

SCREENING-LEVEL HAZARD CHARACTERIZATION

4-Hydroxyanisole (CASRN 150-76-5)

The High Production Volume (HPV) Challenge Program¹ was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set^{1,2}) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance^{2,3} and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor’s responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

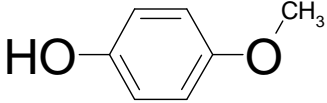
OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

² U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

³ U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

Chemical Abstract Service Registry Number (CASRN)	150-76-5
Chemical Abstract Index Name	Phenol, 4-methoxy-
Structural Formula	
<p style="text-align: center;">Summary</p> <p>CASRN 150-76-5 is a solid with moderate vapor pressure and high water solubility. It possesses high mobility in soil. Volatilization is considered moderate based on the estimated Henry's Law constant. The rate of hydrolysis is negligible. The rate of atmospheric photooxidation is considered moderate. CASRN 150-76-5 is expected to have low persistence (P1) and low bioaccumulation potential (B1).</p> <p>The acute oral toxicity of CASRN 150-76-5 is low in rats. In a 7-week oral dietary, repeated-dose toxicity study in rats, a dose related decrease in growth was observed at ~250 mg/kg-bw/day and above in males; the NOAEL for systemic toxicity is 50 mg/kg-bw/day. In a 9-week oral dietary, repeated-dose toxicity study in rabbits, reduced body weight and organ weight changes were observed at ~3000 mg/kg-bw/day; the NOAEL for systemic toxicity is ~1500 mg/kg-bw/day. There are no adequate reproductive or developmental toxicity studies. CASRN 150-76-5 was not mutagenic in bacteria <i>in vitro</i> but was mutagenic in mammalian cells <i>in vitro</i>. CASRN 150-76-5 induced chromosomal aberrations in mammalian cells <i>in vitro</i>. CASRN 150-76-5 was equivocal in a mouse erythrocyte micronucleus test <i>in vivo</i>. CASRN 150-76-5 is irritating to rabbit skin and eyes and produced depigmentation in the guinea pig and in the miniature pig. Dietary exposure to CASRN 150-76-5 is associated with an increased incidence of forestomach papillary or nodular hyperplasia in male rats. CASRN 150-76-5 showed no evidence of carcinogenicity in female mice or rabbits (both sexes) via the dermal route of exposure.</p> <p>The 96-h LC₅₀ for fish exposed to CASRN 150-76-5 ranges from 29-110 mg/L. No adequate data were submitted to assess the aquatic toxicity of CASRN 150-76-5 to aquatic invertebrates or aquatic plants.</p> <p>Reproductive/developmental toxicity, acute toxicity to aquatic invertebrates and toxicity to aquatic plants are data gaps under the HPV Challenge Program.</p>	

The sponsor, Hydroquinone Precursors and Derivatives Panel (HQPD) Hydroquinone Monomethyl Ether (HQMME) Task Force of the American Chemistry Council, submitted a test plan and robust summaries to EPA for 4-hydroxyanisole (CAS No. 150-76-5) dated December 20, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on January 21, 2003 (<http://www.epa.gov/oppt/chemrtk/pubs/summaries/4hydroxy/c14160tc.htm>). EPA comments on the original submission were posted to the website on May 13, 2003. The sponsor submitted updated/revised documents on December 15, 2003, which were posted to the ChemRTK website on February 25, 2004.

1. Chemical Identity

1.1 Identification and Purity

The following description is taken from the 2003 Test Plan and Robust Summary. CASRN 150-76-5 is the reaction product of hydroquinone, sodium hydroxide and methyl chloride. This reaction produces crude 4-hydroxyanisole and a minor co-product 1,4-dimethoxybenzene. The crude 4-hydroxyanisole is distilled to remove trace impurities. Test substance purity was not provided in the Robust Summaries.

1.2 Physical-Chemical Properties

The physical-chemical properties of CASRN 150-76-5 are summarized in Table 1. CASRN 150-76-5 is a solid with moderate vapor pressure and high water solubility.

