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Benzenamine, 4-nitro-N-phenyl
CAS N°: 836-30-6

SIDS Initial Assessment Report
for
SIAM 8
(Paris, 28-30 October 1998)

Chemical name: ANILINE, 4-NITRO-N-PHENYL

CAS N°: 836-30-6

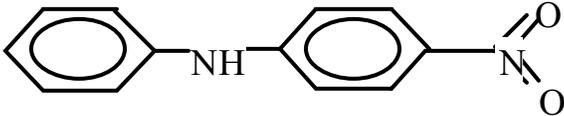
Sponsor country: Belgium
SIDS Contact Point
in sponsor country: Dr Thaly LAKHANISKY
Toxicology
Scientific Institute of Public Health
Rue J. Wytsman 14
B-1050 Brussels, Belgium

HISTORY: SIDS dossier and Testing Plan were discussed at the 2nd SIDS Review Meeting in March 1993. It was agreed that no further testing was required and that SIAR could be prepared. The original SIAR was discussed at the 5th SIAM. It has been modified in light of comments from Member countries & OECD Secretariat.
International Chemical Safety Card available.

COMMENTS: At SIAM 6, Member countries recommended to redraft the report in confirming the release and PEC values and circulate for comments under the written procedure.

Date of circulation: July 1997

SIDS INITIAL ASSESSMENT PROFILE

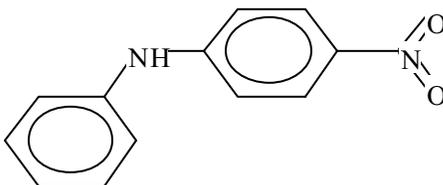
CAS No.	836-30-6
Chemical Name	Benzenamine, 4-nitro-N-phenyl
Structural Formula	
CONCLUSIONS AND RECOMMENDATIONS	
<p>Environment</p> <p>This chemical is not biodegradable, but bioaccumulative and toxic to aquatic species. However, PEC/PNEC is less than 1. It is currently considered of low potential risk and low priority for further work.</p> <p>Health</p> <p>This chemical may cause methemoglobinaemia, but exposure is low. It is currently considered of low potential risk and low priority for further work</p>	
SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS	
<p>The substance is manufactured at a limited number of sites world-wide. It is manufactured solely for use as a chemical intermediate for industrial uses and thus is essentially fully consumed in chemical reductive alkylation reaction downstream of manufacture. There is no consumer exposure.</p> <p>The substance is not acutely toxic neither orally nor by inhalation. Subchronic studies showed a decrease in the body weight gain, histopathological effects on kidney, liver and spleen, slight anaemia and increased methaemoglobinaemia. Neither adverse reproductive nor genotoxic effects have been detected.</p> <p>The substance is not a skin or eye irritant and there is no evidence of it producing skin sensitisation.</p> <p>In humans, due to its nitroaromatic structure, 4NDPA is considered to have the potential to cause methaemoglobin formation.</p> <p>4-NDPA is acutely toxic to aquatic invertebrates. It is not readily biodegradable and its partition coefficient shows a potential for bioaccumulation. The substance is persistent and only slowly photodegradable.</p> <p>Sources of environmental release arise during manufacturing, in very low quantities. For the representative facilities, the liquid effluents are treated on site previous to effluent discharge into the aquatic environment. Solid process wastes, consisting of distillation residues from production sites, are incinerated.</p> <p>In conclusion, 4NDPA is tested persistent in the environment and no environmental residues from production activity have been detected. It is currently considered of low potential risk and low priority for further work but because of its high aquatic toxicity, there may be a risk from production sites.</p>	
NATURE OF FURTHER WORK RECOMMENDED	

SIDS Initial Assessment Report

1. IDENTITY

Chemical name: Benzenamine, 4-nitro-N-phenyl
Synonyms: 4-nitrodiphenylamine
p-nitrophenylamine
4NDPA

CAS-number: 836-30-6
Empirical formula: C₁₂ H₁₀ N₂ O₂
Structural formula:



Molecular weight: 214

Degree of purity: 97,4%

Identity of major impurities: aniline: < 0,2% w/w

2. EXPOSURE

2.1 General discussion:

The substance is manufactured at a limited number of sites worldwide. It is manufactured solely for use as a chemical intermediate for industrial uses and thus is essentially fully consumed in chemical reductive alkylation reactions downstream of manufacture.

Worldwide production is reportedly up to 30,000 tonnes annually.

Sources of environmental release arise primarily during manufacturing. Due to its physical properties, a negligible amount of 4-NDPA would be lost in the atmosphere. Solid process wastes, consisting of distillation residues from production sites are incinerated. At the representative facilities, the liquid process effluents are treated on site by physical chemical treatment and by passing through an activated sludge treatment plant. The sludge is destroyed by incineration. Treated effluents are discharged to river.

