付録 IV

三つのデータセット(Vitic Nexus、Leadscope FDA Genetox データ、および、NIHS により提供された Kirkland データセットの一部)の組み合わせの中の少なくとも一つの陽性化合物がヒットした in vitro 染色体異常アラートに対する in vivo 染色体異常の陽性予測率

アラート番号	アラート名	陽性 [a]	陰性 [b]	陽性予測率 [c] (%)
007	N-Nitro or N-nitroso compound	8	7	53
019	Epoxide	9	6	60
023	vic-Dihalide	2	7	22
027	Alkylating agent	20	41	33
028	Mono- or di-alkylhydrazine	3	1	75
033	Hydrazine or monoacyl- or monosulphonyl-hydrazine	1	1	50
051	Azirine or aziridine	7	0	100
069	Nitrogen or sulphur mustard	7	1	88
306	Alkyl aldehyde or precursor	7	13	35
308	Alkyl carbamate	3	5	38
309	alpha,beta-Unsaturated ketone	5	12	29
314	Thiuram disulphide or dithiocarbamate	1	3	25
323	Aryldialkyltriazene	1	0	100
328	Halogenated methane	1	8	11
329	Aromatic nitro compound	11	38	22
334	Alkyl nitrite, nitrous acid or nitrite salt	2	0	100
339	Polycyclic aromatic hydrocarbon or hetero-analogue	5	1	83
341	Pyrroline ester, pyrroline N-oxide ester, pyrrole ester or pyrrole alcohol	1	2	33
362	Vinyl carbamate	1	0	100
470	Phenol	2	1	67
516	Triarylmethane salt	1	2	33
517	2,4-Diaminopyrimidine or analogue	2	1	67

521	N-Polyhaloalkylthio compound	1	0	100
529	Xanthine	1	0	100
577	Purine base	8	3	73
578	5-Fluoropyrimidine	1	1	50
580	Aryl N-alkylcarbamate	2	2	50
585	Indole or benzotriazole	2	3	40
625	Catechol	1	15	6
626	Aromatic hydrocarbon	1	3	25
627	Inorganic cadmium compound	1	0	100
642	Bisdioxopiperazine	1	0	100
674	Allylbenzene	1	2	33

(a): in vivo 細胞遺伝学的試験において総合的に陽性であった化合物の個数; (b): in vivo 細胞遺伝学的試験において総合的に陰性であった化合物の個数; (c): 陽性予測率 = 陽性化合物数 / (陽性化合物数 + 陰性化合物数). 背景色が付けられたアラートは、拡張候補とされたアラート。

付録 V

DfW13 NIHS 020211_1 に実装された in vivo 染色体異常アラート

In Vivo 染色体異常	アラート番号	アラート名
拡張された in vivo 染色体異常アラート (関連する reasoning rule が付属)	028	Mono- or di-alkylhydrazine
	051	Azirine or aziridine
	069	Nitrogen or sulphur mustard
	470	Phenol
	627	Inorganic cadmium compound
in vivo 染色体異常に関連 – in vivo 染色体異常データがアラートに追加された。	517	2,4-Diaminopyrimidine or analogue
新規 in vivo 染色体異常アラート	719	Polycyclic aromatic hydrocarbon or hetero-analogue

ジメチルアニリンの構造異性体における物理化学的性状の情報収集に関する調査

研究目的

既存化学物質の物理化学的性質及び分解性・蓄積性試験結果に基づいて構造分類を行うために、各種の毒性データを収集し、翻訳整理すると共に、カテゴリー分類のための基礎的研究を行う。

研究方法

ジメチルアニリンの構造異性体における物理化学的性状に関し、文献調査を行うとともに、必要に応じて構造活性相関手法を用いて推定を行った。これらの結果より、ジメチルアニリンの構造異性体に関し、カテゴリーとしての評価の妥当性を検討した。これらの結果を基に、SIAP、SIAR 及び IUCLID Dossier を作成した。

調査対象物質

今回の調査における対象物質を以下に示す。

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

研究結果

上記 6 物質は、3,4-ジメチルアニリンを除いて、常温で液体であり、互いに非常に近い物理化学的性状を示していた。また、アニリンに二つのメチル基が連結すると云う、互いに類似した構造を示している。これらのことより、ジメチルアニリン異性体 6 物質をカテゴリーとして評価することは妥当であると考えられた。調査により得られた物理化学的性状値を経済協力開発機構の高生産量既存化学物質点検プログラムにおける SIAP、SIAR 及び IUCLID Dssier としてまとめた。これらの書類を付録に添付する。

