FOREWORD INTRODUCTION

p-Toluidine

CAS N°: 106-49-0

SIDS Initial Assessment Report

For

SIAM 21

Washington, DC, 18–21 October 2005

1. Chemical Name:	**p-Toluidine**
2. CAS Number:	**106-49-0**
3. Sponsor Country:	Germany Contact Point: BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Postfach 12 06 29 D- 53048 Bonn
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	Bayer AG, Germany Contact person: Dr. Burkhardt Stock D-51368 Leverkusen Building 9115
• Process used	The BUA Peer Review Process : see next page
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme?	by ICCA-Initiative
7. Review Process Prior to the SIAM:	last literature search (update): 14 April 2004 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms 26 March 2004 (Ecotoxicology): databases CA, biosis; search profile CAS-No. and special search terms OECD/ICCA
8. Quality check process:	IUCLID was used as a basis for the SIDS dossier. All data were checked and validated by BUA. A final evaluation of the human health part has been performed by the Federal Institute for Risk Assessment (BfR) and of the ecotoxicological part by the Federal Environment Agency (UBA).
9. Date of Submission:	Deadline for circulation: 22 July 2005
10. Date of last Update:	Last literature search: IUCLID Chapters 1-4: 2003-08-26, Chapter 5: 2004-01-02

11. Comments:

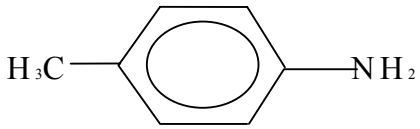
OECD/ICCA - The BUA* Peer Review Process

Qualified BUA personnel (toxicologists, ecotoxicologists) perform a quality control on the full SIDS dossier submitted by industry. This quality control process follows internal BUA guidelines/ instructions for the OECD/ICCA peer review process and includes:

- a full (or update) literature search to verify completeness of data provided by industry in the IUCLID/HEDSET
- Review of data and assessment of the quality of data
- Review of data evaluation
- Check of adequacy of selection process for key studies for OECD endpoints, and, where relevant, for non-OECD endpoints by checking original reports/publications
- Review of key study description according to robust summary requirements; completeness and correctness is checked against original reports/publications (if original reports are missing: reliability (4), i.e. reliability not assignable)
- Review of validity of structure-activity relationships
- Review of full SIDS dossier (including SIAR, SIAP and proposal for conclusion and recommendation for further work)
- In case of data gaps, review of testing plan or rationale for not testing

* BUA (GDCh-Beratergremium für Altstoffe): Advisory Committee on Existing Chemicals of the Association of German Chemists (GDCh)

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	106-49-0
Chemical Name	p-Toluidine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There are no specific studies available which evaluate the possible potential of p-toluidine to affect fertility or to cause developmental toxicity. Information from m-toluidine is used to fill the data gap. Therefore the SIAR contains a short comparison of p-toluidine and m-toluidine for all endpoints. The isomer m-toluidine was already discussed and concluded in SIAM 11, 2001; the data are published by UNEP in 2003. A comparison of the intrinsic toxicological properties of m-toluidine with these properties of p-toluidine showed that m-toluidine is more potent in methemoglobin forming than the p-isomer. Taking into account that methemoglobinemia in pregnant rats is causally linked to developmental toxicity it can be assumed that extrapolation of the results with m-toluidine to p-toluidine would imply a tendency to lead to an overestimation of the developmental toxicity of p-toluidine. Furthermore developmental toxicity data from the structurally related p-isopropylaniline were included in the assessment. This seems to be justified due to the structural similarity of both substances as both aniline derivatives have substituents in para position of nearly the same influence on the reactivity of the respective molecule. This could be demonstrated with the data on acute toxicity as well as with repeated toxicity data. For all three substances methemoglobinemia and/or erythrocyte toxicity seem to be the most relevant mechanism for systemic toxicity. In addition, with respect to mutagenicity, the comparison of results of the respective tests with these substances demonstrates the inconsistency, which is typical for aromatic amines.

p-Toluidine is absorbed via gastrointestinal tract and is distributed, metabolized and excreted via urine and feces. The identification of 2-amino-5-methylphenol indicates that the metabolism in rat proceeds through ring hydroxylation with subsequent conjugation. There are no specific toxicokinetic data on absorption via skin and respiratory tract; absorption via these administration routes can be reasonably be predicted due to the molecular size of p-toluidine.
m-Toluidine (SIAM 11) is rapidly absorbed via gastrointestinal tract, via skin and is metabolized by ring hydroxylation. Although 2-amino-4-methyl-phenol and 4-amino-2-methylphenol were identified in the rat urine with a small amount of the parent compound, there is no sufficient information on quantitative metabolism of m-toluidine or on toxicokinetics. **Overall conclusion:** Both isomers, p- and m-toluidine are absorbed via gastrointestinal tract and via skin and distributed. They are metabolized by ring hydroxylation with subsequent conjugation and excreted via urine and feces.
For **p-toluidine**, the LC_{50} (inhalative, rat) is > 0.64 mg/l, and LD_{50} (dermal, rabbit) is 890 mg/kg bw. LD_{50} (oral, rat) was determined 656 mg/kg bw and 620 mg/kg bw. Signs of intoxication include hypoactivity, muscular weakness, convulsions, cyanosis and narcosis. p-Toluidine is a methemoglobin forming chemical in rats. Levels up to 21.7 % following oral application to rats and up to 40 % following dermal application to rats were measured. p-Toluidine is a methemoglobin forming chemical in humans as it produces the same toxic effects as aniline from 22 mg/m³ onwards with less cyanosis but more stranguria and hemoglobinuria.
For **m-toluidine**, LD_{50} values are from 450 to 1430 mg/kg bw by oral route to rats and 3250 mg/kg bw by dermal route to rabbits (no information on study quality available). Severe methemoglobin formation is reported

following single exposure to m-toluidine ranging up to 36.4 % in rats after oral application and 40 % in rats after dermal application (these data as well as those given above for p-toluidine are derived from a study which examined the methemoglobin formation of m- and p-toluidine in parallel) and up to 60.2 % in cats (i.v.). For **p-isopropylaniline,** LD_{50} values of 985 mg/kg bw and 757 mg/kg bw were reported of rats following single oral application. Single oral application of 25 mg/kg bw to cats resulted in elevated methemoglobin level and an increase in Heinz bodies. **Overall conclusion:** Based on the available data, p- and m-toluidine are of moderate acute toxicity. Main toxic signs result from the methemoglobin formation in rats as well as in humans. m-Toluidine is considerably more active in methemoglobin formation than p-toluidine when tested at equal dosages and under similar experimental conditions. p-Isopropylaniline led to an increase in methemoglobin after oral application of 25 mg/kg bw to cats (no quantitative data available).

p-Toluidine causes irritation to the eyes of rabbits which recovered within 7 days. No irritational effects were observed when applied to the rabbit's ear for 24 hours under occlusive conditions. **p-Toluidine** is a sensitizer by skin contact as shown in a patch test with guinea pigs. There is no valid human data available.

There are no adequate repeated dose toxicity studies available for **p-toluidine**. There are a number of limited studies sufficient to support a weight of evidence approach. Limitations include documentation of the experiments in general, number of animals under test, treatment time as well as the lack of necessary investigations. Nevertheless, the overall weight of evidence indicates low systemic toxicity with liver and blood as target organs. Based on increased liver to body weight ratio in the available subacute feeding study a NOAEL of 165 ppm (corresponding to 13.8 mg/kg bw/day) can be derived for rats. In studies over a period of 6 months dose-related (40 - 160 mg/kg bw/day) increases in methemoglobin level up to ≥ 10 % are reported for rats. In addition, it is demonstrated that prolongation of treatment time up to 12 months does not result in further increase in methemoglobin levels in rats. Treatment of rats and mice with p-toluidine in feed for 18 months resulted in a NOAEL (systemic toxicity) of 2000 ppm in rats (highest dose tested, approximately 150 mg/kg bw/day). In mice treated with 500 ppm (approximately 75 mg/kg bw/day) no influence on body weight and/or mortality rate was reported, however hepatomas occurred in males.
With **m-toluidine** there has been reported a valid combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD TG 422 on rats with gavage application of the structurally closely related isomer m-toluidine which has been assessed during OECD-ICCA SIAM 11 in 2001. In this study m-toluidine leads to deposit pigmentations and extramedullary hematopoiesis in spleen starting already at the lowest dose of 30 mg/kg bw/day representing the LOAEL. There are sufficient evidences that this chemical induces methemoglobinemia, but methemoglobin content was not determined in this study.
With **p-isopropylaniline** there has been reported a valid combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD TG 422 on rats with gavage application resulting in a NOEL (systemic toxicity) of 6 mg/kg bw/day based on erythrocyte toxicity including secondary effects. **Overall conclusion:** Following repeated dosing both toluidine isomers as well as p-isopropylaniline reveal as main targets the erythrocytes (methemoglobin formation) and liver (increased liver weight/m-toluidine and p-isopropylaniline and slight hepatocyte swelling/p-toluidine in rats; liver tumors in mice/m- and p-toluidine). The NOELs in rats for all three substances are roughly in the same dose range; main toxic principle of all three substances is the methemoglobin formation with accompanying symptoms.

p-Toluidine does not induce point mutations in the vast majority of *in vitro* Ames tests. In Chinese hamster lung cells p-toluidine is clastogenic in the presence but not in the absence of S9-mix. *In vivo*, DNA single strand breaks are detected in liver and kidneys of mice using alkaline-elution technique after single intraperitoneal injection of 2/3 of the respective LD_{50} (35 mg/kg bw), therefore it cannot be decided definitely whether the effects occurred due to cytotoxicity or real genotoxic mechanisms. Overall, there is some indication for clastogenic activity *in vitro* and some residual suspicion for such action *in vivo*.

