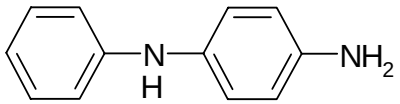
# SIDS INITIAL ASSESSMENT PROFILE

| | |
|---|---|
| **CAS No.** | 101-54-2 |
| **Chemical Name** | 4-Aminodiphenylamine (4-ADPA) |
| **Structural Formula** |  |

## SUMMARY CONCLUSIONS OF THE SIAR

### Human Health

4-Aminodiphenylamine (4-ADPA) can be taken up into the body by the oral and dermal routes of exposure as evidenced by the results of animal studies. In rats the substance and/or its metabolites are eliminated mainly with the feces, but can also be detected in the urine. An indirect evidence of dermal absorption in humans is provided by the detection of 4-ADPA in the urine of one worker after a single dermal contact with the substance. 4-ADPA can bind to hemoglobin and proteins.

Methemoglobinemia was observed in cats after single oral administration. In rats, the oral $LD_{50}$ value was determined as 720 mg/kg bw. Clinical signs of toxicity included ataxia, nasal, oral and ocular discharge, difficult breathing, and hypoactivity. The acute dermal toxicity of 4-ADPA was very low with an $LD_{50}$ value of greater than 5,000 mg/kg bw in rabbits. The only clinical signs noted in some animals were nasal and ocular discharge and single occurrences of red and/or swollen eyes.

4-ADPA was not irritating to the skin of rabbits (OECD TG 404). Transient irritant effects were observed after instillation of 4-ADPA into the eyes of rabbits (OECD TG 405). 4-ADPA is a skin sensitizer in guinea pigs. Skin sensitizations have been reported also in humans. In the majority of human case reports, however, there was evidence that the sensitizing effects observed were due to cross-reactivity with antibodies to structural analogues of 4-ADPA such as p-phenylenediamine.

The NOAEL in a rat 90-day feeding study with male rats was 1,000 ppm (approximately 100 mg/kg bw/day). In this study slight anemia and changes in liver enzyme levels were seen at approximately 250 mg/kg bw/day (2,500 ppm). At 5,000 ppm (approximately 435-500 mg/kg bw/day) pathological changes in the liver were found at the histological examination, and at 7,500 ppm (approximately 555-750 mg/kg bw/day) histopathological changes were found in the testes (degeneration of seminiferous tubules). The NOAEL in a rat carcinogenicity study with dietary exposure over 78 weeks was 1,200 ppm (approximately 60-120 mg/kg bw/day; highest dose tested).

4-ADPA did not induce gene mutations in standard bacterial and mammalian cell tests (Ames, HPRT) with and without metabolic activation. The substance was, however, genotoxic in the mouse lymphoma test, and also demonstrated the potential to induce chromosomal aberrations *in vitro*. 4-ADPA did not induce unscheduled DNA synthesis in rat hepatocytes *in vitro* and *ex vivo*. A bone marrow micronucleus test in male mice was negative. Although some systemic toxicity was observed in the high dose animals, there was no evidence that an adequate exposure of the target tissue was achieved. Based on the weight-of-evidence, and taking into account structure-activity relationship information, an in vivo genotoxic activity of 4-ADPA cannot be excluded.

Early feeding studies in rats and mice revealed no evidence of carcinogenicity but they were not adequate to judge the carcinogenic potential of 4-ADPA, mainly because of the shortened period of administration of the test substance, i.e. only 78 weeks in rats, and 41-48 weeks in mice, respectively.

There was no fertility study available. In a 90-day feeding study on male rats, degeneration of seminiferous tubules in the testes, accompanied by marginal changes in enzyme activities (LDH and hyaluronidase) were found at a severely toxic dose level (about 7,500 ppm = 555-750 mg/kg bw/day). The NOAEL for testicular toxicity was determined as 5,000 ppm (approximately 435-500 mg/kg bw/day). In early NTP carcinogenicity studies with rats and mice no histological changes in the reproductive organs of both sexes were observed up to and including the highest doses tested (corresponding to approximately 60-120 mg/kg bw/day for the rat. Due to severe limitations in the study no reliable dose could be derived for the mice).

Developmental toxicity (significantly increased resorptions, reduced fetal weight and increased fetal anomalies) was observed in two reliable gavage studies on CD rats, exposed from gestational day 6 to 15 to doses (vehicle: corn oil) that caused clear maternal toxicity (≥ 100 mg/kg bw/day), as evidenced by significantly decreased weight gain and food consumption. The maternal and developmental NOAELs were identified at 50 mg/kg bw/day.

**Environment**

4-ADPA is a brown to purple crystalline solid substance with a melting point of 72.1 to 74.6 °C. According to the flask method the substance is soluble in water to a value of 504 mg/l at 20 °C. pKa-values of 4.4 (pKa1) and 0.72 (pKa2) are reported. The vapor pressure was experimentally determined to be $7.6 \times 10^{-5}$ Pa at 20 °C. A log $K_{ow}$ value of 1.82 was calculated. The flash point of the substance is 193 °C. From the water solubility and vapor pressure, a Henry´s Law Constant of $2.8 \times 10^{-5}$ Pa $m^3$ $mol^{-1}$ at 20 °C is calculated indicating a low potential for volatilization from surface waters. According to Mackay fugacity model level I the main target compartment for 4-ADPA is water (99 %).

In air, the substance is indirectly photodegraded with a calculated $t_{1/2}$ = 1.9 h and will also undergo direct photolysis. In water, indirect photodegradation was shown to occur in the presence of a photosensitizer. In anaerobic buffer solutions with acid till neutral pH, the half life period of 4-ADPA is in the range of months. At higher pH the abiotic degradation was faster, however, a half-life could not be derived. Under aerobic conditions and in presence of nutrient medium containing traces of heavy metals, stability of the substance is clearly reduced. A half-life of 2.5 d can be estimated for 20 °C.