添付資料

添付資料１　ジメチルアニリン異性体 6 物質カテゴリーの SIAP
添付資料２　ジメチルアニリン異性体 6 物質カテゴリーの SIAR

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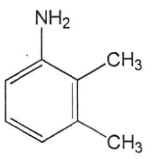
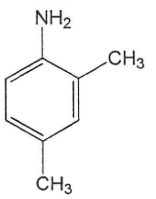
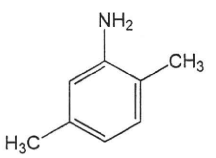
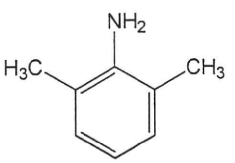
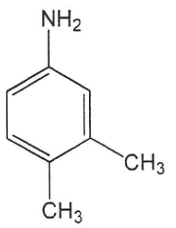
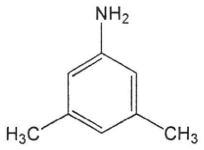
知的所有権の取得状況

(該当なし)

添付資料 1

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/analogue rationale

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).

Based on the sameness of basic molecular structures, which is direct connection of one methyl functional group ($-CH_3$) and two amino functional groups ($-NH_3$) to a benzene-ring, all physical-chemical properties are very close in this category. This sameness of basic molecular structure enables the category assessment.

Physical-chemical properties

All category member substances are liquid at standard temperature and pressure except for 3,4-dimethylaniline. The melting points are in the range of <-15 °C – 15.5 °C on 2,3-, 2,4-, 2,5-, 2,6- and 3,5-isomers, although 3,4-isomer has 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 2.5-6.6 g/L at 20/25 °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 4.72-5.14 at 20/25 °C, which means the member substances exist in un-dissociated form in environmental water. According to the close molecular structure, no remarkable differences are observed in the field of physical-chemical properties except for the melting point of 3,4-dimethylaniline.

Human Health

Environment

Exposure

Production volume

2,3-dimethylaniline

Volume of import into Japan was 30 tons/year – 40 tons/year around 2005. It is though that most of them is import.

2,4-dimethylaniline

Total volume of production and import in Japan was 512 tons 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 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 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 tons. Production and/or import volume of 2,5-dimethylaniline in USA was less than 500,000 pounds 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 tons.

添付資料２

COVER PAGE

SIDS Initial Assessment Report

For

SIAM XX

City name, Country name, Date Month, Year

1. Chemical Name:	Dimethylaniline Category
2. CAS Number:	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
3. Sponsor Country:	Japan Contact Point: Mr. Hiroshi Kamitsuji Deputy Director OECD Division Ministry of Foreign Affairs, Japan
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners: • Name of industry sponsor /consortium	
• Process used	
6. Sponsorship History • How was the chemical or category brought into the	Dimethylaniline Category is sponsored by Japan and is submitted for first discussion at SIAM XX.
7. Review Process Prior to the SIAM:	Japanese government peer-reviewed the documents and audited selected studies.
8. Quality check process:	Japanese government peer-review committee performed spot checks on randomly selected endpoints and compared original studies with data in the SIDS Dossier.
9. Date of Submission:	Date, Month, Year
10. Date of last Update:	Date, Month, Year
11. Comments:	

CONTENTS

Tables

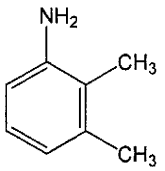
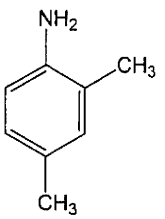
SIDS Initial Assessment Report

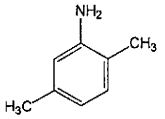
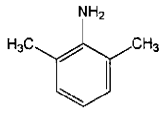
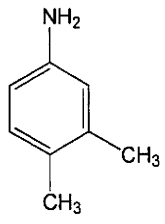
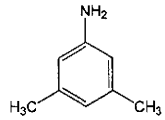
1 IDENTITY

1.1 Identification of chemicals

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). The chemical identifiers of the dimethylaniline category members are displayed in Table 1.