Property	Value
CASRN	150-76-5
Molecular Weight	124.14
Physical State	Solid
Melting Point	57°C (measured)
Boiling Point	243°C (measured)
Vapor Pressure	8.3×10 ⁻³ mm Hg at 25°C (estimated) ² ; 0.014 mm Hg at 25°C (estimated) ³
Water Solubility	40,000 mg/L at 25°C (measured)
Dissociation Constant (pK _a)	10.21 (measured)
Henry's Law Constant	5.35×10 ⁻⁷ atm·m ³ /mole (estimated) ²
Log K _{ow}	1.34 (measured)

¹ American Chemistry Council. 2003. Revised Test Plan and Robust Summary for 4-Hydroxyanisole. Available online at <http://www.epa.gov/chemrtk/pubs/summaries/4hydroxy/c14160tc.htm> as of July 13, 2010.

² U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at <http://www.epa.gov/opptintr/exposure/pubs/episutedl.htm> as of July 12, 2010.

³ NOMO5. 1987. Programs to Enhance PC-Gems Estimates of Physical Properties for Organic Compounds. The Mitre Corp.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

CASRN 150-76-5 had an aggregated production and/or import volume in the United States between 1 and 10 million pounds during calendar year 2005.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include resin and synthetic rubber manufacturing as intermediates; and other basic organic chemical manufacturing as “other.” Non-confidential commercial and consumer uses of this chemical include “other.”

2.2 Environmental Exposure and Fate

The environmental fate properties of CASRN 150-76-5 are provided in Table 2. CASRN 150-76-5 is expected to be highly mobile in soil. CASRN 150-76-5 was found inherently biodegradable in an anaerobic screening test in which 90% degradation, measured as methane production, was reached after 7 days of incubation. CASRN 150-76-5 was found readily biodegradable using a modified MITI test (OECD 301C), achieving 86% degradation after 4 weeks. The rate of volatilization is considered moderate based on the estimated Henry’s Law constant. The rate of hydrolysis is negligible. CASRN 150-76-5 is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Property	Value
Photodegradation Half-life	4.3 hours (estimated) ²
Hydrolysis Half-life	Stable
Biodegradation	90% after 7 days (inherently biodegradable anaerobically) 86% after 4 weeks (readily biodegradable) ³
Bioaccumulation Factor	BAF = 2.6 (estimated) ²
Log K _{oc}	1.75 (measured in a Brookston clay loam) ⁴ ; 2.0 (estimated) ²
Fugacity (Level III Model) ²	
Air (%)	0.8
Water (%)	27.0
Soil (%)	72.1
Sediment (%)	0.2
Persistence ⁵	P1 (low)
Bioaccumulation ⁵	B1 (low)

¹American Chemistry Council. 2003. Revised Test Plan and Robust Summary for 4-Hydroxyanisole. Available online at <http://www.epa.gov/chemrtk/pubs/summaries/4hydroxy/c14160tc.htm> as of July 13, 2010.

²U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at <http://www.epa.gov/opptintr/exposure/pubs/episuite.html> as of July 12, 2010.

³National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. Available online at

http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html as of July 14, 2010.

⁴ Boyd SA. 1982. Adsorption of substituted phenols by soil. *Soil Science* 134:337–343.

⁵ Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: CASRN 150-76-5 is a solid with moderate vapor pressure and high water solubility. It possesses high mobility in soil. Volatilization is considered moderate based on the estimated Henry's Law constant. The rate of hydrolysis is negligible. The rate of atmospheric photooxidation is considered moderate. CASRN 150-76-5 is expected to have low persistence (P1) and low bioaccumulation potential (B1).

3. Human Health Hazard

The human health data submitted for SIDS endpoints is provided in Table 3.

Acute Oral Toxicity

Rats (1 to 10 per group; strain/sex not specified) were administered CASRN 150-76-5 via gavage at doses of ~ 689 to 2400 mg/kg and observed for 14 days. Mortalities were 4/10 and 5/6 at ~ 1379 and 2069 mg/kg, respectively.

LD₅₀ ~ 1630 mg/kg

Acute Dermal Toxicity

New Zealand white rabbits (5/sex/dose) were administered CASRN 150-76-5 via dermal application to clipped skin, at 2000 mg/kg under occluded conditions for 24 hours and observed for 14 days. No mortalities were observed. This study was summarized from a TSCATS submission (OTS0557192-1).