There are no adequate studies with **p-toluidine** to evaluate carcinogenicity in rats and mice. There are a number of limited studies sufficient to support a weight of evidence approach. The limitations include e.g. only one dose in the dermal study, limited number of animals, treatment time too short and are only reported in brief. Following oral and dermal (one dose only) application to rats no tumors can be identified at any dose level. In mice, hepatomas are identified in males in all dose groups whereas females showed liver tumors only in the high dose group. In a study with subcutaneous injection of p-toluidine to rats only a slight, not significant increase in the number of tumors at the injection site and in the liver are reported.

There are no specific data on toxicity for reproduction for **p-toluidine.** Data from repeated dose toxicity studies give no evidence for possible effects of p-toluidine on reproductive organs. Developmental toxicity studies with p-toluidine are not available.
In an OECD TG 422 guideline study with **m-toluidine** on rats it is shown that an impairment of reproductive

function as well as adverse effects on development might occur after applying systemically toxic doses to the parents leading to methemoglobin formation. The NOEL for reproductive toxicity of m-toluidine in rats is 30 mg/kg bw/day. At this dose there is already some degree of hemolytic anemia present as indicated by deposit pigmentation and extramedullary hematopoiesis in the spleen. The NOEL for developmental toxicity for m-toluidine in rats is considered to be 100 mg/kg bw/day. In an OECD TG 422 guideline study with **p-isopropylaniline** on rats there is no impairment of reproductive ability until the highest dose tested (60 mg/kg bw/day) although indications for methemoglobinemia has been detected already at 20 mg/kg bw/day. The NOEL for developmental toxicity for p-isopropylaniline in rats is considered to be 20 mg/kg bw/day. **Overall Conclusion:** There are no specific data on toxicity for reproduction for p-toluidine. Data from repeated dose toxicity studies give no evidence for possible effects of p-toluidine on reproductive organs. Developmental toxicity studies with p-toluidine are not available. But taking into account the results from an OECD TG 422 guideline study performed with the structurally closely related isomer m-toluidine as well as with the structurally related p-isopropylaniline on rats it can be deduced that an impairment of reproductive function as well as adverse effects on development might occur after applying systemically toxic doses to the parents leading to methemoglobin formation. The NOELs for reproductive toxicity in rats are 30 mg/kg bw/day for m-toluidine and 60 mg/kg bw/day for p-isopropylaniline. At these doses there is already some degree of hemolytic anemia present as indicated by deposit pigmentation and extramedullary hematopoiesis in the spleen. The NOELs for developmental toxicity for m-toluidine in rats are considered to be 100 mg/kg bw/day for m-toluidine and 20 mg/kg bw/day for p-isopropylaniline.
In view of the fact that m-toluidine is more potent in methemoglobin formation than p-toluidine and taking into account that methemoglobinemia in pregnant rats may be causally linked to developmental toxicity it can be assumed that extrapolation of the results with m-toluidine to p-toluidine would imply a tendency to lead to an overestimation of the developmental toxicity of p-toluidine. Since there is no evidence for adverse effects on reproduction or developmental effects for m-toluidine or p-toluidine through a direct mechanism of action further testing of p-toluidine is not regarded to be necessary.

Environment

p-Toluidine consists of lustrous plates or leaflets with a melting point of 44 °C, and a boiling point of 200.5 °C. The density is 0.9619 g/cm^3 at 20 °C. The interpolated vapor pressure at 25 °C is 38.1 Pa. The measured log K_{ow} is 1.39. The solubility in water is 7.4 g/l at 25 °C. The flash point is 87 °C, the auto-ignition temperature 482 °C.

In the atmosphere, p-toluidine is degraded by photochemically produced OH radicals. The half-life is calculated to be ca. 2.9 hours.
With regard to the chemical structure, p-toluidine is not expected to hydrolyze due to the lack of hydrolysable functions.
p-Toluidine is inherently biodegradable (MITI test OECD TG 301 C: > 30 % after 14 days; OECD TG 302 B: 94 % after 8 days (industrial sludge), OECD TG 302 B: 94 % after both 10 and 13 days, OECD TG 302 B: 97.7 % after 5 days (adapted sludge), study similar to OECD TG 301 D: biodegradation 68 % after 20 days (study poorly documented)).

According to the Mackay fugacity model level I, the favorite target compartment of p-toluidine is water with 83.7 %, followed by air with 16.0 %. The experimentally determined Henry's law constant (0.20 Pa m^3/mol at 25 °C) proves a low to moderate potential for volatilization from surface waters.
In a sparsely documented study with fish, bioconcentration factors of < 1.3 were obtained at 100 µg/l and < 13 at 10 µg/l. The bioconcentration factor BCF = 2.35 for p-toluidine, calculated from the octanol-water partition coefficient, indicates that there is a low potential for bioaccumulation of p-toluidine in fish. The available experimental data concerning uptake and elimination of p-toluidine in *Mytilus edulis,* indicates its low potential for bioaccumulation in mussels: 85 % elimination of the steady state body burden after 4 hours.
Experimentally obtained adsorption coefficients (K_{oc}) revealed a low to high sorption potential of p-toluidine. The experimentally achieved K_{oc} values were in the range of 102.2 to 1903.4 depending on soil properties. In addition, K_{oc} values were calculated with PCKOCWIN v. 1.66 (K_{oc} = 72.5) and with the TGD equation for the anilines (K_{oc} = 52). These results indicate a low sorption potential of p-toluidine onto the organic phase of soil or sediments. It can be assumed that at low pH the protonated form of p-toluidine with its electrostatic forces may play an important role in soil sorption processes.

Concerning the toxicity of p-toluidine to aquatic species reliable experimental results of tests with fish, *Daphnia*, and algae are available. The tests were performed according to standard procedures or similar methods. The lowest effect values from short-term tests, as well as from a prolonged fish toxicity test are:

Danio rerio:	96 h-LC_{50} = 115 mg/l (m)
Poecilia reticulata:	14 d-LC_{50} = 10.7 mg/l (n)

Daphnia magna: 48 h-EC_{50} = 0.12 mg/l (m)
Scenedesmus obliquus: 48 h-E_rC_{50} = 62.9 mg/l (n)
Scenedesmus quadricauda: 96 h-E_bC_3 = 8.0 mg/l (n)

Data for algal toxicity (*S. capricornutum*, 72 h-E_bC_{50}) of m-toluidine (SIAM 11) and o-toluidine (SIAM 19) is 17.7 and 30.9 mg/l, respectively. For *Chlorella pyrenoidosa* the 96 h-E_rC_{50} for o-toluidine is 55 mg/l.
Tests on chronic toxicity of p-toluidine to aquatic species are not available.
Concerning the effects on terrestrial organisms the following data was obtained for plants in a root elongation test with a duration of 5 days:
Brassica campestris: 5 d-LC_{50} = 102.2 mg/l (n).
The lowest toxicity of p-toluidine to microorganisms measured in a test according to OECD TG 209. A 3h-EC_{50} value of 100 mg/l was obtained with predominantly domestic sewage.
As acute test results of p-toluidine for three trophic levels are available, an assessment factor of 1000 was applied for the derivation of the $PNEC_{aqua}$ according to the EU Technical Guidance Document. The lowest of the available $L(E)C_{50}$ values was obtained for *Daphnia magna*, 48 h-EC_{50} = 0.12 mg/l, therefore resulting in a $PNEC_{aqua}$ = 0.12 µg/l.

Exposure

p-Toluidine is commercially manufactured by reduction of p-nitrotoluene. In 2000, the global production volume of p-toluidine was estimated to be 19 600 tonnes by 23 producers: Western Europe 8000 tonnes/a, USA 3000 tonnes/a, Japan 1200 tonnes/a, South Korea 2400 tonnes/a, China 3800 tonnes/a, and India 1200 tonnes/a. In the Sponsor country, one company has a total production volume of 2000 -10 000 tonnes/a. The total production of this company is used as an intermediate in chemical synthesis, either onsite or offsite by customers. The total end use volume of Western Europe (approximately 5700 tonnes/a of p-toluidine) is used as an intermediate in chemical synthesis as well.