Table 1: Identification of the Substance

CAS Number	IUPAC Name	Molecular Formula	Structural Formula	Molecular Weight	Synonyms
87-59-2	2,3-Dimethylaniline	$C_8H_{11}N$		121.18	2,3-Dimethylbenzenamine 2,3-Dimethylphenylamine 2,3-Xylylamine 2,3-Xylidine *o*-Xylidine 1-Amino-2,3-dimethylbenzene 3-Amino-*o*-xylene Benzeneamine, 2,3-dimethyl- Benzene, 1-amino-2,3-dimetyl-
95-68-1	2,4-Dimethylaniline	$C_8H_{11}N$		121.18	2,4-Dimethylbenzenamine 2,4-Dimethylphenylamine 2,4-Xylylamine 2,4-Xylidine *m*-Xylidine 1-Amino-2,4-dimethylbenzene 4-Amino-1,3-dimethylbenzene 4-Amino-3-methyltoluene 4-Amino-1,3-xylene Aniline, 2,4-dimethyl- Benzeneamine, 2,4-dimethyl- 4-Methyl-*o*-toluidine 2-Methyl-*p*-toluidine *m*-Xylidine *m*-4-Xylieine

95-78-3	2,5-Dimethylaniline	$C_8H_{11}N$		121.18	2,5-Dimethylbenzenamine 2,5-Dimethylphenylamine 2,5-Xylylamine 2,5-Xylidine *p*-Xylidine 1-Amino-2,5-dimethylbenzene 3-Amino-1,4-dimethylbenzene 5-Amino-1,4-dimethylbenzene 2-Amino-1,4-xylene Aniline, 2,5-dimethyl- Benzeneamine, 2,5-dimethyl- Benzene, 2-amino-1,4-dimethyl- 6-Methyl-*m*-toluidine 5-Methyl-*o*-toluidine
87-62-7	2,6-Dimethylaniline	$C_8H_{11}N$		121.18	2,6-Dimethylbenzenamine 2,6-Dimethylphenylamine 2,6-Xylylamine 2,6-Xylidine 1-Amino-2,6-dimethylbenzene 2-Amino-1,3-dimethylbenzene 2-Amino-*m*-xylene 2-Amino-1,3-xylene Aniline, 2,6-dimethyl- Benzene, 2-amino-1,3-dimethyl- Benzene, 2-amino-1,3-dimethyl- *o*-xylidine
95-64-7	3,4-Dimethylaniline	$C_8H_{11}N$		121.18	3,4-Dimethylbenzenamine 3,4-Dimethylphenylamine 3,4-Xylylamine 3,4-Xylidine 1-Amino-3,4-dimethylbenzene 4-Amino-1,2-dimethylbenzene Benzenamine, 3,4-dimethyl- Benzene, 4-amino-1,2-dimethyl- 3,4-Dimethylaminobenzene
108-69-0	3,5-Dimethylaniline	$C_8H_{11}N$		121.18	3,5-Dimethylbenzenamine 3,5-Dimethylphenylamine 3,5-Xylylamin 3,5-Xylidine 1-Amino-3,5-dimethylbenzene 5-Amino-1,3-dimethylbenzene 5-Amino-1,3-xylene Benzeneamine, 3,5-dimethyl- Benzene, 1-amino-3,5-dimethyl-

In addition to each CAS number, CAS number 1300-73-8 exists which covers the mixture of isomers.

1.2 Purity/Impurities/Additives

Purity of a typical commercial product of 2,6-dimethylaniline in Japan is more than 99 % and no additives is added [CERI (2002a)]. Purity of a typical commercial product of 3,4-dimethylaniline in Japan is more than 99 %, impurity is 2,3-dimethylaniline and no additives is added [CERI (2002b)]. There is no more information on the purity of the category member substances in Japan.

1.3 Physico-Chemical properties

Physico-chemical properties of category member substances are shown in the following tables. If no reliable data is obtained, computer-modeled data is used. All category member substances are liquid at standard temperature and pressure except for 3,4-dimethylaniline. Because of relatively high similarity of the molecular structures of the category member substances, all physical-chemical properties are very close in this category.

- Physical state/appearance

Physical state/appearance of the category member substances are shown in Table 2. All category member substances are liquid at standard temperature and pressure except for 3,4-dimethylaniline.

Table 2: Physical state/appearance of dimethylanilines

Substance	Value	Reliability	Reference
2,3-Dimethylaniline	Pale red-brown, transparent liquid	2	CERI, 1989a
2,4-Dimethylaniline	Liquid	2	Seidel A. (ed), 2004
2,5-Dimethylaniline	Colourless liquid	2	CERI, 1989b
2,6-Dimethylaniline	Colourless liquid	2	Seidel A. (ed), 2004
3,4-Dimethylaniline	Solid	2	Seidel A. (ed), 2004
3,5-Dimethylaniline	Orange-brown, transparent liquid	2	CERI, 1989c

- Melting point

Melting points of the category member substances are shown in Table 3. As melting point of 2,6-isomer is more than 25 °C, only this chemical is solid at the standard temperature in the category members.

