SIDS INITIAL ASSESSMENT PROFILE

Category Name	Dimethylaniline Category
CAS No.	87-59-2 95-68-1 95-78-3 87-62-7 95-64-7 108-69-0
Chemical Name	2,3-Dimethylaniline 2,4-Dimethylaniline 2,5-Dimethylaniline 2,6-Dimethylaniline 3,4-Dimethylaniline 3,5-Dimethylaniline
Structural Formula	87-59-2 2,3-Dimethylaniline 95-68-1 2,4-Dimethylaniline 95-78-3 2,5-Dimethylaniline 87-62-7 2,6-Dimethylaniline 95-64-7 3,4-Dimethylaniline 108-69-0 3,5-Dimethylaniline

SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

The dimethylaniline category consists of six chemicals: 2,3-dimethylaniline (87-59-2), 2,4-dimethylaniline (95-68-1), 2,5-dimethylaniline (95-78-3), 2,6-dimethylaniline (87-62-7), 3,4-dimethylaniline (95-64-7) and 3,5-dimethylaniline (108-69-0).

There are a number of unifying considerations, which together justify the inclusion of members within the Dimethylaniline Category. These include:

1. Similarity of chemical structure and Functional Groups.
   Direct connection of two methyl groups and one amino group to a benzene ring

2. Similarity of Physical / Chemical Properties
   Melting points, boiling points, water solubility, log Kow, dissociation constants in the water.

3. Similarity of Mammalian Toxicity
   Acute toxicity, repeated dose toxicity (anemia, liver and kidney damages), genotoxicity

4. Similarity in Health Effects and Mechanism of Toxic Action
   Methemoglobinemia, mutagenic and clastogenic

5. Similarity of Environmental Toxicity and Fate Properties
   Acute toxicity, chronic toxicity, toxicity to Microorganisms

The read across approach is used for genotoxicity, carcinogenicity and reproductive/developmental toxicity for the human health section. The similar toxicological effects identified in the repeated dose studies support the applicability of the read across approach.

CAS	87592	95681	95783	87627	95647	108690
Substance name	2,3-DMA	2,4-DMA	2,5-DMA	2,6-DMA	3,4-DMA	3,5-DMA
Mammalian toxicity endpoints						
Acute toxicity	x	x	x	x	x	x
Repeated dose toxicity	x	x	x	x	x	x
Gene mutation *in vitro*	x	x	x	x	x	x
Chromosomal aberration *in vitro*	x	x	RA	x	x	x
Gene mutation *in vivo*	RA	RA	x	x	RA	x
Micronucleus assay *in vivo*	x	x	x	x	x	x
Carcinogenicity	RA	x	x	x	RA	RA
Reproductive/Developmental toxicity	RA	RA	RA	x	RA	RA
Environmental toxicity endopoints						
Acute toxicity						
Fish	x	RA	x	x	x	x
Aquatic Invertebrates	x	x	x	x	x	x
Aquatic Plants	x	RA	x	x	x	x
Chronic toxicity						
Fish	ND	ND	ND	ND	ND	ND

Aquatic Invertebrates	x	RA	x	x	x	x
Aquatic Plants	x	RA	x	x	x	x
Toxicity to Microorganisms	x	x	x	x	x	x

x: Reliable data available
RA: Read across
ND: No data available

Physico-chemical properties

All category member substances are liquids at standard temperature and pressure except for 3,4-dimethylaniline. The melting points are in the range of <-15 °C – 15.5 °C for 2,3-, 2,4-, 2,5-, 2,6- and 3,5-dimethylaniline, although that of 3,4-dimethylaniline is 51 °C. The boiling points are in the range of 214-228 °C, and the vapour pressures are in the range of 3.72 – 63.2 Pa at 20/25 °C. The water solubility values are in the range of 3.8-6.98 g/L at 22/25 °C, and the partition coefficients between octanol and water (log K_{ow}) are in the range of 1.68-1.91. Dissociation constants in the water are in the range of 4.02-5.17 at 20/25 °C, which means the member substances exist predominantly in un-ionized form in environmental water.

