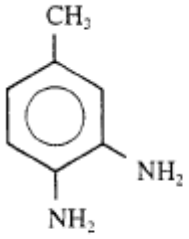
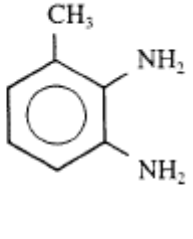
SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	2687-25-4, 496-72-0, 25376-45-8 and 26966-75-6
Chemical Names	o-TDA category: 2,3-toluenediamine (2,3-TDA), 3,4-toluenediamine (3,4-TDA) and commercial TDA mixture (2,3/3,4-TDA (40/60))
Structural Formula	 Toluene-3,4-diamine  Toluene-2,3-diamine

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The o-TDA category consists of two individual compounds, 3,4-TDA (CAS No. 496-72-0) and 2,3-TDA (CAS No. 2687-25-4), and a commercially supplied mixture in which these isomers are the major constituents in a 60/40 ratio, respectively (CAS No. 25376-45-8 and 26966-75-6 referred to as commercial TDA mixture (2,3/3,4-TDA (40/60))). Only the isometric mixture (2,3/3,4-TDA (40/60)) is available commercially. The following structural analogue of the sponsored substances is used to address the endpoints for biodegradation, repeat dose toxicity and reproductive toxicity: 2,4-toluenediamine (2,4-TDA; CAS number 95-80-7, presented and agreed upon at SIAM 22). 2,4-TDA is a structural isomer of the sponsored substances, differing in the substitution pattern of the amine groups on the tolyl ring; having similar physical chemical properties; similar environmental fate; and similar health effects (acute toxicity and genotoxicity). As a result, data from 2,4-TDA can be used for read across to 2,3- TDA, 3,4-TDA and commercial TDA mixture (2,3/3,4-TDA (40/60)).

It should be noted that CAS number 25376-45-8 is used to represent all of the individual mixed TDA isomers (m, o, and p). In the context of this assessment, the sponsored mixed isomer data consist of only o-TDA which is a commercial TDA mixture of 2,3/3,4-TDA (40/60) using CAS numbers 25376-45-8 and 26966-75-6. A dossier for m-TDA CAS number 25376-45-8 was previously created and presented at SIAM 22 and only consisted of those data representing m-TDA commercial mixture (2,4/2,6-TDA (80/20) isometric mixture. In order to distinguish between the two isomeric mixtures that are represented by the same CAS number (25376-45-8), two separate dossiers were created.

Human Health

Metabolism data are not available on commerical TDA mixture (2,3/3,4-TDA (40/60)), 2,3- and 3,4-TDA. Data on the close structural analogue 2,4-TDA are available. 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. The excretion of metabolites predominantly occurs via urine in rats and mice. Similar findings are anticipated for commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3- and 3,4-TDA.

The oral LD_{50} of mixed commercial TDA mixture (2,3/3,4-TDA (40/60)) in rats was = 660 mg/kg bw; for 2,3-TDA the value was = 812 mg/kg bw. Clinical signs during exposure to commercial TDA mixture (2,3/3,4-TDA (40/60)) included decreased locomotor activity, ptosis, piloerection and death. 2,3-TDA exposure produced clinical signs including ruffed fur and very sluggish behaviour. Gross necropsy revealed congestion throughout the lungs and abdominal viscera, mottled livers, and effects on the stomach and intestines. The dermal LD_{50} of commercial TDA mixture (2,3/3,4-TDA (40/60)) and 2,3-TDA (rabbits) was = >5750 mg/kg bw (highest dose tested) and = 1120 mg/kg bw, respectively.

Mild/slight skin irritation is expected following exposure to commercial TDA mixture (2,3/3,4-TDA (40/60)). Mild/slight eye irritation was observed following exposure to commercial TDA mixture (2,3/3,4-TDA (40/60)). Similar effects are anticipated for 2,3- and 3,4-TDA.

Repeated dose studies are not available for the commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA or 3,4-TDA. Based on structural similarities, data from 2,4-TDA presented at SIAM 22 are used to fulfil this endpoint. Animal studies have shown that the 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/d, 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 vitro, 3,4-TDA is considered positive in bacterial gene mutation assays and mammalian mutagenicity studies

In vivo, there was a clear indication of a clastogenic effect of the commercial TDA mixture (2,3/3,4-TDA (40/60)) administered i.p. in a somatic cell test system (mouse micronucleus assay). 3,4-TDA induced chromosomal damage in the bone marrow of mice at doses of 244 mg/kg bw and above following i.p. injection. Inhibition of DNA synthesis was observed in mice injected i.p. once with 500 mg/kg bw. The available data suggest that commerical TDA mixture (2,3/3,4-TDA (40/60)) and 3,4-TDA are likely to be genotoxic.

