

# I U C L I D

## Data Set

**Existing Chemical** : ID: 100-02-7  
**CASNo.** : 100-02-7  
**EINECS Name** : 4-nitrophenol  
**EINECS No.** : 202-811-7  
**TSCA Name** : Phenol, 4-nitro-  
**Molecular Formula** : C6H5NO3

**Producer Related Part**  
**Company** : Solutia Inc.  
**Creation date** : 04.04.2002

**Substance Related Part**  
**Company** : Solutia Inc.  
**Creation date** : 04.04.2002

**Memo** :

**Printing date** : 25.10.2002  
**Revision date** :  
**Date of last Update** : 24.10.2002

**Number of Pages** : 22

**Chapter (profile)** : Chapter: 1, 2, 3, 4, 5, 7  
**Reliability (profile)** : Reliability: without reliability, 1, 2, 3, 4  
**Flags (profile)** : Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE),  
Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

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### 2.1 MELTING POINT

**Value** : = 114 °C  
**Sublimation** :  
**Method** : other  
**Year** : 1996  
**GLP** : no data  
**Test substance** : no data  
**Reliability** : (2) valid with restrictions  
Cited as a Peer reviewed reference in HSDB (2002) for 4-nitrophenol; also cited as a definitive value in IPCS CICAD Document 20 - Mononitrophenols (2000).  
**Flag** : Critical study for SIDS endpoint  
24.10.2002 (2)

### 2.2 BOILING POINT

**Value** : > 279 °C at  
**Decomposition** :  
**Method** : other  
**Year** : 1987  
**GLP** : no data  
**Test substance** : no data  
**Reliability** : (2) valid with restrictions  
Cited as Peer reviewed reference in HSDB (2002) for 4-nitrophenol; Cited as definitive value in IPCS CICAD Document 20 - Mononitrophenols (2000).  
**Flag** : Critical study for SIDS endpoint  
24.10.2002 (19)

### 2.3 DENSITY

#### 2.3.1 GRANULOMETRY

### 2.4 VAPOUR PRESSURE

**Value** : = .0067 hPa at 20° C  
**Decomposition** :  
**Method** : other (calculated)  
**Year** : 1988  
**GLP** : no data  
**Test substance** : no data  
**Reliability** : (2) valid with restrictions  
Cited as Peer reviewed reference in HSDB (2002) for 4-nitrophenol.  
**Flag** : Critical study for SIDS endpoint  
24.10.2002 (11)

### 2.5 PARTITION COEFFICIENT

**Log pow** : <= 1.91 at °C  
**Method** : other (calculated)

## 2. Physico-Chemical Data

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Year : 1985  
GLP : no data  
Test substance : no data  
Reliability : (2) valid with restrictions  
Value of <2.4 cited as definitive value in IPCS CIDAD Document 20 -  
Mononitrophenols (2000).  
Flag : Critical study for SIDS endpoint  
24.10.2002 (7)

### 2.6.1 WATER SOLUBILITY

Value : = 16000 mg/l at 25 ° C  
Qualitative :  
Pka : at 25 ° C  
PH : at and ° C  
Method : other  
Year : 1996  
GLP : no data  
Test substance : no data  
Reliability : (2) valid with restrictions  
Cited as a Peer reviewed reference in HSDB (2002) for 4-nitrophenol.  
Flag : Critical study for SIDS endpoint  
24.10.2002 (18)

### 2.6.2 SURFACE TENSION

### 2.7 FLASH POINT

### 2.8 AUTO FLAMMABILITY

### 2.9 FLAMMABILITY

### 2.10 EXPLOSIVE PROPERTIES

### 2.11 OXIDIZING PROPERTIES

### 2.12 ADDITIONAL REMARKS



### 3. Environmental Fate and Pathways

Id 100-02-7  
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rates were 1000 kg/hr for each of the three main compartments, air, water and soil.

Level III Fugacity Model (Full-Output):

=====

Chem Name : p-Nitrophenol  
Molecular Wt: 139.11  
Henry's LC : 1.3e-008 atm-m3/mole (user-entered)  
Vapor Press : 0.005 mm Hg (user-entered)  
Log Kow : 1.91 (user-entered)  
Soil Koc : 33.3 (calc by model)

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	4.98	19	1000
Water	36.3	20	1000
Soil	58.7	20	1000
Sediment	0.0147	60	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)
Advection (percent)				
Air	7.37e-012	153	42	5.1
1.4 Water	1.43e-014	1.06e+003	30.6	35.4
1.02 Soil	2.33e-013	1.71e+003	0	57.1
0 Sediment	1.61e-015	0.143	0.000248	0.00477
8.27e-006				

Persistence Time: 28.1 hr  
Reaction Time: 28.8 hr  
Advection Time: 1.16e+003 hr  
Percent Reacted: 97.6  
Percent Advected: 2.42

Half-Lives (hr), (estimated from experimental data):  
Air: 19  
Water: 20  
Soil: 20  
Sediment: 60

Advection Times (hr):  
Air: 100  
Water: 1000  
Sediment: 5e+004

**Reliability** : (2) valid with restrictions  
Estimated value based on accepted model. Second soil value was for sediment.