Human Health

2,6-Dimethylaniline is readily absorbed through the oral route and subsequently is distributed through the body in rats. After a single oral dose of [^{14}C]-2,6-dimethylaniline, most of the radiolabel was eliminated in the urine and small amounts of the radiolabel were recovered in tissues. Rats receiving 10 daily doses had higher levels of radioactivity in the blood and other tissues, and the greatest concentrations of radioactivity were found in the red blood cells and liver. More rapid excretion of radioactivity was observed after 10 daily doses compared to a single dose. The slower clearance at later time points (biphasic elimination) were observed after i.p. administration of 2,6- and 3,5-dimethylaniline indicating metabolites bound to tissue components. 2,6-Dimethylaniline was excreted in the urine of rats as parent compound and metabolites (4-hydroxy-2,6-dimethylaniline (4-HDMA), and a trace level of N-2,6-trimethylaniline). 2,4-Dimethylaniline was excreted in the urine of rats mainly as parent compound, N-acetyl-4-amino-3-methylbenzoic acid, and a trace level of N-2,4-trimethylaniline. 2,6-Dimethylaniline was excreted in the urine of dogs as parent compound and metabolites, (4-HDMA and 2-amino-3-methylbenzoic acid). N-2,3-trimethylaniline, 2,6-dimethylnitrosobenzene and the glycine conjugate of 2-amino-3-methylbenzoic acid were also detected after 2,6-dimethylaniline treatment. 2,4-Dimethylaniline was excreted in the urine of dogs as parent compound, 6-hydroxy-2,4-dimethylaniline, 4-amino-3-methylbenzoic acid, and trace level of N-2,4-trimethylaniline. Compared to 2,6-dimethylaniline the species difference in metabolism is greater between rats and dogs for 2,4-dimethylaniline. 2,5-Dimethylaniline was excreted in the urine of rats mainly as parent compound and 4-hydroxy-2,5-dimethylaniline, and trace level of 2-amino-4-methylbenzoic acid and 3-amino-4-methylbenzoic acid. The metabolism of N-(2,6-dimethylphenyl)hydroxylamine and 4-HDMA were found as metabolites by using human liver microsomes and recombinant human P450 enzymes (CYP2A6 and CYP2E1). In addition the nonenzymatic oxidation of 4-HDMA to 3,5-dimethyl-4-iminoquinone was reported.

Based on an acute toxicity study conducted according to OECD TG 423 under GLP using female rats where all animals survived at 300 mg/kg bw while all animals died at 2000 mg/kg bw, the oral LD_{50} for 2,6-dimethylaniline was between 300 and 2000 mg/kg bw. At 300 mg/kg bw clinical signs included a slight decrease in motor activity and ptosis. At 2000 mg/kg bw, clinical signs included a severe decrease in locomotor activity, adoption of a prone position, abnormal gait, hypotonia and deep respiration. In other oral studies by NTP, the LD_{50}s for 2,6-dimethylaniline were 1160 or 1270 mg/kg bw for females and between 620 and 1250 mg/kg bw or 1310 mg/kg bw/day for male rats. In another experiment for the single oral dose toxicity of dimethylanilines in rats and mice, the following LD_{50} values (in mg/kg bw) were determined: 2,3-dimethylaniline: rats 930, mice 1070; 2,4-dimethylaniline: rats 470, mice 250; 2,5-dimethylaniline, rats 1300, mice 840; 2,6-dimethylaniline, rats 1230, mice 710; 3,4-dimethylaniline, rats 810, mice 710; 3,5-dimethylaniline, rats 710, mice 420. No reliable information is available for the dermal route, and no information is available for the inhalation route regarding acute toxicity. For the category, LD_{50}s between 450-1310 mg/kg bw were observed in rats and 250-1070 mg/kg bw in mice suggesting all substance cause acute toxicity via the oral route.

2,4-Dimethylaniline has a weak irritant effect on the skin and irritant effects on the eyes of rabbits. 2,6-Dimethylaniline has an irritant effect on the skin and a weak irritant effect on the eyes of rabbits. 3,5-Dimethylaniline has no irritant effect on the skin and is a weak irritant in contact with the eyes of rabbits. Category members were considered to be weekly irritant to the skin and eyes of rabbits.

No information wais available concerning skin sensitisation in animals for any of the dimethylaniline isomers.