Table 3: Melting point of dimethylanilines

Substance	Value	Reliability	Reference
2,3-Dimethylaniline	< -15 °C	2	Lide D.R. (ed), 2008
2,4-Dimethylaniline	-14.3 °C	2	Lide D.R. (ed), 2008
2,5-Dimethylaniline	15.5 °C	2	Lide D.R. (ed), 2008
2,6-Dimethylaniline	7.5 °C[1)]	1	CERI, 2003a
3,4-Dimethylaniline	51 °C	2	Lide D.R. (ed), 2008
3,5-Dimethylaniline	9.8 °C	2	Lide D.R. (ed), 2008

1) Test result according to OECD test-guideline 102 "Melting point: Differential scanning calorimetry" in compliance with GLP.

- Boiling point

Boiling points of the category member substances are shown in Table 4. All member substances have close values on boiling point.

Table 4: Boiling point of dimethylanilines

Substance	Value	Reliability	Reference
2,3-Dimethylaniline	221.5 °C	2	Lide D.R. (ed), 2008
2,4-Dimethylaniline	214 °C	2	Lide D.R. (ed), 2008
2,5-Dimethylaniline	214 °C	2	Lide D.R. (ed), 2008
2,6-Dimethylaniline	217.8 °C[1)]	1	CERI, 2003b
3,4-Dimethylaniline	228 °C	2	Lide D.R. (ed), 2008
3,5-Dimethylaniline	220.5 °C	2	Lide D.R. (ed), 2008

1) Test result according to OECD test-guideline 103 "Boiling point: Ebulliometer" in compliance with GLP.

- Density

Densitys of the category member substances are shown in Table 5.

Table 5: Density of dimethylanilines

Substance	Value	Reliability	Reference
2,3-Dimethylaniline	0.9931 g/cm^3 at 20 °C	2	Lide D.R. (ed), 2008
2,4-Dimethylaniline	0.9723 g/cm^3 at 20 °C	2	Lide D.R. (ed), 2008
2,5-Dimethylaniline	0.9790 g/cm^3 at 21 °C	2	Lide D.R. (ed), 2008
2,6-Dimethylaniline	0.9842 g/cm^3 at 20 °C	2	Lide D.R. (ed), 2008
3,4-Dimethylaniline	1.076 g/cm^3 at 18 °C	2	Lide D.R. (ed), 2008
3,5-Dimethylaniline	0.9706 g/cm^3 at 20 °C	2	Lide D.R. (ed), 2008

- Vapour pressure

Values of the vapour pressure of the category member substances are shown in Table 6. As vapour pressure of 3,5-dimethylamine is not obtained, an estimation value is used for this chemical.

Table 6: Vapour pressure of dimethylanilines

Substance	Value	Reliability	Reference
2,3-Dimethylaniline	10.0 Pa at 25 °C	2	Howard P.H. et al., 1997
2,4-Dimethylaniline	13.1 Pa at 25 °C[1)]	2	Lide D.R. (ed), 2008
2,5-Dimethylaniline	20.0 Pa at 20 °C	2	Howard P.H. et al., 1997
2,6-Dimethylaniline	63.2 Pa at 25 °C[2)]	1	CERI, 2003c
3,4-Dimethylaniline	3.72 Pa at 25 °C	2	Jayasinghe D.S. et al., 1992
3,5-Dimethylaniline	17 Pa at 25 °C by MPBPWIN[3)]	2	US EPA, 2008a

1) Vapour pressure at 25 °C is intra-porated from the vapour pressure at -2 °C, 21 °C, 51 °C, 88 °C, 139.1 °C and 210.9 °C.
2) Test result according to OECD test-guideline 104 "Vapour pressure: Static method" in compliance with GLP.
3) Calculation by MPBPWIN (version 1.43) with boiling point of 220.5 °C.

- Water solubility

Values of water solubility on the category member substances are shown in Table 7. As reliable data is not obtained on 2,4-isomer and 3,4-isomer, estimation values are used for these chemicals. The category member substances have relatively high water solubility in the order of g/L.

Table 7: Water solubility of dimethylanilines

Substance	Value	Reliability	Reference
2,3-Dimethylaniline	6.6 g/L at 25 °C[1)]	2	CERI, 1989a
2,4-Dimethylaniline	6.1 g/L at 25 °C by WSKOW[2)]	2	US EPA, 2008b
2,5-Dimethylaniline	5.6 g/L at 25 °C[3)]	2	CERI, 1989b
2,6-Dimethylaniline	6.98 g/L at 20 °C[4)]	1	CERI, 2003d
3,4-Dimethylaniline	2.5 g/L at 25 °C by WSKOW[5)]	2	US EPA, 2008b
3,5-Dimethylaniline	4.6 g/L at 25 °C[3)]	2	CERI, 1989c

1) Test result according to OECD test-guideline 105 "Water solubility: Flask method".
2) Calculation by WSKOW (version 1.41a) with melting point of -14.3 °C and log K_{ow} of 1.68.
3) Test result according to OECD test-guideline 105 "Water solubility: Flask method".
4) Test result according to OECD test-guideline 105 "Water solubility: Flask method" in compliance with GLP.
5) Calculation by WSKOW (version 1.41a) with melting point of 51 °C and log K_{ow} of 1.84.

