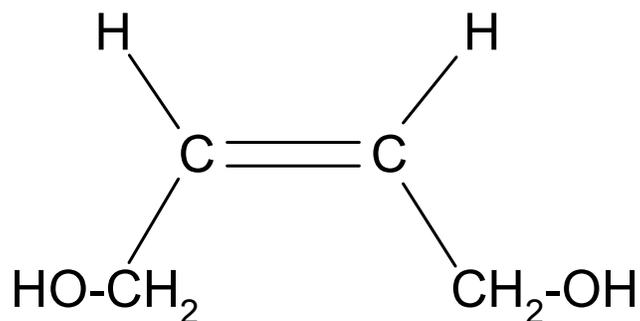


## 2-Butene-1,4-diol



**CAS Number 110-64-5**

### **U.S. EPA HPV Challenge Program Revised Submission**

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Submitted by:

**BPPB Consortium**

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## Executive Overview

2-Butene-1,4-diol, CAS Number 110-64-5, is a four-carbon unsaturated diol that is used as a chemical intermediate. It is a colorless, odorless liquid at room temperature, has a very low vapor pressure and a boiling point of 240° C. It is miscible with water and many organic solvents. There are no known consumer uses for this industrial material.

Degradation in the atmosphere is facile with the material reacting readily with photo-generated hydroxyl radicals and ozone. In water, the material is considered hydrolytically stable, but it is subject to rapid bacterial biodegradation. Data indicate that it will be rapidly degraded in a wastewater treatment plant. Based on its physical properties and degradation, calculations show that environmentally it will distribute primarily to water and secondarily to soil.

The toxicity of 2-Butene-1,4-diol to fish, aquatic invertebrates, and aquatic plants is low but higher to fish and daphnids than predicted by a simple narcosis model. In mammals the acute toxicity by the oral route is low with a rat oral LD<sub>50</sub> in the range of 850 mg/kg-bw. Limited dermal, inhalation and injection studies indicate low hazard by all routes of exposure. Genetic toxicology testing shows that this material is inactive in bacterial and mammalian systems.

Repeated-dose testing data for this material is sparse. The metabolism of this material can be inferred from the available data on 2-Butene-1,4-diol and similar compounds. The probable primary route of metabolism is to maleic acid, which has an acute toxicity and genotoxicity profile similar with 2-Butene-1,4-diol. Although an experimental data-based link cannot be made to efficient metabolism of 2-Butene-1,4-diol to maleic acid, the limited available data on bioactivation and toxicity of 2-Butene-1,4-diol and other allylic alcohols, and the data on maleic acid support this as the probable mechanism. Maleic acid, tested as maleic anhydride, has low repeated-dose and chronic toxicity and is not a specific reproductive or developmental toxin. Because the link showing efficient metabolism of 2-Butene-1,4-diol to maleic acid is weak, and because there is the possibility of metabolic intermediates on the way to maleic acid showing specific toxicity, the maleic acid data cannot be considered fully representative of 2-Butene-1,4-diol. The maleic acid (as the anhydride) data are presented as supporting information in hazard and risk assessment.

The following studies are proposed:

- ❑ OECD 203 fish study to strengthen the available information for toxicity to fish.
- ❑ OECD 422 *Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test* to fill the remaining mammalian HPV data elements. This study will provide data for the repeated-dose, reproductive and developmental toxicity data elements.

