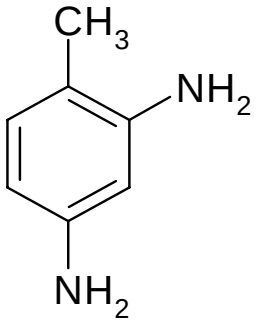
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	95-80-7
Chemical Name	Toluene-2,4-diamine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The 80/20% mixture of 2,4-TDA/2,6-TDA was used as read across in cases that inhalation data of 2,4-TDA was not available (acute toxicity and repeated dose toxicity).

Toluene-2,4-diamine (2,4-TDA) is almost completely absorbed via the gastrointestinal tract in animals and well absorbed via the skin (54% in monkeys and 24% in humans over an exposure time of 24 h). No data are available on absorption by inhalation. In rats the highest tissue concentrations were measured in liver and kidney after oral or i.p. administration. Concentrations in heart, lungs, spleen, and testes were significantly lower. There are no species-related differences in tissue distribution between mice and rats. In rats, rabbits, and guinea pigs unchanged 2,4-TDA was excreted via urine in concentrations from 0.1 to 3%. 2,4-TDA is mainly hydroxylated at the ring under formation of aminophenols (major pathway) and additionally N-acetylation occurs. Mono- as well diacetyl derivates were observed in different quantities in the urine of rats, mice, rabbits, and guinea pigs. In dogs, however, only very small amounts of the monoacetyl derivative were detected. Elimination of sulfate conjugates was shown in the 24-hour urine in rats and mice, whereas glucuronic acid conjugates occurred at a higher level in mice than in rats. The excretion of metabolites predominantly occurs via urine in rats and mice.

2,4-TDA has proven to be toxic with oral LD50 values between 73 and 350 mg/kg bw in rats and mice. A dermal LD50 value of 1200 mg/kg bw was detected in rats. No animal nor human data are available on acute inhalation toxicity of 2,4-TDA. A mixture of 80% 2,4-TDA and 20% 2,6-TDA (CAS-No. 25376-45-8) has a similar oral and dermal acute toxicity profile as pure 2,4-TDA (oral LD50 values between 50 and 500 mg/kg bw for rats, mice, rabbits, and cats and a dermal LD50 value of 463 mg/kg bw for rats). Thus results of tests with that 80/20 mixture are used to assess the acute inhalation toxicity of the pure 2,4-TDA. No mortality occurred after a 4 hour inhalation to concentrations of approx. 5.57 mg/l of the 80/20 mixture of 2,4-/2,6-TDA, but all animals appeared in a bad health state.

In a Draize test with rabbits according to OECD TG 404 2,4-TDA did not cause skin irritation. The substance demonstrated only slight conjunctival redness after instillation to the eye in a Draize test with rabbits according to OECD TG 405. In a Magnusson Kligman test with 2,4-TDA (in compliance with OECD TG 406) up to 100% of the guinea pigs demonstrated a positive reaction. Human data demonstrate a possible cross sensitivity to p-phenylenediamine.

Animal studies have shown that main toxic effect associated with dietary exposure of 2,4-TDA is hepatotoxicity. In short-term studies effects were characterized by a decrease in body weight and an increase in the liver: body weight ratios. In long-term studies toxic effects on the liver accelerated the development of chronic renal disease in rats, an

effect that contributed to a marked decrease in survival. In a 2-year feeding study in rats (doses 5.9 and 13 mg/kg bw/day, OECD TG 452), the lower dose of 5.9 mg/kg bw/d showed toxic effects in the liver and kidneys and increased tumor incidences in the liver (male rats, female rats, female mice), and in the mammary gland (female rats) (LOAEL). An overall NOAEL was not demonstrated. In 28-day inhalation studies of limited test design the 2,4-/2,6-TDA mixture gave 9.5 mg/m^3 (approx. 1 mg/kg bw/day) as a NOAEL for systemic effects in rats. At a concentration of 83 mg/m^3 (approx. 9 mg/kg bw/d) reduced body weight gain, an increase of the relative weight of the liver, kidneys, and thyroid glands, and a relative lymphopenia were observed. In cats the concentration of 9.5 mg/m^3 already caused a slight formation of methaemoglobin (2.1%). At a concentration of 41.6 mg/m^3 (approx. 4.5 mg/kg bw/d) cats showed severe methaemoglobinemia (30%), retarded body weight gain, and pathomorphological findings in the lungs, liver, and kidneys.

In vitro 2,4-TDA induces gene mutations in bacteria using standard Ames test conditions (OECD TG 471). Mammalian cell gene mutation tests carried out in various cells according to OECD TG 476 resulted in negative results. In cultivated mammalian cells 2,4-TDA produced chromosomal aberrations and SCE (OECD TG 473, OECD TG 479). 2,4-TDA was positive for induction of UDS (OECD TG 482), and of DNA strand breaks , and DNA adducts. In general, rodent *in vivo* micronucleus tests were negative in bone marrow or peripheral blood (OECD TG 474). A weak positive effect on one rat strain (PVG) was limited to a dose with high acute toxicity. However, in other in vivo assays generally weak genotoxic effects were obtained, e.g. gene mutations, UDS, DNA strand breaks and DNA adducts were observed in rodent livers. It cannot be excluded that 2,4-TDA has genetic effects on germ cells.

