# SIDS INITIAL ASSESSMENT PROFILE

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| **CAS No.** | 99-88-7 |
| **Chemical Name** | 4-Isopropylaniline |
| **Structural Formula** |  |

## SUMMARY CONCLUSIONS OF THE SIAR

### Physical-chemical properties

4-Isopropylaniline is a liquid. The melting point and the boiling point are <-100 °C (measured) and 226-227 °C at 745 mmHg (measured), respectively. The density is 0.953 g/m$^3$ at 20 °C (measured). The vapour pressure at 25 °C extrapolated from the experimental value is 5.62 Pa (measured). The partition coefficient between octanol and water (log Kow) is 2.3 at 25 °C (measured) and the water solubility is 2390 mg/L at 20 °C (measured). The dissociation constant (pKa) is 5.00 and shows that 4-isopropylaniline exists primarily as its neutral species in the environment at pH values between 6 and 9 (measured). Soil adsorption coefficient (log $K_{oc}$) is 2.53 by KOCWIN ver. 2.00. The Henry's law constant of 0.318 Pa.m$^3$/mol at 20/25 °C is calculated by vapour pressure of 5.62 Pa at 25 °C divided by water solubility of 2390 mg/L at 20 °C.

### Human Health

No specific studies were conducted on absorption, distribution, metabolism, or excretion in mammals. The following experimental data on the acute oral toxicity and repeated oral toxicity indicate that 4-isopropylaniline was absorbed via the gastrointestinal tract in rats and distributed via the circulatory system.

The oral $LD_{50}$ value was 985 mg/kg bw (95 % CL: 846–1146 mg/kg bw) in rats (OECD TG 401). 4-Isopropylaniline caused various changes in movement (abnormal gait and hypoactivity), posture (prone, lateral and hunchback position) and general condition (abnormal distention, lacrimation, salivation and dirty hair). Although there were no reliable data for acute inhalation and dermal toxicity, the dermal $LD_{50}$ value was reported to be 1000-1030 mg/kg bw in rats in the secondary literature.

In a primary dermal irritation study in rabbits (OECD TG 404), 4-isopropylaniline caused irreversible skin reaction (erythema, edema, scar formation, etc.) after 4-hour exposure. It was concluded that this chemical was corrosive to the skin. No data are available for eye irritation, but eye corrosivity is expected due to the physicochemical properties.

No data are available for skin sensitization.

The combined investigation of repeated dose toxicity and reproduction/developmental toxicity screening of 4-isopropylaniline with the application of OECD TG 422 is reported. 4-Isopropylaniline was administered by gavage to 12 animals/sex/dose at 0 (vehicle, corn oil), 6, 20, and 60 mg/kg bw/day for 48 days in males or from 14 days before mating to the third day of lactation in females (total, 41–45 days). One female of the 60 mg/kg bw/day group was found dead at day 25 of gestation (43$^{rd}$ administration day). No death was observed in male animals. Test substance-related effects such as anemic eyeballs and transient salivation were observed in both sexes (≥20 mg/kg bw/day) and pallor was noted in females during gestation (60 mg/kg bw/day). Hematology and clinical chemistry parameters showed anemia, and methemoglobin levels were significantly increased (≥20 mg/kg bw/day). The absolute and/or relative weights of the liver and spleen increased significantly in both sexes (60 mg/kg bw/day or≥20 mg/kg bw/day). Abnormal histopathological findings were observed in the bone marrow (increase of hematopoiesis), spleen (congestion, deposits of pigment, and extramedullary

hematopoiesis), and liver (extramedullary hematopoiesis, deposits of pigment, and hypertrophy of hepatocytes) in both sexes (60 mg/kg bw/day or 20 mg/kg bw/day). Based on these findings, methemoglobinemia and/or anemia data, and related abnormal clinical signs and pathological findings, the no-observed-adverse-effect level (NOAEL) for repeated-dose oral toxicity was determined to be 6 mg/kg bw/day for both sexes.

In a bacterial reverse mutation assay performed according to OECD TG 471, 4-isopropylaniline was mutagenic to *Salmonella typhimurium* TA100 and TA1535 with exogenous metabolic activation. This chemical was negative in *Salmonella* strains TA98 and TA1537 and *Escherichia coli* WP2 *uvrA* with or without metabolic activation. In the HPRT-test with V79 Chinese hamster cells, 4-isopropylaniline did not induce gene mutations either with or without metabolic activation (OECD TG 476). In *in vitro* chromosomal aberration tests (OECD TG 473) in Chinese hamster lung fibroblast (CHL/IU) cells and V79 Chinese hamster cells, 4-isopropylaniline did not induce chromosomal aberrations with and without metabolic activation. In an *in vivo* micronucleus assay performed in mice according to OECD TG 474, 4-isopropylaniline did not induce chromosomal aberrations. Based on these results, 4-isopropylaniline was not considered to be clastogenic *in vitro* and *in vivo*, but it is not possible to exclude the genotoxicity of this chemical because the potential to cause gene mutations has not been investigated *in vivo*.