LD₅₀ > 2000 mg/kg

Repeated-Dose Toxicity

(1) Rats (10/sex/dose; strain not specified) were administered CASRN 150-76-5 via the diet at concentrations of 0, 0.02, 0.1, 0.5, 2.0 or 5.0% (approximately 0, 10, 50, 250, 1000 or 2500 mg/kg-bw/day)⁴ for 5 to 7 weeks. No mortality was observed in any group. A dose-related decrease in body weight (neither quantitative nor statistical information was provided) was observed at $\geq 0.5\%$ in males and $\geq 2.0\%$ in females. Urine glucose levels in males increased with increasing concentration. No other treatment related effects were observed on hematology endpoints or at necropsy.

LOAEL ~ 250 mg/kg-bw/day (based on decreased body weight in males)

NOAEL ~ 50 mg/kg-bw/day

(2) Rabbits (6/group, strain/sex not specified) were administered CASRN 150-76-5 via the diet at concentrations of 0, 1.0, 5.0 or 10% (~ 0, 300, 1500, or 3000 mg/kg-bw/day)⁵ for 5-9 weeks.

⁴ mg/kg-bw/day calculated by converting % in diet to ppm and multiplying result by 0.05 food factor in rats.

⁵ mg/kg-bw/day calculated by converting % in diet to ppm and multiplying result by 0.03 food factor in rabbits.

Body weight and clinical chemistry were conducted on all animals. Hematological analysis was conducted on 3 rabbits at 5 days prior to the start of the experiment and again at 24 and 59 days of the experiment. No mortality was observed in any group. Weight loss was observed in animals in the 10% treatment group (neither quantitative nor statistical information was provided). No treatment related effects on clinical chemistry were observed. Rabbits fed the highest concentration had low red blood cell counts during interim evaluation and animals in the 5% or higher treatment group had decreased red blood cell counts at the completion of the study (neither quantitative nor statistical information was provided). Average weights of the heart, lungs and testes were smaller and average weights of the liver and brain were larger in the 10% treatment group (neither quantitative nor statistical information was provided). Histological examination of the heart, lungs, spleen, liver, kidneys, brain, testes, and gastrointestinal tract showed no treatment related pathological changes.

LOAEL ~ 3000 mg/kg-bw/day (based on decreased red blood cell counts and decreased body weight)

NOAEL ~ 1500 mg/kg-bw/day

Reproductive/Developmental Toxicity

No adequate data were provided for these endpoints.

Genetic Toxicity – Gene Mutation

In vitro

(1) In a reverse-mutation assay, *S. typhimurium* strains TA100 and TA1530 were exposed to CASRN 150-76-5 at concentrations up to 4 µmol/plate, in the presence and absence of metabolic activation. Positive and negative controls were tested concurrently and responded appropriately. The assay was negative for mutagenicity.

CASRN 150-76-5 was not mutagenic in this assay.

(2) In a National Toxicology Program (NTP) study, *S. typhimurium* strains TA 98, TA100, TA1535 and TA 1537 were exposed to CASRN 150-76-5 at concentrations of 0, 100, 333, 1000, 3333, 5000 or 6666 µg/plate, in the presence and absence of metabolic activation. Positive and negative controls were tested concurrently, and responded appropriately. Cytotoxicity was observed at concentrations of 5000 µg/plate and higher. The assay was negative for mutagenicity (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=salmonella.salmonellaData&activetab=detail&endpointlist=SA&cas%5Fno=150%2D76%2D5).

CASRN 150-76-5 was not mutagenic in this assay.

(3) In a mammalian cell gene mutation assay, L5178Y mouse lymphoma cells were exposed to CASRN 150-76-5 at concentrations of 8 – 1500 µg/mL in the absence of metabolic activation and 0.75 – 56 µg/mL in the presence of metabolic activation. Positive and negative controls were tested concurrently, and responded appropriately. Cytotoxicity was observed at concentrations >1125 µg/mL in the absence of metabolic activation and >13 µg/mL in the presence of metabolic activation. CASRN 150-76-5 induced gene mutations in the absence but not in the presence of metabolic activation. TSCATS (OTS0545512-1).