## **Testing Plan and Rationale**

## Testing Plan in Tabular Format

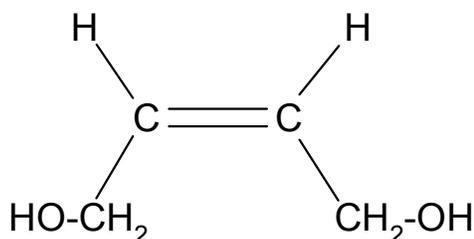
CAS Number 110-64-5  2-Butene-1,4-diol	Information Available?							Testing Recommended?
	OECD Study?	GLP Study?	Supporting Information?	Estimation Method?	Acceptable?	Testing Recommended?		
HPV Endpoint								
<b>Physical Chemical</b>								
Melting Point	Y	N	N	Y	N	Y	N	
Boiling Point	Y	N	N	Y	N	Y	N	
Vapor Pressure	Y	N	N	Y	N	Y	N	
Partition Coefficient	Y	Y	N	Y	N	Y	N	
Water Solubility	Y	N	N	Y	N	Y	N	
<b>Environmental &amp; Fate</b>								
Photo-Degradation	Y	N	N	N	Y	Y	N	
Water Stability	Y	N	N	Y	Y	Y	N	
Transport	Y	N	N	N	Y	Y	N	
Biodegradation	Y	Y	N	Y	N	Y	N	
<b>Ecotoxicity</b>								
96-Hour Fish	Y	N	N	Y	N	N	Y	
48-Hour Invertebrate	Y	N	N	Y	N	Y	N	
72-Hour Algae	Y	Y	N	Y	N	Y	N	
<b>Toxicity</b>								
Acute	Y	N	N	Y	N	Y	N	
Repeated Dose	Y	N	Y	Y	Y	N	Y	
Genetic Toxicology <i>in vitro</i>	Y	N	N	Y	N	Y	N	
Genetic Toxicology <i>in vivo</i>	Y	Y	Y	Y	N	Y	N	
Reproductive	Y	N	N	Y	Y	N	Y	
Developmental	Y	N	N	Y	Y	N	Y	

## Introduction

2-Butene-1,4-diol, CAS no. 110-64-5, is an olefinic diol most commonly prepared by the high pressure reaction of acetylene and formaldehyde to give 2-Butyne-1,4-diol, which is partially reduced using a poisoned-Palladium or a Raney nickel catalyst to give predominantly cis 2-Butene-1,4-diol (1). The CAS number above is for the cis-trans mixture of 2-Butene-1,4-diol, but it is the CAS number typically used for this material in commerce even though most of the commercial material is of cis configuration.

2-Butene-1,4-diol is a clear to light yellow liquid at room temperature and is odorless (2). It has low volatility and is miscible with water and most organic solvents (2).

This material has numerous industrial applications due to its chemical structure as it undergoes the typical reactions of both alcohols and olefins including the Diels-Alder addition typical of olefins. The bulk of 2-Butene-1,4-diol production is used as an intermediate in the synthesis of various products (1).



The structure of 2-Butene-1,4-diol is shown above. This material is also known as:

- 2-Butene-1,4-diol (ACN)(8CI9CI)
- Agrisynth b2d
- 2-Buten-1,4-diol
- 2-Butene, 1,4-dihydroxy-
- Butenediol
- 1,4-Butenediol
- 1,4-Dihydroxy-2-butene
- Penitricin C

Exposure in industrial applications is limited by process controls, protective equipment and a very low vapor pressure. No occupational exposure level set by any governmental agency was located. There are no known uses of 2-Butene-1,4-diol in consumer products.

Several physicochemical, fate and toxicity studies have been conducted with 2-Butene-1,4-diol (and its metabolites). These studies are briefly reviewed in this testing rationale document, which also describes how these studies meet the SIDS (Screening Information Data Set) end-points of the United States Environmental Protection Agency (USEPA) High Production Volume Challenge (HPV) program. Robust summaries have been prepared for key studies; supporting studies are referenced in these summaries or given as shorter summaries using the IUCLID format. The available data set satisfactorily fulfills the data requirements for most of the data elements of the EPA Program. Additional testing is proposed to fill data elements not adequately covered by existing data.

## Physicochemical Data

Physicochemical data for 2-Butene-1,4-diol are available from the literature and manufacturer's information.

Melting Point	10° C (3)
Boiling Point	240° C @ 1013 hPa (3)
Density	1.067 –1.074 @ 20° C (4)
Vapor Pressure	0.0087 hPa @ 25° C (5)
Partition Coefficient	Log $K_{o/w}$ = -0.90 (6)
Water Solubility	Very soluble (3) or miscible (2)

**Table 1: Physical-chemical data for 2-Butene-1,4-diol**

These properties indicate that 2-Butene-1,4-diol is a slightly volatile liquid with high water solubility. The value of the partition coefficient suggests that 2-Butene-1,4-diol partition preferentially into water and, therefore, has little potential for bioaccumulation. The  $K_{o/w}$  of 2-Butene-1,4-diol has been determined experimentally and is validated by literature values. As this material has no dissociation constant in the nominal range of water solution pH values and is water stable, the  $K_{o/w}$  determination is relatively uncomplicated. Its solubility has been described as both miscible and very soluble; in either case, the information fills the needs of the HPV program.