No data for carcinogenicity are available for mixed commercial TDA mixture (2,3/3,4-TDA (40/60)), 3,4-TDA and 2,3-TDA. Supplemental data from 2,4-TDA is provided for informational purposes. 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). The available data suggest that commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA and 3,4-TDA may have a carcinogenic potential.

Effects on fertility studies are not available for the commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA and 3,4-TDA. Data from the close structural analogue, 2,4-TDA are used to address this endpoint. Severe testicular atrophy in rats was shown at 28 mg/kg bw/d 2,4-TDA in a 15-month 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 ca. 5 and 15 mg/kg bw/d. 5 mg/kg bw day is considered as marginal LOAEL for effects in reproductive organs as it causes a decrease in epididymal sperm reserves. No NOAEL was established.

Rats exposed to the commercial TDA mixture (2,3/3,4-TDA (40/60)) showed significantly reduced body weights and body weight gains at 300 mg/kg bw/day. Fetal body weights at 300 mg/kg bw/day were also significantly reduced, along with a significant increase in the number of incomplete vertebrae at 100 and 300 mg/kg bw/day. Fetuses at 300 mg/kg bw/day also showed increased incidence of missing sternebrae and incomplete skull closure. The occurrence of hemorrhagic abdomen was increased at 10, 100 and 300 mg/kg/day. The NOAEL (maternal) = 100 mg/kg bw/day and the NOAEL (developmental) = 30 mg/kg bw/day. In rabbits, swollen, red or pink eyelids were documented and in maternal animals body weight and body weight gains were significantly reduced at 100 mg/kg/day bw. The percentage of dams that resorbed their entire litter was significantly increased and fetal weights were significantly reduced at 100 mg/kg bw/day. Fetal survival was significantly reduced at 100 mg/kg/day. Examination of the skeletal and soft tissue revealed no significant differences between any of the test groups and the controls. The NOAEL (maternal) = 30 mg/kg bw/day and the NOAEL (developmental) = 30 mg/kg bw/day. As a result of these data the commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA and 3,4-TDA are considered to be reproductive and developmental toxicants.

Environment

The commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA and 3,4-TDA are in solid form for shipping but are heated into a molten liquid for transfer. The melting points of the commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA and 3,4-TDA range from 40 - 50°C, 63-64 °C and 88.5-93 °C, respectively. The boiling points for the commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA and 3,4-TDA are >250°C, 255 °C and 265 °C at 1013 hPa. The vapor pressures are 2.96 hPa at 100 °C (commercial TDA mixture (2,3/3,4-TDA (40/60))) and, 0.00074 hPa (2,3-TDA) and 0.00084 hPa (3,4-TDA) at 25 °C. In the case of 2,3-TDA measured vapor pressure values are also available indicating 6.66, 26.6 and 133 hPa at 119, 149 and 198ºC, respectively. Model estimates of water solubility and partition coefficient estimates are not appropriate for mixtures such as the commercial TDA mixture (2,3/3,4-TDA (40/60)) isomer. However, estimates are available for 2,3-TDA and 3,4-TDA. The estimated water solubility for both 2,3-TDA and 3,4-TDA is 13.85 g/L at 25 °C. The estimated partition coefficient for 2,3-TDA is 0.71 at 25°C while the experimental value for 3,4-TDA is 0.66 at 25°C. The Henry's Law Constant is estimated to be $7.43E^{-10}$ for both 2,3 and 3,4 TDA via the bond method.

Photodegradation half-lives based on default input parameters in EPIWIN v3.12 for both 2,3- and 3,4-TDA indicate a half-life of 0.6 hours with the overall OH rate constant being $200.1360E^{-12}$(cm^3/(molecule*sec). Model estimates for the mixed isomer are not appropriate.

A hydrolysis study was attempted on the commercial TDA mixture (2,3/3,4-TDA (40/60)) mixture following OECD TG 111. Results of this study conclude that the commercial TDA mixture (2,3/3,4-TDA (40/60)) shows degradation reactions in aqueous buffer solutions which are easily influenced by different factors (pH with faster degradation occurring at lower pHs and oxidation).