Information on the sub-acute repeated dose toxicity in rats was available from 28-d studies following OECD TG 407 for 2,3-, 2,4-, 2-5-, 3,4- and 3,5- dimethylanilines and a screening study following OECD TG 422 for 2,6-dimethylaniline. Other reliable studies included a NTP study (2-week, 13-week and 2-year) for 2,6-dimethylaniline, a non-GLP 28-day study for 2,4-, 2,5-, and 2,6-dimethylanilines, a 6-month feeding study for 2,4- and 2,6-dimethylanilins, and a 5 to 20-day study for 2,4- and 2,6-dimethylanilines in rats. The toxic effects of dimethylanilines in these studies were closely comparable.

The most general target for dimethylanilines was the blood. Increased methemoglobin resulted in hemolysis, reduction of hemoglobin and erythrocyte concentration and cyanosis at sufficiently high doses of 50 mg/kg bw/day for 2,6-, 2,3-, 2,5-, 3,4- and 3,5-dimethylanilines while hematological changes were observed at 10 mg/kg bw/day for 2,4-dimethylaniline (OECD TG 422 and 407). Hemosiderin deposition in the liver, kidney and spleen were similarly observed as a secondary effect to the loss of functional erythrocytes. Especially, hemosiderin deposition in the spleen was observed for 2,3-dimethylanin at 12 mg/kg bw/day (lowest dose) in females (OECD TG 422). Extramedullary haematopoiesis, increased size of erythrocytes and swelling of the spleen occurred as compensatory actions. Additionally, the hemolysis led to changes in other blood parameters like WBC count, or increase of reticulocytes (OECD TG 422 and 407). In the NTP study for 2,6-dimethylaniline, toxic effects occurred in the hematopoietic systems at ≥40 mg/kg bw/day (13-week) and ≥ 310 mg/kg (2-week); however, male rats are more sensitive than female rats for effects on the hematopoietic systems. In the NTP study (2-year), body weight gains and survival were decreased at the high dose, but no indicative anemia was observed in rats fed 2,6-dimethylaniline.

Also, high urine volumes along with a decrease of the specific density, reduced pH and reduction of urinary levels of protein and ketone bodies generally occurred in treated with any category substances, generally at high doses (TG 422 and 407).

Effects on the kidney such as papillary necrosis, dilatation of renal tubules, and/or hyaline droplets were observed at 10 mg/kg bw/day in animals treated with 2,4-dimethylaniline, at 50 or 60 mg/kg bw/day in animals treated with 2,3-, 2,5- or 3,4-dimethylanilines, and at 250 or 360 mg/kg bw/day (highest dose) in animals treated with 2,6- or 3,5-dimethylanilines (OECD TG 422 and 407). 2,4-Dimethylaniline also showed stronger renal effects comparing to 2,6-dimethylaniline dosing (6-month feeding study).

There were increased relative and/or absolute weights of the liver (enlarged liver) or hypertrophy at 10 mg/kg bw/day in animal treated with 2,4- dimethylaniline, at 50 or 60 mg/kg bw/day in animals treated with 2,3-, 2,6-, 3,4- and 3,5-dimethylanilines, and at 300 mg/kg bw/day (highest dose) in animals treated with 2,5-dimethylaniline (OECD TG 422 and 407). In the NTP study for 2,6-dimethylaniline, toxic effects occurred in the hepatic systems (13-week). 2,4-Dimethylaniline showed stronger hepatic effects comparing to 2,5- and 2,6-dimethylanilines dosing (non-GLP 28-day study). This finding was also comparable with the 6-month feeding study, and more severe liver enlargement was observed in 2,4-dimethylaniline treatment (6-month feeding study). Similarly, 2,4-dimethylaniline showed hepatotoxicty after 5-20 days dosing at 117 mg/kg bw/day (25% of the estimated oral LD_{50}) while no hepatotoxity was observed at 157.5 mg/kg bw/day (25% of the estimated oral LD_{50}) after 20 days dosing of 2,6-dimethylaniline (5 to 20-day study).

Increased absolute or relative weights of the thyroid were observed at 250 or 360 mg/kg bw/day (highest dose) in animals treated with 2,6- or 3,5-dimethylanilines (OECD TG 422 and 407).

Hyperkeratosis of the forestomach was observed in rats treated with 2,4-, 2,5- or 2,6-dimethylanilines (non GLP 28-day study) and 2,4-dimethylanilines (6-month feeding study). 2,5-Dimethylaniline was the only isomer for which hyperkeratosis of the forestomach were reported in the 28-day studies (OECD TG 407). However, these effects may be due to local irritating effects of the chemicals.