**Flag** : Critical study for SIDS endpoint  
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#### 3.3.2 DISTRIBUTION

#### 3.4 MODE OF DEGRADATION IN ACTUAL USE

#### 3.5 BIODEGRADATION

**Type** : aerobic  
**Inoculum** :

### 3. Environmental Fate and Pathways

Id 100-02-7  
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**Contact time** :  
**Degradation** : 1 - 100 % after 10 day  
**Result** : other  
**Deg. Product** :  
**Method** : other  
**Year** : 1979  
**GLP** : no data  
**Test substance** : no data  
**Method** : Report contains a comparative assessment of a series of Biodegradability studies all performed in accord with OECD Guideline 301. Studies included: Coupled Units test, Zahn-Wellens test, MITI test, AFNOR test, Sturm test, OECD Screen test and Closed bottle test.  
**Result** : With the exception of the Closed bottle test and the MITI test, which yielded low results, PNP was considered sufficient or even readily biodegradable in all other tests conducted. The degree (% DOC removed) for each test (days to complete) was: Coupled Units test - 100+/-4 % (7d); Zahn-Wellens test - 92%(10d); MITI test - 1%; French ANFOR test - 97%; Sturm test - 97%; and Closed bottle test - 60% (30d).  
**Test substance** : No data cited in article, but typical technical grade PNP has purity of 99% and was likely used in these studies.  
**Reliability** : (1) valid without restriction  
Use of OECD methodology acceptable for regulatory review and decision-making.  
**Flag** : Critical study for SIDS endpoint

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#### 3.6 BOD5, COD OR BOD5/COD RATIO

#### 3.7 BIOACCUMULATION

#### 3.8 ADDITIONAL REMARKS

## 4.1 ACUTE/PROLONGED TOXICITY TO FISH

<b>Type</b>	:	static
<b>Species</b>	:	Lepomis macrochirus (Fish, fresh water)
<b>Exposure period</b>	:	96 hour(s)
<b>Unit</b>	:	mg/l
<b>Analytical monitoring</b>	:	no
<b>LC50</b>	:	c >= 5.8
<b>Method</b>	:	other
<b>Year</b>	:	1977
<b>GLP</b>	:	no
<b>Test substance</b>	:	other TS
<b>Method</b>	:	This study preceded development of OECD Test Guideline 203 but was conducted in a manner consistent with that guideline. Groups of bluegill fingerlings (mean length of 2.8 cm); fish were not fed 48 h prior to nor during the 96 hr exposure period. Groups of 10 fish were added to glass vessels containing 15 l water at 5 test concentrations (8.7, 5.6, 3.7, 2.4 and 1.6 mg/L PNP dissolved in acetone. Both a negative control and an acetone-containing control group were also used. No aeration was performed during the test. Water temperature was maintained at 22+/-1%, with a pH ranging between 6.7-6.3. Dissolved oxygen ranged from 93% saturation at study start to 7% at study termination. Observations and mortality were checked every 24 hr. At the end of the study, test concentrations and observed mortality were converted to logarithms and probits, respectively, and analyzed by a least square regression method for determination of LC50 and CI at 24, 48, and 96 hr timepoints.
<b>Result</b>	:	All deaths occurred during the first 24 hr of the study, hence the LC50 and CI values for each of the study time points (24, 48, 96 hr) were the same, i.e. LC50 = 5.8 (3.7-9.2) mg/L. Mortality (%) observed at each PNP concentration was: 100% @ 8.7 mg/L, 10% @ 5.6 mg/L, and 0% @ 3.7 mg/L, 2.4 mg/L, 1.6 mg/L, untreated control and acetone control.
<b>Test substance</b>	:	Purity of 99%.
<b>Reliability</b>	:	(2) valid with restrictions This study was conducted prior to, but consistent with OECD Guideline # 203 and, US GLP guidelines effective in 1979 for nonclinical laboratory studies. Reduction in oxygen over time is not considered a factor in interpretation of results since all deaths (10%) occurred within first 24 hrs of study.
<b>Flag</b>	:	Critical study for SIDS endpoint
09.10.2002		

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## 4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

