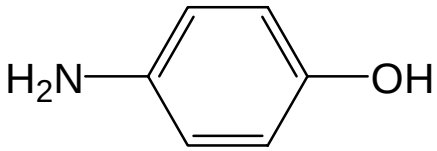
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	123-30-8
Chemical Name	*p*-Aminophenol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical properties

p-Aminophenol is a white or reddish yellow crystalline solid with a water solubility of 15.7 g/L at 20 °C. The melting point and boiling point are 187.5 °C and 284 °C (decomposition point) respectively. A partition coefficient between octanol and water (Log Kow) is 0.04 at pH 7.4. A calculated vapour pressure of p-aminophenol is 0.00436 Pa at 25 °C.

p-Aminophenol is an amphoteric substance with both hydroxyl and amino functional groups. Dissociation constants of pKa1 = 5.48 and pKa2 = 10.30 show that p-aminophenol exists primarily as its neutral species in the environment at pH values between 6 and 9.

Human Health

Following oral administration to rabbits, 100 % of p-aminophenol is absorbed. In rabbits, the substance is excreted in the urine. Aminophenol conjugates and acetaminophenol and its conjugates were major urinary metabolites in rats subcutaneously administered with p-aminophenol. The dermal absorptions of p-aminophenol in rats and humans are 11% and 6-8% of the applied dose, respectively.

The oral LD_{50} value was 671 mg/kg bw for male and female rats. P-Aminophenol caused lethargy, piloerection and oedematous swelling of the salivary glands. There are no reliable information for acute inhalation and dermal studies; however the inhalation LC_{50} value is reported to be more than 5.91 mg/L and the dermal LD_{50} value is reported to be more than 5000 mg/kg bw in the secondary literature.

The irritant effects on the skin were tested in accordance with standard guideline. p-Aminophenol was slightly irritating to rabbit skin. It led to slight edema of both the intact and abraded sites in one rabbit at 24hr after application and recovered within 72 hr (a primary irritation score of 0.2 out of 8). p-Aminophenol was slightly irritating to rabbit eyes, but caused no corneal opacity. All the lesions disappeared within 2 days of the instillation in rabbits. No experimental data were available for respiratory tract irritation in animals.

p-Aminophenol gave positive results for skin sensitization in a patch test in guinea pigs. Various human skin sensitisation studies showed positive reactions to p-aminophenol in hairdressers/barbers.

The repeated dose toxicity of p-aminophenol has been investigated in three studies. In a repeated dose oral toxicity study in rats following OECD TG No.407, the substance was administered via gavage to (6 animals/sex/dose) at 0, 4, 20, 100 or 500 mg/kg bw/day, for 28 days with a 14-day recovery period. Death was observed in one male due to renal damage at 500 mg/kg bw/day. Anemia-like findings were observed in males and females at 500 mg/kg bw/day. Brown urine was found in males and females at 100 and 500 mg/kg bw/day. There were increases in extramedullary hematopoiesis in 1 male and 5 females (2 females in the recovery group) and in hemosiderin pigment of the spleen in 5 females (6 females in the recovery group). Basophilic tubules in the kidney were observed in 1 male and 4 females at 100 mg/kg bw/day, and 4 males (3 males in the recovery group) and all females at 500 mg/kg bw/day. In addition, there were significantly increased absolute kidney

weights in females at 100 and 500 mg/kg bw/day and relative kidney weights in both sexes at 500 mg/kg bw/day. Significant increases in relative spleen weights in females at 500 mg/kg/day and in absolute and/or relative liver weights in both sexes at 500 mg/kg/day were also observed. Absolute brain weight was significantly decreased in the recovery group females at 100 and 500 mg/kg/day. Based on these results, the NOAEL for repeated dose oral toxicity was considered to be 20 mg/kg bw/day.

In a reproductive and developmental toxicity screening test in rats following OECD TG No.421, the substance was administered via gavage to (12 animals/sex/dose) at 0, 20, 100 and 500 mg/kg bw/day, for 40-60 days. Four males and 2 females died at 500 mg/kg/day. In these dead animals, renal pathological changes including tubular necrosis, basophilic tubules or protein cast etc. were observed. In the surviving animals, decreases in body weight gain and food consumption, and brown urine were observed. Histopathological changes in the kidney (basophilic tubules, protein cast, and granular cast) and spleen (deposits of hemosiderin in the red pulp and extramedullary hematopoiesis) were observed in both sexes. In males, testicular toxicities such as histopathological changes and decreased absolute and relative weights of the testes and epididymides were indicative of treatment related effects. These findings were observed in male and female groups at 500 mg/kg bw/day; brown urine in both sexes and decreased food consumption in females were also found at 100 mg/kg bw/day. Based on these effects, the NOAEL for repeated dose oral toxicity was considered to be 20 mg/kg bw/day.