In the Sponsor company, p-toluidine is manufactured and processed in closed systems. The effluent concentration from the wastewater treatment plant was below the detection limit of 20 µg/l (With a dilution factor of 700 at that site the concentration in the receiving river is below 0.03 µg/l). p-Toluidine is transported in rolling channel drums and also in rail or road tankers. The transported goods are classified and labeled according to the relevant national and international transport regulations. There are 2 other companies which produce p-toluidine in the Sponsor country. However, no information is available from these companies.

p-Toluidine is used exclusively as an intermediate in chemical processes, e.g. for the manufacturing of 4B acid (intermediate for pigments) and of other pigments, dyestuff, pesticides, and pharmaceuticals. No consumer use is known for p-toluidine. p-Toluidine is listed in the Danish and Norwegian Product Registers as an industrial product. It is not listed in the Finnish and Swedish Product Registers. In the Swiss Product Register p-toluidine is registered to occur in a consumer product (acrylate glue) with a p-toluidine concentration of 0.01 %. Thus, an exposure of consumers and of the environment due to releases from (consumer) products appears to be negligible.

Toluidine (isomers not specified) was detected in certain vegetables and liquid fuels. p-Toluidine was identified in gasoline. It is released from *Penicillium viridicatum* and from *Methylobacterium mesophilicum* biofilm interlaced with *Penicillium viridicatum*. p-Toluidin is an intermediate in the biodegradation of p-nitrotoluene, e.g. at former munitions sites. p-Toluidine is formed during pyrolysis.

In 1979, p-toluidine was detected in the river Rhine, with the highest p-toluidine concentration of 1 µg/l. In 1991, p-toluidine was not detected in several rivers in North Rhine-Westfalia in Germany (detection limit: 0.1 - 1 µg/l). In 2001, p-toluidine could also not be detected in 3 Indian water samples (detection limit: 23 ng/l). p-Toluidine occurs in air and tobacco smoke with emissions of up to 2.4 µg/cigarette.
Measurements at the workplaces have been performed according to German Technical Guidance TRGS 402. In Germany up to 2004, for occupational settings, a legally binding maximum admissible concentration (technical based) of 1.0 mg/m³ was set for p-toluidine. With the new German Ordinance on hazardous substances at January 1, 2005, this limit value was officially withdrawn by the German Ministry of Labour. In the Sponsor country, as also confirmed by one company, the exposure of workers is below this limit. p-Toluidine has a TWA (Time-weighted average) value of 2 ppm and is also classified in the TLV list A3 as a confirmed animal carcinogen with unknown relevance to humans.
Concentrations of p-toluidine in urine of occupationally exposed workers were similar to these of the general population. Prominent differences were found between males and females. 3 out of 4 studies found elevated levels of p-toluidine hemoglobin adducts in blood of smokers, compared to non-smokers.

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

Human Health: The chemical possesses properties indicating a hazard for human health (acute and subacute toxicity, methemoglobin formation, skin sensitization, eye irritation, possible genotoxicity and carcinogenicity). Based on the data presented by the Sponsor country (relating to production by one producer in one country which accounts for 10 - 50 % of global production and relating to the use pattern in several OECD countries), exposure is controlled in occupational settings, and exposure of consumers appears to be negligible. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country. The substance is currently of low priority for further work.

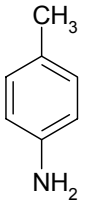
Environment: The chemical possesses properties indicating a hazard for the environment (acute aquatic toxicity to *Daphnia magna*). Based on data presented by the Sponsor country (relating to production by one producer in one country which accounts for 10 - 50 % of global production and relating to the use pattern in several OECD countries), exposure to the environment is anticipated to be low. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country. The substance is currently of low priority for further work.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 106-49-0
IUPAC Name: p-Toluidine
Molecular Formula: C_7H_9N
Structural Formula:



Molecular Weight: 107.16 g/mol
Synonyms: 1-Amino-4-methylbenzene
4-Amino-1-methylbenzene
4-Aminotoluene
p-Methylaniline
4-Methylaniline
4-Methylbenzenamine
p-Tolylamine
Benzenamine, 4-methyl-
p-Aminotoluene
p-Methylbenzenamine

1.2 Purity/Impurities/Additives

Purity of the commercial product: > 99.5 %
Impurities:

- m-Toluidine < 0.5 % w/w (Bowers, 2002)
- o-Toluidine < 0.5 % w/w (Bowers, 2002)
- Water 0.1 - 0.2 % w/w (Bowers, 2002)

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties of p-toluidine

Property	Value	Reference	IUCLID
Substance type	Organic, aromatic, amino compound		1.1.1
Physical state	Lustrous plates or leaflets	Merck Index, 2001	1.1.1
Melting point	44 °C	Bowers, 2002	2.1
Boiling point at 1013 hPa	200.5 °C	Bowers, 2002	2.2
Density at 20 °C	0.9619 g/cm3	Bowers, 2002	2.3
Vapour pressure at 25 °C	38.1 Pa	Chao, Lin and Chung, 1983	2.4
Octanol/water partition coefficient (log Kow)	1.39 (measured)	Hansch, Leo and Hoekman, 1995	2.5
Water solubility	7.4 g/l	Merck Index, 2001	2.6.1
Flash point (Closed cup)	87 °C	Bowers, 2002	2.7
Auto flammability (auto-ignition temperature)	482 °C	Bowers, 2002	2.8
Dissociation constant (pKa)	4.98 (calculated)	Lu, Wang and Bao, 2003	2.12

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Commercial toluidine manufacturing starts with the mononitration of toluene by mixed-acid (nitric acid/sulfuric acid) which yields the three isomers of nitrotoluene, mostly o- and p-nitrotoluene, and to a smaller extend m-nitrotoluene. In general, the nitrotoluene isomers are separated by distillation before the nitro group is reduced (Bowers, 2002).

Most important method for the manufacture of p-toluidine is the catalytic vapor-phase reduction of p-nitrotoluene with hydrogen according to

$CH_3\text{-}C_6H_4\text{-}NO_2 + 3\ H_2 \rightarrow CH_3\text{-}C_6H_4\text{-}NH_2 + 2\ H_2O$

The process is performed in a closed system. The catalysts applied may include various metals like Raney nickel, copper, molybdenum, tungsten, vanadium, and noble metals. The catalyst is immobilized in a column or bed. A mixture of p-nitrotoluene and excess hydrogen is passed over it at about 250 °C. The products are condensed and excess hydrogen is recycled. The aqueous phase is separated from the organic phase. The aqueous phase is stripped to remove organics and the water is led to the wastewater treatment plant. The organic product is dried and distilled (Bowers, 2002).

Rarely applied methods for commercial reduction of nitrotoluene involve utilization of such reducing agents like hydrazine, sulfide, and sodium hydrosulfite (Bowers, 2002).

In 2002 in Western Europe, about 1/3 of the p-nitrotoluene manufacturing volume was used for the production of p-toluidine (Srour, 2002).

In 2000, the global production volume of p-toluidine is estimated to be 19 600 tonnes (Table 2) by 23 producers (Srour, 2002).

In the Sponsor country, Bayer has a total production volume of 2000 -10 000 tonnes/a. This production is used as an intermediate in chemical synthesis, either onsite or offsite by customers (Bayer Chemicals, 2004). There are 2 other companies which produce p-toluidine in the Sponsor country. However, no information is available from these companies (Srour, 2002).

Table 2 Estimated production volume in 2000 (Srour, 2002)

Region	Estimated production volume (tonnes/a)
Western Europe (4 producers)	8000
USA (1 producer)	3000
Japan (1 producer)	1200
South Korea (1 producer)	2400
China (13 producers)	3800
India (2 producers)	1200

p-Toluidine is used exclusively as an intermediate in chemical processes (Bowers, 2002; Srour, 2002). The largest subsequent product of p-toluidine is 4B acid (4-toluidine-3-sulphonic acid, an intermediate for pigment production) which amounts to about 2/3 of world p-toluidine demand. p-Toluidine is also used in minor amounts for the manufacturing of

- m-Nitro-p-toluidine, acetoacetate-p-toluidine, di-p-toluidinoterephthalic acid, which all are intermediates in the production of pigments
- Dehydro-p-toluidine, an intermediate in the production of dyestuff
- Pesticides and pharmaceutical intermediates, and others intermediates (Bowers, 2002; Srour, 2002).

In Western Europe the total demand of p-toluidine (5700 tonnes/a) is exclusively used as an intermediate in chemical synthesis. Its use pattern is well-known (Srour, 2002):

- For the production of different azo-pigments, quinacridone-pigments and paper dyes 4100 tonnes/a p-toluidine are processed by multi step synthesis followed by purification procedures. Therefore it can be assumed that the concentration of p-toluidine is negligible in these pigments. With respects to the chemical structure of those products, e.g. pigment red 57, pigment yellow 1, pigment red 3, pigment orange 34 and others, no p-toluidine can be released by metabolisation.
- About 1000 tonnes/a of p-toluidine is used as an intermediate for pesticides, e.g. for the insecticide fipronil and the fungicide tolylfluanid. These pesticides are covered by special legal regulations.
- Another group of valuable chemical intermediates with an amount of about 600 tonnes/a is synthesised by substitution of the amino group of p-toluidine. The most important substances of

this group are p-fluorotoluene, p-fluorobenz-aldehyde, p-fluorobenzylchloride and p-bromo-toluene. Based on the substitution of the amino group no p-toluidine can be released by metabolism. For the end products, in all cases, the residues of p-toluidine are assumed to be negligible.

