA98, TA100, and TA1535. Tested with and without metabolic activation. Dosing: 0-10,000 mg/plate. OECD Guideline 471.	Zeiger et al. 1988	NOTOX 2004, 2007
pTSA (surrogate)	Bacteria (<i>Salmonella typhimurium</i>)	Genotoxicity	<i>in vitro</i> mutation	Positive/Negative	Negative	Ames test. Cell type: <i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537, and TA1538. Tested with and without metabolic activation. Dosing: 0-5,000 mg/plate.	Hoechst 1988a	NOTOX 2004, 2007 Product Investigations Inc. 1992
pTSA (surrogate)	V79 Chinese Hamster cells	Genotoxicity	Chromosomal aberration	Positive/Negative	Negative	Tested with and without metabolic activation. Dosing: 0-1,902 mg/mL. Endpoint criteria: classified as positive if test substances induce significantly increased aberration rate compared to controls. OECD Guideline 471.	Hoechst 1988b	NOTOX 2004, 2007 Product Investigations Inc. 1992
Acute Toxicity								
BSA	Rat	Mortality	Mortality over 14 days	LD50	1,100 mg/kg	Test population: Cartworth-Wistar rats; 5 males/dose. Dosing: oral by unspecified method, a logarithmic series of single doses differing by a factor of 2.	Smythe et al. 1962	NOTOX 2004, 2007
BSA	Cat	Mortality	ND	LDLo	10,000 mg/kg	Administration to the skin.	Graham and Kuizenga 1945	RTECS 2007c
pTSA (surrogate)	Rat	Mortality	Mortality over 28 days	LD50	1,410 mg/kg	Test population: Wistar rats; 5/sex/dose. Dosing: oral gavage; females at 1250, 1600, and 2000 mg/kg; males dosed at 2000 mg/kg. Endpoint: Clinical signs also measured. OECD Guideline 401.	Hoechst 1988c	NOTOX 2004, 2007 Product Investigations Inc. 1992 Greim et al. 1994
Repeated Dose Toxicity								
pTSA (surrogate)	Rat	Morbidity and Mortality	Bodyweight, Hematology, Clinical biochemistry, Pathology, Histopathology, Mortality	NOAEL	>500 mg/kg-day	Test population: Wistar rats; male/female (unspecified number of animals). Dosing: oral daily, 28 days, by unspecified method; 0, 4, 20, 100, 500 mg/kg bw/d OECD Guide-line 407.	Hoechst 1990	NOTOX 2004, 2007 Product Investigations Inc. 1992 Greim et al. 1994

Notes: BSA = benzenesulfonic acid
LD50 = median lethal dose
LDLo = lowest published lethal dose
ND = not defined
NOAEL = no-observed-adverse-effects level
pTSA = p-toluenesulfonic acid

^a Effects listed are those evaluated in the study. In cases that specific endpoints tested for were not described, test effects are listed as ND. For mortality, if the duration over which mortality was evaluated was not described, the test effect is additionally listed as ND.

Table 3-2. Ecological Toxicity Data for Benzenesulfonic Acid and p-Toluenesulfonic Acid.

Chemical of Interest	Receptor (pathway)	Organism	Common Name	Endpoint	Measure	Result	Primary Reference	Secondary Reference
BSA	Bird (Oral)	ND	ND	Mortality	LD50	75 mg/kg	Schafer 1972	RTECS 2007c
pTSA (surrogate)	Bird (Oral)	<i>Coturnix coturnix</i>	Quail	Mortality	LD50	>316 mg/kg	Schafer et al. 1982	--
BSA	Invertebrate	ND	ND	Morbidity	EC50 (48h) ^a	963,000 mg/L	Hoechst 1981	NOTOX 2004
BSA	Fish	ND	ND	Mortality	LC50 (96h) ^a	1,120,000 mg/L	Hoechst 1981	NOTOX 2004
BSA	Cat (Dermal)	ND	ND	Mortality	LDLo	10,000 mg/kg	Graham and Kuizenga 1945	RTECS 2007c
BSA	Rodent (Oral)	ND	Rat	Mortality	LD50	1,100 mg/kg	Smythe et al. 1962	NOTOX 2004
pTSA (surrogate)	Rodent (Oral)	ND	Rat	Mortality	LD50	1,410 mg/kg	Hoechst 1988a	NOTOX 2004
pTSA (surrogate)	Rodent (Oral)	ND	Rat	Morbidity, Morality	NOAEL	>500 mg/kg-day	Hoechst 1990	NOTOX 2007

Notes: BSA = benzenesulfonic acid
 EC50 = median effective concentration
 LC50 = median lethal concentration
 LD50 = median lethal dose
 LDLo = lowest published lethal dose
 ND = not defined
 NOAEL = no-observed-adverse-effects level
 pTSA = p-toluenesulfonic acid
 -- = not applicable

^a Calculated value as presented in NOTOX 2004.