2,4-TDA is carcinogenic in long-term animal studies similar to OECD TG 453. In F344 rats, liver tumors are produced in both genders and mammary tumors in females after oral administration with doses of 5.9 and 13 mg/kg bw/d. 2,4-TDA was also carcinogenic for female B6C3F1 mice, inducing hepatocellular carcinomas at doses of 15 and 30 mg/kg bw/d. Local sarcomas were demonstrated after subcutaneous application of 25 mg/kg bw/d to SD rats over a 2-year period (doses 8.3 and 25 mg/kg bw/d).

Severe testicular atrophy in rats was shown at 28 mg/kg bw/d in a 15-months study. Inhibited spermatogenesis (66%) associated with a significant reduction in the weights of seminal vesicles and epididymides, morphological damage of Sertoli cells as well as with a diminished level of serum testosterone and an elevation of serum LH was observed at 15 mg/kg bw/d in a 10-week male rat feeding study with dose levels of approx. 5 and 15 mg/kg bw/d.
5 mg/kg bw/d is considered as marginal LOAEL for effects on reproductive organs as it causes a decrease in epididymal sperm reserves. No NOAEL was established.

No valid data are available to assess the endpoint developmental toxicity. Further testing on developmental toxicity is considered to be not necessary, since reduction of occupational risks is effective due to the implemented exposure reduction measures because of genotoxic and carcinogenic properties of the chemicals. Results from human epidemiological studies with various diaminotoluenes concerning reproductive health are inconclusive to assess any developmental impairment by 2,4-TDA.

Environment

2,4-TDA is a clear colourless solid with a boiling point of 288 °C and a melting point of 99 °C. Its density is 1.256 g/cm^3. It has a water solubility of 38 g/l at 25 °C, a vapor pressure of 0.017 Pa (at 25 °C) and a measured log K_{OW} of 0.074 (at 25 °C). With a Henry's law-constant of 5.46.10-5 Pa.m^3.mol^{-1} for 2,4-TDA no significant volatilization from water is expected.

2,4-TDA is not readily biodegradable. In a MITI-II test on inherent biodegradation performed with the 80:20 mixture of 2,4-TDA and 2,6-TDA and unadapted inoculum only 4 % degradation was found after 28 d. However, biodegradation of 2,4-TDA reached 51% of theoretical CO_2 yield over 36 days in the Modified Sturm Test (OECD 301B), using an unadapted inoculum. A Zahn-Wellens-Test conducted with sludge from an industrial sewage treatment plant as inoculum assumed to be adapted to TDA showed elimination of 100 % after 6 days for 2,4-TDA and of 89 % after 28 days for 2,6-TDA. Therefore, it can be concluded that both isomers are inherently biodegradable by adapted inoculum.
Biodegradation studies in soil using ^{14}C-labelled TDA showed that biodegradation started immediately after mixing with the aerobic soil. The degradation rates indicate that biodegradation slowed down after TDA had formed covalent bounds to humic substances. It is not possible to calculated a half-life for biodegradation of TDA in soil (because of competing reactions with soil organic matter.), but it can be assumed that TDA covalently bound to organic matter is degraded almost similar to the humic acids themselves. A mean half-life of 1000 d can be

assumed for this humified TDA, whereas unbound TDA is rapidly biodegraded in soil.
Based on the molecular structure, hydrolysis of TDA is not expected under environmental conditions. The UV-spectra (λmax at 295 nm for 2,4- TDA indicate that direct photolysis in water may occur. Half-lives in the range of 29 d (summer) to > 1 year (winter) have been calculated. However, under real environmental conditions half-lives should be at least one order of magnitude higher than the calculated half-lives because turbidity and adsorption are not considered.
The calculated half-life for the photo-oxidation (reaction with hydroxyl radicals) of TDA in air is 2 h (2,4-TDA). This half-live is based on an assumed tropospheric hydroxyl radical concentration of 5 x 10^5 molecules/cm^3.

Experiments with radiolabelled 2,4-TDA revealed that the substances form covalent bonds with the organic fraction in soil. A Koc-value of 9,763 l.kg-1 for 2,4-TDA has been measured. According to a fugacity model (Mackay level I) soil (64 %) and sediment (32 %) are identified as target compartments for TDA in the environment. Measured BCF values in fish of < 5 and < 50 do not indicate a significant potential for bioaccumulation.

