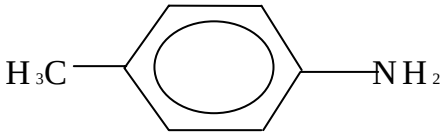
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	106-49-0
Chemical Name	p-Toluidine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There are no specific studies available which evaluate the possible potential of p-toluidine to affect fertility or to cause developmental toxicity. Information from m-toluidine is used to fill the data gap. Therefore the SIAR contains a short comparison of p-toluidine and m-toluidine for all endpoints. The isomer m-toluidine was already discussed and concluded in SIAM 11, 2001; the data are published by UNEP in 2003. A comparison of the intrinsic toxicological properties of m-toluidine with these properties of p-toluidine showed that m-toluidine is more potent in methemoglobin forming than the p-isomer. Taking into account that methemoglobinemia in pregnant rats is causally linked to developmental toxicity it can be assumed that extrapolation of the results with m-toluidine to p-toluidine would imply a tendency to lead to an overestimation of the developmental toxicity of p-toluidine. Furthermore developmental toxicity data from the structurally related p-isopropylaniline were included in the assessment. This seems to be justified due to the structural similarity of both substances as both aniline derivatives have substituents in para position of nearly the same influence on the reactivity of the respective molecule. This could be demonstrated with the data on acute toxicity as well as with repeated toxicity data. For all three substances methemoglobinemia and/or erythrocyte toxicity seem to be the most relevant mechanism for systemic toxicity. In addition, with respect to mutagenicity, the comparison of results of the respective tests with these substances demonstrates the inconsistency, which is typical for aromatic amines.

p-Toluidine is absorbed via gastrointestinal tract and is distributed, metabolized and excreted via urine and feces. The identification of 2-amino-5-methylphenol indicates that the metabolism in rat proceeds through ring hydroxylation with subsequent conjugation. There are no specific toxicokinetic data on absorption via skin and respiratory tract; absorption via these administration routes can be reasonably be predicted due to the molecular size of p-toluidine.
m-Toluidine (SIAM 11) is rapidly absorbed via gastrointestinal tract, via skin and is metabolized by ring hydroxylation. Although 2-amino-4-methyl-phenol and 4-amino-2-methylphenol were identified in the rat urine with a small amount of the parent compound, there is no sufficient information on quantitative metabolism of m-toluidine or on toxicokinetics. **Overall conclusion:** Both isomers, p- and m-toluidine are absorbed via gastrointestinal tract and via skin and distributed. They are metabolized by ring hydroxylation with subsequent conjugation and excreted via urine and feces.
For **p-toluidine**, the LC_{50} (inhalative, rat) is > 0.64 mg/l, and LD_{50} (dermal, rabbit) is 890 mg/kg bw. LD_{50} (oral, rat) was determined 656 mg/kg bw and 620 mg/kg bw. Signs of intoxication include hypoactivity, muscular weakness,

convulsions, cyanosis and narcosis. p-Toluidine is a methemoglobin forming chemical in rats. Levels up to 21.7 % following oral application to rats and up to 40 % following dermal application to rats were measured. p-Toluidine is a methemoglobin forming chemical in humans as it produces the same toxic effects as aniline from 22 mg/m³ onwards with less cyanosis but more stranguria and hemoglobinuria.
For **m-toluidine**, LD_{50} values are from 450 to 1430 mg/kg bw by oral route to rats and 3250 mg/kg bw by dermal route to rabbits (no information on study quality available). Severe methemoglobin formation is reported following single exposure to m-toluidine ranging up to 36.4 % in rats after oral application and 40 % in rats after dermal application (these data as well as those given above for p-toluidine are derived from a study which examined the methemoglobin formation of m- and p-toluidine in parallel) and up to 60.2 % in cats (i.v.). For **p-isopropylaniline,** LD_{50} values of 985 mg/kg bw and 757 mg/kg bw were reported of rats following single oral application. Single oral application of 25 mg/kg bw to cats resulted in elevated methemoglobin level and an increase in Heinz bodies. **Overall conclusion:** Based on the available data, p- and m-toluidine are of moderate acute toxicity. Main toxic signs result from the methemoglobin formation in rats as well as in humans. m-Toluidine is considerably more active in methemoglobin formation than p-toluidine when tested at equal dosages and under similar experimental conditions. p-Isopropylaniline led to an increase in methemoglobin after oral application of 25 mg/kg bw to cats (no quantitative data available).