Table 4-1. Human Health Toxicity Data for p-Chlorobenzenesulfonic Acid, by Test Category.

Test Organism	Endpoint	Test Effects ^a	Measure	Result	Study Detail	Primary Reference	Secondary Reference
Genotoxicity							
Bacteria (<i>Salmonella typhimurium</i>)	Genotoxicity	<i>in vitro</i> mutation	Positive/Negative	Negative	Ames test. Dosing: 50-1,000 mcg/ml. Tested with and without metabolic activation.	Pharmakon Research International, 1985a	MDEQ 2006
L5178 Y Mouse lymphoma cells	Genotoxicity	Mutation frequency	--	No increase	Dosing: 50-1,000 mcg/mL. Tested with and without metabolic activation. Endpoint: Mutations at the thymidine kinase location.	Pharmakon Research International, 1985b	MDEQ 2006
Rat	Genotoxicity	Chromosomal aberrations in bone marrow, incidence	--	No increase	Test population: male rats. Dosing: oral gavage, 2,000 mg/kg. Sacrifice: 6, 12, and 24 hours post treatment.	Pharmakon Research International, 1985c	MDEQ 2006
Repeated Dose Toxicity							
Rat	Morbidity, Mortality, Growth	ND	NOAEL	Female: 2,000 mg/kg-day; Male: 1,000mg/kg-day	Test population: 10 rats/sex/dose group. Dosing: daily, 28 days via oral gavage; 0, 10, 50, 1,000, and 2,000 mg/kg-bw.	American Biogenics Inc. 1985	MDEQ 2006
Rat	Reproductive, Developmental	Number of live births; newborn weight	--	No dose related effects	Test population: pregnant female rats. Dosing: high doses of pCBSA on days 7 and 16 of pregnancy (method unspecified).	Chernoff and Rosen 1985	MDEQ 2006

Notes: ND = not defined
 NOAEL = no-observed-adverse-effects level
 pCBSA = p-chlorobenzenesulfonic acid
 -- = not applicable

^a Effects listed are those evaluated in the study. In cases that specific endpoints tested for were not described, test effects are listed as ND. For mortality, if the duration over which mortality was evaluated was not described, the test effect is additionally listed as ND.

Table 4-2. Ecological Toxicity Data for p-Chlorobenzenesulfonic Acid.

Receptor (pathway)	Organism	Common Name	Endpoint	Measure	Result	Primary Reference	Secondary Reference
Invertebrate	<i>Daphnia magna</i>	Water flea	Mortality	LC50 (24h)	8,600 mg/L	Dowden and Bennett 1965	--
Invertebrate	<i>Daphnia magna</i>	Water flea	Mortality	LC50 (48h)	7,659 mg/L	Dowden and Bennett 1965	--
Invertebrate	<i>Daphnia magna</i>	Water flea	Mortality	LC50 (72h)	3,964 mg/L	Dowden and Bennett 1965	--
Invertebrate	<i>Daphnia magna</i>	Water flea	Mortality	LC50 (96h)	2,150 mg/L	Dowden and Bennett 1965	--
Rodent (Oral)	ND	Rat	Morbidity, Mortality, Growth	NOAEL	Female: 2,000 mg/kg-day; Male: 1,000 mg/kg-day	American Biogenics Corp. 1985	MDEQ 2006
Rodent (Oral)	ND	Rat	Reproductive, Developmental	--	No dose related effects	Chernoff and Rosen 1985	MDEQ 2006

Notes: LC50 = median lethal concentration
 ND = not defined
 NOAEL = no-observed-adverse-effects level
 -- = not applicable

Table 5-1. Human Health Toxicity Data for Phthalic Acid and Phthalic Anhydride, by Test Category.