- Partition coefficient between octanol and water

Values of the partition coefficient between octanol and water on the category member substances are shown in Table 8. All member substances have close values on partition coefficient between octanol and water.

Table 8: Partition coefficient between octanol and water of dimethylanilines

Substance	Value	Reliability	Reference
2,3-Dimethylaniline	Log K_{ow} = 1.84[1)]	1	CERI, 1989d
2,4-Dimethylaniline	Log K_{ow} =1.68	2	Hansch C. et al., 1995
2,5-Dimethylaniline	Log K_{ow} = 1.91[1)]	1	CERI, 1989e
2,6-Dimethylaniline	Log K_{ow} = 1.78[1)]	1	CERI, 2001a
3,4-Dimethylaniline	Log K_{ow} =1.84	2	Jayasinghe D.S. et al., 1992
3,5-Dimethylaniline	Log K_{ow} = 1.83[1)]	1	CERI, 1989f

1) Test result according to OECD test-guideline 105 "Partition coefficient: Shake flask method" in compliance with GLP.

- Soil adsorption coefficient

Values of the partition soil adsorption coefficient on the category member substances are shown in Table 9. As no data is available on this endpoint for the category member substances, estimation method with KOCWIN (version 2.00) with log K_{ow} value is used. Log K_{oc} values of 1.8 – 2.0 indicate that the category member substances have relatively low mobility in soil.

Estimation result of KOCWIN with molecular connectivity method does not distinguish the difference of the structure of the category member substances. In this estimation, all results of the soil adsorption coefficient (log K_{oc}) is 2.3.

Table 9: Soil adsorption coefficient of dimethylanilines

Substance	Value	Reliability	Reference
2,3-Dimethylaniline	Log K_{oc} = 1.9 by KOCWIN[1)]	2	US EPA, 2009
2,4-Dimethylaniline	Log K_{oc} = 1.8 by KOCWIN[2)]	2	US EPA, 2009
2,5-Dimethylaniline	Log K_{oc} = 2.0 by KOCWIN[3)]	2	US EPA, 2009
2,6-Dimethylaniline	Log K_{oc} = 1.9 by KOCWIN[4)]	2	US EPA, 2009
3,4-Dimethylaniline	Log K_{oc} = 1.9 by KOCWIN[5)]	2	US EPA, 2009
3,5-Dimethylaniline	Log K_{oc} = 1.9 by KOCWIN[6)]	2	US EPA, 2009

1) Calculation by KOCWIN (version 2.00) with log K_{ow} of 1.84.
2) Calculation by KOCWIN (version 2.00) with log K_{ow} of 1.68.
3) Calculation by KOCWIN (version 2.00) with log K_{ow} of 1.91.
4) Calculation by KOCWIN (version 2.00) with log K_{ow} of 1.78.
5) Calculation by KOCWIN (version 2.00) with log K_{ow} of 1.84.
6) Calculation by KOCWIN (version 2.00) with log K_{ow} of 1.83.

- Dissociation constant

Values of the dissociation constant on the category member substances are shown in Table 10. As the pK_a of the category member substances is about 4-5 at 20-25 °C in water, the member substances exist in un-dissociated form in environmental water.

Table 10: Dissociation constant t of dimethylanilines

Substance	Value	Reliability	Reference
2,3-Dimethylaniline	pK_a = 4.72 at 25 °C[1)]	2	CERI, 1989g
2,4-Dimethylaniline	pK_a = 4.89 at 25 °C	2	Speight J.G., 2005
2,5-Dimethylaniline	pK_a = 4.51 at 25 °C[1)]	2	CERI, 1989h
2,6-Dimethylaniline	pK_a = 4.02 at 20 °C[2)]	1	CERI, 2003e
3,4-Dimethylaniline	pK_a = 5.17 at 25 °C	2	Speight J.G., 2005
3,5-Dimethylaniline	pK_a = 4.84 at 25 °C[1)]	2	CERI, 1989i

1) Test result according to OECD test-guideline 112 "Dissociation constants in water: titration method".
2) Test result according to OECD test-guideline 112 "Dissociation constants in water: Spectro-photometric method" in compliance with GLP.