<b>Type</b>	:	static
<b>Species</b>	:	Daphnia magna (Crustacea)
<b>Exposure period</b>	:	48 hour(s)
<b>Unit</b>	:	mg/l
<b>Analytical monitoring</b>	:	no
<b>NOEC</b>	:	m >= 13
<b>EC50</b>	:	c >= 22
<b>Method</b>	:	OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilisation Test"
<b>Year</b>	:	1980
<b>GLP</b>	:	no data
<b>Test substance</b>	:	other TS
<b>Method</b>	:	Methods used followed protocol as found in US EPA, 1975 for Macroinvertebrate testing, which are consistent with OECD Guideline 202. D. magna, <24h old, were used as the tester strain. Culture water was reconstituted as outlined in US EPA, 1975 guidance, such that it contained

reconstituted as outlined in US EPA, 1975 guidance, such that it contained a total hardness of 173+/-13 mg/l as CaCO<sub>3</sub> and a pH of 8.0+/-0.2. Temperature was maintained at 22+/-1 degree C. A stock solution of the chemical in distilled water was prepared and used to provide a series of graded concentrations (reportedly 5-8) for testing. PNP was added to 500 mL diluent water in 2-L jars to prepare for each test solution. The 500 mL volume of test solution was divided into three 150-mL aliquots to provide triplicate exposures at each concentration. Five Daphnids were randomly placed in each test solution within 30 min of preparation. A negative control was also tested. Measurements were taken to confirm dissolved oxygen concentration, pH, and temperature in the high, medium and low test concentrations. Observations were made at 24 and 48 hours of exposure and any mortalities were recorded. Mortality data were used to calculate an LC50 and CI using a moving average angle method.

**Result** : LC50 (CI) values for 24 hr and 48 hrs were, respectively, 24 (22-26) mg/L and 22 (20-24) mg/L. ; The No Discernable Effect level was 13 mg/L. Dissolved oxygen concentrations ranged from 6.5-9.1 mg/L, pH values measured 7.4-9.4 units.

**Test substance** : Test compound purchased from commercial chemical supplier, hence technical grade PNP was likely used and had purity of 99%.

**Reliability** : (1) valid without restriction GLP compliance was not stated in the article but adequate documentation can be assumed as this study was performed for the US EPA under contract no. 68-01-4646.

**Flag** : Critical study for SIDS endpoint

23.08.2002 (10)

#### 4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

**Species** : Scenedesmus subspicatus (Algae)

**Endpoint** : growth rate

**Exposure period** : 96 hour(s)

**Unit** : mg/l

**Analytical monitoring** : no

**EC10** : c >= 8

**EC50** : c >= 32

**Method** : OECD Guide-line 201 "Algae, Growth Inhibition Test"

**Year** : 1985

**GLP** : no data

**Test substance** : other TS

**Method** : Following test guidelines set by OECD, 1983 and German Umweltbundesamt, 1982. Experiments were incubated at 22+/-2 degrees C. at constant photosynthetically effective light intensity. Due to a distinct change of pH value caused by inclusion of PNP in sterilized double distilled water used as the diluent in this study, the pH of the stock solution was adjusted to pH 7 using NaOH. Experiments were performed by preparing two parallel dilution series in 300-ml Erlenmeyer flasks containing a saturated test chemical solution, medium and 5 ml algae suspension of approx. 10E4 cells/ml. Each Erlenmeyer flask was shaken 2-3 times per day and continuously illuminated from the side by two fluorescent lamps. After 0, 72 and 96 hrs, the cell growth of a 10-mm layer of cell suspensions from each test culture and from the controls was measured at 578 nm using a spectrophotometer. The extinction units were converted to cell numbers using a standard curve and the cell numbers determined using the Utermoehl method. The concentration-effect relationships were plotted on semilogarithmic paper and EC10 and EC50 values determined graphically.

**Test substance** : Commercial grade PNP, and thus with purity of 99%.

**Reliability** : (1) valid without restriction  
While not explicitly stated, the fact that this study was conducted according

## 4. Ecotoxicity

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Flag 23.08.2002 : to national (Ger) and international (OECD) test guidelines it most likely was conducted consistent with or actually followed GLP guidance.  
: Critical study for SIDS endpoint (6)