4-ADPA is not readily biodegradable. In a Zahn-Wellens test with industrial sludge 100 % DOC elimination was observed within 7 days. The calculated log $K_{ow}$ value (log $K_{ow}$ = 1.82) and a calculated BCF of 7 indicate that there is a low potential for bioaccumulation in aquatic organisms. The calculated $K_{oc}$ ($K_{oc}$ = 95) suggests that 4-ADPA has a low sorption potential. However, as it cannot be excluded that significant adsorption to sewage sludge was observed in the Zahn Wellens test, a higher adsorption than predicted from the log Kow could be expected also in the soil compartment. Using EPIWIN a Koc value of 3000 can be estimated.

Concerning the toxicity of 4-ADPA towards aquatic species experimental results of tests with fish, *Daphnia*, and algae are available. In the acute studies no analytical monitoring of the test substance concentration was performed. Therefore, the half-life of 2.5 d was used to derive effective concentrations from the nominal values.

In an acute fish test (*Danio rerio*) a 96 h $LC_{50}$ of 1.9 mg/l (nominal, 1.1 mg/l effective) was observed. According to a standard procedure equivalent to OECD Guideline 202 an $EC_{50}$ (48 h) of 0.37 (nominal, 0.28 mg/l effective) was reported for *Daphnia magna*. The toxicity of 4-ADPA to algae was studied in a test according to DIN 38412, part 9, without analytical monitoring. *Desmodesmus subspicatus* showed 72 h $EC_{50}$ values (nominal) on growth rate of 4.8 mg/l 4-ADPA (3.2 mg/l effective). and on biomass of 2.4 mg/l (1.6 mg/l effective). In this test a nominal 72 h $EC_{10}$ value of 1.8 mg/l (1.2 mg/l effective) was obtained which is considered as a NOEC.
The inhibitory effect of 4-ADPA to nitrification was studied with microorganisms of non-adapted sludge in both a semi-continuous and continuous culture system. An $EC_{50}$ of nominal 30 mg/l 4-ADPA (26 mg/l effective) was determined.

A chronic test was performed with *Daphnia magna* during 21 days for immobilisation and reproduction in semi-

static system with analytical monitoring by GC/MSD. Nominal $EC_{50}$ values for immobilisation of 0.52 mg/l (0.34 mg/l effective) and of 0.1 mg/l (0.07 mg/l effective) for reproduction rate were observed. The nominal NOEC for reproduction was 0.04 mg/l (lowest tested concentration). The effective NOEC for reproduction is estimated to </= 0.01 mg/l.

It has to be considered that the toxicity observed in the reported studies was caused both by the 4-ADPA as well as by the degradation products due to the instability of the test substance.

From the lowest acute effect value of 0.28 mg/l a PNEC of 0.28 ug/l can be derived using an assessment factor of 1000, as no definitive NOEC can be derived from the chronic *Daphnia* study.

Tests on terrestrial species are not available.

**Exposure**

The global manufacturing capacity of 4-ADPA was about 140,000 tons in 1995. 4-ADPA is nearly exclusively used as an intermediate for the manufacturing of antiozonants (ca. 20 producers) for the rubber industry. Further uses are as a dye intermediate and as component for hair dyes.

The manufacturing of dyes is assumed to be equivalent to 200 - 300 t/a of 4-ADPA, less than 0.5 % of the 4-ADPA manufactured. In Germany the production of these textile dyes has been discontinued in 1990. The use of 4-ADPA in hair dyes is currently allowed in the EU. 4-ADPA is not used as an ingredient in hair dyeing products manufactured by the major suppliers in Europe, but 4-ADPA containing products are offered by other companies via the Internet. Consumers may also be exposed to 4-ADPA through contact with rubber products containing 4-ADPA as residue. According to the SPIN database 4-ADPA was present in 9 consumer preparations in Sweden in 2002.

Releases of 4-ADPA into the environment may occur during manufacturing and processing, in the rubber industry from the use of antiozonants containing 4-ADPA as residue, from the utilization of rubber products and from hair dyeing and other direct uses of the substance.

At the only manufacturing and processing site in the Sponsor country nearly no 4-ADPA was emitted into the environment in 2002. The effluent concentrations were below the detection limit of 10 µg/l. No information is available from other sites.

Losses of 4-ADPA from rubber articles into the environment, including tyre abrasion, evaporation from rubber surfaces, and losses from landfilled rubber wastes, is estimated to be 4 t/a in Germany.

Workplace air sampling of precursors and auxiliaries, which are thought to be indicators of any exposure, suggest that the exposure of workers to airborne 4-ADPA is negligible in these manufacturing and processing workplaces. Biological monitoring for 4-ADPA in workers show that urinary 4-ADPA levels and blood levels of 4-ADPA adducts with hemoglobin are below the detection limits.

## RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

**Human Health:** The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health. Based on data presented by the Sponsor country, exposure is controlled in occupational settings. Consumers may be exposed to 4-ADPA through the use of hair dye products and rubber products. It is therefore recommended that countries perform an exposure assessment, and, if then indicated, a risk assessment.

**Environment:** The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for the environment. Releases of 4-ADPA into the environment may occur during manufacturing and processing, in the rubber industry from the use of antiozonants containing 4-ADPA as residue, from the utilization of rubber products and from hair dyeing and other direct uses of the substance (cf. information from product registers). Therefore, an exposure assessment and, if then indicated an environmental risk assessment is recommended. This should also include further investigations on the identities and properties of degradation products.