**Recommendation:** No additional physicochemical studies are recommended. The available data fill the HPV required endpoints.

## Environmental Fate and Pathways

Biodegradation potential has been determined using an OECD Guideline 302B test and a closed-bottle test. In the closed-bottle test, a degradation of 67% was reported in 30 days, after what appeared to be an extended lag phase (7), indicating that this material is considered readily biodegradable. Although the closed bottle test lacked full documentation, the validity of the method was validated by results of other test materials examined in the same protocol corresponding well with literature reports (see robust summary for the closed bottle test). In the modified Zahn Wellens test (OECD 302B) with non-acclimated sludge, a removal of ~99 % was recorded after only 3 days of incubation (8). Although the Zahn-Wellens test is only indicative of inherent biodegradation, the rapidity of the total DOC breakdown further supports the material being considered readily biodegradable. Additional support for ready biodegradation comes from inspection of the structure and the probable initial rapid attack of dehydrogenases and the linear structure. In addition, the structurally similar compound allyl alcohol is known to be readily biodegradable, even in the MITI test (9).

Photodegradation was estimated using version 1.90 of the Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) that estimates the rate constant for the atmospheric, gas-phase reaction between organic chemicals with photochemically produced hydroxyl radicals or ozone. The estimated rate constant is used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radical and ozone. The program produced an estimated rate constant of  $63.23 \text{ E-12 cm}^3/\text{molecule-sec}$ . Using the default atmospheric hydroxyl radical concentration in APOWIN and the estimated rate constant for reaction of 2-Butene-1,4-diol with hydroxyl radical, the estimated half-life of 2-Butene-1,4-diol vapor in air is approximately 2 hours (see accompanying robust summary) (10). In addition to reactivity with hydroxyl radical, 2-Butene-1,4-diol is expected to react with atmospheric ozone based on the olefinic group. The reaction rates for ozone with cis and trans olefins vary with trans being faster. In this case, as most commercial 2-Butene-1,4-diol is the cis isomer, the slower cis reaction rate was used in the estimate to give a half-life of approximately 2 hours with ozone at  $700 \text{ E6 molecules/cm}^3$

Water stability for this material has been estimated using established chemical principles (see accompanying robust summary for details and considerations). It was estimated that in nominally neutral solutions there would be no hydrolytic reaction as there are no hydrolysable groups (11). It is concluded that the water stability is well characterized and the half-life in water is greater than one year.

Theoretical Distribution (Fugacity) of 2-Butene-1,4-diol in the environment was estimated using the MacKay EQC level III model with standard defaults in EPIWIN v 3.05 but using the measured vapor pressure, the measured  $\log K_{o/w}$ , and data-verified estimates for half-life in water, soil and sediment. (12). The results for distribution using measured major physicochemical properties, a model calculated  $K_{o/c}$  (adsorption coefficient based on organic carbon content) of 0.0516 and equal initial distribution to air, water and soil are:

○ Air	0.38 %
○ Water	53.5 %
○ Soil	46.0 %
○ Sediment	0.08 %

**Table 2: Theoretical Distribution (Fugacity) of 2-Butene-1,4-diol in the environment**

**Recommendation:** No additional environmental fate and pathway studies are recommended. The available data fill the HPV required data elements.

## Ecotoxicity

An unpublished study of the acute toxicity of 2-Butene-1,4-diol to the freshwater fish *Leuciscus idus* showing a LC<sub>50</sub> of 390 mg/L (7) suggests that this material presents little acute hazard to freshwater fish; however, important details about this study are lacking. A guideline daphnia study indicates an EC<sub>50</sub> of 65.2 mg/L (13). Green algae tests indicate an IC<sub>50</sub> of 79 mg/L (14). These values, with references, are shown in the table along with results of ECOSAR modeling using the “Neutral Organics” model and the ECOSAR fish toxicity estimate using the “vinyl/allylic alcohols” model, based on the measured K<sub>o/w</sub> of -0.90, for comparison. The measured data do not fit either the ECOSAR Neutral organics or the Vinyl/allyl alcohol model well. In addition, the aquatic toxicity of allyl alcohol to fathead minnows and *Daphnia magna* is very high with 96-hour LC<sub>50</sub> and EC<sub>50</sub> values of 0.35 and 0.25 mg/L respectively (15).