CASRN 150-76-5 was mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Chinese hamster ovary (CHO) cells were exposed to CASRN 150-76-5 at concentrations of 0, 954, 1269, and 1692 µg/mL in the presence and absence of metabolic activation. Positive and negative controls were tested concurrently, and responded appropriately. Cytotoxicity was observed at concentrations of 1692 µg/mL. CASRN 150-76-5 induced chromosomal aberrations at ≥ 954 µg/mL in the absence of metabolic activation and ≥ 1269 µg/mL in the presence of metabolic activation. TSCATS (OTS0545451-1).

CASRN 150-76-5 induced chromosomal aberrations in this assay.

In vivo

CD-1 mice (5/sex/dose) were injected (ip) with CASRN 150-76-5 at concentrations of 175, 875, and 1750 mg/kg. A positive control was included. Bone marrow was harvested at 24, 48, and 72 hours after dosing. Mortality occurred at 1750 mg/kg (data not provided) and extra animals were treated to maintain treated animal numbers. A statistically significant increase (but not a dose-dependent increase) in micronucleated polychromatic erythrocytes (PCEs) was observed in mice treated with 175 mg/kg at 24 hours. No other treatment related effects were observed. TSCATS (OTS0558712-1).

CASRN 150-76-5 was equivocal for induction of micronuclei in bone marrow in this assay.

Additional Information

Eye Irritation

New Zealand White rabbits (3/sex) were instilled with 0.1 mL of a neat solution of CASRN 150-78-7 into the right eye. The rabbits' eyes were rinsed after 24 hours. Effects included slight to moderate conjunctival irritation (6 animals), corneal opacity (1 animal), corneal ulceration (5 animals), and iridial changes (2 animals). All animals were free of significant ocular irritation within 3 to 7 days of initial treatment.

CASRN 150-78-7 was irritating to rabbit eyes in this study.

Carcinogenicity

(1) In a 2-year feeding study, male Fischer 344 rats (30-31/concentration) received CASRN 150-76-5 in the diet at a concentration of 0 or 0.4%. All surviving animals were sacrificed at the end of 104 weeks. Liver and kidneys were weighed and stomach tissues were processed for hemotoxylin/eosin staining. Final average body weights were significantly lower than the basal diet controls; however relative liver and kidney weights were not significantly different. A significant increase in forestomach papillary or nodular hyperplasia incidence (31%) was observed in the treated group (n=26) as compared to controls.

CASRN 150-76-5 increased the incidence of forestomach papillary or nodular hyperplasia in rats in this study.

(2) Female Swiss mice (50/test concentration, 100/control) were administered CASRN 150-78-7 by dermal application (in acetone or methanol), at concentrations of 0, 5 or 10% twice a week on an area of dorsal skin, which was shaved regularly, for 100 weeks. Treatment began at 7 weeks.

Complete autopsies were performed on all animals. No significant differences in survival rates, body weights, or tumor incidence were observed in either dose group as compared to controls. **No evidence of carcinogenicity was reported in this study.**

(3) New Zealand White rabbits (5/concentration; male and female mixed) were administered CASRN 150-78-7 by dermal application (in acetone or methanol) to the interior left ear at concentrations of 0, 5 or 10%, twice a week for 80 weeks. Complete autopsies were performed on all animals. No treatment-related decrease in survival rates or local dermal changes were noted in either dose group. No tumors were seen in test animals. **No evidence of carcinogenicity was reported in this study.**

Depigmentation

(1) Black guinea pigs (strain/sex/number not specified) were administered CASRN 150-78-7 in a lanolin vehicle, by dermal application at a concentration of 20%, to the back of the ears once per day for a period of 1 to 8 weeks. Complete depigmentation occurred starting within 5-10 days of the beginning of treatment (Riley, 1969).

CASRN 150-78-7 was a depigmenting agent in the black guinea pig.

(2) Two female Yucatan miniature pigs were administered CASRN 150-78-7 in a 50:50 propylene glycol/ethanol vehicle, by dermal application at a concentration of 5%, to 5-7 sites (12.5 cm²), 2 times/day, 7 days/week for 90 days. Depigmentation (Grade 2) was noted for the test chemical after 70 days of exposure (Nair and Tramposch, 1991).

CASRN 150-78-7 was a depigmenting agent in the Yucatan miniature pig.