No consumer use is known for p-toluidine (Bayer Chemicals, 2004). p-Toluidine is listed in the Danish and Norwegian Product Registers as an industrial product (SPIN, 2004). It is not listed in the Finnish and Swedish Product Registers. In the Norwegian Product Register there is a confidential listing. In the Danish Product Register there are 28 product listings for p-toluidine in 2001, the latest year of reporting. According to this register, for the manufacturing of these products, in total "0.0 tonnes" of p-toluidine were used in 2001, signifying that p-toluidine is not added intentionally into these products. There were registrations as stopping and filling material, and registrations for the sale, repair and maintenance of motor vehicles and motorcycles, and for retail sale of automotive fuel. No consumer application is registered. Consistently, it is stated that p-toluidine is used in closed system and is used non-dispersively (SPIN, 2004).

In the Swiss Product Register (2004) p-toluidine is registered to occur in an acrylate glue with a p-toluidine concentration of 0.01 % (*cf.* Chapter 2.3.2).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Environmental information from manufacturing and processing of p-toluidine is available for the Bayer Chemicals plants in Germany. There are 2 other companies which handle p-toluidine in Germany. However, no information is available from these companies (Srour, 2002, Bayer Chemicals, 2004).

At the Bayer site p-toluidine is manufactured and processed in closed systems (Bayer Chemicals, 2004).

The exhausts from hydrogenation, distillation, and processing are connected to thermal exhaust purification plants and air washing units. Thus, at Bayer Chemicals, during production virtually no p-toluidine is emitted into the atmosphere. In 2000, according to the current Official Emission Declaration, no p-toluidine (< 25 kg/a) was emitted into the atmosphere (Bayer Chemicals, 2004).

Waste from the manufacturing process is incinerated in an incinerator for hazardous wastes (Bayer Chemicals, 2004).

The wastewater from hydrogenation is stripped and led to the Leverkusen industrial and municipal wastewater treatment plant (Bayer Chemicals, 2004).

24 h/d, 365 d/a, the air and water emissions of the Bayer production site are monitored by an Environmental Surveillance Group which operates independently of any manufacturing unit. This group is equipped with mobile detectors and sampling devices for various potential emissions. It also operates stations with measuring and sampling devices for air and water. Within the daily monitoring program p-toluidine was not detected in the effluent of the wastewater treatment plant with a detection limit of 20 µg/l (Bayer Chemicals, 2004).

The effluent of the Bayer Leverkusen wastewater treatment plant passes into the Rhine. Taking into account the 10 percentile of the river flow (1050 m^3/s), the dilution factor (700), and the detection limit (20 µg/l), for the receiving water a

Predicted Environmental Concentration (PEC) of < 0.028 µg/l

is calculated (Bayer Chemicals, 2004).

Exposure information from other companies is not available.

Exposure of consumers and of the environment due to releases from consumer products appears to be negligible (*cf.* chapters 2.1 and 2.3.2).

2.2.2 Photodegradation

p-Toluidine entering in the atmosphere is expected to be degraded by OH-radicals with a reaction rate constant of $1.32 \cdot 10^{-11}$ cm^3/molecule · sec. The calculated half-life of p-toluidine in air due to indirect photodegradation is $t_{1/2air}$ = 2.9 hours, considering a daily mean OH-radicals concentration of 500 000 radicals per cm^3 (Bayer Industry Services, 2004).

p-Toluidine has UV absorption which extends beyond 290 nm (Méallier, 1969) and may potentially undergo direct photolysis in the environment due to absorbance of environmental UV light.

The photodegradation data are compiled in Table 3.

Table 3 Photodegradation of p-toluidine (IUCLID 3.1.1)

Parameter	Method	Result	Reference
Indirect photodegradation in air	Calculation with AOPWIN, v. 1.91 for 24 h-day, 500 000 OH/cm3	t1/2 = 2.9 h	Bayer Industry Services, 2004
Direct photodegradation in air	Absorption spectra at UV-radiation between 220 and 320 nm	Two bands of absorption: 236 and 289 nm	Méallier, 1969

2.2.3 Stability in Water

p-Toluidine is not expected to undergo hydrolysis in the environment due to the lack of hydrolysable functional groups (Harris, 1990).

2.2.4 Transport between Environmental Compartments

The distribution of p-toluidine between environmental compartments was calculated according to the Mackay Fugacity Model Level I (v. 2.11). The main target compartment for p-toluidine is water with 83.7 % followed by air with 16.0 %. Results and input parameters are presented on Table 4 (Bayer Industry Services, 2004).

Table 4 Input parameters and results of the Mackay Fugacity Model Level I (IUCLID 3.3.2)

Input Parameters	Value
Temperature	25°C
Vapour Pressure	38.1 Pa
Water Solubility	7.4 g/l
Log Kow	1.39
Melting Point	44 °C

Compartment	Calculated distribution
Water	83.69 %
Air	15.98 %
Sediment	0.16 %
Soil	0.16 %
Suspended Sediment	<0.01 %
Fish	<0.01 %
Aerosol	<0.01 %

The distribution coefficient of p-toluidine between aqueous solutions and air was calculated using the Bond-method. The Henry´s law constant (HLC) was 0.21 Pa m^3/mol (Bayer Industry Services, 2004). The Group-method leads to a HLC of 0.24 Pa m^3/mol (Bayer Industry Services, 2004). Using the characteristic vapour pressure and solubility of p-toluidine at 25 °C from Table 1 (see also Table 5), and applying the HLC formula (vapour pressure/water solubility) a Henry´s law constant of 0.52 Pa m^3/mol is obtained.

The experimentally determined Henry's law constant confirmed the above calculated constants. Jayasinghe et al. (1992) obtained a HLC of 0.20 Pa m^3/mol by using the gas-liquid equilibration method.

A summary of the available HLC-values are presented on Table 5.

These data indicate that p-toluidine has a low to moderate potential for volatilization from aqueous solutions according to the scheme of Thomas (1990).

Table 5 Distribution in the environment (IUCLID 3.3.2)

Parameter	Method	Result	Source
Henry´s law constant	Calculated with HENRYWIN, v. 3.10 (Bond-method)	0.21 Pa m3/mol	Bayer Industry Services, 2004
Henry´s law constant	Calculated with HENRYWIN, v. 3.10 (Group-method)	0.24 Pa m3/mol	Bayer Industry Services, 2004
Henry´s law constant	Ratio between vapour pressure and water solubility	0.52 Pa m3/mol	Bayer Industry Services, 2004
Henry´s law constant	Gas-liquid equilibration method	0.20 Pa m^3/mol	Jayasinghe et al., 1992

2.2.5 Biodegradation

A large number of tests on biodegradability are available for p-toluidine. Several experimental data give a hint on ready biodegradation and also prove that p-toluidine is inherently biodegradable.

A ready test was conducted with activated sludge, according to a test procedure similar to the OECD TG 301 D Closed Bottle method. Although the study is only poorly documented and only raw data are available, the results are here considered, because they give a hint on ready biodegradation. In this test p-toluidine was emulgated; the initial concentration was 3 mg/l and a BOD of the stock solution (initial concentration 1000 mg/l = 2470 mg COD/l) of 1670 mg/l was calculated after 20 days, which corresponded to a biodegradation rate of 68 % (Bayer AG, 1974).

Additionally an aerobic ready test was performed according to the national Japanese standard method comparable to the OECD TG 301 C guideline. After a period of 14 days p-toluidine was judged to be "well biodegradable" according to the criteria used at that time. The percentage of biodegradation determined from the oxygen consumption exceeded 30 % after 2 weeks from the beginning of the test (Sasaki, 1978). The database of NITE (2002) contains contradictory poorly documented data on biodegradation in MITI I-tests: TOC elimination of 1 %, 6 % and 98 % after 28 days.

A test designed to evaluate the inherent biodegradability of organic substances, was conducted with industrial activated sludge following OECD TG 302 B. The initial test substance concentrations were in the range of 50 to 400 mg/l DOC. Lag phase duration was about 3 days. Elimination of p-toluidine by physical mechanisms was approx. 10 %. Within the 4-day lasting log phase 79 % of p-toluidine was eliminated resulting in a total elimination of 94 % after 8 days (Wellens, 1990).

Further Zahn-Wellens tests (OECD TG 302 B) were performed at concentrations of p-toluidine of 189.9 mg/l and 383.6 mg/l, respectively. After 10 days and 13 days, respectively, 94 % of the test substance was degraded. No information on the origin and adaptation of the inoculum is given (Hoechst AG, 1986).

These results were confirmed by another Zahn-Wellens test. The inoculum used in a concentration of 100 mg/l dry matter, was previously adapted to the test substance for 20 days. After 5 days 97.7 % of the initial concentration (200 mg/l COD) as the sole source of carbon had been removed (Pitter, 1976).

The key data of the biodegradation studies are listed in Table 6.