The lowest NOAEL of 2 mg/kg bw/day was derived in 2,4-dimethylaniline due to effects on the blood, liver and kidneys at 10 mg/kg bw/day. The changes were usually fully recovered within a 2 week period except for the hemosiderin deposition and in some cases, the kidney necrosis. Nevertheless both of these effects are reduced in their severity during recovery (OECD TG 422 and 407).

The LOAEL of 2 mg/kg bw/day for 2,6-dimethylaniline in dogs was derived from a non-GLP 28-day study, in which dogs were dosed 2,4-, 2,5- or 2,6-dimethylanilines at 0, 2, 10 or 50 mg/kg bw/day, and fatty degeneration of the liver was observed at 2 mg/kg bw/day in the 2,6-dimethylaniline treatment. In contrast to rats, 2,6-dimethylaniline showed stronger toxicity comparing to 2,4- and 2,5-dimethylaniline in dogs.

Based on these effects, the NOAEL of repeated oral dose ranged between 2-12 mg/kg bw/day and the LOAEL of dimethylaniline category for repeated oral dose ranged between 10-60 mg/kg bw/day in rats. Target organ systems were the blood, spleen, liver and kidneys.

In bacterial reverse mutation assays with multiple strain of *S. typhimurium* and *E. coli* (OECD TG 471), 2,3-dimethylaniline and 2,4-dimethylaniline were found to be mutagenic in TA100 and 2,6-dimethylaniline in TA100 and TA1535, both only with activation by S9 mix. On the other hand, one study by NTP showed negative results on 2,6-dimethylaniline with or without S9 mix. One bacterial reverse mutation study conducted for all six isomers showed positive results on 2,3-, 2,4-, 2,5-, and 3,4-dimethylanilines with rat or hamster S9 mix while 2,6- and 3,5-dimethylanilines were judged weakly mutagenic with rat or hamster S9 mix. In *in vitro* chromosome aberration studies (TG 473), 2,3-dimethylaniline, 2,4-dimethylaniline and 3,5-dimethylaniline showed chromosomal aberrations while 3,4-dimethylaniline did not with or without S9 mix. 2,6-Dimethylaniline induced chromosomal aberrations (TG 473) and sister chromatid exchanges in mammalian cells *in vitro* with and without S9 mix. In addition, a BALB/c-3T3 cell transformation assay showed a positive response by 2,6-dimethylaniline.

In *in vivo* gene mutation assays with Muta^{TM} mice (nasal tissue, bone marrow and liver), 2,5- and 2,6-dimethylanilines increased mutation frequency of lacZ and cII genes in the nasal tissue, and 2,5-dimethylaniline also increased mutation frequency of lacZ gene in the bone marrow. On the other hand, 3,5-dimethylaniline showed a negative result in the *in vivo* gene mutation assay. In *in vivo* micronucleus assays, all six isomers of dimethylanilines was non-clastogenic in the bone marrow and 2,5-, 2,6- or 3,5-dimethylaniline in the peripheral blood in mice. 2,6-Dimethylaniline did not affect DNA repair in a DNA repair host-mediated assay or an unscheduled DNA synthesis assay *in vivo*. In SCG (Comet) assays *in vivo*, all six isomers of dimethylanilines induced DNA damage in the bone marrow (only for 3,4- and 3,5-dimethylanilines), lung, kidney or liver in mice.

In summary, the results from the available studies suggested that members of dimethylaniline category are mutagenic *in vitro* and *in vivo*.

In a 2-year carcinogenicity study, male and female rats were fed diets containing 0, 300, 1000 or 3000 ppm 2,6-dimethylaniline from 5 weeks of age and mated at 16 weeks of age. Females continued to receive dosed or control diets during pregnancy and lactation. The offspring were weaned at 21 days of age and groups of males and females (56/sex/group) were fed the same study diets as their parents. There were significant increases in the incidences of adenocarcinomas or carcinomas of the nasal cavity (28/56 high dose males, 24/56 high dose females and 1/56 mid dose females) and of the papillary adenomas (10/56 high dose males, 2/56 mid dose males, and 6/56 high dose females). A rhabdomyosarcoma, a rare tumour of the nasal cavity, was observed in dosed rats of each sex. In addition, the increased incidences of subcutaneous fibromas and fibrosarcomas in male and female rats and the increased incidence of neoplastic nodules of the liver in female rats may have been related to the administration of 2,6-dimethylaniline. In a two-stage nasal carcinogenesis model using male rats, the tumour-promoting activity of 2,6-dimethylaniline was evidenced. Another carcinogenicity study demonstrated that 2,4-dimethylaniline induced pulmonary tumours in female mice, and 2,5-dimethylaniline led to an increase in subcutaneous fibromas and fibrosarcoma in male rats, and in vascular tumours in male mice. It can be predicted that all members of the category may be carcinogenic due to their *in vivo* genotoxic activity.