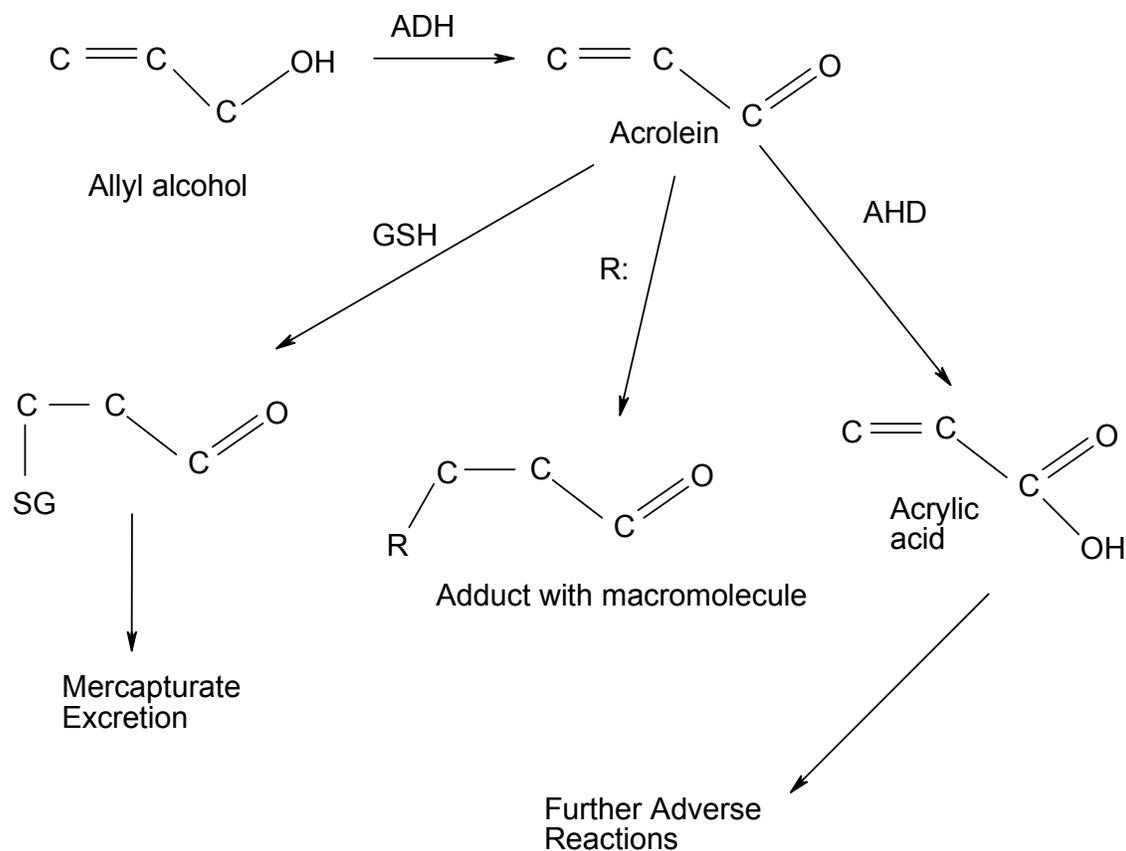
Aquatic Toxicity of 2-Butene-1,4-diol			
	Reported Values	ECOSAR Prediction Neutral Org Model	ECOSAR Prediction Allylic Alcohols Model
Fish, LC <sub>50</sub>	390 mg/L (7)	35,500 mg/L*	0.53 mg/L
Daphnia, 48 hour EC <sub>50</sub>	65.2 mg/L (13)	31,200 mg/L*	
Algae, 72 hour EC <sub>50</sub>	290 mg/L (13)	16.5 mg/L*	

\* Estimated using ECOSAR with measured K<sub>o/w</sub> (16)

**Table 3: Aquatic Toxicity of 2-Butene-1,4-diol.**

One method of judging the specific aquatic toxicity as compared to the nonspecific toxicity of an organic compound due to simple narcosis is to measure the “excess toxicity” as a ratio of the LC value observed to that predicted by the neutral organics model. Veith et al. (17) used this concept to infer that certain acetylenic alcohols acted by a specific toxic mechanism beyond simple narcosis. By that criterion, 2-Butene-1,4-diol has an “excess toxicity” of about 100 fold for fish and about 500 fold for daphnids. This suggests that a specific mechanism of toxicity is involved for fish and daphnids. On the other hand, the algal toxicity is lower than predicted. This suggests that fish and daphnids are capable of bioactivating 2-Butene-1,4-diol while algae are not.