Table 6 Tests on biodegradation of p-toluidine (IUCLID 3.5)

Inoculum	Procedure	Result	Reference
Aerobic predominantly domestic sewage	comparable to OECD TG 301 D	68 % after 20 days	Bayer AG, 1974
Aerobic activated sludge	comparable to OECD TG 301 C	> 30 % after 14 days	Sasaki, 1978
Aerobic industrial activated sludge	OECD TG 302 B	94 % after 8 days	Wellens, 1990
Aerobic activated sludge	OECD TG 302 B	94 % after 10 and 13 days	Hoechst AG, 1986
Activated sludge, adapted	OECD TG 302 B	97.7 % after 5 days	Pitter, 1976

2.2.6 Bioaccumulation

Concerning the bioaccumulation potential of p-toluidine only data from one sparsely documented study are available.

In this study with carp (*Cyprinus carpio*), bioconcentration factors of < 1.3 and < 13 were obtained at 100 µg/l and 10 µg/l, respectively (NITE 2002).

Taking into account the octanol-water partition coefficient, a bioconcentration factor (BCF) can be calculated with the BCFWIN Program (v. 2.15). Using log K_{ow} = 1.39, the calculated BCF was 2.35 (log BCF = 0.37) (Bayer Industry Services, 2004).

Knezovich, Lawton and Harrison (1988) studied uptake, depletion and metabolism of ^{14}C-labeled p-toluidine in the marine mussel *Mytilus edulis*. Mussels were exposed to a concentration of 2 x 10^{-5} mol/l of p-toluidine under marine ambient conditions. The steady state of the body burden was reached after 4 hours of exposure, however, the "static" BCF for the steady-state is not available . Rapid elimination was observed resulting in a depuration of ≥ 85 % of the tissue residues within 4 hours. Concerning the metabolism of p-toluidine in *Mytilus edulis* it was found that 17.5 % of the steady state body burden was converted to the corresponding N-acetyl derivative as the only metabolite.

The high elimination rate suggests that there is a low bioaccumulation potential.

Table 7 Bioaccumulative properties of p-toluidine (IUCLID 3.7)

Organism	Method	Result	Source
Fish	Calculated with BCFWIN, v. 2.15	BCF = 2.35	Bayer Industry Services, 2004
Cyprinus carpio (Carp)	Not specified	BCF < 13 (at 10 µg/l)	NITE, 2002
Mytilus edulis (Common bay mussel)	14C-p-Toluidin; under marine ambient conditions	≥ 85 % elimination within 4 h after steady-state 17.5 % of body burden were metabolized after 8 h	Knezovich, Lawton and Harrison, 1988

2.2.7 Geoaccumulation

Experimental K_{oc} values were published by Gawlik et al. (1998). Four soil types were treated with p-toluidine solutions according to OECD TG 106 . Three soils achieved K_{oc} in the range of 102.2 - 200.2 at a pH of 5.2 to 7.4 indicating that p-toluidine is a substance with low geoaccumulation potential according to Litz (1990). However, high soil sorption potential was observed in one single soil type of low pH and high clay content (K_{oc} = 1903.4). In addition, the mean K_{oc} of p-toluidine to four silt loam soils was 79, obtained by Briggs (1981). The pH of the soil ranged from 6.1 to 7.5.

The distribution of p-toluidine between the organic phase of soil or sediments and the pore water was calculated using QSAR. A K_{oc} of 72.5 was calculated with PCKOCWIN v. 1.66 (Bayer Industry Services, 2004). Using a K_{ow} of 1.39, the TGD equation for anilines

$\log K_{oc} = 0.62 \log K_{ow} + 0.85 = 1.71$

results in K_{oc} = 52.

The results of the calculated values correspond to the experimental values, achieved according to the OECD TG 106 and the study by Briggs (1981).

A sequential extraction procedure was used to show that p-toluidine binds soils in two phases (Graveel, Sommers and Nelson, 1985). The experiments were carried out with ring-labeled p-toluidine. Binding to soil was shown to give a rapid reversible equilibrium which may involve electrostatic interactions, hydrophobic bonding or irreversible imine linkages followed by covalent bonding of the substance to the soil organic matter. During the 63 day incubation period, by decomposition, measured by CO_2 evolution, 15 % CO_2 was released.

Investigations of Graveel, Sommers and Nelson (1986) on soil sorption/desorption of p-toluidine supported the correlation of soil pH and clay content as observed in the study by Gawlik et al. (1998). The obtained K_{oc} values in this study are 323, 496, and 508, depending on soil properties. The pH was 4.0, 4.3, and 5.9, respectively.

The range of investigated K_{oc} values reflects the influence on pH. It can be assumed that at low pH the protonated form of p-toluidine with its electrostatic forces may play an important role in soil sorption processes as shown by Graveel, Sommers and Nelson (1986).

The available K_{oc} values are compiled in Table 8.

Table 8 Geoaccumulative properties of p-toluidine (IUCLID 3.3.1)

Parameter	Method	Result	Reference
Soil organic carbon-water distribution coefficient	OECD TG 106 (modified)	Soil-Type: Koc silt loam: 102.2 loam: 200.2 silt: 121.4 clay: 1903.4	Gawlik et al., 1998
Soil organic carbon-water distribution coefficient	Adsorption/desorp-tion from soils	Koc = 79 (pH 6.1 - 7.5)	Briggs, 1981
Soil organic carbon-water distribution coefficient	Adsorption/desorption from equilibrated soils	Koc = 323 (pH 4.0) Koc = 496 (pH 4.3) Koc = 508 (pH 5.9)	Graveel, Sommers and Nelson, 1986
Soil organic carbon-water distribution coefficient	Calculated with PCKOCWIN, V1.66	Koc = 72.5	Bayer Industry Services, 2004
Soil organic carbon-water distribution coefficient	Log Koc = 0.62 log Kow + 0.85 = 1.71	Koc = 52	Bayer Industry Services, 2004

2.2.8 Environmental Monitoring

Occurrence

Toluidine (isomers not specified, but p-toluidine likely to be present) occurs in vegetables like cabbage (*Lactuca sativa*), carrots (*Daucus carota*), celery (*Apium graveolens*), and peas (*Pisum sativum*) (Neurath et al., 1977).

The filamentous fungus *Penicillium viridicatum* evolved p-toluidine and other volatile organic compounds during growth on malt extract agar and under several conditions mimicing colonization of automobile air conditioning systems. p-Toluidine was also released from a bacterial biofilm of *Methylobacterium mesophilicum* interlaced with *Penicillium viridicatum* (Rose et al., 2000).

At former munitions sites p-toluidine is an degradation intermediate of p-nitrotoluene. It is degraded much faster than its precursor, p-nitrotoluene (Van Aken and Agathos, 2002).

Toluidine (isomers not specified) was detected as a component of coal oil at a concentration of 135 mg/kg (Tomkins and Ho, 1982) and in two liquid fuels (Potter, 1996). p-Toluidine was identified in gasoline (Schmidt, Kleinert and Haderlein, 2000).

Water

In 1979, Wegmann and De Korte (1981) found several aromatic amines in surface waters of the Netherlands. In 46 water samples (containing sediments) of the river Rhine from Lobith, the mean p-toluidine concentration was 0.17 µg/l (26 samples above the determination limit of 0.02 µg/l, maximum 1.0 µg/l). In its tributaries Boven Merwede and Issel the mean p-toluidine concentration was 0.07 µg/l (5 samples of 12 above detection limit, maximum 0.35 µg/l) and 0.08 µg/l (6 samples of 13 above detection limit, maximum 0.39 µg/l), respectively (Wegmann and De Korte, 1981). 3 ground water samples from the vicinity of an US underground coal gasification site, contained toluidine in concentrations of up to 9.2 µg/l (sum of o- and p-isomers) (Stuermer, Ng and Morris, 1982).

In 1991, p-toluidine was monitored in several rivers in North Rhine-Westfalia in Germany (LWA NRW, 1992). It was neither detected in the Rhine (3 sampling sites) nor in any of 6 of its tributaries with a detection limit of 1 µg/l (detection limit in the Wupper 0.1 µg/l).

There are no recent reports on the occurrence of p-toluidine in environmental media in the Sponsor country.

With a limit of detection of 23 ng/l, p-toluidine could not be detected in samples of drinking water of Jabalpur (India), river water and treated paper mill effluent (Mishra et al., 2001).

Air/Tobacco smoke

p-Toluidine occurs in tobacco smoke (Pailer, Huebsch and Kuhn, 1966; Neurath, 1969; Schmeltz and Hoffmann, 1977).

Patrianakos and Hoffmann (1979) found high levels of aromatic amines in tobacco smoke. The p-toluidine load of the main stream smoke (primary smoke [which is inhaled by the smoker]) was 7 - 59 ng/cigarette depending on the protein and nitrate content of the cigarettes. The side stream smoke (secondary smoke [which is also inhaled by the non-smoker]) contained 1 - 2 orders of magnitude more p-toluidine (1730 ng/cigarette). The authors concluded that aromatic amines like p-toluidine are formed by pyrolysis.