Chemical of Interest	Test Organism	Endpoint	Test Effects ^a	Measure	Result	Study Detail	Primary Reference	Secondary Reference
Reproductive Toxicity								
Phthalic acid	Rat	Reproduction	Corpora lutea per litter; live fetuses/litter; postimplantation loss; sex ratios of live fetuses; external, internal and skeletal malformations in fetuses; fetal weight; degree of ossification.	NOAEL	1,763 mg/kg-day	Teratogenicity study. Test population: pregnant Wistar rats;11 females/dose. Dosing: dietary, ad libitum at 0, 1.25, 2.5, or 5.0% (mean daily intake of 0, 1,021, 1,763, and 2,981 mg/kg-bw) on day 7 through 16 of pregnancy.	Ema et.al. 1997	--
Phthalic acid	Rat	Reproduction	Decreased fetal weight in males, lesser degree of ossification.	LOAEL	2,981 mg/kg-day	Teratogenicity study. Test population: pregnant Wistar rats;11 females/dose. Dosing: dietary, ad libitum at 0, 1.25, 2.5, or 5.0% (mean daily intake of 0, 1,021, 1,763, and 2,981 mg/kg-bw) on day 7 through 16 of pregnancy.	Ema et.al. 1997	--
Phthalic acid	Rat	Growth	Maternal food consumption, maternal weight gain.	NOAEL	1,021 mg/kg-day	Maternal toxicity evaluation in teratogenicity study. Test population: pregnant Wistar rats;11 females/dose. Dosing: dietary, ad libitum at 0, 1.25, 2.5, or 5.0% (mean daily intake of 0, 1,021, 1,763, and 2,981 mg/kg-bw) on day 7 through 16 of pregnancy.	Ema et.al. 1997	--
Phthalic acid	Rat	Growth	Maternal food consumption, maternal weight gain.	LOAEL	1,763 mg/kg-day	Maternal toxicity evaluation in teratogenicity study. Test population: pregnant Wistar rats;11 females/dose. Dosing: dietary, ad libitum at 0, 1.25, 2.5, or 5.0% (mean daily intake of 0, 1,021, 1,763, and 2,981 mg/kg-bw) on day 7 through 16 of pregnancy.	Ema et.al. 1997	--
Phthalic acid	Mouse	Reproduction	Percent pregnant females, live implants/female, dead implants/female	LOAEL	40 mg/kg-day	Dominant lethality assay. Test population: male Swiss albino mice, 10-12 weeks old, 20/group. Dosing: 1 intraperitoneal injection of 40 mg/kg-bw or 80 mg/kg-bw per day for 5 days. Each male bred to 2 different females for each period 1-7, 8-14, 15-21, and 22-28 days post treatment.	Jha et.al. 1998	--
Phthalic acid	Mouse	Reproduction	Number of abnormal sperm	NOAEL	50 mg/kg	Spermhead abnormality assay. Test population: male Swiss albino mice, 5/group. Dosing: 1 intraperitoneal injection of 50, 100, 150, 200, and 300 mg/kg-bw.	Jha et.al. 1998	--
Phthalic anhydride (surrogate)	Rat	Reproduction	Sperm motility	NOAEL	0.02 mg/m ³	Male reproduction study. Test population: rats, 6/group.	Protsenko 1970	OEHA 2000
Phthalic anhydride (surrogate)	Rat	Reproduction	Sperm motility	LOAEL	0.2 mg/m ³	Male reproduction study. Test population: rats, 6/group.	Protsenko 1970	OEHA 2000
Genotoxicity								
Phthalic acid	Bacteria (<i>Salmonella typhimurium</i>)	Genotoxicity	<i>in vitro</i> mutation	Positive/Negative	Negative	Ames test. Tested with and without metabolic activation.	Agarwal et.al. 1985	--
Phthalic acid	Bacteria (<i>Salmonella typhimurium</i>)	Genotoxicity	<i>in vitro</i> mutation	Positive/Negative	Negative	Ames test. Dosing: 33 - 10,000 mcg/ml. Tested with and without metabolic activation. Test year - 1987.	NTP 2007	--
Phthalic acid	Chinese hamster ovary cells	Genotoxicity	<i>in vitro</i> clastogenic activity	Positive/Negative	Negative	Test for clastogenic activity in cultured Chinese hamster ovary cells.	Phillips et al. 1982	--
Acute Toxicity								
Phthalic acid	Mouse	Mortality	Behavioral somnolence and ataxia. Gastrointestinal hypermotility, diarrhea.	LD50	2,530 mg/kg	Dosing: oral	1992. <i>J. American College of Toxicol.</i> 1(Part B): 711	RTECS 2007a ^b
Repeated Dose Toxicity								
Phthalic acid	Rat	Morbidity	Changes in blood serum composition (TP, Bilirubin, cholesterol).	TDLo	102 mg/kg/26W intermittent	Dosing: oral	1967. <i>Gigiena i Sanitariya.</i> 32(8): 12	RTECS 2007a ^b
Phthalic anhydride (surrogate)	Mouse	Carcinogenicity	Lung and kidney histopathology	LOAEL	1,562 mg/kg-day	Test population: B6C3F1 male and female mice, 50/sex/group. Dosing: average dietary concentrations of 16,346 and 32,692 ppm for males and 12,019 and 24,038 ppm for females for 104 weeks.	NCI 1979	USEPA 2007a
Phthalic anhydride (surrogate)	Rat	Carcinogenicity	Survival, body weight, gross and microscopic signs of clinical toxicity.	NOAEL	748 mg/kg-day	Test population: F344 male and female rats, 50/sex/group. Dosing: Dietary concentrations of 7,500 or 15,000 ppm for 105 weeks. Concentrations approximately equal to 374 and 748 mg/kg-day.	NCI 1979	USEPA 2007a