Information on reproductive toxicity in animals is only available for 2,6-dimethylaniline. In the combined repeated dose toxicity study with reproduction/developmental toxicity screening test [OECD TG 422] described above, rats were administered 2,6-dimethylaniline by gavage at 0 (vehicle), 2, 10, 50 or 250 mg/kg bw/day. The males exhibited no alterations in reproductive parameters. At 250 mg/kg bw/day, the number of implantation sites in females was significantly lower than controls. The numbers of corpora lutea decreased with increasing dose, but the changes were not significant. There was a decrease in the numbers of pups born as the dose increased, however the decrease was not significant at any dose. There was a significant decrease in the total number of live pups on day 0 of lactation at 250 mg/kg bw/day. The NOAEL for reproductive performance of parental animals in this study was 250 mg/kg bw/day for males and 50 mg/kg bw/day for females based on a decrease in the number of implantation. The NOAEL for offspring was 50 mg/kg bw/day. However the effects were only observed in the presence of severe maternal toxicity (e.g. mortalilty). In the above described repeated dose toxicity studies, reproductive organ were not affected (organ weight and histopathological examinations) in males and females up to highest dose tested. A read-across approach on reproductive/developmental toxicity can be used for the other dimethylanilines.

Category dimethylaniline may have properties that are hazardous for human health (acute toxicity, skin and eye irritation, repeated-dose toxicity, genotoxicity and carcinogenicity). Adequate screening data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

All category members are not expected to undergo hydrolysis in the environment due to the lack of hydrolysable functional groups. A hydrolysis test [OECD TG 111] for 2,6-dimethylaniline showed no hydrolysis at pH4, pH7

and pH9 at 50 °C for 5 days.

In the atmosphere, indirect photo-oxidation for 2,3-dimethylaniline, 2,4-dimethylaniline, 2,5-dimethylaniline, 2,6-dimethylaniline, 3,4-dimethylaniline and 3,5-dimethylaniline by reaction with hydroxyl radicals are predicted to occur with a half-life of 0.053, 0.066, 0.053, 0.066, 0.053 and 0.053 days, respectively.

Ready biodegradation tests [OECD TG 301C] for 2,3-dimethylaniline, 2,5-dimethylaniline, 2,6-dimethylaniline and 3,5-dimethylaniline resulted in 3, 1, 0 and 3 % biodegradation after 28 days, respectively. Inherent biodegradation test [OECD TG 302C] for 2,4-dimethylaniline and 3,4-dimethylaniline resulted in 0 and 7 % biodegradation after two weeks, respectively. All category member substances are not readily biodegradable under aerobic conditions.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that 2,3-dimethylaniline will distribute mainly to the soil (77.9 %) and water (21.7%) compartments with minor distribution to the sediments compartment (0.24%) and negligible amount in the air compartment (0.07%). If released only to the water compartment, 2,3-dimethylaniline stays in the water compartment (98.9%) with negligible amounts in other compartments. A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments for other category member substances showed the same distribution as 2,3-dimethylaniline.

Henry's law constant values calculated with vapour pressure divided by water solubility are 0.18-1.1 Pa.m3/mole at 20-25°C, which suggests that volatilization of category member substances from water phase is not expected to be high. A log K_{oc} of 1.8-2.0 was estimated for category member substances based on the log K_{ow} and this figure indicates a low sorption to soil and sediment. However, aromatic amines have high affinity for soil organic matter due to the high reactivity of the aromatic amine group. Therefore, dimethylamines have a low mobility in soils.