2.2 Environmental exposure:

Exposure relevant properties:

Water solubility: 4,1 mg/l at 24 °C

Partition coefficient log P_{ow}: 3,82 at 25 °C (calc.: 4,00)

The logKow value of 3.82 indicates that the substance has some potential for bioaccumulation.

Vapour pressure: 1.067 kPa at 240 °C

0,133 kPa at 192 °C

< 0,02 kPa at 25 °C (calculated)

Biodegradation: no biodegradation, no aerobic biodegradability or chemical degradation after 8 weeks in river water; no ultimate degradation to CO₂ after up to 35 days.

Photolysis: Photo transformation in water: 7% in 7 days, t_{1/2}: 70 days.(based on the UV absorption spectrum of 4NDPA, which indicates strong absorption in the solar spectral region)

Partitioning and fate: Based on the physical-chemical properties of the substance, in the environment, it would tend to partition mostly to soil and sediment. Furthermore, taking into account the strictly industrial use of this substance as an intermediate and its estimated substantive soil particulate binding characteristics (based on its LogKow of 3.82), the exposure of the aquatic environment is considered low.

Effluents concentrations:

Plant location	Year	Concentration (mg/l)	Discharge rate (m ³ /day)	
Antwerp	once a week	below detect.limit		
Newport	1994	14	3.223	*
	1995	14	3.130	
	1996	6		

* limit concentration imposed by local authorities: 100 mg/l + effluents discharged only at high tide (dilution factor: 10 000, based on the US EPA BOX model: from an average daily effluent of 3 000 m³/day and two tidal cycles per day, a dilution factor of 221 833 can be derived. A dilution factor of 10 000 seems therefore conservative and appropriate for the calculations).

Stack emissions: not required by BE national authorities for solids with an emission rate lower than 0.5 kg/h (= conc. limit of 50 mg/m³)

2.3 Consumer exposure:

There is no significant consumer exposure.

The large quantity of 4-NDPA is used in a closed system by the producer as an intermediate for synthesis.

A worst case assumption, i.e. that drinking water containing up to the maximum solubility limit (4 ppm) of 4NDPA is consumed daily, 2l water x 4 mg/l 4NDPA x 100% absorption x 1/70 kg = 0,11 mg/kg/d. This scenario results in a margin of safety of at least 500-fold for repeated dose effects and a safety margin of >2200-fold for developmental toxicity.

2.4 Occupational exposure:

The primary routes of potential occupational exposure are inhalation and, to a lesser extend, dermal.

Prior to 1979, the mean exposure to 4NDPA was at most 0.46 mg/m³ (Antwerp Monsanto plant). Since 1979, 90% of all values have been less than 0.25 mg/m³ and the highest value recorded was 1.6 mg/m³.

At the Newport plant, the grand mean value over 15 years has been less than 0.11 mg/m³ and the highest individual value recorded was 6.16 mg/m³.

The mean occupational dust inhalation exposure level was 0.15 mg/m³ across all manufacturing operations.

The manufacturer's internal atmospheric occupational exposure guide is 3 mg/m³ set on SAR basis to substances known to produce methaemoglobin in humans.

3. TOXICITY

3.1 Health effects

3.1.1 Acute toxicity

Oral: rat LD50 > 7.940 mg/kg

Dermal: rat LD50 > 7.940 mg/kg

Skin irritation: rabbit: FHSA 500 mg/24 hr exposure on abraded and non-abraded skin: 0.0/8.0

Eye irritation: FHSA 100 mg/24 hr exposure: 2,6/110

No test results on sensitisation are available, but extensive experience within Monsanto has not produced any reports of sensitisation.

3.1.2 Repeated dose toxicity

In two subchronic studies in rats (oral, up to 5000 ppm in the diet, 90 days), the most notable clinical pathology findings occurred in the haematological parameters (increased reticulocyte counts, dose related increase in methaemoglobin, decreased hematocrits, haemoglobin and RBC counts, in females and to a lesser extent, in males.). Besides decreased body weight gain, histopathological effects on the kidneys (discoloration, tubulointerstitial nephropathy of the cortex and medulla, mostly in males at high dose), elevated liver weights (in high dose females), splenic congestion and hemosiderin deposition and slight anaemia were observed. Treated animals of both sexes had yellow/orange urine and yellow stained fur resembling the test material colour. No significant toxicological effects (NOEL) were seen at 800 ppm (57 mg/kg/d).

In a subacute dust inhalation study in rats (up to 52 mg/m³, 21 days, 6h/d, 5d/week) effects on respiratory irritation, elevated liver weights and methaemoglobin were observed. Minimal effects were noted at the intermediate level of 29 mg/m³ with no discernible effects seen at 8,5 mg/m³ (NOEL).

In neither case was an effect on the male or female gonads observed.