Level III Fugacity modeling, using loading rates for Air, Soil, and Water of 300 kg/h for each media, using default input parameters shows the following percent distribution for the individual constituents, 2,3-TDA: Air = 0.0142%, Water =48%, Soil = 51.9%, and Sediment = 0.0928%; and 3,4-TDA: Air = 0.0143%, Water = 48.3, Soil = 51.6% Sediment = 0.0929%. Fugacity estimations are not applicable to mixtures such as the commercial TDA mixture (2,3/3,4-TDA (40/60)).

Available data on 3,4-TDA indicate the substance to not be readily biodegradable (0% degradation after 28 days) this is further supported by data from 2,4-TDA. Similar findings are anticipated for the commercial TDA mixture (2,3/3,4-TDA (40/60)) and 2,3-TDA. These substances are not anticipated to bioaccumlate. The estimated BCF for 2,3-TDA and 3,4-TDA is 3.16. Model estimates are not appropriate for the commercial TDA mixture (2,3/3,4-TDA (40/60)), but BCF values are expected to be similar.

In fish (*Brachydanio rerio)*, the 96-hour LC_{50} was = 20 mg/L for 3,4-TDA. Results from ECOSAR v0.99h

indicate that the predicted 96 hr LC_{50} = 14.769 mg/L for both 3,4 and 2,3-TDA.
In an acute aquatic invertebrate study in *Daphnia magna* conducted with the commercial TDA mixture (2,3/3,4-TDA (40/60)), the 48h EC50 is 1.73 mg/L (nominal). Analyses were only conducted on the three highest test concentrations (1, 3, and 10 mg/L). Recoveries were within 20% of nominal in the two highest concentrations. In the lowest concentration (1 mg/L) recovery was within 60% of nominal concentration. Results from ECOSAR v0.99h indicate that the predicted 48 hr LC_{50} = 0.421 mg/L for both 3,4 and 2,3-TDA. In an inhibition of growth to aquatic plants study (OECD TG 201), the following 72 hour EC50 values were reported based on nominal concentrations: (E_rC_{50}) = 0.94 mg/L and (E_yC_{50}) = 0.040 mg/L. However, in the test concentrations decreased markedly by test end and analysis wase only conducted on the three highest concentrations (1, 3 and 10 mg/L.) From the analytical recoveries recorded for these three concentrations a general correction was made for all test concentrations. On this basis the 72 hour EC50 measured values are: (E_rC_{50}) = 0.38 mg/L and (E_yC_{50}) = 0.021 mg/L. As effects were seen at all test concentrations a NOEC can not determined. Results from structure activity relationship tools, ECOSAR v0.99h indicate that the predicted 96 hr EC_{50} = 0.134 mg/L for both 3,4 and 2,3-TDA.

Exposure

Global production volumes of the commercial TDA mixture (2,3/3,4-TDA (40/60)), including 2,3-TDA and 3,4-TDA, are not available. United States production volumes are estimated to be in the range of 1 to 10 million pounds. The commercial TDA mixture (2,3/3,4-TDA (40/60)) is manufactured in closed systems and primarily used on-site.

The only potential for exposure as a result of manufacture is during loading of the product(s). Occupational monitoring records indicate that occupational levels are kept below the American Industrial Hygiene Association recommended value. The commercial TDA mixture (2,3/3,4-TDA (40/60)) is available in 55 gallon non-returnable drums, 5,000 gallon tank trucks, 5,000 gallon isocontainers and 20,000 gallon tank rail cars.

There is no known use in consumer products.

Under normal use, the only potential exposures to the environment from the commercial TDA mixture (2,3/3,4-TDA (40/60)), 2,3-TDA and 3,4-TDA would be due to accidental spills or releases.

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

Human Health: The chemicals in this category are candidates for further work. These chemicals possess properties indicating a hazard for human health (repeated dose toxicity (body weight, lung, liver and kidney), genotoxic, carcinogenic, reproductive and developmental effects). Member countries are invited to perform an exposure assessment and if then indicated a risk assessment.

Environment: The chemicals in this category are candidates for further work. These chemicals possess properties indicating a hazard for the environment (acute toxicity to aquatic invertebrate and algae (< 1 mg/L)). Member countries are invited to perform an exposure assessment and if then indicated a risk assessment.