p-Toluidine causes irritation to the eyes of rabbits which recovered within 7 days. No irritational effects were observed when applied to the rabbit's ear for 24 hours under occlusive conditions. **p-Toluidine** is a sensitizer by skin contact as shown in a patch test with guinea pigs. There is no valid human data available.

There are no adequate repeated dose toxicity studies available for **p-toluidine**. There are a number of limited studies sufficient to support a weight of evidence approach. Limitations include documentation of the experiments in general, number of animals under test, treatment time as well as the lack of necessary investigations. Nevertheless, the overall weight of evidence indicates low systemic toxicity with liver and blood as target organs. Based on increased liver to body weight ratio in the available subacute feeding study a NOAEL of 165 ppm (corresponding to 13.8 mg/kg bw/day) can be derived for rats. In studies over a period of 6 months dose-related (40 - 160 mg/kg bw/day) increases in methemoglobin level up to $\geq$ 10 % are reported for rats. In addition, it is demonstrated that prolongation of treatment time up to 12 months does not result in further increase in methemoglobin levels in rats. Treatment of rats and mice with p-toluidine in feed for 18 months resulted in a NOAEL (systemic toxicity) of 2000 ppm in rats (highest dose tested, approximately 150 mg/kg bw/day). In mice treated with 500 ppm (approximately 75 mg/kg bw/day) no influence on body weight and/or mortality rate was reported, however hepatomas occurred in males.
With **m-toluidine** there has been reported a valid combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD TG 422 on rats with gavage application of the structurally closely related isomer m-toluidine which has been assessed during OECD-ICCA SIAM 11 in 2001. In this study m-toluidine leads to deposit pigmentations and extramedullary hematopoiesis in spleen starting already at the lowest dose of 30 mg/kg bw/day representing the LOAEL. There are sufficient evidences that this chemical induces methemoglobinemia, but methemoglobin content was not determined in this study. With **p-isopropylaniline** there has been reported a valid combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD TG 422 on rats with gavage application resulting in a NOEL (systemic toxicity) of 6 mg/kg bw/day based on erythrocyte toxicity including secondary effects. **Overall conclusion:** Following repeated dosing both toluidine isomers as well as p-isopropylaniline reveal as main targets the erythrocytes (methemoglobin formation) and liver (increased liver weight/m-toluidine and p-isopropylaniline and slight hepatocyte swelling/p-toluidine in rats; liver tumors in mice/m- and p-toluidine). The NOELs in rats for all three substances are roughly in the same dose range; main toxic principle of all three substances is the methemoglobin formation with accompanying symptoms.

p-Toluidine does not induce point mutations in the vast majority of *in vitro* Ames tests. In Chinese hamster lung cells p-toluidine is clastogenic in the presence but not in the absence of S9-mix. *In vivo*, DNA single strand breaks are detected in liver and kidneys of mice using alkaline-elution technique after single intraperitoneal injection of 2/3 of the respective LD_{50} (35 mg/kg bw), therefore it cannot be decided definitely whether the effects occurred due to cytotoxicity or real genotoxic mechanisms. Overall, there is some indication for clastogenic activity *in vitro* and some residual suspicion for such action *in vivo*.