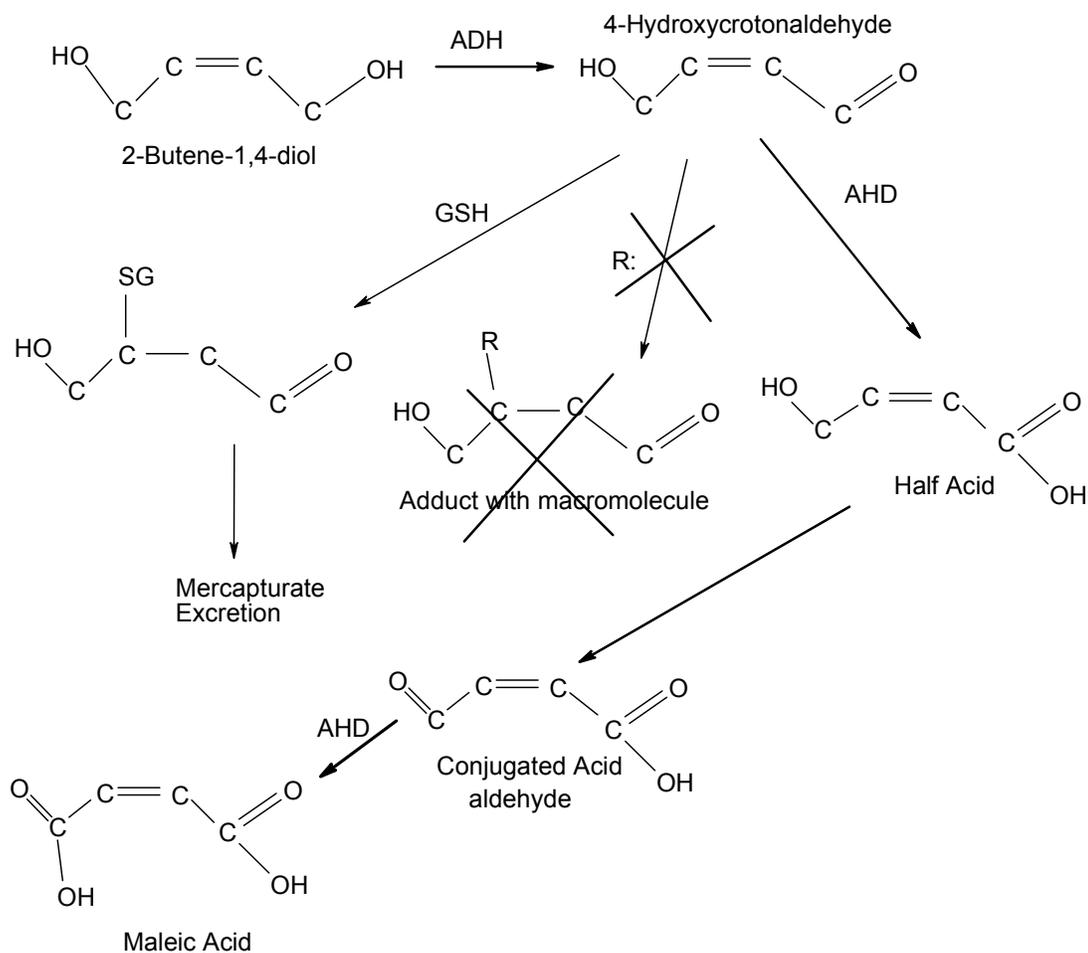
If the probable mechanism of bioactivation is considered these aquatic toxicity results are logical. Evidence concerning the mechanism of allyl alcohol points to activation by means of alcohol dehydrogenase to acrolein; a very reactive material that depletes cellular glutathione and can covalently bind to nucleophilic cellular macromolecules.