No data were available on the carcinogenicity of 4-isopropylaniline.

4-Isopropylaniline was investigated in a reproductive and developmental toxicity screening test conducted in rats according to OECD TG 422. One female parent of the 60 mg/kg bw/day group died during delivery at day 25 of gestation (43$^{rd}$ administration day). No abnormalities were observed on the reproductive organs and other reproductive parameters of parental animals. Effects on the offspring included a significant reduction of the viability index of male pups on day 4 after birth and body weight of male and female pups on the day of birth in the 60 mg/kg bw/day group. Based on these results, the NOAEL for reproductive toxicity in parental animals was determined to be 60 mg/kg bw/day, and the NOAEL for developmental toxicity in offspring was determined to be 20 mg/kg bw/day. However, developmental effects were observed only at a dose which induced significant systemic/maternal toxicity, and there were no other significant effects on developmental parameters of offspring.

**4-Isopropylaniline possesses properties indicating a hazard for human health (corrosivity, repeated-dose toxicity and gene mutation *in vitro*). Adequate screening data are available to characterize the human health hazard for the purpose of the OECD Cooperative Chemicals Assessment Programme.**

**Environment**

In the atmosphere, 4-isopropylaniline is expected to be degraded by hydroxyl radicals. A calculated half-life time of 0.081days (sunlight is irradiated as 12 hours a day) is obtained by AOPWIN (version 1.92a) for the indirect photo-oxidation by reaction with hydroxyl radicals in air. This chemical is expected to photodegrade rapidly in the atmosphere.

A study according to OECD test-guideline 111 showed no hydrolysis of 4-isopropylaniline in water at pH 4, 7 and 9 in 50 °C after five days.

An OECD test guideline 301C test was conducted with 4-isopropylaniline with activated sludge for four weeks. The concentration of the test substance was 100 mg/L and the concentration of the activated sludge was 30 mg/L as suspended solid matters. The test result showed 1 % degradation by BOD. According to the result, 4-isopropylaniline is considered to be not-readily biodegradable.

In a study performed according to OECD test-guideline 305 with carp exposed to 4-isopropylaniline, steady-state bio-concentration factors of 8.0 and 6.4 were obtained for the concentration of 10 µg/L and of 100 µg/L respectively for 28-day exposure period. Using an octanol-water partition coefficient (log Kow) of 2.3, a bio-concentration factor of 21.7 was calculated with BCFBAF, version 3.01. This chemical is not expected to bioaccumulate.

Fugacity level III calculations show that 4-isopropylaniline is mainly distributed to the water compartment (19.9 %) and soil compartment (79.6 %) if equally and continuously released to the air, soil and water. A Henry's law constant of 0.318 Pa.m$^3$/mole at 25 °C suggests that slight volatilization of 4-isopropylaniline from water is expected. A soil adsorption coefficient of log Koc = 2.53 indicates 4-Isopropylaniline has moderate adsorption to soil and sediment.

The following acute toxicity test results have been determined for aquatic species:

Fish [*Oryzias latipes*]: 96 h $LC_{50}$ = 46 mg/L (nominal; all measured concentrations were

within 20% of the nominal, semistatic), OECD TG 203

Daphnid [*Daphnia magna*]: 48 h $EC_{50}$ = 1.5 mg/L (nominal, static), OECD TG 202

Algae[*Pseudokirchneriellasubcapitata*]: 72 h $ErC_{50}$ = 18 mg/L (measured, growth rate, static) , OECD TG 201

The following chronic toxicity test results have been determined for aquatic species:

Daphnid [*Daphnia magna*]: 21 d LOEC = 0.0093 mg/L (nominal, semistatic) , OECD TG 211

21 d NOEC =0.0051 mg/L (nominal, semistatic, ) , OECD TG 211

Algae[*Pseudokirchneriellasubcapitata*]:

72 h LOErC = 1.73 mg/L (measured; growth rate, static) , OECD TG 201

72 h NOErC = 0.68 mg/L (measured; growth rate, static) , OECD TG 201

**4-Isopropylaniline possesses properties indicating a hazard for the environment (acute aquatic toxicity values between1and 100 mg/L for fish, invertebrate and algae and chronic toxicity less than 1 mg/L for invertebrate and algae). This chemical is considered not readily biodegradable and has a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purpose of the OECD Cooperative Chemicals Assessment Programme.**

**Exposure**

Production and/or import volume of 4-isopropylaniline in Japan (sponsor country) was reported to be <100 tonnes/year in fiscal year 2009. Production volume in the world is not available.

4-Isopropylaniline is manufactured with aniline and isopropyl alcohol or manufactured by nitration and subsequent reduction of cumene. 4-Isopropylaniline is used as a raw material for herbicide, dye and pigment. 4-Isopropylaniline results in the limited release to the environment as a chemical of raw materials for herbicide, dye and pigment in Japan.

Occupational exposure through inhalation of vapour and dermal route is anticipated when a worker handles this chemical directly.

As 4-isopropylaniline is used as an intermediate in herbicides, dyes and pigments, consumer exposure is considered to be negligible.