### 4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

#### 4.5.1 CHRONIC TOXICITY TO FISH

#### 4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

#### 4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

#### 4.6.2 TOXICITY TO TERRESTRIAL PLANTS

#### 4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

### 4.7 BIOLOGICAL EFFECTS MONITORING

### 4.8 BIOTRANSFORMATION AND KINETICS

### 4.9 ADDITIONAL REMARKS

## 5.1.1 ACUTE ORAL TOXICITY

<b>Type</b>	: LD50
<b>Species</b>	: rat
<b>Strain</b>	: Sprague-Dawley
<b>Sex</b>	: male/female
<b>Number of animals</b>	: 50
<b>Vehicle</b>	: other
<b>Value</b>	: = 230 mg/kg bw
<b>Method</b>	: OECD Guide-line 401 "Acute Oral Toxicity"
<b>Year</b>	: 1983
<b>GLP</b>	: yes
<b>Test substance</b>	: other TS
<b>Method</b>	: Administered by gavage using propylene glycol as vehicle to 5 groups of rats (5 male and 5 female) given 70, 110, 171, 268 or 420 mg/kg/d; Clinical signs recorded 3X during first 8-hr after dosing and 2X daily for the remainder of the 14-d observation period. Body weights recorded on test days 0, 7 and 14. All survivors were necropsied on test day 15. Food and water administered ad libitum. LD50 and CI determined using method of Finney, DJ. 1971. Probit Analysis, Cambridge Univer. Press.
<b>Result</b>	: LD50 +/- Confidence Limits (95%): 230 mg/kg (182-289 mg/kg); Deaths: 70 mg/kg (0/10), 110 mg/kg (0/10), 171 mg/kg (3/10), 268 mg/kg (8/10) and 420 mg/kg (8/10); Deaths all occurred within the first 8 hrs of dosing and exhibited the following clinical signs: convulsions, prostration and dyspnea prior to death; Clinical signs observed in survivors during the first three days after dosing included: tremors, ptosis, salivation and lethargy. No untoward effects were noted at necropsy of survivors.
<b>Test substance</b>	: Technical grade purity of > 99%
<b>Reliability</b>	: (1) valid without restriction
<b>Flag</b>	: Critical study for SIDS endpoint
	09.10.2002

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## 5.1.2 ACUTE INHALATION TOXICITY

## 5.1.3 ACUTE DERMAL TOXICITY

<b>Type</b>	: LD0
<b>Species</b>	: rabbit
<b>Strain</b>	: New Zealand white
<b>Sex</b>	: male/female
<b>Number of animals</b>	: 10
<b>Vehicle</b>	: physiol. saline
<b>Value</b>	: > 5000 mg/kg bw
<b>Method</b>	: OECD Guide-line 402 "Acute dermal Toxicity"
<b>Year</b>	: 1983
<b>GLP</b>	: yes
<b>Test substance</b>	: other TS
<b>Method</b>	: One group of 5 male and 5 female rabbits were administered 5000 mg/kg/d test material on the shaved and abraded dermal surface. After administration the site was occluded and test material left in place for 24 hours. After test material removal, animals were observed for the remainder of the 14-d observation period. Clinical signs were recorded 3X during the first 8 hrs and 2X daily for the remainder of the study. Body weights were recorded on test days 0, 7 and 14. Necropsies were performed on all animals on test day 15. Food and water were administered ad libitum.

## 5. Toxicity

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**Result** : No deaths occurred and no signs of systemic toxicity were seen during the study or at necropsy. Erythema and edema were observed during visual observations and at necropsy.  
**Test substance** : Technical grade purity of > 99%  
**Reliability** : (1) valid without restriction  
09.10.2002

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### 5.1.4 ACUTE TOXICITY, OTHER ROUTES

### 5.2.1 SKIN IRRITATION

### 5.2.2 EYE IRRITATION

### 5.3 SENSITIZATION

### 5.4 REPEATED DOSE TOXICITY

**Species** : rat  
**Sex** : male/female  
**Strain** : Sprague-Dawley  
**Route of admin.** : gavage  
**Exposure period** : 13 weeks  
**Frequency of treatment** : Once daily throughout the exposure period  
**Post obs. period** : None  
**Doses** : 0, 25, 70 and 140 mg/kg/d  
**Control group** : yes, concurrent vehicle  
**NOAEL** :  $\geq 25$  mg/kg  
**LOAEL** : = 70 mg/kg  
**Method** : OECD Guide-line 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"  
**Year** : 1989  
**GLP** : yes  
**Test substance** : other TS  
**Method** : Groups of 20M and 20F S-D rats were administered 0, 25, 70 or 140 mg PNP/kg daily in distilled water for 13 weeks by gavage at a constant volume of 10 ml/kg. Dose levels were verified by spectrophotometric analysis. Mortality checks and signs of intoxication were made twice daily, and detailed clinical signs, individual body weights and food consumption recorded weekly. Pre and post study ophthalmoscopic examinations were also conducted on all animals available. At weeks 7 and 14 extensive hematology (RBC, RETIC, HGB, HCT, PLATELET, WBC, differential Leukocytes, and cell morphology) and serum chemistry (GLU, BUN, CREAT, AST, ALT, GGT, T PROT., ALBU, GLOB, CA, T BILI, PHOS, NA, POTAS, CL) parameters were conducted on blood samples from 10 animals/sex/group. No urinalysis was performed. At termination brain, liver, kidney, spleen and testes with epididymides were weighed for all survivors and a full necropsy performed. A full set of approx. 40 tissues and organs (including gonads) were collected from all surviving animals and sections were examined microscopically from these tissues for the control and high dose animals. Microscopic examination of tissues was also performed on tissues of premature deaths exhibiting gross autopsy findings. Temperature, lighting and humidity were controlled throughout the study. Body weights and weight gains, food consumption, hematology and clinical chemistry parameters and organ weights (absolute and relative) were initially analyzed using Levine's test of homogeneity of variances. If