**Figure 2. Bioactivation of Allyl Alcohol**

In the bioactivation mechanism of allyl alcohol, evidence points to acrolein formation as the initial step. Acrolein is highly reactive as it has a reactive terminal conjugated olefin.

In the case of 2-Butene-1,4-diol, the initial reaction with alcohol dehydrogenase is expected to proceed rapidly; however, the reaction product, 4-hydroxycrotonaldehyde, is partially blocked from Michael addition reactions by both steric and electronic factors. The major pathways remaining to the unsaturated aldehyde are the reaction with either aldehyde dehydrogenase to the conjugated acid (which is even more stable) or reaction with alcohol dehydrogenase to the dialdehyde. In either case, the molecule will continue to react with dehydrogenases, provided  $\text{NAD}^+$  is not depleted, to the oxidation product maleic acid.



**Figure 3. The Proposed Primary Metabolism of 2-Butene-1,4-diol**

**Recommendation:** No additional ecotoxicity studies are recommended for algae or invertebrates. The available data fill the HPV required endpoints at these two trophic levels. Toxicity testing of fish using an OECD 203 compliant protocol is recommended to better define toxicity to fish.

## Health Effects

Several studies have been conducted to estimate the acute health effects and potential genotoxicity of 2-Butene-1,4-diol to man. Repeated-dose duration studies are limited and no specific tests have been conducted to investigate the reproductive and developmental toxicity of 2-Butene-1,4-diol itself.

## Metabolism

Data on the metabolism of 2-Butene-1,4-diol was not found in the open literature and, at this point, metabolic and bioactivation pathways (see Figure 3) are speculative. Metabolic information can be inferred from the known toxicologic properties of this compound and its chemical class of unsaturated alcohols. The proposed major oxidative metabolic pathway of 2-Butene-1,4-diol to maleic acid is supported by the relative toxicities of allyl alcohol, 2-Butene-1,4-diol and maleic acid (or the anhydride which is rapidly converted to maleic acid in the body after gavage administration). The acute toxicity of allyl alcohol is high ( $LD_{50} = 64 \text{ mg/kg-bw}$  (18)) while the acute toxicity of 2-Butene-1,4-diol and maleic acid are low and approximately equal. ( $LD_{50}$  2-Butene-1,4-diol =  $856 \text{ mg/kg}$ ;  $LD_{50}$  maleic acid =  $708 \text{ mg/kg}$  (MA data from HSDB)). Additional support comes from the target organ data that are available showing the target organ for allyl alcohol is the liver while the target organ for maleic acid and 2-Butene-1,4-diol is the kidney, Likewise the acute fish and daphnia toxicity for allyl alcohol is very high, dissimilar from 2-Butene-1,4-diol and maleic acid, which have low and essentially equal acute toxicities for fish and daphnids.

This proposed pathway is in accord with the toxicity data and is supported by metabolic data from crotyl alcohol and allyl alcohol which are both bioactivated to the unsaturated aldehyde, and offers a logical explanation for the low degree of 2-Butene-1,4-diol toxicity to mammals, fish and daphnids.

## Acute Toxicity

### Oral Exposure

The oral  $LD_{50}$  of 2-Butene-1,4-diol has been determined to be  $\sim 856 \text{ mg/kg}$  in the rat and  $\sim 480 \text{ mg/kg}$  in the mouse (19). The only pathological finding reported was “suspicion of kidney toxicity”. These results are supported by a limited rabbit oral study showing and oral  $LD_{50}$  between  $214$  and  $535 \text{ mg/kg}$  (20) and an extensive investigation of the acute toxicity of 2-Butene-1,4-diol by i.p. injection in Wistar rats showing a steep dose-response curve and a  $LD_{50}$  of  $327 \text{ mg/kg}$  (21).

## Inhalation Exposure

It has been reported that there were no deaths when rats were exposed to saturated vapor of 2-Butene-1,4-diol for 8 hours (19). This is referred to as an “inhalation risk test” and was conducted using a 20 ° C saturated atmosphere of 2-Butene-1,4-diol vapor. The actual concentration was not measured but based on the vapor pressure, the vapor concentration is calculated to be in the range of 7 ppm.