Bioaccumulation potential for 2,3-dimethylaniline and 3,5-dimethylaniline are predicted to be low based on a BCF value of 7.6 and 7.5 estimated with BCFWIN (version 3.01), respectively. 2,4-Dimethylaniline, 2,5-dimethylaniline, 2,6-dimethylaniline and 3,4-dimethylaniline are not expected to bioaccumulate in the aquatic environment based on a measured bioconcentration factor of <10, <3.8, 2.4 and <10, respectively. These results show a low potential for bioaccumulation of dimethylanilines for aquatic organisms.

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

2,3-Dimethylaniline

Fish [*Oryzias latipes*]: 96 h LC_{50} > 94 mg/L (measured) [OECD TG 203, semi-static]

Invertebrate [*Daphnia magna*]: 48 h EC_{50} = 8.9 mg/L (measured) [OECD TG 202, static]

Algae [*Pseudokirchneriella subcapitata*]: 72 h ErC_{50} = 41.4 mg/L (growth rate method) (measured) [OECD TG 201, static]

2,4-Dimethylaniline

Fish: No reliable studies were identified. The predicted 96-hour LC_{50}, based on read across from 3,5-dimethylaniline = 33.9 mg/L; The predicted 96-hour LC_{50}, based on ECOSAR (v 1.11) = 37.2 mg/L

Invertebrate [*Daphnia magna*]: 48 h EC_{50} = 9.9 mg/L [DIN38412, static]

Algae: No reliable studies were identified. The predicted 72-hour EC_{50}, based on read across from 3,4-dimethylaniline = 8.59 mg/L; The predicted 96-hour EC50, based on ECOSAR (v 1.11) = 37.0mg/L

2,5-Dimethylaniline

Fish [*Oryzias latipes*]: 96 h LC_{50} > 110 mg/L (measured) [Other Guideline; Chemical Substances Control Law, Japan, semi-static]

Invertebrate [*Daphnia magna*]: 48 h EC_{50} = 18 mg/L (measured) [Other Guideline; Chemical Substances Control Law, Japan, static]

Algae [*Pseudokirchneriella subcapitata*]: 72 h ErC_{50} = 30 mg/L (growth rate method) (measured) [Other Guideline; Chemical Substances Control Law, static]

2,6-Dimethylaniline

Fish [*Oryzias latipes*]:	96 h LC_{50} > 97.9 mg/L (measured) [OECD TG 203, semi-static, limit test]
Invertebrate [*Daphnia magna*]:	48 h EC_{50} = 20 mg/L (measured) [OECD TG 202, static]
Algae [*Pseudokirchneriella subcapitata*]:	72 h ErC_{50} > 100 mg/L (growth rate method) (nominal) [OECD TG 201, static]

<u>3,4-Dimethylaniline</u>

Fish [*Oryzias latipes*]:	96 h LC_{50} > 97.9 mg/L (measured) [Other Guideline; Chemical Substances Control Law, Japan, semi-static]
Invertebrate [*Daphnia magna*]:	48 h EC_{50} = 1.09 mg/L (measured) [Other Guideline; Chemical Substances Control Law, Japan, static]
Algae [*Pseudokirchneriella subcapitata*]:	72 h ErC_{50} = 8.59 mg/L (growth rate method) (measured) [Other Guideline; Chemical Substances Control Law, static]

<u>3,5-Dimethylaniline</u>

Fish [*Oryzias latipes*]:	96 h LC_{50} = 33.9 mg/L (measured) [OECD TG 203, semi-static]
Invertebrate [*Daphnia magna*]:	48 h EC_{50} = 2.2 mg/L (nominal) [OECD TG 202, static]
Algae [*Pseudokirchneriella subcapitata*]:	72 h ErC_{50} = 29.1 mg/L (growth rate method) (nominal) [OECD TG 201, static]

The following chronic toxicity test results have been determined:

<u>2,3-Dimethylaniline</u>

Invertebrate [*Daphnia magna*]:	21 d NOEC = 0.1 mg/L (measured) [Provisional procedure proposed by Federal Environmental Agency (Umweltbundesamt), semi-static]
Algae [*Pseudokirchneriella subcapitata*]:	72 h NOEC = 4.32 mg/L (growth rate method) (measured) [OECD TG 201, static]

<u>2,4-Dimethylaniline</u>

Invertebrate:	No reliable studies were identified. The predicted 21 d NOEC, based on read across from 3,4-dimethylaniline = 0.0095 mg/L
Algae:	No reliable studies were identified. The predicted 72 h NOEC, based on read across from 2,5-dimethylaniline = 2.03 mg/L