<b>Result</b>	: initially analyzed using Levine's test of homogeneity of variances. If nonhomogeneous, data were transformed and then analyzed via ANOVA (p<0.05). Dunnett's t-test (2-tail, p<0.05) was used to compare treated and control groups. Cumulative survival was assessed using the National Cancer Institute statistical package and analyzed for trend.
<b>Test substance</b>	: Early deaths were seen in groups of male and female rats given 70 and 140 mg/kg/d PNP. Total premature deaths observed in 0, 25, 70 and 140 mg/kg males were 0,0,1, 15, respectively; for females - 0,1,1,6, respectively; Several of these premature deaths (1-70 mg/kg male, 2 @ 140 mg/kg male, 3 @ 140 mg/kg female) died shortly after bleeding at wk 7, which likely exacerbated deaths, while 1 HD male was found to have died from gavage error. All other deaths at 70 mg/kg and 140 mg/kg were considered related to PNP exposure as they exhibited significant clinical signs of toxicity (pale appearance, languid behavior, prostration, wheezing and dyspnea), died shortly after dosing and exhibited moderate to severe congestive liver, kidney, lungs and adrenal cortex pathology (which correlated with necropsy findings) after microscopic examination; The presence of clinical signs of toxicity and absence of specific histopathological changes in these premature deaths suggests a relationship to acute pharmacologic/toxicologic effect. The single premature death observed in the LD female group was not considered treatment-related as there were no clinical signs observed, it did not die shortly after dosing (was found dead overnight) and had little in the way of organ congestion. Significant increases were observed in segmented neutrophils and absolute monocytes and eosinophil counts, as well as polychromasia of erythrocytes in 140 mg/kg animals of both sexes; these findings were considered of no toxicological significance. No treatment-related effects were observed in clinical signs, body weights, food consumption, ophthalmoscopic examination, organ weights or histopathology of survivors. Specifically, no effects were observed on gonads in this study. A NOEL was established as 25 mg/kg/d.
<b>Reliability</b>	: Purity of 99%
<b>Flag</b>	: (1) valid without restriction
09.10.2002	: Critical study for SIDS endpoint
<b>Species</b>	: rat
<b>Sex</b>	: male/female
<b>Strain</b>	: Sprague-Dawley
<b>Route of admin.</b>	: inhalation
<b>Exposure period</b>	: 4 weeks
<b>Frequency of treatment</b>	: 6 hr/d, 5 days/week
<b>Post obs. period</b>	: none
<b>Doses</b>	: 0, 1, 5, and 30 mg/m <sup>3</sup>
<b>Control group</b>	: yes
<b>NOAEL</b>	: >= 5 mg/m <sup>3</sup>
<b>LOAEL</b>	: = 30 mg/m <sup>3</sup>
<b>Method</b>	: OECD Guide-line 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study"
<b>Year</b>	: 1984
<b>GLP</b>	: yes
<b>Test substance</b>	: other TS
<b>Method</b>	: Groups of 15 male and 15 females S-D rats were exposed to target concentrations of 0, 1, 5 or 30 mg/m <sup>3</sup> of PNP dust via whole body exposure in 1000 L glass and stainless steel chambers. Chamber concentrations were generated via use of a Wright dust feed and determined 3X daily by gravimetric analysis. Particle size determinations were measured weekly. Food and water were available ad libitum at all times other than during exposure. Temperature and humidity, as well as light:dark cycle were controlled. Animals were observed twice daily for mortality and signs of toxicity. Each animal was carefully examined and weighed weekly. Hemoglobin and methemoglobin concentrations were