3.1.3 Reproductive toxicity

25 Pregnant Sprague-Dawley rats were treated by gavage with 4NDPA at dose levels of 250, 1000 and 3000 mg/kg/day on days 6 through 15 of gestation. Moderate to severe signs of maternal toxicity were evidenced by mortality (one female in the mid-dose group and eight females in the high dose group), clinical signs (few or no faeces, faecal stain and dark material around the mouth and nose) and dose-dependent reduced body weight gains. No treatment-related clinical signs of toxicity were noted in the 250 mg/kg/day. In all of the treated groups, yellow-orange coloured faeces, urine, fluid in the cage/tray and staining of the haircoat and extremities were observed.

Foetal body weight was statistically reduced at the 3000 mg/kg/day level when compared to the control group. A slight but not statistically significant reduction in gravid uterine weight at 3000 mg/kg/day was also observed. All

other caesarean parameters (mean number of corpora lutea, implantation sites, viable foetuses, early and late resorptions and foetal sex ratio) were generally comparable between the control and treated groups.

No treatment-induced foetal malformations were observed in the study. A statistically significant increase in the number of litters with 27 presacral vertebrae and a slight but not statistically significant increase in the number of foetuses/litters with 14th full ribs were noted at 3000 mg/kg/day level. These changes occurred at a dosage level with 32% maternal mortality, which is considered excessive for the evaluation of potential teratogenic effects. At the 1000 mg/kg/day level, a slight but not statistically significant increase was noted in the number of foetuses/litters with 14 full ribs.

The data suggest a no-observed effect level (NOEL) of 250 mg/kg/day for maternal and developmental toxicity.

The malformations appearing either in presence of maternal toxicity or at a not statistically significant level, the substance was not considered as a selective reprotoxicant

3.1.4 Genetic toxicity

There was no evidence to suggest genotoxicity of 4NDPA when tested in a battery of tests [Salmonella typhimurium (TA98, TA100, TA1535, TA1537, TA1538) or CHO (Chromosomal aberrations)].

In vivo, at 5.000 mg/kg, no increase in aberrations was seen in bone marrow cells.

3.2 Effects on the environment

3.2.1 Acute fish toxicity

a. Rainbow trout (*Oncorhynchus mykiss*):
LC50, 96 hr= 16 mg/l (carrier solvent: acetone)

Bluegill sunfish (*Lepomis macrochirus*):
LC50, 96 hr= 17 mg/l (carrier solvent: acetone)

Results:

Hours	LC50 (CI) mg/l Rainbow trout	LC50 (CI) mg/l Bluegill sunfish
24	33 (23-49)	>32 <49
48	31 (21-47)	28 (22-36)
96	16 (11-20)	17 (13-23)
NOEC	6,5	14

Test concentration and observed percentage mortality were converted to logarithms and probits, respectively, and these values were utilised in a least square regression analysis. The LC50's and the 95% confidence intervals were calculated from the regression equation.

b. Fathead minnow (*Pimephales promelas*):
LC50, 96hr = 2,4 mg/l (95% CI = 1,8-3,2 mg/l)
(carrier solvent: acetone)

Maximum concentration at which no effect was observed within the period of test (NOEC) = 1,8 mg/l

- c Acute fish toxicity - time independent study:
Fathead Minnow (*Pimephales promelas*):
LC50, 15 days flow-through = >1,18 <2,13 mg/l
LC50, 24 hours = 2,2 mg/l (95% CI = 2,03-2,39).
(carrier solvent: acetone)

3.2.2 Acute daphnia toxicity (*Daphnia magna*)

EC50: 48 hr = 1,0 mg/l (carrier solvent: acetone)
EC50: 24 hr = 2,1 mg/l (carrier solvent: acetone)
= most sensitive species.

3.2.3 Acute algae toxicity (*Selenastrum capricornutum*)

EC50, 96 hr = 27 mg/l (based on cell growth)
EC50, 96 hr = 36 mg/l (based on chlorophyll a)
Lowest Observed Effect Concentration based on cell growth
(LOEbC): 10 mg/l

4. INITIAL ASSESSMENT

The substance is manufactured at a limited number of sites worldwide. It is manufactured solely for use as a chemical intermediate for industrial uses and thus is essentially fully consumed in chemical reductive alkylation reaction downstream of manufacture.

Considerable air monitoring data have indicated a mean occupational dust inhalation exposure level of 0.15 mg/m³ across all manufacturing operations.

In calculation of worst-case exposure potential in the workplace, one can assume the mean dust value of 0,15 mg/m³ x 10 m³ /d and 100 % absorption/retention, which amounts to 1,5 mg 4-NDPA/d. For a 70 kg person, this amounts to 0,02 mg/kg/d. Safety margin of 60-200 when compared to the NOEL (8.5 mg/m³)/LOEL (29 mg/m³) by inhalation and >2.800 for repeated dose toxicity (oral subchronic/ NOEL = 57 mg/kg/d)) and > 12.000 for oral developmental/reproductive toxicity (NOEL = 250 mg/kg/d).

There is no consumer exposure.

