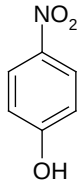
SCREENING-LEVEL HAZARD CHARACTERIZATION

4-Nitrophenol
(CASRN 100-02-7)

Chemical Abstract Service Registry Number (CASRN)	**100-02-7**
Chemical Abstract Index Name	**Phenol, 4-nitro-**
Structural Formula	 SMILES: N(=O)(=O)c(ccc(O)c1)c1

Summary

4-Nitrophenol is a solid with low vapor pressure and high water solubility. It is expected to have moderate mobility in soil. Volatilization of 4-nitrophenol is considered low based on its Henry's Law constant and the fact that it will partially exist as an anion under environmental conditions, and anions do not volatilize. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered slow. 4-Nitrophenol is not readily biodegradable and is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Acute oral toxicity of 4-nitrophenol to rats is moderate and the acute dermal toxicity to rabbits is low. In a 13-week oral gavage repeated-dose toxicity study with 4-nitrophenol in rats, mortality was observed at 70 mg/kg-day; the NOAEL for systemic toxicity is 25 mg/kg-day. In a four week inhalation toxicity study in rats, diffuse anterior capsular cataracts and corneal keratitis sicca were observed at 0.03 mg/L-day; the NOAEC is 0.005 mg/L-day. In a dermal two-generation reproductive toxicity study in rats, no adverse reproductive or developmental effects were observed; the NOAEL for reproductive, maternal and developmental toxicity is 250 mg/kg-day (highest dose tested). In a prenatal oral gavage developmental toxicity study in rats, maternal toxicity in the form of decreased body weight and body weight gain was observed at 27.6 mg/kg-day; the NOAEL for maternal toxicity is 13.8 mg/kg-day. No treatment-related effects on developmental parameters were observed; the NOAEL for developmental toxicity is 27.6 mg/kg-day (highest dose tested). 4-Nitrophenol was not mutagenic in bacteria and induced chromosomal aberrations in mammalian cells in the presence of metabolic activation *in vitro*. 4-Nitrophenol did not increase the incidence of tumors following dermal exposure in mice.

For 4-nitrophenol, the 96-h LC_{50} for acute toxicity to fish is 5.8 mg/L, the 48-h EC_{50} for acute toxicity to aquatic invertebrates is 22 mg/L, and the 72-h EC_{50} for toxicity to aquatic plants is > 32 mg/L for growth rate.

No data gaps were identified under the HPV Challenge Program.

The sponsor, Solutia, Inc., submitted a Test Plan and Robust Summaries to EPA for 4-nitrophenol (PNP; CASRN 100-02-7; CA Index name: phenol, 4-nitro-) on April 9, 2003. EPA posted the submission on the ChemRTK HPV Challenge website on April 17, 2003 (http://www.epa.gov/oppt/chemrtk/pubs/summaries/4ntrophn/c14390tc.htm). EPA comments on the original submission were posted to the website on August 25, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on March 25, 2004, which were posted to the ChemRTK website on June 30, 2004.

1. Chemical Identity

1.1 Identification and Purity

4-Nitrophenol is a solid with low vapor pressure and high water solubility.

1.2 Physical-Chemical Properties

The physical-chemical properties of 4-nitrophenol are summarized in Table 1.

Table 1. Physical-Chemical Properties of 4-Nitrophenol[1]

Property	Value
CASRN	100-02-7
Molecular Weight	139.11
Physical State	Solid
Melting Point	114°C (measured)
Boiling Point	>279°C with decomposition (measured)
Vapor Pressure	9.8×10^{-5} mm Hg at 20°C (measured)
Dissociation Constant (pK_a)	7.15 (measured)[2]
Henry's Law Constant	4.2×10^{-10} atm-m^3/mole (estimated)[3]
Water Solubility	16,000 mg/L at 25°C (measured)
Log K_{ow}	1.91 (measured)[2]

[1]Solutia Industries Inc. 2004. Revised Test Plan and Robust Summary for p-Nitrophenol. Available online at http://www.epa.gov/chemrtk/pubs/summaries/4ntrophn/c14390tc.htm as of December 19, 2011.
[2]SRC. 2011. The Physical Properties Database (PHYSPROP). Syracuse, NY: SRC Inc. Available online at http://www.syrres.com/esc/physprop.htm as of December 19, 2011.
[3]U.S. EPA. 2011. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of December 19, 2011.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

4-Nitrophenol was not reported in the 2006 IUR.

2.2 Environmental Exposure and Fate

The environmental fate characteristics of 4-nitrophenol are summarized in Table 2.