Short-term and long-term tests with fish, invertebrates and algae are available for TDA. The lowest effects values from the short-term tests are: *Pagrus major* (marine): 96h-LC_{50} = 0.161 mg/l (TDA 80:20), *Daphnia magna*: 48h-EC_{50} = 1.6 mg/l (2,4-TDA), *Selenastrum capricornutum* 96h-EC_{50} = 9.54 mg/l (2,4-TDA). In a test with *Danio rerio* that investigated the toxicity of TDA 80:20 on the embryo and sac-fry stages a 10d-NOEC of 3.61 mg/l was found for the endpoint behaviour abnormality. In a reproduction test with Daphnia magna a 21d-NOEC of 0.282 mg/l was found for TDA 80:20.
Compared to other fish species, *Pagrus major* showed the highest sensitivity to 2,4-TDA and the isomeric mixture (effect values were more than a factor of 1000 lower than for other fish species tested; *Pimephales promelas* (96 h) 1420 mg/l (flow-through; analytical monitoring), 2,4-TDA; *Oryzias latipes* (96 h) 912mg/l (flow-through, analytical monitoring) 2,4-TDA). The reason for this high sensitivity is not clear.
The PNECaqua is derived by applying an assessment factor of 100 to the 96h-LC50 for *Pagrus major* resulting in a PNEC of 1.6 µg/l because in this short-term test a lower effect value was found than in the available long-term tests.
Tests with benthic organisms are available. The effect levels are:
Chironomus riparius: 28d-NOEC of 500 mg/kg dw (TDA 80:20)
Lumbriculus variegatus: 28d-NOEC 12.3 mg/kg dw (TDA 80:20).
For the terrestrial compartment short-term tests with plants and earthworms are available. The following results were obtained: *Lactuca sativa* and *Avena sativa*: 14d-EC_{50} = 320 mg/kg dw; *Eisenia fetida*: 14d-LC_{50} > 1000 mg/kg dw. With an assessment factor of 1000, a PNECsoil of 320 µg/kg dw was derived.

Exposure

The total amount of TDA (technical mixture of 2,4- and 2,6-isomers in the ratio 80:20) produced in the EU is about 280 000 t/a for the year 1999/2000. Additionally, about 10,000 t/a are imported. No information is available about export volumes. Therefore, the total volume of TDA handled in the EU amounts to 290,000 t/a.

In the EU, TDA is almost exclusively used as an intermediate in the chemical industry to produce TDI (toluylene diisocyanate). A small volume of 2,4-TDA is processed to dyes.

Releases into the environment may occur from production of TDA and from processing to dyes. During processing to TDI no releases into the wastewater occur as it is a water-free process. From processing of TDA to dyes environmental releases can occur. TDI is not stable in water and hydrolyses to TDA and oligourea.
Diffuse releases can occur from TDA or TDI (after hydrolysis) chemically reacted in polyurethane or epoxy matrices during use and disposal of polymer products. Trace amounts of residual monomers may be released via migration and leaching. No significant releases of TDA into the atmosphere during production and processing to TDI are expected. For a German site, an emission of 10 kg/a is stated, at further sites the exhaust gases are incinerated. A study on the gas phase reaction of TDI with moisten air revealed that no TDA was formed. It can be concluded that a relevant TDA exposure does not occur from TDI emissions.

There are no indications for any direct application of 2,4-TDA by consumers.

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 (acute and subacute toxicity, skin sensitisation, genotoxicity, carcinogenicity and reproductive toxicity).

A risk assessment was performed in the context of the EU Existing Substances Regulation. For human health, concerns were identified regarding occupational exposure. For all three TDA scenarios at the workplace (production and further processing as a chemical intermediate, production of 2,4-TDA pastilles and use of 2,4-TDA pastilles for the production of dyes) carcinogenicity in combination with mutagenicity and skin sensitisation lead to concern. Extensive technical and organisational reduction measures have already led to very low levels of exposure. Other member countries are invited to perform an exposure assessment and if necessary a risk assessment for occupational settings. Based on data presented by the Sponsor Country exposure of consumers appears to be negligible.

Risks of skin sensitisation are considered to be small. However, because the corresponding risk cannot be quantified or excluded, a general concern for skin sensitisation is expressed. Carcinogenicity risk assessment was conducted with a quantitative approach. Additionally a risk evaluation for this endpoint was done by calculating with different levels of risk acceptance. The specific conclusions for the different occupational exposure scenarios critically depend on the chosen level of risk acceptance. This comparison may be helpful for risk managers in order to evaluate the necessity and priority of further risk reduction measures beyond those that has already been successfully implemented.

Environment: The chemical is a candidate for further work.

The chemical possesses properties indicating hazard for the environment (acute and chronic aquatic toxicity to invertebrates, acute toxicity to fish (*Pagrus major*)) and algae). Other member countries are invited to perform an exposure assessment, and if necessary a risk assessment for the environment.

Note: A risk assessment for this chemical is currently under discussion in the EU in the context of the EU Regulation 793/93. Risk was identified for the generic scenario for process 2,4 TDA to dyes (wastewater treatment plant, surface water and sediment).