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	weighed weekly. Hemoglobin and methemoglobin concentrations were determined by orbital sinus during week 2. Ophthalmic exams were conducted just prior to terminal sacrifice on all animals. The following hematology (RBC, HCT, HGB, PLATELETS, RBC morph, and total and differential leukocyte counts, and clotting time) and blood chemistry (ALT, AST, BUN, TOT BILI, GLU, LD, CHOL, NA, POTAS, CA, CL, PROT, ALBU, GLOB) were evaluated after 4 weeks. No urinalysis was performed. Complete necropsies were conducted on all animals on test. The following organ weights were recorded: lungs, liver, kidneys, brain, heart, adrenals, spleen and testes with epididymides. Thymus wt was not recorded. Histopathological examinations were conducted on approximately 40 tissues and organs, and all gross lesions observed at necropsy, on all high dose and control animals. Clinical pathology, hematology, weekly body weights and weight gains, organ weights and weight ratios of control groups were compared statistically to treated groups of the same sex. Box test was used to determine homogeneity of variances followed by a 1-way classification by ANOVA if variances were homogeneous or use of rank transformation if nonhomogeneous. If found significant ( $p < 0.05$ ) Dunnett's t-test was used to compare groups ( $p < 0.05$ ).	
<b>Result</b>	: Mean gravimetric chamber concentrations were 1.09, 5.27, and 29.2 mg/m <sup>3</sup> . MMD ranged from 5.4-6.9 $\mu$ . Prestudy analysis indicated that the PNP dust was homogeneously distributed in the stainless steel chamber. No deaths occurred during the study. Except for dose-related yellow staining attributed to test material, no abnormal physical observations were noted. Ophthalmoscopic examinations revealed 11 cases of diffuse anterior capsular cataracts only in HD males and females. Corneal keratitis sicca (inflammation and drying of the cornea and conjunctiva) was noted in 3 HD animals. Periodic changes in body weights were seen inconsistently and in opposite directions for each sex and thus not considered treatment-related. No consistent, dose-related effect was noted in METH values, while some very slight changes in HGB and HCT were seen in HD males. The relationship of these effects to PNP treatment is unclear. No treatment-related effects were seen in other hematologic or clinical chemistry parameters. No gross or microscopic pathological effects or organ weight changes were noted that were attributed to PNP. No effects on the gonads was observed. A NOEL was established as 5 mg/m <sup>3</sup> .	
<b>Test substance</b>	: Purity of 99 %.	
<b>Reliability</b>	: (1) valid without restriction	
09.10.2002		(13)
<b>Species</b>	: rat	
<b>Sex</b>	: male/female	
<b>Strain</b>	: Sprague-Dawley	
<b>Route of admin.</b>	: gavage	
<b>Exposure period</b>	: 4 weeks	
<b>Frequency of treatment</b>	: once daily for the entire test period	
<b>Post obs. period</b>	: none	
<b>Doses</b>	: 0, 1, 10, 50, and 100 mg/kg	
<b>Control group</b>	: yes, concurrent vehicle	
<b>NOAEL</b>	: $\geq 50$ mg/kg	
<b>LOAEL</b>	: $\geq 100$ mg/kg	
<b>Method</b>	: other	
<b>Year</b>	: 1989	
<b>GLP</b>	: yes	
<b>Test substance</b>	: other TS	
<b>Method</b>	: Groups of 5 male and 5 female S-D rats were administered PNP in distilled water by gavage at doses of 0, 1, 10, 50 and 100 mg/kg at a constant volume of 10 ml/kg. Daily clinical signs were recorded and individual body weights and food consumption were taken weekly for all animals. Hematological (HGB, HCT, RBC, TOT /DIFF LEUKO, MET HGB ) and clinical pathological (BUN, GLU, CREAT, ALT, ATS, T PROT, ALBU, GLOB, T BILI, PHOS, NA, K, CL) parameters were measured prior to	

GLOB, T BILI, PHOS, NA, K, CL) parameters were measured prior to study termination after 4 weeks. Gross necropsy examinations were conducted at the terminal sacrifice and brain, liver, kidneys, spleen and testes with epididymides were trimmed and weighed. Collected tissues (approx. 40/animal) were preserved and gross lesions, kidneys, livers and spleen were prepared from all animals and examined microscopically. Dosing solutions were analyzed by spectrophotometric means for stability and concentration.

**Result** : Analysis of dosing solutions indicated stability and accuracy. One female rat at the 100 mg/kg dose level died shortly after bleeding followed by dosing and is likely treatment-related. Mean body weights and food consumption in treated groups were comparable to control values. No changes were observed in hematology or clinical chemistry values between treated and control groups. No clinical signs of toxicity were observed in survivors. Organ weights, necropsy findings and microscopic examination of treated rats were similar to controls.

**Test substance** : Purity of 99 %.

**Conclusion** : This study was a range-find study to set dose levels for study no. HL-88-372. As such, no statistical treatment of data was ascertained.

**Reliability** : (2) valid with restrictions  
09.10.2002

(14)

**5.5 GENETIC TOXICITY 'IN VITRO'**

**Type** : Ames test

**System of testing** : Salmonella typhimurium strains TA100, TA98, TA1535 and TA1537

**Concentration** : 0, 10, 33, 100, 166, 333, 666, 1000 ug/plate

**Cycotoxic conc.** : 1000 ug/plate (TA100)

**Metabolic activation** : with and without

**Result** : negative

**Method** : OECD Guide-line 471 "Genetic Toxicology: Salmonella typhimurium Reverse Mutation Assay"

**Year** : 1983

**GLP** : yes

**Test substance** : other TS

**Method** : Methodology used by NTP based on Ames test plate incorporation assay and consistent with OECD 471. All tests were run in duplicate and three plates were assayed at each dosage for each run both with and without metabolic activation; S9 obtained from male S-D rats injected with Arochlor 1254 (500 mg/ml) five days before they were killed; all tester strains obtained originally from B. Ames; the high dose was designed to produce toxicity (reduced background lawn or solubility limits; sterile DSMO was used as the solvent; negative (solvent) and positive controls (2-aminoanthracene, 4-nitro-o-phenylenediamine, sodium azide and 9-aminoacridine) used were appropriate to detect mutagenicity with or without metabolic activation in each of the 4 tester strains used. A positive response was detected if a reproducible, dose related increase (>2X) was seen in revertant colonies according to a model described by Margolin et al 1981.