High levels of p-toluidine were also measured by Luceri et al. (1993). Both the main stream smoke of cigarettes and the side stream smoke of cigarettes, contain significant amounts of all toluidine isomers and other aromatic amines. Depending on the brand, the p-toluidine content is 14 - 42 ng/cigarette in the main stream smoke, and 10 - 100 times higher in the side stream smoke (562 – 2390 ng/cigarette). These authors also examined several aromatic amines as tracers of cigarette smoke in air and found a strong correlation of p-toluidine (and other aromatic amines) levels in indoor air with the smoking status of the inhabitants (Table 11). Thus, the ubiquitous distribution of these aromatic amines in indoor air samples was attributed to tobacco smoke (Luceri et al., 1993).

Table 9 Concentrations of p-toluidine in indoor air (Luceri et al., 1993)

Air source	**p-Toluidine concentration (ng/m^3)**
Office of a non-smoker with smokers in contiguous room	3.7
Office of a non-smoker with smokers in contiguous room after overnight ventilation	0.5
Office with 1 smoker	2.9
Office with 2 smokers	6.3
Club room	11.3
Non-smoking train compartment	1.1
Hair-dresser saloon	4.8

Palmiotto et al. (2001) examined the occurrence of 10 aromatic amines in air in several Italian sites. In the most heavily polluted outdoor air of the cities examined (air of the centre of Brindisi), the p-toluidine concentration was approximately 20 ng/m^3. In air from a smokers room the p-toluidine concentration was approximately 8 ng/m^3 (Palmiotto et al., 2001).

Neurath (1969) reports that the ring-substituted aromatic amines of tobacco smoke are most likely formed during pyrolysis. Thus, p-toluidine is formed by several sources where pyrolysis of nitrogen-containing material occurs, e.g. uncontrolled biomass burning and food curing with smoke.

2.3 Human Exposure

2.3.1 Occupational Exposure

Occupational exposure to p-toluidine is most likely to occur through inhalation and dermal contact.

Workplaces

At the Bayer manufacturing sites, workplaces where p-toluidine is manufactured or processed (Bayer Chemicals, 2004), include

- Manufacturing processes: Conversion of p-nitrotoluene to p-toluidine, distillation (*cf* Chapter 2.1)
- Processing: In chemical synthesis for production of chemical intermediates (*cf* Chapter 2.1).

At the Bayer sites, p-toluidine is manufactured and processed in closed systems (*cf* Chapter 2.2.1). p-Toluidine is transported in rolling channel drums and also in rail or road tankers inside and outside the Bayer industrial sites. The means of consignments depend on the demands of the costumer. (Bayer Chemicals, 2004). The transported goods are classified and labeled according to the relevant national and international transport regulations e.g. UN-no. 1708, GGVSee/IMDG-code/ADNR/ RID/ADR: 6.1 (Bayer Chemicals, 2003).

Precautionary measures at the workplace

In accordance with the principles of Responsible Care and Sustainable Development, at Bayer Chemicals the exposure of workers is reduced to the lowest technically practicable level (Bayer Chemicals, 2004).

Surveys of the Bayer workplaces are performed according to German Technical Guidances TRGS 402 and TRGS 901. This includes regular surveys in the working area for any possible exposure to p-toluidine and other dangerous substances under all relevant work situations, and appropriate control measures (Bayer Chemicals, 2004).

To protect workers from exposure, several precautionary and protective measures are taken. E.g. sampling takes place in a widely closed system. The filling and drumming takes place in a closed system with special suction devices. Repair and maintenance work is only carried out on parts of the manufacturing or processing systems, which have been emptied. Prior to repair and maintenance the parts are flushed with solvent and water to remove residual substances. Special written permits are required which include a detailed description of the protective measures depending on the work to be done (e.g. full protective clothing and gas filter masks (classification ABEK) (Bayer Chemicals, 2004).

Down stream users of p-toluidine are informed by way of a material safety data sheet on the recommended safety measures (see above) (Bayer Chemicals, 2004).

Potential exposure at the workplace

Measurements at the workplaces have been performed according to German Technical Guidance TRGS 402. In Germany up to 2004, for occupational settings, a legally binding maximum admissible concentration (technical based) of 1.0 mg/m³ was set for p-toluidine. At Bayer Chemicals production and processing sites, the exposure of workers was below this limit (Bayer Chemicals, 2004). With the new German Ordinance on hazardous substances at January 1, 2005, this limit value was officially withdrawn by the German Ministry of Labour. According to the new German Ordinance there are now only health-based occupational exposure limits accepted as standards. The pre-existing technical exposure limit, which is a factor of ten lower than the current USA TLV value, might still serve as a orientating value until a health-based limit value for p-toluidine is derived in the future. p-Toluidine has also been classified on the MAK 3B list as a substance for which a carcinogenic potential is suspected from in vitro or animal experiments (assessment based on the cancerogenicity studies as reported in chapter 3.1.7). Therefore no MAK (maximum admissible concentration) is set (Greim, 2004). p-Toluidine has a TWA (Time-weighted average) value of 2 ppm and is also classified in the TLV list A3 as a confirmed animal carcinogen with unknown relevance to humans (ACGIH, 2004).

Biological monitoring

Hemoglobin adducts of p-toluidine were detected in an exposed worker but, unfortunately, neither the results nor the exposure to tobacco smoke or other hazardous substances were detailed by the authors (Sabbioni and Beyerbach, 1995). Riffelmann et al. (1995) examined occupationally exposed workers from 3 chemical plants (presumably in Germany). The urinary p-toluidine concentrations were similar in occupationally exposed smokers (n = 22) and non-smokers (n = 21), 2.1 µg/l and 2.4 µg/l, respectively (difference not significant). The level was independent from the acetylator status of the workers (2.1 and 2.2 µg/l for fast and slow acetylators, respectively). However, there was a 2/3 increase in the urinary p-toluidine levels in unexposed smokers (mean 2.2 µg/l, n = 8), compared to unexposed non-smokers (1.3 µg/l, n = 8).

2.3.2 Consumer Exposure

p-Toluidine is used exclusively as an intermediate in chemical processes (Bowers, 2002; Srour, 2002). No consumer use is known for p-toluidine (Bayer Chemicals, 2004). End-products made from p-toluidine do not contain significant p-toluidine levels, because p-toluidine is - as can be seen from the variety of products synthesized from p-toluidine - used as a basic intermediate in chemical synthesis (*cf.* Chapter 2.1). Synthetic p-toluidine is not present in end-products at levels relevant for classification as a hazardous substance (Bayer Chemicals, 2004). However, p-toluidine occurring in smoke might contaminate e.g. foodstuffs (*cf.* Chapter 2.2.8 and below).

p-Toluidine is not listed in the Danish and Norwegian Product Registers as a consumer product (*cf.* Chapter 2.1). It is not listed in the Finnish and Swedish Product Registers (SPIN, 2004).

Although it is reported that p-toluidine might occur at trace concentrations in consumer products, the level relevant for classification is not reached:

In the Swiss Product Register (2004) p-toluidine is registered to occur in an acrylate glue with a p-toludine concentration of 0.01 %. This glue contains diisopropyl-p-toluidine with a concentration of approximately 2 % and it is assumed that p-toluidine is not added on purpose but is a synthesis residue (Swiss Product Register, 2004).

The anthraquinone color Acid Violett 43 (CI 60730), which is safe for use in hair dye formulations, may contain traces of p-toluidine (less than 0.1 %) (Fiume, 2001). According to the US Food and

Drug Administration, in the early 1980s there were 31 cosmetic products containing Acid Violett 43 in the USA. In 1998, it was used in 1 out of 1478 hair dyes, in 1 out of 32 coloring hair rinses, and (in violation of the US Food, Drug and Cosmetics Act) in 1 out of 241 underarm deodorants. In the EU and Japan, Acid Violett 43 is approved only for limited uses in cosmetics. In US hair colouring formulations Acid Violett 43 was used at concentrations of less than 0.1 % (one exception [out of 31] with 0.1-1 %) in the early 1980s (Fiume, 2001). In the EU, toluidines and their salts and halogenated and sulphonated derivatives are not permitted for use in cosmetic products (EU, 1999).

Thus, an exposure of consumers and of the environment due to releases of synthetic p-toluidine from these consumer products appears to be negligible.

Environmental tobacco smoke contains several aromatic amines including p-toluidine. Tobacco smoke contaminates the air of virtually all inhabited environments (*cf.* Chapter 2.2.8). Since several ring-substituted aromatic amines are formed by pyrolysis (Neurath, 1969; Patrianakos and Hoffmann, 1979), it is likely that any smoke derived from nitrogen-containing fuels contains p-toluidine and contaminates consumer products including food (expert judgement).

El-Bayoumy et al. (1986) determined the levels of aniline and toluidines in human urine. They found p-toluidine in 2 out of 11 smokers and in 4 out of 9 non-smokers and concluded that diet as a source other than cigarette smoke, may contribute significantly to the urinary p-toluidine.