The substance is not acutely toxic neither orally nor by inhalation. Subchronic studies showed a decrease in the body weight gain, histopathological effects on kidney, liver and spleen, slight anaemia and increased methaemoglobin.

Adverse reproductive and genotoxic effects have not been detected.

The substance is not a skin or eye irritant and there is no evidence of its producing skin sensitisation.

In humans, due to its nitroaromatic structure, 4-NDPA is considered to have the potential to cause methaemoglobin formation.

4-NDPA is acutely toxic to aquatic invertebrates. It is not readily biodegradable and its partition coefficient shows a potential for bioaccumulation. The substance is persistent and only slowly photodegradable.

Environmental contamination with 4-NDPA results primarily from chemical manufacturing.

In current manufacturing processes the effluent containing 4NDPA is treated by means of activated sludge wastewater treatment. In this process 4-NDPA is not biodegraded but removed from the effluent through adsorption onto the sludge. The sludge is separated from the effluent afterwards and burnt in an incinerator. The effluent of the wastewater treatment plants is regularly monitored and no 4-NDPA could be detected. The detection limit of the analytical method used is 10 µg/l. The actual concentration of 4NDPA in these effluents can thus be considered to be less than 10 µg/l.

If the EU default dilution factor of 10 in surface water is applied to calculate the PEC, the concentration to be used for risk assessment is 1 µg/l. It should be emphasised, however, that the dilution obtained at the European 4-NDPA manufacturing plants is at least 1400 times. This means that the PEC should be considered as much less than 1 µg/l.

The PNEC for 4-NDPA can be derived from the EC50 obtained for Daphnia. The EC50 of 1 mg/l and the uncertainty factor of 1000 to extrapolate the EC50 to long-term exposure yield a PNEC of 1 µg/l. From the exposure and environmental no-effect values calculated above, a PEC/PNEC ratio of less than 1 can be derived.

5. CONCLUSIONS AND RECOMMENDATIONS

Based on the initial assessment for environment and human health given and considering that it is used as a chemical intermediate only , 4NDPA does not give cause for concern: despite its ecotoxicity, its environmental release from production plants is not significant.

It can be considered to present a low potential for risk to man and its environment.

**Summary of Responses to the OECD Request for
available Data on HPV Chemicals**

0. General Information

Name of Sponsor country: *Belgium*
Contact point: *Dr T. LAKHANISKY*
Division Toxicology
Institute of Hygiene and Epidemiology
Rue J. Wytsman, 14
B-1050- BRUSSELS, Belgium

Name of Lead organization: *Institute of Hygiene and Epidemiology*

1. Chemical Identity

1.1 CAS-number *836-30-6*

1.2 Name (give the name supplied by the OECD)
Benzenamine, 4-nitro-N-phenyl

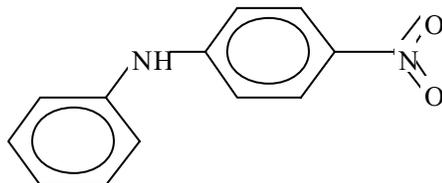
1.3 Common Synonyms

4-nitrodiphenylamine
p-nitrophenylamine
4NDPA

1.4 Empirical formula

C₁₂ H₁₀ N₂ O₂

1.5 Structural formula



1.6 Purity of industrial product

1.6.1 Degree of purity (percentage by weight/volume) *97,4*

1.6.2 Identity of major impurities: *xylene, aniline, formanilide*

1.6.3 Essential additives (stabilizing agents, inhibitors, other additives), if applicable

2. Physical-Chemical Data**2.1 Melting or Decomposition Point:** *132 ° Centigrade*Method (e.g., OECD, others): *not specified*GLP: YES []
NO [x]Reference: *Monsanto Product Assessment Report - 4NDPA,
September 1979***2.2 Boiling Point (including temperature of decomposition, if relevant):***343 °C at 101.33 kPa*Method (e.g., OECD, others): *not specified*GLP: YES []
NO [x]Reference: *Monsanto Product Assessment Report - 4NDPA,
September 1979***2.3 Vapour pressure:** *1.067 kPa at 240 °C (a)*
*0,133 kPa at 192 °C (b)**< 0,02 kPa at 25°C (calculated)(c)*Method (e.g., OECD, others): *not specified*GLP: YES []
NO [x]Reference: (a) and (b): *Monsanto Product Assessment Report - 4NDPA
September 1979*
(c) *US Contact Point***2.4 Partition coefficient n-Octanol/water:** *log Pow = 3,82 a t 25°C; Calculated: 4,00*Method: calculated [x]
Measured [x]GLP: YES []
NO [x]Analytical Method: *HPLC (EPA Guidelines)*Comments (e.g., is the compound surface active or dissociative?):
*Samples analysed at one test concentration only*Reference: *SRI n° 8669***2.5 Water solubility:** *4,1 mg/l at 24 °C*

Method (e.g., OECD, others):

GLP: YES []
NO [x]

Analytical Method: *HLPC*

Comments (e.g., the detection limit for insoluble substances):

Solubility was determined at 3 pH values: 4.0 mg/l at pH 5; 4.1 mg/l at pH 7 and 4.1 mg/l at pH 9.