<u>2,5-Dimethylaniline</u>

Invertebrate [*Daphnia magna*]:	21 d NOEC = 0.096 mg/L (measured) [OECD TG 211, semi-static]
Algae [*Pseudokirchneriella subcapitata*]:	72 h NOEC = 2.0 mg/L (growth rate method) (measured) [OECD TG 201, static]

<u>2,6-Dimethylaniline</u>

Invertebrate [*Daphnia magna*]:	21 d NOEC = 2.23 mg/L (measured) [OECD TG 211, semi-static]
Algae [*Pseudokirchneriella subcapitata*]:	72 h NOEC = 32 mg/L (growth rate method) (nominal) [OECD TG 201, static]

<u>3,4-Dimethylaniline</u>

Invertebrate [*Daphnia magna*]:	21 d NOEC = 0.0095 mg/L (measured) [OECD TG 211, semi-static]
Algae [*Pseudokirchneriella subcapitata*]:	72 h NOEC = 2.94 mg/L (growth rate method) (measured) [Other Guideline; Chemical Substances Control Law, Japan, static]

3,5-Dimethylaniline

Invertebrate [*Daphnia magna*]: 21 d NOEC = 0.03 mg/L (nominal) [OECD TG 211, semi-static]

Algae [*Pseudokirchneriella subcapitata*]: 72 h NOEC = 5.8 mg/L (growth rate method) (nominal) [OECD TG 201, static]

Acute aquatic toxicity data were available for category members except fish and algae tests on 2,4-dimethylaniline. For fish, LC_{50} values were generally greater than 100 mg/L except 3,5-dimethylaniline (33.9 mg/L). For daphnids, EC_{50} values were between 1.09 and 25 mg/L. For algae, EC_{50} values were between 8.59 and >100 mg/L.

No chronic toxicity data are available on fish. Chronic aquatic toxicity data on daphnids and algae were available for category member substances except 2,4-dimethylaniline. For daphnids, NOEC values were generally less than 0.1 mg/L except 2,6-dimethylaniline (2.23 mg/L). For algae, NOEC values were generally less than 10 mg/L except 2,6-dimethylaniline (32 mg/L).

Chemicals in the category dimethylaniline possess properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L; chronic aquatic toxicity less than 1.0 mg/L). Chemicals in the category are not readily biodegradable and have a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

2,3-Dimethylaniline

Volume of import into Japan was 30 – 40 tonnes/year around 2005.

2,4-Dimethylaniline

Total volume of production and import in Japan was 512 tonnes in fiscal year of 2009 according to the notification based on the Chemical Substances Control Law in Japan. Production and/or import volume on 2,4-dimethylaniline in USA was 500,000 pounds – 1 million pounds (226.8 tonnes – 453.6 tonnes) in 2006 according to IUR information by US-EPA.

2,5-Dimethylaniline

No detailed information is obtained on the production and import volume in Japan. Production and/or import volume on 2,5-dimethylaniline in USA was less than 500,000 pounds (226.8 tonnes) in 2006 according to IUR information by US EPA.

2,6-Dimethylaniline

According to the notification based on the Chemical Substances Control Law in Japan, total volume of production and import on this chemical in fiscal year 2009 was less than 100 tonnes. Production and/or import volume of 2,6-dimethylaniline in USA was less than 500,000 pounds (226.8 tonnes) in 2006 according to IUR information by US-EPA.

3,4- Dimethylaniline, 3,5-Dimethylaniline

According to the notification based on the Chemical Substances Control Law in Japan, total volume of production and import on 3,5-dimethylaniline in fiscal year 2009 was less than 100 tonnes.

According to the results of the environmental survey and wildlife monitoring and PRTR data in Japan, the release of dimethylanilines to the environment from its manufacturing and formulation plants is minimal.

According to the inquiry survey, employees in the processing site of 2,4-dimethylaniline in a Japanese company wear gloves, protective goggles and other proper protect equipments. Therefore, occupational exposure is thought to be minimal.

All category member substances are used mainly as intermediates for the production of dyes, pigments, pharmaceuticals and agrochemicals. Some are used as intermediate for photographic chemicals, antioxidants, synthetic resins, fragrances and riboflavin. Therefore, consumer exposure is not expected.