In the general population (84 adults from Western Germany), the level of p-toluidine in urine was 1.2 µg/l (median, 0 - 27 µg/l). For 34 males, the median was 3.1 µg/l, and for 50 females, the median was 0.69 µg/l (Weiss et al., 2000). Higher values were observed by Riffelmann et al. (1995), who also found a 2/3 increase in the urinary p-toluidine levels in unexposed smokers (mean 2.2 µg/l, n = 8), compared to unexposed non-smokers (1.3 µg/l, n = 8). There were no significant differences in renal excretion of p-toluidine between occupationally exposed smokers (mean 2.1 µg/l, n = 22) and nonsmokers (mean 2.4 µg/l, n = 21).

In human milk from 7 smokers and 24 non-smokers, DeBruin, Pawliszyn and Josephy (1999) found several aromatic amines of cigarette smoke, but they did not detect p-toluidine with a detection limit of 0.01 ppb.

In a study on hemoglobin adducts of aromatic amines in children from three different-sized Bavarian towns, Richter et al. (2001) found no influence of exposure to environmental tobacco smoke (determined by interview) on p-toluidine hemoglobin adduct levels, but observed the highest mean adduct level in the largest town. In contrast, Lewalter and Neumann (1996) report that the hemoglobin adduct background level of toluidine (no isomer specified) is 1 - 10 µg/l for the general population due to tobacco smoke.

Stillwell, Bryant and Wishnok (1987) found that the p-toluidine hemoglobin adduct level was doubled in smokers (0.13 ng/g hemoglobin, n = 12), compared to non-smokers (0.07 ng/g hemoglobin, n = 10). Skipper, Bryant and Tannenbaum (1988) confirmed these results with smokers and non-smokers from Turin (Italy) and Boston (USA). In the Boston cohort, the p-toluidine hemoglobin adduct level was 0.18 - 0.42 ng/g hemoglobin for different groups of smokers, and 0.09 ng/g hemoglobin for non-smokers. In the Turin cohort, the average p-toluidine hemoglobin adduct level was 0.31 ng/g hemoglobin in 40 smokers, and 0.21 ng/g hemoglobin in 25 non-smokers. Significant differences between smokers and non-smokers were also observed by Bryant et al. (1988) for slightly different cohorts from Turin. In these cohorts, the p-toluidine hemoglobin adduct level was 0.31 - 0.41 ng/g hemoglobin in smokers, and 0.21 ng/g hemoglobin in non-smokers.

It is concluded that smoke is the predominant source of p-toluidine in humans.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

There are no specific studies available which evaluate the possible potential of p-toluidine to affect fertility or to cause developmental toxicity. Information from m-toluidine is used to fill the data gap. Therefore the SIAR contains a short comparison of p-toluidine and m-toluidine for all endpoints.

The isomer m-toluidine was already discussed and concluded in SIAM 11, 2001; the data are published by UNEP in 2003. A comparison of the intrinsic toxicological properties of m-toluidine with these properties of p-toluidine showed that m-toluidine is more potent in methemoglobin forming than the p-isomer. Taking into account that methemoglobinemia in pregnant rats is causally linked to developmental toxicity it can be assumed that extrapolation of the results with m-toluidine to p-toluidine would imply a tendency to lead to an overestimation of the developmental toxicity of p-toluidine. Furthermore developmental toxicity data from the structurally related p-isopropyl-aniline were included in the assessment. This seems to be justified due to the structural similarity of both substances as both aniline derivatives have substituents in para position of nearly the same influence on the reactivity of the respective molecule. This could be demonstrated with the data on acute toxicity as well as with repeated toxicity data. For all three substances methemoglobinemia and/or erythrocyte toxicity seem to be the most relevant mechanism for systemic toxicity. In addition, with respect to mutagenicity, the comparison of results of the respective tests with these substances demonstrates the inconsistency, which is typical for aromatic amines.

3.1.1 Toxicokinetics, Metabolism and Distribution

Studies in Animals

In vivo Studies

There are no specific toxicokinetic studies with p-toluidine on absorption via skin and respiratory tract but based on molecular size of p-toluidine absorption via these administration routes can be reasonably predicted.

Following oral application of 500 mg p-toluidine/kg bw to 4 rats peak blood level after 12 and 24 hours was observed. As half-life time of plasma elimination 12 to 15 hours was derived (Brock, Hundley and Lieder, 1990); i.v. application to 4 dogs yielded a half-life time of plasma elimination of 1 hour (Kiese, 1963). 72 hours following oral application of labeled p-toluidine to 4 rats, radioactivity was detected in decreasing range: abdominal fat > liver > abdominal skin > kidney > whole blood > spleen > urinary bladder > lung > gastrointestinal tract > heart > bone marrow > muscle > brain > testes (Brock, Hundley, and Lieder, 1990). Cheever, Richards and Plotnik (1980) concluded that metabolism of p-toluidine in 4 rats (500 mg/kg bw) proceeds through ring hydroxylation with subsequent conjugation. They identified as metabolite 2-amino-5-methylphenol (quantification not given) and unchanged p-toluidine (2.5 % of the dose in 24-hour urine).

In further studies, which were only reported in brief, groups of female Wistar rats (n = 8) received 0, 40, 80 and 160 mg/kg bw/day p-toluidine together with protein-rich (24 %) or together with protein-low (8 %) diet over 6 or 12 months (160 mg/kg bw/day only), respectively (Malik-Brys and Senczuk, 1995a, b). Due to the available graphics, at the end of the 6 months treatment time, p-toluidine content was dose-relatedly increased in blood and urine not only when given together with protein-rich diet but also when given with protein-low diet although the respective values were

lower. Additionally, prolongation of treatment time up to 12 months did not result in further increased p-toluidine content in blood and urine.

Conclusion

p-Toluidine is absorbed via gastrointestinal tract and is distributed, metabolized and excreted via urine and feces. The identification of 2-amino-5-methylphenol indicates that the metabolism in rat proceeds through ring hydroxylation with subsequent conjugation. There are no specific toxicokinetic data on absorption via skin and respiratory tract; absorption via these administration routes can reasonably be predicted due to the molecular size of p-toluidine.

m-Toluidine (SIAM 11)

m-Toluidine is rapidly absorbed via gastrointestinal tract, via skin and is metabolized by ring hydroxylation (BUA, 1995). Although 2-amino-4-methyl-phenol and 4-amino-2-methylphenol were identified in the rat urine with a small amount of the parent compound, there is no sufficient information on quantitative metabolism of m-toluidine or on toxicokinetics (UNEP, 2003).

Overall conclusion:

Both isomers, p- and m-toluidine are absorbed via gastrointestinal tract and via skin and distributed. They are metabolized by ring hydroxylation with subsequent conjugation and excreted via urine and feces.

3.1.2 Acute Toxicity

Studies in Animals

There are no animal studies available, which are performed according to the current guidelines. Nevertheless the studies are considered of sufficient good quality to allow the evaluation of this endpoint:

Inhalation

In an inhalation hazard test, 6 rats were exposed for one hour against vapor concentrations of approximately 0.64 mg p-toluidine/l. Signs of intoxication during and post exposure included generalized inactivity, rhinitis and lacrimation, which ceased one day post exposure. No animal died during the exposure or during the 14-day observation period. Gross autopsy revealed no significant findings (Industrial Bio-Test Laboratory Inc., 1973, questionable reliability).

Dermal

Dermal application of 464 - 1470 mg/kg bw moistened p-toluidine (exposure time not mentioned) to 5 rabbits/dose group resulted in an LD_{50}-value of 890 mg/kg bw. Signs of intoxication from day 4 post exposure in the lowest dose group and within 4 hours post exposure in the highest dose group were hypoactivity, muscular weakness, convulsions and vocalisation just prior to death which occurred in all dose groups. Additionally, moderate to severe erythema, mild edema, focal chemical burns and subdermal hemorrhages were seen in the skin of the rabbits. Pathological investigations showed granular livers in the decedents whereas from survivors no significant findings were noted (Industrial Bio-Test Laboratory Inc., 1973, questionable reliability).

Single dermal application of p-toluidine resulted in methemoglobin level up to 20 %, and recovery occurred within 48 hours. Dermal application of 0.5, 0.75, 1, or 1.25 % solution of p-toluidine to rats for 2 - 6 hours (no further detail) resulted in dose-related increase in methemoglobin level up to

40 %. As the experimental performances of the tests are described poorly these results are difficult to interpret (Senczuk and Rucinska, 1984).

Oral

To determine LD_{50} values of p-toluidine, there are 2 studies, which could be taken into account. In the first one 10 male rats per dose received dosages ranging from 100 mg/kg bw up to 900 mg/kg bw dissolved in lutrol (Bayer AG, 1978) Signs of intoxications were hypoactivity, increase of urinary excretion, emaciation, bloody eyes, cyanosis, anorexia and narcosis which led to dose-related death during the 14 day post exposure observation period. The resulting LD50 value is 620 mg/kg bw. This data correspond to another study which was carried out to an earlier timepoint and which is of questionable reliabilty. In that study 5 rats per dose group were treated with up to 1000 mg/kg bw dissolved in corn oil. Hypoactivity, cyanosis, anorexia and death and no significant findings at gross autopsy were reported. The resulting LD_{50} value was 656 mg/kg bw (Industrial Bio-Test Laboratory Inc., 1973;).