**Result** : No increase in revertants were observed with or without metabolic activation in any of the 4 tester strains.

**Test substance** : Purity = 99%.

**Reliability** : (1) valid without restriction  
While no statistical methods were used, none were needed to visually inspect and render a conclusion of no increases observed in revertants in any tester strain; further, these findings are consistent with other literature citations using similar methodology

**Flag** : Critical study for SIDS endpoint  
09.10.2002

(8)

## 5. Toxicity

Id 100-02-7

Date 25.10.2002

<b>Type</b>	:	Chromosomal aberration test
<b>System of testing</b>	:	Chinese Hamster Ovary cell culture
<b>Concentration</b>	:	100 to 2500 ug/ml
<b>Cycotoxic conc.</b>	:	not stated
<b>Metabolic activation</b>	:	with and without
<b>Result</b>	:	positive
<b>Method</b>	:	other
<b>Year</b>	:	1987
<b>GLP</b>	:	yes
<b>Test substance</b>	:	other TS
<b>Method</b>	:	Study performed under auspices of US NTP program. Doses were based on a preliminary test of cell survival 24 hr after treatment. Cells were collected 10.5 h after treatment by mitotic shaking-off. Slides stained with Giemsa and coded. 100 cells were scored from each of the 3 highest dose groups having sufficient metaphases for analysis (cells with 19-23 metaphases chosen); Positive control groups treated with triethylenemelamine, mitomycin C or Cyclophosphamide), solvent control also used.. Aberrations were typed and recorded separately but analyzed grouped into categories of simple (breaks and terminal deletions), complex (rearrangements and exchanges) and other (i.e pulverized chromosomes). Gaps and endoreduplications were recorded but not included in totals. Aberrations in polyploid cells were not scored. Linear regression of the percentage of cells with aberrations vs. the log-dose was used as the test for trend. A binomial sampling assumption was used and data were analyzed according to the method of Margolin et al Environ Mutag 8:183 (1981). P values were adjusted by Dunnett's method to take multiple dose comparisons into account.
<b>Remark</b>	:	In a concurrent study PNP was negative for SCE induction up to doses that caused severe cell cycle delay (25 ug/ml -S9; 1700 ug/ml +S9).
<b>Result</b>	:	No treatment-related increase in the frequency of structural aberration were noted up to severe cytotoxic levels (>750 ug/ml -S9; Reproducible , dose-related and significant increases in cells with structural chromosomal aberrations were seen at test levels of 1500 to 2000 ug/ml +S9 that induced severe cell cycle delay.
<b>Test substance</b>	:	Purity of 99 %.
<b>Reliability</b>	:	(2) valid with restrictions
<b>Flag</b>	:	Critical study for SIDS endpoint
15.10.2002		

(4)

### 5.6 GENETIC TOXICITY 'IN VITRO'

### 5.7 CARCINOGENITY

### 5.8 TOXICITY TO REPRODUCTION

<b>Type</b>	:	Two generation study
<b>Species</b>	:	rat
<b>Sex</b>	:	male/female
<b>Strain</b>	:	Sprague-Dawley
<b>Route of admin.</b>	:	dermal
<b>Exposure period</b>	:	F0: males - 113 doses; females- 118 doses; F1: males - 190 doses; females - 180 doses
<b>Frequency of treatment</b>	:	once per day, 5 days per week
<b>Premating exposure period</b>	:	
<b>Male</b>	:	140 days (100 doses)

## 5. Toxicity

Id 100-02-7

Date 25.10.2002

**Female** : 140 days (100 doses)

**Duration of test** : Through prebreeding, breeding, gestation, lactation and development through two full generations (1 litter per generation), F2 pups observed through 30 days postweaning.