Reference: *SRI n° 8669*

2.6 Flash point (liquids)

190 °C closed cup [] open cup []

Method (e.g., OECD, others including reference to the standard test used): *not specified*

GLP: YES []
NO []

Reference: *US Contact Point*

2.7 Flammability (solid/gases)

Method (e.g., OECD, others): *not specified*

GLP: YES []
NO [x]

Test results: *non-flammable*

Comments: *Burning stopped when flame removed*

2.8 pH in water

pH at mg/l (water)
pKa

Comments: *not applicable*

2.9 Other data e.g., relative density, surface tension (of aqueous solution), fat solubility, explosivity, oxidizing properties and particle size distribution

Comments: *specific gravity: 1,16 at 150 °C (a)*
Ignition temp. : 220°C (b)

Reference: *(a) Monsanto Product Assessment Report - 4NDPA / September 1979*
(b) US Contact Point

3. Source of Exposure

3.1 Production levels expressed as tons per annum: Information on production levels should be provided in ranges (e.g., 100-1000 tons, etc.) per responder or country and the date for which those ranges apply should be given.

20-30.000 tonnes (Monsanto worldwide, 1989)

3.2 Processes: Describe sources of potential human or environmental exposure including workplace concentrations and emission data (in % release), if available for both manufacturing and user areas.

Reference: *Monsanto has established a Monsanto Work Place Exposure Guideline for 4NDPA of 3 mg/m³ based on its potential for methaemoglobin formation.*

3.3 Information concerning Uses (including categories and types of uses expressed in percentage terms): Examples of use categories are dyestuffs, intermediates, solvents, adhesives, building material agents, detergents, cleaning agents, fertilizers, plastic agents, surface treatment agents, etc.

Types of uses are divided into three: industrial use (open system and closed system), public use and export:

Isolated intermediate chemical converted in anti-degradants for rubber.

3.4 Options for disposal: Mode of disposal (e.g., incineration, release to sewage system) for each category and type of use, if appropriate; recycling possibility)

4. Environmental Fate and Pathways

Reporting of studies should give the test method, test conditions (lab versus field studies), test results (e.g., % degradation in specified time period) and reference. Information on breakdown products (transient and stable) should be provided when available.

4.1 Degradability (biotic and abiotic)

4.1.1 Biodegradability

Test substance: 4NDPA

Test type, aerobic [x], anaerobic []

Test medium: *water, water-sediment, soil, and sewage treatment*

In the case of poorly soluble chemicals, treatment given (nature, concentration, etc.):
DMSO

Test method (e.g., OECD, ISO, others): EPA Guidelines

GLP: YES []
NO []

Test results: *No biodegradation or chemical degradation after 8 weeks in river water.*

Comments: *No ultimate degradation to CO₂ after up to 35 days*

Reference: *SRI N° 8669*
Monsanto Report ES-79-SS-25

4.1.2 Sewage Treatment: Information on treatability of the substance

4.1.3 Stability in air (e.g., photo degradability) and in water (e.g., hydrolysis)

Test substance: 4NDPA

Test method or estimation method (e.g., OECD, others): *EPA Guidelines*

If available, information on degradation products, dissociation constants and half-life should be given.

GLP: YES []
NO [x]

Test results: *Photo transformation in water*

Percentage of degradation after certain period: *7% in 7 days; half-life time: 70 days based on the UV absorption spectrum of 4-NDPA which indicated strong absorption in the solar spectral region.*

Remark: *Dissolved in ionised water and exposed to sunlight. Measured loss of parent material. Study carried out from September 12 to 19, 1979 in Menlo Park, California, US. Control samples were at 23 degrees C and no temperature was listed for sunlight-exposed samples.*

Comments: *based on SAR evaluation, the substance is not hydrolysed.*

Reference: *SRI N° 8669*

4.1.4 Identification of main mode of degradability in actual use

Since 4NDPA is primarily used as an intermediate in producing p-phenylenediamine antidegradants, it is consumed in the reductive alkylation process.

Reference: *Monsanto*

4.2 Bioaccumulation

Test substance: 4-NDPA

Test method (e.g., OECD, others): *not specified*

. Type of test: static [], semi-static [], flow-through []

. Other (e.g., field test) []

GLP: YES []

NO []

Test results: Bioaccumulation factor: $BCF = 580,0$
log fish BCF = 2,8

Reference: *US Contact Point*

5. Ecotoxicological Data

5.1 Toxicity to fish

5.1.1 Results of acute tests

Test species: *a. Rainbow trout (Oncorhynchus mykiss)*
Bluegill sunfish (Lepomis macrochirus)

Test method (e.g., OECD, others): *not specified*

- . Type of test static , semi-static , flow-through
- . Other (e.g., field observation)

GLP: YES
NO

Results:

Hours	LC50 (CI) mg/l Rainbow trout	LC50 (CI) mg/l Bluegill sunfish
24	33 (23-49)	>32 <49
48	31 (21-47)	28 (22-36)
96	16 (11-20)	17 (13-23)
NOEC	6,5	14

Comments: *Test concentration and observed percentage mortality were converted to logarithms and probits, respectively, and these values were utilised in a least square regression analysis. The LC50's and the 95% confidence intervals were calculated from the regression equation.*

Test species: *b. Fathead minnow (Pimephales promelas):* LC50, 96hr = 2,4 mg/l
(95% CI = 1,8-3,2 mg/l)

Maximum concentration at which no effect was observed within the period of test :(NOEC)
= 1,8 mg/l

Additional data: BCF = 580.0 (*)
Log fish BCF = 2.8

Reference: *Monsanto Studies: BN-77-60 and BN-79-324*
(*) US Contact Point

5.1.2 Results of long-term test e.g., prolonged toxicity, early life-stage

Test substance: 4-NDPA

Test species: *Fathead minnow (Pimephales promelas):*

Test method (e.g., OECD, others):

- . Type of test: static , semi-static , *flow-through*
- . Other (e.g., field observation [15-days/ time independent study])

GLP: YES
NO

Test results: LC50, 15 days, flow-trough: >1,18 <2,13 mg/l
LC50, 24 hours = 2,2 mg/l (95% CI = 2,03-2,39).

Maximum concentration at which no effect was observed within the period of the test
 Minimum concentration at which effect was observed within the period of the test

Reference: *Monsanto*

5.2 Toxicity to daphnids

5.2.1 Results of acute tests

Test substance: 4NDPA

Test species: *Daphnia magna*

Test method (e.g., OECD, others): *EPA Guidelines*
Solvent: acetone

GLP: Yes []
 NO [x]

Test results: EC50 - values after 24 and 48 hours, and method used to calculate these values:

EC50, 48 hr = 1,0 mg/l (Litchfield and Wilcoxon data analysis)
EC50, 24 hr = 2,1 mg/l
NOEC = 0.56 mg/l

Reference: *BN-79-323 (Monsanto Study)*

5.2.2 Results of long-term e.g., reproduction

Test substance:

Test species:

Test method (e.g., OECD, others):
 . Type of test: static [], semi-static [], flow-through []
 . Other (e.g., field observation) []

GLP: YES []
 NO []

Test results:
 Maximum concentration at which no effect was observed within the period of the test
 Minimum concentration at which effect was observed within the period of the test

Comments: *data not available*

5.3. Toxicity to algae

Test substance: 4NDPA

Test species: *Algae (Selenastrum capricornutum)*

Test method (e.g., OECD, others): *EPA Guidelines*

GLP: YES []
NO [x]

Test results: EC50 (duration, e.g. 24, 48, 72 hours):
EC50, 96 hr = 27 mg/l (based on cell growth)
EC50, 96 hr = 36 mg/l (based on chlorophyll a)

Maximum concentration at which no effect was observed within the period of the test
Minimum concentration at which effect was observed within the period of the test:
Lowest Observed Effect Concentration based on cell growth (LOEbC): 10 mg/l

Reference: BN-79-3122 (Monsanto Study)

5.4 Toxicity to other aquatic organisms

Test substance: 4-NDPA

Test species: Midge (Paratanytarsus portthenogenetica)

Test method (e.g., OECD, others): EPA Guidelines, 48 hr, and static

GLP: YES [x]
NO []

Test results: LC50, 24 hr > 180 mg/l
EC50, 48 hr = 120 mg/l (95% CI = 95-160 mg/l)

Reference: ABC-27138 (Monsanto Study)

5.5 Toxicity to bacteria

Test substance:

Test species:

Single species tests such as "Microtox Photobacterium luminescence test" and tests on overall processes such as nitrification or soil respiration are included in this item.

Test method (e.g., OECD, others):
. Type of test
. Other (e.g., field observation) []

GLP: YES []
NO []

Test results:

Comments: data not available

5.6 Toxicity to terrestrial organisms

5.6.1 Toxicity to soil dwelling organism

Test substance:

Test species:

Test method (e.g., OECD, others):

GLP: YES []
NO []

Test results: LC50 (at 7 and 14 days for earthworms)

5.6.2 Toxicity to plants

Test substance:

Test species:

Test method (e.g., OECD, others):

GLP: YES []
NO []

Test results: EC50 for 7 and 14 days or LC50

Maximum concentration at which no effect was observed within the period of the test

Minimum concentration at which effect was observed within the period of the test

Comments: *data not available*

5.6.3 Toxicity to birds

Test substance:

Test species:

Test method (e.g., OECD, others):

GLP: YES []
NO []

Test results: EC50 for 7 and 14 days or LC50

Maximum concentration at which no effect was observed within the period of the test

Minimum concentration at which effect was observed within the period of the test

Comments: *data not available*

5.7 Biological Effects Monitoring (including biomagnifications): Studies on variation of predominant species in certain ecosystems and monitoring of biological effects (e.g., thinning of eggshell) etc. are included.