Table 2. Environmental Fate Characteristics of 4-Nitrophenol[1]

Property	Value
Photodegradation Half-life	2.5 days (estimated)[2]
Hydrolysis Half-life	Stable
Biodegradation	0% after 30 days (not readily biodegradable); 1% after 14 days (not readily biodegradable); 60% after 30 days (not readily biodegradable); 90% after 28 days (readily biodegradable); 92% after 10 days (inherently biodegradable); 4.3% after 14 days (not readily biodegradable)[3]
Bioaccumulation Factor	BCF = 2.5–7.8 (measured in carp at 0.2 mg/L)[3]; BCF = 2.6–5.4 (measured in carp at 0.02 mg/L)[3]; BAF = 6.1 (estimated)[2]
Log K_{oc}	2.5 (estimated)[2]
Fugacity (Level III Model)[2]	
Air (%)	<0.1
Water (%)	17.3
Soil (%)	82.5
Sediment (%)	0.2
Persistence[4]	P1 (low)
Bioaccumulation[4]	B1 (low)

[1]Solutia Industries Inc. 2004. Revised Test Plan and Robust Summary for p-Nitrophenol. Available online at http://www.epa.gov/chemrtk/pubs/summaries/4ntrophn/c14390tc.htm as of December 19, 2011.
[2]U.S. EPA. 2011. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of December 19, 2011.
[3]National 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 December 13, 2011.
[4]Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

4-Nitrophenol is expected to have moderate mobility in soil. Mixed results were obtained using ready biodegradability tests; however, it was shown that 4-nitrophenol is inherently biodegradable. It achieved 1% and 4.3% of its theoretical biochemical oxygen demand (BOD) in 14 days using the modified MITI test (OECD TG 301 C) and was classified as not readily

biodegradable. It did not degrade after 30 days at 1 mg/L related to dissolved organic carbon using the closed bottle (OECD TG 301D) test; however, it achieved 60% of its theoretical BOD in 30 days in a separate OECD TG 301D test in which trace metals and vitamins were added to the medium. 4-Nitrophenol degraded 90% after 28 days, as measured by CO_2 evolution and the standard Sturm (OECD TG 301B) test and was readily biodegradable. It was degraded 92% in 10 days using the Zahn-Wellens (OECD TG 302B) test and was inherently biodegradable. The rate of hydrolysis is considered negligible. Volatilization of 4-nitrophenol is considered low based on its Henry's Law constant and the fact that it will partially exist as an anion under environmental conditions, and anions do not volatilize. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered slow. 4-Nitrophenol is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Conclusion: 4-Nitrophenol is a solid with low vapor pressure and high water solubility. It is expected to have moderate mobility in soil. Volatilization of 4-nitrophenol is considered low based on its Henry's Law constant and the fact that it will partially exist as an anion under environmental conditions, and anions do not volatilize. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered slow. 4-Nitrophenol is expected to have low persistence (P1) and low bioaccumulation potential (B1).

3. Human Health Hazard

A summary of health effects data submitted for SIDS endpoints is provided in Table 3.

Acute Oral Toxicity

Sprague-Dawley rats (five/sex/dose) were administered 4-nitrophenol in propylene glycol via gavage at 70, 110, 171, 268 or 420 mg/kg. Mortality was observed at ≥ 171 mg/kg. All deaths occurred within the first 8 hours.
LD_{50} = 230 mg/kg

Acute Dermal Toxicity

New Zealand White rabbits (five/sex/dose) were dermally administered 4-nitrophenol in physiological saline at 5000 mg/kg to the shaved and abraded skin of the back for 24 hours under occlusive conditions. No deaths, clinical signs of toxicity or changes in body weight were observed.
LD_{50} > 5000 mg/kg

Repeated-Dose Toxicity

(1) In a 13-week oral gavage repeated-dose toxicity study, Sprague-Dawley rats (20/sex/dose) were treated with 4-nitrophenol at 0, 25, 70 and 140 mg/kg-day. Deaths were observed at all

dose levels. Adverse effects observed in animals that died in the 70 and 140 mg/kg-day groups included pale appearance, languid behavior, prostration, wheezing, dyspnea and severe congestive liver, kidney, lungs and adrenal cortex pathology. Increases were observed in segmented neutrophils and absolute monocytes and eosinophil counts, as well as polychromasia of erythrocytes at 140 mg/kg-day in both sexes. One animal died at 25 mg/kg-day which was identified as the NOAEL in the robust summary because the death was not treatment-related; two animals died at the next highest dose (70 mg/kg-day).
LOAEL = 70 mg/kg-day (based on mortality)
NOAEL = 25 mg/kg-day