There are no adequate studies with **p-toluidine** to evaluate carcinogenicity in rats and mice. There are a number of limited studies sufficient to support a weight of evidence approach. The limitations include e.g. only one dose in the dermal study, limited number of animals, treatment time too short and are only reported in brief. Following oral and dermal (one dose only) application to rats no tumors can be identified at any dose level. In mice, hepatomas are identified in males in all dose groups whereas females showed liver tumors only in the high dose group. In a study with subcutaneous injection of p-toluidine to rats only a slight, not significant increase in the number of tumors at the injection site and in the liver are reported.

There are no specific data on toxicity for reproduction for **p-toluidine.** Data from repeated dose toxicity studies give no evidence for possible effects of p-toluidine on reproductive organs. Developmental toxicity studies with p-toluidine are not available.
In an OECD TG 422 guideline study with **m-toluidine** on rats it is shown that an impairment of reproductive function as well as adverse effects on development might occur after applying systemically toxic doses to the parents leading to methemoglobin formation. The NOEL for reproductive toxicity of m-toluidine in rats is 30 mg/kg bw/day. At this dose there is already some degree of hemolytic anemia present as indicated by deposit pigmentation and extramedullary hematopoiesis in the spleen. The NOEL for developmental toxicity for m-toluidine in rats is considered to be 100 mg/kg bw/day. In an OECD TG 422 guideline study with **p-isopropylaniline** on rats there is no impairment of reproductive ability until the highest dose tested (60 mg/kg bw/day) although indications for methemoglobinemia has been detected already at 20 mg/kg bw/day. The NOEL for developmental toxicity for p-isopropylaniline in rats is considered to be 20 mg/kg bw/day. **Overall Conclusion:** There are no specific data on toxicity for reproduction for p-toluidine. Data from repeated dose toxicity studies give no evidence for possible effects of p-toluidine on reproductive organs. Developmental toxicity studies with p-toluidine are not available. But taking into account the results from an OECD TG 422 guideline study performed with the structurally closely related isomer m-toluidine as well as with the structurally related p-isopropylaniline on rats it can be deduced that an impairment of reproductive function as well as adverse effects on development might occur after applying systemically toxic doses to the parents leading to methemoglobin formation. The NOELs for reproductive toxicity in rats are 30 mg/kg bw/day for m-toluidine and 60 mg/kg bw/day for p-isopropylaniline. At these doses there is already some degree of hemolytic anemia present as indicated by deposit pigmentation and extramedullary hematopoiesis in the spleen. The NOELs for developmental toxicity for m-toluidine in rats are considered to be 100 mg/kg bw/day for m-toluidine and 20 mg/kg bw/day for p-isopropylaniline.
In view of the fact that m-toluidine is more potent in methemoglobin formation than p-toluidine and taking into account that methemoglobinemia in pregnant rats may be causally linked to developmental toxicity it can be assumed that extrapolation of the results with m-toluidine to p-toluidine would imply a tendency to lead to an overestimation of the developmental toxicity of p-toluidine. Since there is no evidence for adverse effects on reproduction or developmental effects for m-toluidine or p-toluidine through a direct mechanism of action further testing of p-toluidine is not regarded to be necessary.

Environment

p-Toluidine consists of lustrous plates or leaflets with a melting point of 44 °C, and a boiling point of 200.5 °C. The density is 0.9619 g/cm^3 at 20 °C. The interpolated vapor pressure at 25 °C is 38.1 Pa. The measured log K_{ow} is 1.39. The solubility in water is 7.4 g/l at 25 °C. The flash point is 87 °C, the auto-ignition temperature 482 °C.

In the atmosphere, p-toluidine is degraded by photochemically produced OH radicals. The half-life is calculated to be ca. 2.9 hours.
With regard to the chemical structure, p-toluidine is not expected to hydrolyze due to the lack of hydrolysable functions.
p-Toluidine is inherently biodegradable (MITI test OECD TG 301 C: > 30 % after 14 days; OECD TG 302 B: 94 % after 8 days (industrial sludge), OECD TG 302 B: 94 % after both 10 and 13 days, OECD TG 302 B: 97.7 % after 5 days (adapted sludge), study similar to OECD TG 301 D: biodegradation 68 % after 20 days (study poorly documented)).