Test substance:

Organism or ecosystem studied:

Effects monitored:

Information on monitoring conditions (water characteristics: suspended matter, pH, temperature, hardness) (Soil/sediment characteristics: % organic matter, clay content)

Test results:

Chemical analysis:

Comments: *data not available*

5.8 Biotransformation and kinetics in environmental species: Under this item, studies on absorption, distribution, metabolism and excretion etc... should be given. *Data not available*

6. Toxicological Data (oral, dermal and inhalation, as appropriate)

Where observations on humans are available, e.g., irritation, these should be entered in the appropriate "Comments" section.

6.1 Acute toxicity**6.1.1 Acute oral toxicity**

Test substance: 4NDPA
Test species/strain: *rat*
Test method (e.g., OECD, *limit test*, fixed dose test):
GLP: YES []
NO [x]
Test results: *Oral LD50 = > 7.940 mg/kg*
Comments: *0/3 males and 0/2 females died*
Reference: *Y-73-171 (Monsanto Study)*

6.1.2 Acute inhalation toxicity

Test substance:
Test species/strain:
Test method (e.g., OECD, EC, limit test):
GLP: YES []
NO []
Test results: LC50:
Comments: *data not available*

6.1.3 Acute dermal toxicity

Test substance: 4NDPA
Test species/strain: *rat*
Test method (e.g., OECD, *limit test*):
GLP: YES []
NO [x]
Test results: *LD50: > 7.940 mg/kg*
Comments: *0/1 male and 0/1 female died*
Reference: *Y-73-171 (Monsanto Study)*

6.2 Corrosiveness / Irritation**6.2.1 Skin Irritation**

Test substance: 4NDPA

Test species/strain: *rabbit (x6)*

Test method (e.g., OECD, others): *FHSA 500-mg/24 hr exposure on abraded and non-abraded skin*

GLP: YES []
NO [x]

Test results: give maximum scores after .24 hrs = 0

Reference: *Y-73-171 (Monsanto Study)*

6.2.2 Eye Irritation

Test substance: 4NDPA

Test species/strain: *rabbit (6)*

Test method (e.g., OECD, others): *FHSA 100-mg/24 hr exposure*

GLP: YES []
NO [x]

Comments: *2,6/110 (FHSA scores)*

Reference: *Y-73-171 (Monsanto Study)*

6.3 Skin sensitisation

Test substance:

Test species/strain:

Test method (e.g., OECD, others):

GLP: YES []
NO []

Test results: Number of animals with skin reaction at challenge
Number of animals with skin reaction in control group at challenge

Comments: *No tests made, but extensive experience within Monsanto has not produced any reports of sensitisation.*

6.4 Repeated dose toxicity

Test substance: 4NDPA

Test species/strain: *Sprague-Dawley rats*

a. Test method (e.g., OECD, others): *EPA/TSCA
4-week dietary test at dose levels of 0, 2000, 5000, 10 000 and 20 000 ppm to groups of 5 animals per sex.*

GLP: YES [x]

NO []

Test results: *Reduced bodyweight and food consumption at 10 000 and 20 000 ppm in males and females.*

Renal tubular pigments/casts and cysts at 5000, 10 000 and 20 000 ppm.

Dose or concentration at which no toxic effects were observed: 2000 ppm

Reference: ML-83-217 (Monsanto Study)

b. Test method (e.g., OECD, others): EPA/TSCA

Subchronic study: 0, 800, 2000 and 5000 ppm in the diet, 90 days; 30 animals per sex and per dose level.

GLP: YES [x]

NO []

Test results: *Decreased bodyweight gain, histopathological effects on kidneys and spleen, slight anaemia and increased methaemoglobinaemia.*

Dose or concentration at which no toxic effects were observed: 800 ppm

Reference: BD-83-318 (Monsanto Study)

c. Test method (e.g., OECD, others): EPA/TSCA

10 animals/sex/group were exposed by whole body dust inhalation to 8,5, 29 and 52 mg/m³ for 6 hrs/day, 5 days/week for 21 days.