**Doses** : 50, 100, and 250 mg/kg/day

**Control group** : yes, concurrent vehicle

**NOAEL Parental** : > 250 mg/kg bw

**NOAEL F1 Offspr.** : > 250 mg/kg bw

**NOAEL F2 Offspr.** : > 250 - mg/kg bw

**Method** : other

**Year** : 1985

**GLP** : yes

**Test substance** : other TS

**Method** : 5-Week old Charles River CD rats began treatment, consisting of 120 female and 60 male rats housed in wire mesh caging. Humidity, temperature and light:dark cycle were controlled throughout the study. Water and food were available ad libitum. After random assignment, each of the five test groups began the study (F0 generation) with 24 females and 12 male rats per group. All rats were clipped free of hair along the dorsal body line and reshaved as necessary to allow good dermal contact with the test agent. Dosing periods were lengthened over the periods recommended by EPA guidelines to compensate for a 5-day per week dosing period in this study. Test agents were applied dermally using appropriate-sized syringes, once daily, 5 days /week. Animals were individually weighed at the beginning of each study and dose levels adjusted. F0 animals were treated for the first 140 days of the study (100 applications each). Thereafter, one half of the females in each group were paired with corresponding males until either positive mating was achieved (presence of sperm plug and confirmed by vaginal smear) or it became evident that the pair would not mate. In the latter cases additional cohousing occurred until it became apparent that no further mating would ensue. After successful mating, males and females were separated; F0 males were held until all mating ceased, at which time they were sacrificed and testes, epididymis and skin sections were taken for histopathologic evaluation. Dosing of F0 females continued through the breeding, gestation and lactation periods. Females dosed during gestation were based on the last pre-mating weight. Approximately 21 days after birth, the F1 generation was weaned and F0 females sacrificed with their ovaries, uterus and skin sections taken for histopathologic examination. 13 males and 26 females from the F1 generation were randomly selected for continued dosing and breeding in a manner similar to the F0 generation. Application of test materials continued over the next 168 days (120 applications each). Following this period, the F1 rats were mated in a procedure corresponding to the mating of the F0 parental animals. Five males and 5 female pups from the F1 generation were selected at weaning for complete necropsy exam. An additional 5 F2 males and 5 F2 females from each group were randomly selected and retained in wire cages for 30 days after weaning. Dosing of all F1 rats continued throughout breeding, gestation, lactation and until 30 days after all F2 rats had been weaned. Thereafter, all F1 rats and remaining F2 rats were submitted for complete necropsy. All animals dying spontaneously during the course of the study were submitted for necropsy. All rats which underwent necropsy were subjected to histopathological assessment of the following tissues and organs: (brain, spinal cord, eye, salivary gland, heart, thymus, thyroid, lungs, bronchi, esophagus, stomach, small intestine, large intestine, pancreas, adrenal glands, kidneys, liver, testes, epididymis, urinary bladder, male accessory glands, ovaries, corpus uteri, cervix uteri, spleen, lymph nodes, serum, femur, skeletal muscle, mammary gland, treated skin and untreated skin. Organ weights were recorded for scheduled sacrifices from F1 and F2 animals: liver, kidneys, heart, gonads (F0 males also), and brain. Observations for toxic signs, breeding and nesting behavior were recorded daily for all animals. Weights of all dosed rats were recorded weekly. Breeding and litter observations included: litter size, individual pup weights

Breeding and litter observations included: litter size, individual pup weights and viability at birth and on days 4, 7, 14, and at weaning. The following indices were calculated to assess reproductive success: fertility (no. of pregnancies/no. mated) gestation (% of pregnancies resulting in birth of live litters), viability (pups surviving at least to day 4 of life) and lactation (pups surviving at least to day 21 of life). Group-wise statistical ( $p < 0.05$ ) comparisons were made of body weights, absolute and relative organ weights.

The High dose (250 mg/kg/d) was selected based on a range-find study indicating this level to be 1/4 LD50 dermally, and would allow sufficient survival; both an ethanol vehicle (used at 500 mg/ml) control group (0.5 ml/kg/d) and a saline control group (0.5 ml/kg/d) were also evaluated concomittantly. Multigeneration study methodology was modified (dosing took place 5 d/wk rather than 7 d/wk) from test guidelines recommended in TFX Collins Handbook on Teratology, Vol. IV, Chapter 7: Multigeneration Reproduction Studies. 1978.

- Result** : All F0 and F1 rats dosed dermally with PNP or ethanol exhibited a pattern of dermal irritation consisting of varying degrees of erythema, scaling, scabbing and cracking ; some degree of dose-response was noted in PNP-treated groups. No treatment-related mortality was observed in either the F0 or F1 parental generation, and no effects of treatment were noted in body weights in these groups. No evidence of effects in mating, pregnancy, behavior, and growth were found in parents or subsequent F1 and F2 generations. All group-wise comparison of organ weights, including gonads, were unremarkable. No evidence of histopathologic alterations was seen in any tissue examined, including the gonads.
- Test substance** : Purity of test substance used - 99.1%
- Reliability** : (1) valid without restriction
- Study sufficiently adequate to be accepted to fulfill US EPA pesticide reregistration requirement for reproductive toxicity endpoint.

23.08.2002

(1)

**5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY****5.10 OTHER RELEVANT INFORMATION****5.11 EXPERIENCE WITH HUMAN EXPOSURE**

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**Date** 25.10.2002

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7.1 END POINT SUMMARY

7.2 HAZARD SUMMARY

7.3 RISK ASSESSMENT