Notes: LD50 = median lethal dose
 LOAEL = lowest-observed-adverse-effects level
 NOAEL = no-observed-adverse-effects level
 TDLo = lowest published toxic dose
 -- = not applicable

^a Effects listed are those evaluated in the study. In cases that specific endpoints tested for were not described, test effects are listed as ND. For mortality, if the duration over which mortality was evaluated was not described, the test effect is additionally listed as ND.

^b The primary reference as provided in RTECS could not be located and verified, therefore, the primary reference is not listed in the main text.

Table 5-2. Ecological Toxicity Data for Phthalic Acid.

Receptor (pathway)	Organism	Common Name	Endpoint	Measure	Result	Primary Reference	Secondary Reference
Amphibian	<i>Bufo bufo japonicus</i>	Toad	Mortality	LC50 (24h)	40 mg/L	Nishiuchi 1980	USEPA 2007b
Amphibian	ND	Japanese frog	ND	NOEC (24h)	40 mg/L ^a	USEPA 1988	USEPA 1994b
Fish	<i>Oryzias latipes</i>	Medaka	Mortality	LC50 (24h)	1,000 mg/L	Tsuji et al. 1986	USEPA 2007b
Fish	<i>Oryzias latipes</i>	Medaka	Mortality	LC50 (48h)	1,000 mg/L	Tsuji et al. 1986	USEPA 2007b
Fish	<i>Pimephales promelas</i>	Fathead minnow	ND	NOEC (acute)	56 mg/L ^a	USEPA 1988	USEPA 1994b
Fish	<i>Salmo gairdneri</i>	Rainbow trout	ND	NOEC (24h)	5 mg/L ^a	USEPA 1988	USEPA 1994b
Fish	<i>Lepomis macrochirus</i>	Bluegill sunfish	ND	NOEC (24h)	5 mg/L ^a	USEPA 1988	USEPA 1994b
Invertebrate	<i>Chironomus plumosus</i>	Midge	Mortality	LC50 (48h)	72 mg/L	Streufert 1977	USEPA 2007b
Invertebrate	ND	Daphnid	ND	NOEC (48h)	640 mg/L	USEPA 1988	USEPA 1994b
Rodent (Oral)	ND	Rat	Mortality	LD50	8,000 mg/kg-day	Merck 1976	NTP 2006
Rodent (Oral)	ND	Rat	Reproductive	NOAEL	1,763 mg/kg-day	Ema et.al. 1997	--
Rodent (Oral)	ND	Rat	Reproductive	LOAEL	2,981 mg/kg-day	Ema et.al. 1997	--
Rodent (Oral)	ND	Rat	Reproductive	NOAEL	1,021 mg/kg-day	Ema et.al. 1997	--
Rodent (Oral)	ND	Rat	Reproductive	LOAEL	1,763 mg/kg-day	Ema et.al. 1997	--

Notes: LC50 = median lethal concentration

LD50 = median lethal dose

LOAEL = lowest-observed-adverse-effects level

ND = not defined

NOEC = no-observed-effect concentration; no information

NOAEL = no-observed-adverse-effects level

-- = not applicable

^a No information on tested dose range; unknown whether NOECs were highest doses tested.