GLP: YES [x]

NO []

Test results: *Increased methaemoglobin, absolute and relative liver weights and haematological changes were noted at 29 and 52 mg/m³.*

Dose or concentration at which no toxic effects were observed: 8,5 mg/m³

Reference: BD-83-314 (Monsanto Study)

6.5 Genetic toxicity

6.5.1 Bacterial test

Test substance: 4NDPA

Test species/strain: *Salmonella typhimurium (TA98, TA100, TA1535, TA1537, TA1538)*

Test method (e.g., OECD, others): EPA/TSCA

GLP: YES [x]

NO []

Test results: Minimum concentration of test substance at which toxicity to bacteria was observed:

With metabolic activation: 167 ug/plate

Without metabolic activation: 167 ug/plate

Genotoxic effects: + ? -
 With metabolic activation: [] [] [x]
 Without metabolic activation:[] [] [x]

Comments: 4NDPA tested at 5, 16.7, 50, 167 and 500 ug/plate

Reference: PK-86-128 (Monsanto Study)

6.5.2 Non-bacterial in vitro test

Test substance: 4NDPA

Type of cell used: CHO

Test method (e.g., OECD, others): EPA/TSCA

GLP: YES [x]
 NO []

Test results: with metabolic activation: 50 ug/ml: no survival
 Without metabolic activation: 30 ug/ml: no survival

Genotoxic effects: + ? -
 With metabolic activation: [] [] [x]
 Without metabolic activation: [] [] [x]

Comments: Chromosomal aberrations scoring: no clastogenic activity evidenced at 3,10 or 40 ug/ml without S9 or 5,15 and 25 ug/ml with S9.

Reference: PK-86-198 (Monsanto Study)

6.5.3 Non-bacterial test in vivo

Test substance: 4NDPA

Test species/strain: Sprague-Dawley rats

a. Test method (e.g., OECD, others): EPA/TSCA, Chromosomal aberrations

GLP: YES [x]
 NO []

Test results: lowest dose producing toxicity: diarrhoea at 5.000 mg/kg

Genotoxic effect: + ? -
 [] [] [X]

Comments: At 5.000 mg/kg, no increase in aberrations seen in bone marrow cells.
 Bone marrow arrested at 6, 18 and 30 hours after administration.

Reference: PK-86-222 (Monsanto Study)

b. Test method (e.g., OECD, others): EPA/TSCA
 Primary rat hepatoocytes were isolated from groups of rats that had received 0, 50, 250 and 1000 mg/kg 4-NDPA by gavage 16 hours (UDS) or 48 hours (DNA replication) after administration.

GLP: YES [x]
 NO []

Test results: *4-NDPA did not induce UDS or S phase replication indicating that it is not genotoxic nor able to induce immediate cellular proliferation under the conditions of this assay.*

Genotoxic effect: + ? -

Reference: *SR-86-175 (Monsanto Study)*
Carcinogenesis 1, 621-625 (1980)

6.6 Carcinogenicity

Test substance:

Test species/strain:

Test method (e.g., OECD, others):

GLP: YES
 NO

Test results:

6.7 Reproductive and Development toxicity

6.7.1 Reproductive toxicity

Test substance:

Test species/strain:

Test method (e.g., OECD, others):

GLP: YES
 NO

Test results: NOEL for P generation
 NOEL for F1 generation
 NOEL for F2 generation

Maternal and Paternal general toxicity: Reproductive toxicity observed in parental animals (fertility, gestation, reproductive organ toxicity, etc.):

Reproductive toxicity observed in offspring (weights of litter, postnatal growth, viability, etc.):

Comments:

Reference:

6.7.2 Teratogenicity / Developmental toxicity

Test substance: 4NDPA

Test species/strain: *Sprague-Dawley rats*

Test method (e.g., OECD, others):

GLP: YES [x]
NO []

Test results: NOEL for maternal animals: 250 mg/kg/day

Maternal general toxicity: mortality, clinical signs, reduced body weight gains and death at: 3000 mg/kg/day

Pregnancy and litter data: Foetal data (live/dad, sex, external defects, soft tissue and skeletal defects): *decreased body weights, increased, skeletal variations at 3000 mg/kg/day. At 1000, increased number of fetuse s/ litters with 14th full ribs.*

Comments: *dose levels: 0, 250, 1000 and 3000 mg/kg/day (gavage in corn oil)*
Administration of 4-NDPA to pregnant Sprague-Dawley rats on days 6 through 15 of gestation produced moderate to severe signs of toxicity as evidenced by mortality (one female in the mid dose group and eight females in the high dose group), clinical signs and reduced body weight gains. A slight reduction in gravid uterine weight, a statistically significant reduction in foetal body weight, and an increase in skeletal variations were observed at 3000 mg/kg/day. At 1000 mg/kg/day, a slight increase was noted in the number of foetuses/litters with 14th full ribs. No evidence of any maternal or developmental toxicity was observed at 250 mg/kg/day.
Therefore, the no-observed effect level (NOEL) was considered to be 250 mg/kg/day.

Reference: SD-89-471 (Monsanto Study)

6.8 Specific toxicities (Neurotoxicity, immunotoxicity etc.):

6.9 Toxicodynamics, toxico-kinetics

7. **Experience with Human Exposure (give full description of study design, effects of Accidental or Occupational Exposure, epidemiology)**
 - 7.1 **Biological Monitoring (including clinical studies, case reports, etc.)**
8. **Recommended Precautions, Classification (use and/or transportation) and Safety Data Sheets.**
9. **Availability and reference(s) for existing review(s)**
10. **Name of responder**

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