(2) In a four week inhalation repeated-dose toxicity study, Sprague-Dawley rats (15/sex/dose) were exposed (whole-body) to 4-nitrophenol dust (MMD = 5 – 7 :m) at 0, 1, 5 and 30 mg/m^3 (approximately 0, 0.001, 0.005 and 0.03 mg/L). No deaths occurred during the study. Ophthalmoscopic examinations revealed incidences of diffuse anterior capsular cataracts and corneal keratitis sicca in high-dose animals.
LOAEL = 0.03 mg/L-day (based on diffuse anterior capsular cataracts and corneal keratitis sicca)
NOAEL = 0.005 mg/L-day

(3) In a four week oral gavage range-finding study, Sprague-Dawley rats (five/sex/dose) were treated with 4-nitrophenol (purity 99.1%) at 0, 1, 10, 50 and 100 mg/kg-day. One treatment-related death (female) occurred at 100 mg/kg-day. No treatment-related effects were observed in hematology or clinical chemistry values when compared to controls. No clinical signs of toxicity were observed in survivors. Organs weights and histopathology of treated rats were similar to controls.
LOAEL = 100 mg/kg-day (based on mortality)
NOAEL = 50 mg/kg-day

(4) In an 18-month dermal carcinogenicity study, Swiss Webster mice (five/sex/dose) were administered 4-nitrophenol in acetone at 0, 40, 80 and 160 mg/kg-bw/day to intrascapular skin 3 times/week. Survival of the mice treated at 40 mg/kg-bw/day was lower than controls but this was not considered treatment-related. No statistically significant or biologically noteworthy changes occurred in the incidences of non-neoplastic lesions at any site.
NOAEL = 160 mg/kg-bw/day (based on no treatment-related effects at the highest dose tested)

Reproductive Toxicity

In a dermal two-generation reproductive toxicity study, Sprague-Dawley rats (24 female and 15 male rats/dose) were administered to 4-nitrophenol (purity 99.1%) in ethanol at 50, 100 and 250 mg/kg-bw/day. Exposure lasted through pre-breeding, breeding, gestation, lactation and development through two full generations. No treatment-related mortality was observed in the parental generations and no adverse effects on organ weights including gonads and histopathology were observed. The F_0 and F_1 generations exposed to 4-nitrophenol or ethanol exhibited dermal irritation consisting of varying degrees of erythema, scaling, scabbing and cracking. No evidence of effects in mating, pregnancy, behavior and growth were found in parents or F1 and F2 generations.

NOAEL (systemic/reproductive toxicity) = 250 mg/kg-bw/day (based on no adverse effects at the highest dose tested)

Developmental Toxicity

(1) Pregnant Sprague-Dawley rats (20/dose) were exposed to 4-nitrophenol (purity 99.1%) in a propylene glycol solution via gavage at 1.4, 13.8 and 27.6 mg/kg-day on gestation days 6 – 16. Dams exhibited decreased body weight/weight gain at the highest dose. Treatment-related developmental toxicity was not observed.
NOAEL (maternal toxicity) = 13.8 mg/kg-bw/day
LOAEL (maternal toxicity) = 27.6 mg/kg-bw/day (based on decreased body weight and body weight gain)
NOAEL (developmental toxicity) = 27.6 mg/kg-bw/day (based on no treatment-related effects at the highest dose tested)

(2) In the dermal two-generation reproductive toxicity study in rats, described above, no treatment-related developmental effects were observed. The robust summary stated that 250 mg/kg-bw/day was chosen as the highest dose based on a range-finding study that indicated toxicity at higher doses.
NOAEL (maternal/developmental toxicity) = 250 mg/kg-bw/day (based on no adverse effects at the highest dose tested)

Genetic Toxicity – Gene Mutations

In vitro
Salmonella typhimurium strains TA100, TA98, TA1535 and TA1537 were exposed to 4-nitrophenol in dimethyl sulfoxide (DMSO) at 0, 10, 33, 100, 166, 333, 666 and 1000 µg/plate in the presence and absence of metabolic activation. Negative and positive controls were tested, but their responses were not provided. No increases in revertants were observed in the presence or absence of metabolic activation in any of the four tester strains.
4-Nitrophenol was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro
Chinese hamster ovary (CHO) cells were exposed to 4-nitrophenol at concentrations ranging from 100 to 2500 µg/L in the presence and absence of metabolic activation. Reproducible, dose-related increases in cells with structural chromosomal aberrations were seen in the presence of activation at 1500 – 2000 µg/mL. Severe cell-cycle delay was also observed at these dose levels.
4-Nitrophenol induced chromosome aberrations in this study.

Additional Information

Carcinogenicity

In the 18-month dermal carcinogenicity study in mice described above, there were no treatment-related increases in any neoplasms.
4-Nitrophenol did not increase the incidence of tumors in mice.

