# SIDS INITIAL ASSESSMENT PROFILE

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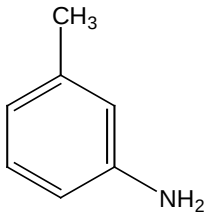
| **CAS No.** | 108-44-1 |
| **Chemical Name** | m-Toluidine |
| **Structural Formula** |  |



## RECOMMENDATIONS

The chemical is a candidate for further work.

## SUMMARY CONCLUSIONS OF THE SIAR

**Human Health**

Although the metabolites, 2-amino-4-methylphenol and 4-amino-2-methylphenol were identified in the rat urine with a small amount of the parent compound, there is not sufficient information on metabolism and toxicokinetics. Acute toxicity of m-toluidine is low because the oral LD50 values in rat, mouse and rabbit are from 450 to 1,430 mg/kg. This chemical is slightly irritating to skin and moderately irritating to eyes. There is no information available on skin sensitisation.

In accordance with an OECD combined repeat dose and reproductive/developmental toxicity screening test [TG 422], m-toluidine was given to Crj: CD (SD) male and female rats by gavage at doses of 0, 30, 100, 300 mg/kg/day for at least 41 days. The critical effect at 100 and 300 mg/kg is a hemolytic anemia, revealed by reduction of erythrocyte counts and hemoglobin concentration, and histological changes such as pigment deposit and extramedullary hematopoiesis in liver and spleen. Other toxicity is renal tubular epithelium lesions accompanied with pigment deposit in kidney. As there is suggestive evidence of hemolytic anemia such as marginal pigment deposit and extramedullary hematopoiesis in spleen at the lowest dose of 30 mg/kg, probably caused by methemoglobin formation, LOAEL for repeat dose toxicity was 30mg/kg/day.

In the above screening test [OECD TG 422], m-toluidine was given from 14 days before mating to 14 days after mating in males and from 14 days before mating to day 3 of lactation in females. As implantation losses were found in all animals at 300 mg/kg and two of ten at 100 mg/kg but not at 30 mg/kg, NOAEL for reproductive toxicity is 30 mg/kg/day. The death of all pups or more than half the number of pups observed at 30 and 100 mg/kg/day is considered as the result of maternal toxicity because there is clear evidence of the lack of the nursing activity, probably due to anemia, and all live offsprings of 30 and 100 mg/kg had normally developed up to 4 days. Therefore the NOAEL for developmental toxicity is considered to be 100 mg/kg/day.

Bacterial genotoxicity studies show negative results in *S. typhimurium* and *E. coli* with and without metabolic activation. In chromosomal aberration test conducted in cultured Chinese hamster lung

(CHL/IU) cells by OECD TG 473, clastogenicity was not observed but significant increase of polyploidy (0.9 to 1.25 %) was found at the highest concentration. However, this result was considered not to be positive because it was within historical control and generally accepted criteria of significance (5 %). Two kinds of *in vivo* studies, sister chromatid exchange and inhibition of DNA-synthesis, also show negative results. Therefore m-toluidine is considered not to be genotoxic. Tumors were not observed in dietary study of male rats at 9,400ppmand male and female mice at 14,700 and 20,400 ppm, respectively. However, the carcinogenicity in rodents is inconclusive because the experimental conditions were insufficient compared to a current carcinogenicity testing protocol.

**Environment**

This chemical is mainly persistent in water and it will be transported to water compartment when released to other environmental compartments. The chemical is not readily biodegradable, and its bioaccumulation potential is low.

This chemical has been tested in a limited number of aquatic species. For algae, 72 h EC50 (biomass change in *Selenastrum capricornutum*) is 17.7 mg/L. For *Daphnia*, the lowest acute toxicity value is 0.73 mg/L (48 h EC50 for immobilization), and the lowest chronic value is 0.01 mg/L (21d NOEC for reproduction). For fish, only acute data were available, the lowest of which is 34 mg/L (96 h LC50, *Oryzias latipes*).

PNEC of 0.0001 mg/L for the aquatic organisms was calculated from the lowest chronic value (NOEC for *Daphnia;* 0.01 mg/L) using an assessment factor of 100. Toxicity of this chemical to aquatic organisms, specially against *Daphnia*, is high.

**Exposure**

The production volume of m-toluidine in Japan was less than 100 tonnes in 1990 - 1992, and imported volume was 97-285 tonnes/year in 1988-1992, however both the production volume and imported volume in Japan in 1998 was 0 ton. This chemical is used as intermediates for pigments, photography agents and others. This chemical is stable in neutral or alkaline solutions, and is classified as "not readily biodegradable". Direct photodegradation is expected. The half-life is estimated to be about 4 months. A generic fugacity model (Mackey level III) shows this chemical would be distributed mainly to water. In the monitoring study of the general environment in Japan in 1977, m-toluidine was detected from surface water and sediment, but in the monitoring study in 1999, it was not detected in water, sediment or air. According to a Japanese manufacturer, 400 kg/year (estimated) of m-toluidine are released with $1 \times 10^{7}$ tonnes/year of effluent into bay. Local predicted environmental concentration (PEClocal) is $4.0 \times 10^{-5}$ mg/l, employing the calculation model. The highest exposure to the general population via the environment would be expected through drinking water processed from surface water. The concentration in drinking water is assumed to be less than $4.0 \times 10^{-5}$ mg/l. Consumer exposure is negligible because m-toluidine is not contained in consumer products. As m-toluidine is mainly produced in a closed system, occupational exposures at production sites may occur by the inhalation and dermal route. Estimated human exposure for a worker who operates sampling (0.1 hr/day), drum filling (1.5 hr/day), and reaction vessel cleaning (2 day/year) without protective equipment is less than 0.21 mg/kg/day. By wearing chemical cartridge respirator during these operations, and ventilation systems during the filling process, exposure level is lower than the estimation.

## NATURE OF FURTHER WORK RECOMMENDED

Local exposure assessment should be considered given the aquatic toxicity of the chemical.