Conclusion: The acute oral toxicity of CASRN 150-76-5 is low in rats. In a 7-week oral dietary, repeated-dose toxicity study in rats, a dose related decrease in growth was observed at ~250 mg/kg-bw/day and above in males; the NOAEL for systemic toxicity is 50 mg/kg-bw/day. In a 9-week oral dietary, repeated-dose toxicity study in rabbits, reduced body weight and organ weight changes were observed at ~3000 mg/kg-bw/day; the NOAEL for systemic toxicity is ~1500 mg/kg-bw/day. There are no adequate reproductive or developmental toxicity studies. CASRN 150-76-5 was not mutagenic in bacteria *in vitro* but was mutagenic in mammalian cells *in vitro*. CASRN 150-76-5 induced chromosomal aberrations in mammalian cells *in vitro*. CASRN 150-76-5 was equivocal in a mouse erythrocyte micronucleus test *in vivo*. CASRN 150-76-5 is irritating to rabbit skin and eyes and produced depigmentation in the guinea pig and in the miniature pig. Dietary exposure to CASRN 150-76-5 is associated with an increased incidence of forestomach papillary or nodular hyperplasia in male rats. CASRN 150-76-5 showed no evidence of carcinogenicity in female mice or rabbits (both sexes) via the dermal route of exposure.

Table 3. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Human Health Data	
Endpoints	SPONSORED CHEMICAL 4-Hydroxyanisole (150-76-5)
Acute Oral Toxicity LD₅₀ (mg/kg)	~ 1630
Acute Dermal Toxicity LD₅₀ (mg/kg)	> 2000
Repeated-Dose Toxicity NOAEL/LOAEL Oral diet (mg/kg-bw/day)	(7 week, rat) NOAEL ~ 50 LOAEL ~ 250 (9 week, rabbit) NOAEL ~ 1500 LOAEL ~ 3000
Reproductive/Developmental Toxicity (mg/kg-day) Maternal/Developmental Toxicity	No adequate data
Genetic Toxicity – Gene Mutations <i>in vitro</i>	Negative (<i>S. typhimurium</i>) Positive (Mouse lymphoma cells)
Genetic Toxicity – Chromosomal Aberrations <i>in vitro</i>	Positive
Genetic Toxicity – Chromosomal Aberrations <i>in vivo</i>	Equivocal
Additional Information Eye Irritation	Irritating
Carcinogenicity	(male rat) Increased incidence of forestomach papillary or nodular hyperplasia (female mouse) Negative (rabbit) Negative
Depigmentation	Positive

Measured data in bold

4. Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 4.

Acute Toxicity to Fish

(1) Fathead minnows (*Pimephales promelas* (20/concentration)) were exposed to measured concentrations of CASRN 150-76-5 at 0, 69.6, 107, 164, 253, or 389 mg/L in a 96-hour flow through test.

96-h LC₅₀ = 110 mg/L

(2) Rainbow trout (*Oncorhynchus mykiss* (10 /concentration)) were exposed to measured concentrations of CASRN 150-76-5 at 0, 100, 180, 320, 560 or 1000 mg/L in a 96-hour flow through test.

96-h LC₅₀ = 29 mg/L

Acute Toxicity to Aquatic Invertebrates

No adequate data.

Toxicity to Aquatic Plants

No adequate data.

Conclusion: The 96-h LC₅₀ for fish exposed to CASRN 150-76-5 ranges from 29-110 mg/L. No adequate data were submitted to assess the aquatic toxicity of CASRN 150-76-5 to aquatic invertebrates or aquatic plants.

Table 4. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Aquatic Toxicity Data	
Endpoints	SPONSORED CHEMICAL 4-Hydroxyanisole (150-76-5)
Fish 96-h LC₅₀ (mg/L)	29 – 110
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	No adequate data
Aquatic Plants 72-h EC₅₀ (mg/L) (growth rate) (biomass)	No adequate data

bold = measured data (i.e., derived from testing)

5. References

Nair, X., and Tramposch, K. M. (1991). The Yucatan miniature swine as an in vivo model for screening skin depigmentation. *J Dermatol Sci* **2**, 428-433.

Riley, P. A. (1969). Hydroxyanisole depigmentation: in-vivo studies. *J Pathol* **97**, 185-191.