In a repeated dose feeding study in rats, 40 male and 45 female rats per dose received concentrations of 0, 0.07, 0.2 or 0.7% p-aminophenol in the diet for up to 6 months (equivalent to ca. 0, 47, 133, or 467 mg/kg bw/day). A reduction of body weight gain was observed in both sexes at 467 mg/kg bw/day. Decreases in RBC and haemoglobin were observed in females of the 467 mg/kg bw/day group at 13 week. In the histopathological examination, nephrosis was observed in both sexes at 47 mg/kg bw/day at 13 weeks. Based on these results, the dose of 47 mg/kg bw/day was considered as the LOAEL for both sexes.

In a bacterial reverse mutation assay with multiple strains of Salmonella typhimurium and Escherichia coli following OECD TG471 and TG 472, p-aminophenol was negative both with and without metabolic activation. An *in vitro* chromosomal aberration test using Chinese hamster lung (CHL/IU) cells following OECD TG473 was positive with and without metabolic activation. An *in vivo* micronucleus test using male mice following OECD TG474 was positive. An *in vivo* dominant lethal mutation test using male rats mated with untreated females was negative. Equivocal results exist concerning genotoxicity based on various *in vitro* and *in vivo* reports, but p-aminophenol is considered to be genotoxic (clastogenic) in vitro and in vivo based on positive results in the TG473 and TG 474 studies.

No reliable data were available for the carcinogenicity of p-aminophenol.

The reproductive toxicity of p-aminophenol has been well investigated in a reproductive and developmental toxicity screening test in rats [OECD TG 421]. In this study, p-aminophenol was administered via gavage to (12 animals/sex/dose) at 0, 20, 100, or 500 mg/kg bw/day, for 40-60 days. Death was observed in both sexes (4 males and 2 females) at 500 mg/kg bw/day. Histopathological examinations revealed decreased spermatocytes and spermatid levels, vacuolation of Sertoli cells, degeneration/necrosis of spermatocytes in the testis, and decreased sperm counts and debris of germ cells in the epididymis lumen at 500 mg/kg/day, but these changes did not affect male reproductive performance, as evidenced by no changes in the copulation index, fertility index or precoital interval. Terminated estrus, longer gestation period, decreased delivery index, increased number of stillborn pups, lowered pup weight, decreased viability of pup on PND4 were observed at 500 mg/kg/day. The NOAEL for reproductive toxicity was considered to be 100 mg/kg bw/day based on terminated estrus and longer gestation period at 500 mg/kg bw/day, and the NOAEL for developmental toxicity was considered to be 100 mg/kg bw/day based on decreased delivery index, increased number of stillborn pups, lowered pup weight and decreased viability of pup on PND4 at 500 mg/kg/day. However, these effects were observed at the high dose, at which significant systemic/maternal toxicity was observed.

In a feeding developmental toxicity study in rats, 25 female rats received concentrations of 0, 0.07, 0.2 or 0.7% p-aminophenol in the diet for 13 weeks (equivalent to ca. 0, 47, 133, or 467 mg/kg bw/day). They were then mated with untreated males. Pregnant females were once again fed with the p-aminophenol containing diet until day 20 of gestation, when they were killed. On day 0 of gestation, maternal body weights in the 133 and 467 mg/kg bw/day dose groups were lower than those of controls. From day 0 to day 20 of gestation, maternal weight gains in the 467 mg/kg bw/day dose group had decreased. Dose-related postimplantation loss was observed at 133 and 467 mg/kg bw/day in the presence of maternal toxicity. No toxicologically significant malformations were observed in the foetuses, but the number of variations (14th rudimentary ribs, unossified fifth or sixth sternebrae) was increased in the 133 and 467 mg/kg bw/day group as a consequence of maternal toxicity. The incidence of 14^{th} rudimentary ribs is comparable with historical control, and increases of variations in the 14^{th} ribs were only significant at the highest dose. Based on decreased maternal body weights at 133 mg/kg bw/day

and higher, the NOAEL for maternal toxicity was considered to be 47 mg/kg bw/day, but no adverse effects were observed on reproductive function. The NOAEL for developmental toxicity was considered to be 47 mg/kg bw/day based on postimplantation loss at 133 and 467 mg/kg bw /day, which is considered to be secondary effects of maternal toxicity.

p-Aminophenol may present a hazard for human health (skin irritation/sensitization, repeated dose toxicity and genotoxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

In the atmosphere, p-aminophenol is expected to be degraded by hydroxyl radicals. A calculated half-life time of 0.144 days and a rate constant of 74.2 × 10-12 cm3/molecule-sec are obtained by AOPWIN for the indirect photo-oxidation by reaction with hydroxyl radicals in air.

p-Aminophenol is not stable to sunlight and turns violet on exposure to sunlight. As p-aminophenol has absorptions with λmax of 294 nm in the environmental UV spectrum, direct photolysis by light may occur. p-Aminophenol is also expected to undergo rapid oxidation in the presence of air. p-Aminophenol is not hydrolysed due to the lack of hydrolysable functional groups. However, it is expected that p-aminophenol is not stable in water because of oxidation process in water. It is known that oxidation process of aminophenols leads to the formation of highly coloured polymeric quinoid structures. Half-life times in water are reported to be 7.67 days in purified water at 100 mg/L at pH 7 at 25 °C and 7.23 hours in de-chlorinated water at 1 mg/L at pH 7.3 – 7.6 at 24 °C The latter value seems to be the most environmentally relevant one. However, there is some uncertainty on the reliability and relevance of both these half lives.