According to the Mackay fugacity model level I, the favorite target compartment of p-toluidine is water with 83.7 %,

followed by air with 16.0 %. The experimentally determined Henry's law constant (0.20 Pa m^3/mol at 25 °C) proves a low to moderate potential for volatilization from surface waters.
In a sparsely documented study with fish, bioconcentration factors of < 1.3 were obtained at 100 µg/l and < 13 at 10 µg/l. The bioconcentration factor BCF = 2.35 for p-toluidine, calculated from the octanol-water partition coefficient, indicates that there is a low potential for bioaccumulation of p-toluidine in fish. The available experimental data concerning uptake and elimination of p-toluidine in *Mytilus edulis*, indicates its low potential for bioaccumulation in mussels: 85 % elimination of the steady state body burden after 4 hours.
Experimentally obtained adsorption coefficients (K_{oc}) revealed a low to high sorption potential of p-toluidine. The experimentally achieved K_{oc} values were in the range of 102.2 to 1903.4 depending on soil properties. In addition, K_{oc} values were calculated with PCKOCWIN v. 1.66 (K_{oc} = 72.5) and with the TGD equation for the anilines (K_{oc} = 52). These results indicate a low sorption potential of p-toluidine onto the organic phase of soil or sediments. It can be assumed that at low pH the protonated form of p-toluidine with its electrostatic forces may play an important role in soil sorption processes.

Concerning the toxicity of p-toluidine to aquatic species reliable experimental results of tests with fish, *Daphnia*, and algae are available. The tests were performed according to standard procedures or similar methods. The lowest effect values from short-term tests, as well as from a prolonged fish toxicity test are:

Danio rerio:	96 h-LC_{50} = 115 mg/l (m)
Poecilia reticulata:	14 d-LC_{50} = 10.7 mg/l (n)
Daphnia magna:	48 h-EC_{50} = 0.12 mg/l (m)
Scenedesmus obliquus:	48 h-E_rC_{50} = 62.9 mg/l (n)
Scenedesmus quadricauda:	96 h-E_bC_3 = 8.0 mg/l (n)

Data for algal toxicity (*S. capricornutum*, 72 h-E_bC_{50}) of m-toluidine (SIAM 11) and o-toluidine (SIAM 19) is 17.7 and 30.9 mg/l, respectively. For *Chlorella pyrenoidosa* the 96 h-E_rC_{50} for o-toluidine is 55 mg/l.
Tests on chronic toxicity of p-toluidine to aquatic species are not available.
Concerning the effects on terrestrial organisms the following data was obtained for plants in a root elongation test with a duration of 5 days:
Brassica campestris: 5 d-LC_{50} = 102.2 mg/l (n).
The lowest toxicity of p-toluidine to microorganisms measured in a test according to OECD TG 209. A 3h-EC_{50} value of 100 mg/l was obtained with predominantly domestic sewage.
As acute test results of p-toluidine for three trophic levels are available, an assessment factor of 1000 was applied for the derivation of the $PNEC_{aqua}$ according to the EU Technical Guidance Document. The lowest of the available $L(E)C_{50}$ values was obtained for *Daphnia magna*, 48 h-EC_{50} = 0.12 mg/l, therefore resulting in a $PNEC_{aqua}$ = 0.12 µg/l.

Exposure

p-Toluidine is commercially manufactured by reduction of p-nitrotoluene. In 2000, the global production volume of p-toluidine was estimated to be 19 600 tonnes by 23 producers: Western Europe 8000 tonnes/a, USA 3000 tonnes/a, Japan 1200 tonnes/a, South Korea 2400 tonnes/a, China 3800 tonnes/a, and India 1200 tonnes/a. In the Sponsor country, one company has a total production volume of 2000 -10 000 tonnes/a. The total production of this company is used as an intermediate in chemical synthesis, either onsite or offsite by customers. The total end use volume of Western Europe (approximately 5700 tonnes/a of p-toluidine) is used as an intermediate in chemical synthesis as well.