Conclusion: Acute oral toxicity of 4-nitrophenol to rats is moderate and the acute dermal toxicity to rabbits is low. In a 13-week oral gavage repeated-dose toxicity study with 4-nitrophenol in rats, mortality was observed at 70 mg/kg-day; the NOAEL for systemic toxicity is 25 mg/kg-day. In a four week inhalation toxicity study in rats, diffuse anterior capsular cataracts and corneal keratitis sicca were observed at 0.03 mg/L-day; the NOAEC is 0.005 mg/L-day. In a dermal two-generation reproductive toxicity study in rats, no adverse reproductive or developmental effects were observed; the NOAEL for reproductive maternal and developmental toxicity is 250 mg/kg-day (highest dose tested). In a prenatal oral gavage developmental toxicity study in rats, maternal toxicity in the form of decreased body weight and body weight gain was observed at 27.6 mg/kg-day; the NOAEL for maternal toxicity is 13.8 mg/kg-day. No treatment-related effects on developmental parameters were observed; the NOAEL for developmental toxicity is 27.6 mg/kg-day (highest dose tested). 4-Nitrophenol was not mutagenic in bacteria and induced chromosomal aberrations in mammalian cells in the presence of metabolic activation *in vitro*. 4-Nitrophenol did not increase the incidence of tumors following dermal exposure in mice.

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Human Health Data

Endpoint	4-Nitrophenol (100-02-7)
Acute Oral Toxicity LD_{50} (mg/kg)	**250**
Acute Dermal Toxicity LD_{50} (mg/kg)	**>5000**
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-day)	**NOAEL= 25 LOAEL = 70**
Repeated-Dose Toxicity NOAEC/LOAEC Inhalation (mg/L-day)	**NOAEC= 0.005 LOAEC = 0.03**
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg-day)	**NOAEL= 250 (highest dose tested)**
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-day) Maternal Toxicity	**NOAEL= 13.8LOAEL = 27.6**
Developmental Toxicity	**NOAEL= 27.6 (highest dose tested)**
Developmental Toxicity NOAEL/LOAEL Dermal (mg/kg-kg/day) Maternal/Developmental Toxicity	**NOAEL= 250 (highest dose tested)**
Genetic Toxicity – Gene Mutation *In vitro*	**Negative**
Genetic Toxicity – Chromosomal Aberrations *In vitro*	**Positive**
Additional Information Carcinogenicity	**Negative (dermal; mouse)**

4. Hazard to the Environment

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

Acute Toxicity to Fish

Bluegill fingerlings (*Lepomis macrochirus*) were exposed to 4-nitrophenol in acetone at nominal concentrations of 1.6, 2.4, 3.7, 5.6, or 8.7 mg/L for 96 hours under static conditions. Negative and vehicle controls were included and responded adequately. All deaths occurred during the first 24 hours of the study, and 100% mortality was observed in groups receiving 8.7 mg/L.
96-h LC_{50} = 5.8 mg/L

Acute Toxicity to Aquatic Invertebrates

(1) Water fleas *(Daphnia magna)* were exposed to 4-nitrophenol at 5 – 8 graded nominal concentrations under unspecified flow conditions for 48 hours. A negative control was included. The no-observed-effect level was 13 mg/L.
24-h EC_{50} = 24 mg/L
48-h EC_{50} = 22 mg/L

Toxicity to Aquatic Plants

Green algae (*Desmodesmus subspicatus)* were exposed to 4-nitrophenol at nominal concentrations of 4.8, 9.6, 19.2, 32.4, 76.8, or 153.6 mg/L under unspecified flow conditions for 96 hours. Exposures were to dilutions of a saturated stock solution of 4-nitrophenol. Exposure concentrations were calculated following completion of the study and were based on the water solubility of 4-nitrophenol and the dilution of the saturated stock solution used in each exposure. The 50% effect concentration based on growth rate was > 32 mg/L.
96-h EC_{50} (growth rate) > 32 mg/L

Conclusion: For 4-nitrophenol, the 96-h LC_{50} for acute toxicity to fish is 5.8 mg/L, the 48-h EC_{50} for acute toxicity to aquatic invertebrates is 22 mg/L, and the 72-h EC_{50} for toxicity to aquatic plants is > 32 mg/L for growth rate.

Table 4. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Aquatic Toxicity Data	
Endpoint	**4-Nitrophenol (100-02-7)**
Fish 96-h LC_{50} (mg/L)	**5.8**
Aquatic Invertebrates 48-h EC_{50} (mg/L)	**22**
Aquatic Plants 72-h EC_{50} (mg/L) (growth rate)	**>32**

Bold = measured data (i.e. derived from testing)