A test result with activated sludge showed 6 % degradation by BOD after four weeks cultivation according to the equivalent protocol with OECD Guideline 301C. After the cultivation period, no p-aminophenol was detected but polymerized substances were detected. BIOWIN estimation predicts that p-aminophenol is not ready biodegradable. According to these results, p-aminophenol is considered to be not readily biodegradable.

In a study performed according to OECD Guideline 305C with carp exposed to p-aminophenol at concentrations of 1.5 µg/L and 0.15 µg/L, bio-concentration factors of 10 – 46 were obtained over an eight-week exposure period. A bio-concentration factor of 3.2 was calculated by BCFBAFWIN using a log Kow of 0.04. These results demonstrate a low bioaccumulation potential of p-aminophenol in aquatic organisms. An estimated log Koc of 1.96 indicates a low potential for accumulation in soil.

Fugacity level III calculations show that p-aminophenol is mainly distributed to the water compartment (99.5 %) if released to the water. A Henry's law constant of 2.01×10-5 Pa.m3/mole at 25 °C suggests that the volatilisation potential of p-aminophenol from the water surface is expected to be low.

The following acute and chronic toxicity test results have been determined for aquatic species. In view of the half-life observed at 1 mg/l, it is possible that the species are exposed to both parent substance and degradation products.

Fish [Oryzias latipes]:	96 h LC50 = 0.93 mg/L (measured)
Invertebrate [Daphnia magna]:	48 h EC50 = 0.098 mg/L (measured)
Algae[Pseudokirchneriella subcapitata]:	72 h ErC50 = 0.15 mg/L (measured; growth rate)
	72 h EbC50 = 0.11 mg/L (measured; biomass)
Fish [Oryzias latipes]:	41 d NOEC = 0.064 mg/L(measured, growth)
Invertebrate [Daphnia magna]:	21 d NOEC = 0.055 mg/L (measured)
Algae[Pseudokirchneriella subcapitata]:	72 h NOEC = 0.036 mg/L (measured; growth rate)
	72 h NOEC = 0.036 mg/L (measured; biomass)

p-Aminophenol possesses properties indicating a hazard for the environment (acute aquatic toxicity values lower than 1 mg/L for fish, invertebrate and algae, chronic aquatic toxicity values lower than 0.1 mg/L for fish, invertebrate and algae and not readily biodegradable). However, the substance has low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD HPV Chemicals Programme.

Exposure

Production of p-aminophenol in Japan was about 400 tonnes in 2007. Production and import volume of aminophenols without distinction of ortho, meta and para isomers was reported to be 1,000 – 10,000 tonnes in Japan in fiscal year 2004. Production volume of p-aminophenol in the USA was between 500,000 to 1 million pounds in 2006 according to IUR information supplied by the US-EPA. Worldwide production volume of p-aminophenol was not available. p-Aminophenol is produced by electrolytic reduction of nitrobenzene in sulphuric acid or manufactured by reduction of p-nitrophenol with iron filings and hydrochloric acid.

p-Aminophenol is used as an intermediate for sulfur dyes, rubber antioxidant, and photo-graphic developer in Japan. This substance is also used as an intermediate for pharmaceutical products, a wood stain, imparting a rose-like colour to timber and a dyeing agent for furs and feathers. p-Aminophenol is used as a developer in oxidation hair dyes.

As p-aminophenol has high water solubility with 15.7 g/L at 20 °C and low vapour pressure with 0.00436 Pa at 25 °C, it is thought that water compartment is the main target if p-aminophenol is released during the industrial processes. No detailed information was available as to what extent p-aminophenol is released during the manufacturing and processing processes in Japan. However, it is mentioned that most production of the technical grade aminophenols occurs on-site as they are chiefly used as intermediate reactants in continuous chemical syntheses. As p-aminophenol is not readily biodegraded, the possibility of environmental release may exist.

A nation-wide environmental survey of chemicals conducted by the Japanese Ministry of Environment in fiscal year 1986 showed that p-aminophenol was not detected in environmental surface water in nine different places with detection limit of 0.8 μg/L. This survey also showed no detection of p-aminophenol in sediment in nine different places (detection limit of 0.05 μg/dry-g). The same survey conducted in the fiscal year 2004, and p-aminophenol was detected in environmental surface water in one place at the level of 0.02 – 0.05 μg/L.

Occupational exposure through inhalation of dust and dermal contact is possible. As p-aminophenol is used as an ingredient in hair dyes, direct consumer exposure does occur.