In the Sponsor company, p-toluidine is manufactured and processed in closed systems. The effluent concentration from the wastewater treatment plant was below the detection limit of 20 µg/l (With a dilution factor of 700 at that site the concentration in the receiving river is below 0.03 µg/l). p-Toluidine is transported in rolling channel drums and also in rail or road tankers. The transported goods are classified and labeled according to the relevant national and international transport regulations. There are 2 other companies which produce p-toluidine in the Sponsor country. However, no information is available from these companies.

p-Toluidine is used exclusively as an intermediate in chemical processes, e.g. for the manufacturing of 4B acid

(intermediate for pigments) and of other pigments, dyestuff, pesticides, and pharmaceuticals. No consumer use is known for p-toluidine. p-Toluidine is listed in the Danish and Norwegian Product Registers as an industrial product. It is not listed in the Finnish and Swedish Product Registers. In the Swiss Product Register p-toluidine is registered to occur in a consumer product (acrylate glue) with a p-toluidine concentration of 0.01 %. Thus, an exposure of consumers and of the environment due to releases from (consumer) products appears to be negligible.

Toluidine (isomers not specified) was detected in certain vegetables and liquid fuels. p-Toluidine was identified in gasoline. It is released from *Penicillium viridicatum* and from *Methylobacterium mesophilicum* biofilm interlaced with *Penicillium viridicatum*. p-Toluidin is an intermediate in the biodegradation of p-nitrotoluene, e.g. at former munitions sites. p-Toluidine is formed during pyrolysis.

In 1979, p-toluidine was detected in the river Rhine, with the highest p-toluidine concentration of 1 µg/l. In 1991, p-toluidine was not detected in several rivers in North Rhine-Westfalia in Germany (detection limit: 0.1 - 1 µg/l). In 2001, p-toluidine could also not be detected in 3 Indian water samples (detection limit: 23 ng/l). p-Toluidine occurs in air and tobacco smoke with emissions of up to 2.4 µg/cigarette.
Measurements at the workplaces have been performed according to German Technical Guidance TRGS 402. In Germany up to 2004, for occupational settings, a legally binding maximum admissible concentration (technical based) of 1.0 mg/m³ was set for p-toluidine. With the new German Ordinance on hazardous substances at January 1, 2005, this limit value was officially withdrawn by the German Ministry of Labour. In the Sponsor country, as also confirmed by one company, the exposure of workers is below this limit. p-Toluidine has a TWA (Time-weighted average) value of 2 ppm and is also classified in the TLV list A3 as a confirmed animal carcinogen with unknown relevance to humans.
Concentrations of p-toluidine in urine of occupationally exposed workers were similar to these of the general population. Prominent differences were found between males and females. 3 out of 4 studies found elevated levels of p-toluidine hemoglobin adducts in blood of smokers, compared to non-smokers.

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

Human Health: The chemical possesses properties indicating a hazard for human health (acute and subacute toxicity, methemoglobin formation, skin sensitization, eye irritation, possible genotoxicity and carcinogenicity). Based on the data presented by the Sponsor country (relating to production by one producer in one country which accounts for 10 - 50 % of global production and relating to the use pattern in several OECD countries), exposure is controlled in occupational settings, and exposure of consumers appears to be negligible. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country. The substance is currently of low priority for further work.

Environment: The chemical possesses properties indicating a hazard for the environment (acute aquatic toxicity to *Daphnia magna*). Based on data presented by the Sponsor country (relating to production by one producer in one country which accounts for 10 - 50 % of global production and relating to the use pattern in several OECD countries), exposure to the environment is anticipated to be low. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country. The substance is currently of low priority for further work.