## Dermal Exposure

One study in rats, which was conducted for DOT labeling purposes, found the dermal LD50 in rats was greater than 200 mg/kg (22).

**Recommendation:** No additional acute toxicity studies are recommended. The available data fill the HPV required endpoints for acute toxicity. Although the available studies do not meet the requirements of the current OECD guidelines in all cases, the weight of evidence shows that the oral toxicity is very low. Conduct of additional studies would not add significantly to our understanding of this material’s toxicity relative to the potential exposures and it is recommended that no additional acute toxicity studies be conducted.

## Repeat Dose Toxicity

### Oral Exposure

The limited data available from rats and rabbits receiving 2-Butene-1,4-diol orally (see robust summaries for details) are not sufficiently informative to draw any conclusions about the repeated-dose toxicity of 2-Butene-1,4-diol. Data from maleic anhydride subchronic and chronic studies suggest that bone marrow may be target organ and data from maleic acid studies suggest the kidney could be a target organ at moderate dose levels.

**Recommendation:** It is recommended that an additional study be conducted using a modern OECD guideline protocol by the oral or other appropriate route..

## Genetic Toxicity

The SIDS/HPV requirement for genetic toxicity screening is for two end-points; one sensitive to point mutation and one sensitive to chromosomal aberrations. In the case of this material, adequate tests have been conducted that cover both of these endpoints.

### Genetic Toxicology in vitro

Two *Salmonella typhimurium* reverse mutation assays have been conducted on this material. The first used a plate incorporation technique and a preincubation technique, both with and without metabolic activation, to demonstrate lack of activity over a wide range of concentrations (23). Because this compound had the possibility of forming an allyl aldehyde and because experience with these types of compounds has shown that the standard Ames procedure can be insensitive to this family of materials, a “liquid suspension” assay was also conducted using crotonaldehyde as a positive control. The result of the liquid suspension assay showed no mutagenic activity in the presence or absence of a metabolic activating system (24).

### Genetic Toxicology in vivo

Mammalian genotoxicity was assessed *in vivo* using the Mouse Micronucleus Test. In this study, groups of NMRI mice received single oral-dose administration of 100, 200 or 400 mg/kg test material in distilled water. Upon sacrifice and slide preparation it was reported that there was no increase in the number of polychromatic erythrocytes containing either small or large micronuclei. No inhibition of erythropoiesis, determined from the ratio of polychromatic to normochromatic erythrocytes, was detected (25).

**Recommendation:** The SIDS requirement for genetic testing has been met as assays sensitive to both point mutation and to clastogenic effects have been conducted using acceptable protocols. No additional testing is recommended.

### Reproductive Toxicity

No standard reproductive studies were found for 2-Butene-1,4-diol. Modern 2-generation data on the probable metabolite, maleic acid, do not indicate any particular reproductive hazard.

**Recommendation:** A reproductive screening study by the oral or other appropriate route is recommended to fill this HPV data element.

### Developmental Toxicity

No standard developmental toxicity studies were found for 2-Butene-1,4-diol. Modern data on the probable metabolite, maleic acid, do not indicate any specific developmental hazard.

**Recommendation:** A developmental toxicity screening study by the oral or other appropriate route is recommended to fill this HPV data element

## Conclusions

With regard to the parameters specified in the EPA HPV Challenge program, available information fills all of the requirements for physicochemical parameters, fate information and two of the three trophic levels for environmental toxicity data. Acute toxicity of 2-Butene-1,4-diol is well defined by available studies and genotoxicity endpoints are filled with appropriate investigations. Probable metabolic pathways suggest that maleic acid is an important metabolite of 2-Butene-1,4-diol and, although data from maleic acid do not imply unusual or specific hazards from 2-Butene-1,4-diol, the possibility that metabolic intermediates on the way to maleic acid might have specific adverse effects cannot be excluded. For this reason, it is considered desirable to fill the HPV data elements of repeated dose, reproductive and developmental toxicity with a modern OECD guideline study. For the purposes of this low exposure material and the HPV program, the OECD 422 Combined *Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test* is proposed as the most appropriate test to fill all three of these HPV data elements with the least animal usage. An OECD 203 guideline test is also recommended to define the toxicity of 2-Butene-1,4-diol to fish.

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