Reported in brief and therefore difficult to interpret, single oral application of 200 mg/kg bw p-toluidine to rat (no further details given) resulted in a methemoglobin level (max) of 21.7 % two hours post application (Senczuk and Rucinska, 1984).

Studies in Humans

It is reported in an earlier publication that toluidines (isomer not specified) due to methemoglobin formation produce the same symptoms, as does aniline (route and duration of exposure is not specified), with less cyanosis but more strangury and hemoglobinuria (Smyth, 1931). Goldblatt (1955) reported in a survey article that, due to effects of their metabolic products on haemoglobin, concentrations of 40 ppm (176 mg/m^3) of toluidine (isomer not specified) in the atmosphere for more than 60 minutes caused severe toxic effects in workers, 10 ppm (44 mg/m^3) lead to symptoms of illness and concentrations in the atmosphere greater than 5 ppm (22 mg/m^3) indicate unsatisfactory conditions (no further details included). In the recent open literature no cases of acute poisoning were reported.

Conclusion

For **p-toluidine**, the LC_{50} (inhalative, rat) is > 0.64 mg/l, and LD_{50} (dermal, rabbit) is 890 mg/kg bw. LD_{50} (oral, rat) was determined 656 mg/kg bw and 620 mg/kg bw. Signs of intoxication include hypoactivity, muscular weakness, convulsions, cyanosis and narcosis. p-Toluidine is a methemoglobin forming chemical in rats. Levels up to 21.7 % following oral application to rats and up to 40 % following dermal application to rats were measured. p-Toluidine is a methemoglobin forming chemical in humans as it produces the same toxic effects as aniline from 22 mg/m^3 onwards with less cyanosis but more stranguria and hemoglobinuria.

m-Toluidine (SIAM 11)

For m-toluidine, LD_{50} values are from 450 to 1430 mg/kg bw by oral route to rats and 3250 mg/kg bw by dermal route to rabbits (no information on study quality available). Severe methemoglobin formation is reported following single exposure to m-toluidine ranging up to 36.4 % in rats after oral application and 40 % in rats after dermal application (these data as well as those given above for p-toluidine are derived from a study which examined the methemoglobin formation of m- and p-toluidine in parallel) and up to 60.2 % in cats (i.v.) (UNEP, 2003).

p-Isopropylaniline

For p-isopropylaniline, LD_{50} values of 985 mg/kg bw (MHW, 1999) and 757mg/kg bw (ECB, 2000) were reported of rats following single oral application. Single oral application of 25 mg/kg bw to cats resulted in elevated methemoglobin level and an increase in Heinz bodies (ECB, 2000).

Table 10 Methemoglobin formation p- and m- toluidine

Species /Route/ mg/kg bw/	% MetHb; m-Toluidine	% MetHb; p-Toluidine	% MetHb; p-Isopropyl-aniline	Reference
Rat oral 200	max. 36.4 %	max. 21.7 %	--	Senczuk and Rucinska, 1984
Cat i.v. 26.8	max. 60.2 %	max. 39.6 %	--	McLean et al., 1966
Cat oral 25	--	--	increased	ECB, 2000
Dog i.v. 111.1	max. 57 %	max. 12 %	--	Kiese, 1963

The data in the Table above show that m-toluidine is considerably more active in methemoglobin formation than p-toluidine when tested at equal dosages and under similar experimental conditions. The acute dermal toxicity of m-toluidine seems to be considerably lower when compared to p-toluidine but the data for m-toluidine is of questionable validity. Overall acute toxicity of both isomers is mainly due to methemoglobin formation, the m-isomer being more active than the p-isomer. p-Isopropylaniline led to an increase in methemoglobin after oral application of 25 mg/kg bw to cats (no quantitative data available).

Overall conclusion

Based on the available data, p- and m-toluidine are of moderate acute toxicity. Main toxic signs result from the methemoglobin formation in rats as well as in humans. m-Toluidine is considerably more active in methemoglobin formation than p-toluidine when tested at equal dosages and under similar experimental conditions. p-Isopropylaniline led to an increase in methemoglobin after oral application of 25 mg/kg bw to cats (no quantitative data available).

3.1.3 Irritation

Skin Irritation

Studies in Animals

No irritational effects were seen following application of 500 mg moistened test substance to the inner surface of one ear of each of 2 rabbits under occlusive conditions for 24 hours. The other ear of each of the 2 rabbits served as control (Bayer AG, 1979).

Eye Irritation

Studies in Animals

50 mg p-toluidine was applied into the conjunctival sac of one eye of each of 2 rabbits and animals were observed for 7 days (Bayer AG, 1979). Over a period of 24 hours conjunctival redness, swelling and lacrimation was observed, but at the end of the observation time no irritational effects were seen. This result is in accordance with the results of an eye irritation study with another one of questionable reliability, which yielded a mean score of 56.7/110 but observation time was too short

(72 hours) to see probable reversibility of the effects (Industrial Bio-Test Laboratory Inc., 1973). Overall, p-toluidine is an irritant to the eyes of rabbits.

Conclusion

p-Toluidine causes irritation to the eyes of rabbits which recovered within 7 days. No irritational effects were observed when applied to the rabbit´s ear for 24 hours under occlusive conditions.

m-Toluidine (SIAM 11)

m-Toluidine is reported to induce slight skin irritation (500 mg/24 hrs) and moderate eye irritation (20 mg/24 hrs) in a publication of limited validity due to poor test description (UNEP, 2003).

Overall conclusion

Based on the available data it can be concluded that both isomers are slight irritants to the skin of rabbits and irritants to the eyes of rabbits.

3.1.4 Sensitisation

Studies in Animals

Skin

Patch test was performed with 10 guinea pigs using a 2 % p-toluidine petrolatum solution and occlusive dressing for induction. 14 days later, 4 concentrations for the challenge procedure were used: 2 %, 1 %, 0.5 %, 0.25 %. p-Toluidine was evaluated as sensitizing because 8/10 guinea pigs showed a positive reaction in the highest concentration (2 %). 6/10, 4/10 and 0/10 animals showed a positive reaction after challenge with 1, 0.5 or 0.25% p-toluidine. As positive control served p-phenylene diamine (Kleniewska and Maibach, 1980).

Studies in Humans

Skin

58 dermatitis patients, known to be hypersensitive to p-phenylene diamine, were patch tested with 2 % p-toluidine in yellow paraffin. 63.8 % (37) of the patients showed positive reactions (Kleniewska, 1975). The study is not assignable because only patients with dermatitis and already sensitized to p-phenylene diamine were included in the test.

Conclusion

p-Toluidine is a sensitizer by skin contact as shown in a patch test with guinea pigs. There is no valid human data available.

m-Toluidine (SIAM 11)

There is no data with **m-toluidine** available on skin sensitization (UNEP, 2003).

Overall conclusion

p-Toluidine is a skin sensitizer when tested in a patch test with guinea pigs. For m-toluidine there are no data available, however, as the higher sensitizing potential for para substituted substances is a known effect, a sensitizing potential of m-toluidine is not necessarily expected.

3.1.5 Repeated Dose Toxicity

The available repeated dose toxicity studies with rats and mice provide only limited information because not all parameters were tested and the documentation of the studies does not meet the criteria of today. However, altogether, main toxic effects seem to be mentioned and target organs can be determined. Therefore the available studies are considered of sufficient quality to evaluate this endpoint.

Studies in Animals

Oral

In a subacute (28 days) feeding study of questionable reliability, 10 male rats received 0, 165, 825 and 1650 ppm p-toluidine (corresponding to 0, 13.8, 66.8, 125.7 mg/kg bw/day), which was blended with basal diet freshly every week. No animal died during the study. No signs of intoxication were noted among any of the animals during the experimental period. Final body weight was significantly reduced at 1650 ppm when compared to the concurrent control. At autopsy, no significant gross pathological lesions were found among any of the rats examined. Organ to body weight ratio was calculated from liver, kidneys, adrenals and testes and were significantly increased only of the livers of the 825 and 1650 ppm dosed groups. No other examined parameters were reported. Thus, based on the findings reported, the NOAEL is 165 ppm (corresponding to 13.8 mg/kg bw/day; Industrial Bio-Test Laboratory Inc., 1973).

In other studies, groups of female Wistar rats received 0, 40, 80 and 160 mg/kg bw/day in protein-rich (24 %) or protein-low (8 %) diet over 6 or 12 months (160 mg/kg bw/day only), respectively (Malik-Brys and Senczuk, 1995a, b). In addition to data on kinetics (see Chapter 3.1.1) the only parameter examined was methemoglobin content in blood. Methemoglobin levels increased dose-relatedly after application of p-toluidine together with protein-rich diet (data not given, graphic only). Protein-low diet together with p-toluidine given for 6 months caused also a dose-related increase in methemoglobin levels (specific control data not given, low, mid and high dose: 2.2 %, 6.7 %, 10.5 %). From the available graphics, these values seem to be lower than those after protein-rich diet. For the prolongation of treatment up to 12 months with 160 mg/kg bw/day p-toluidine together with protein-low diet or together with protein-rich diet, respectively, graphics of results show that the respective methemoglobin levels are lower than after the 6 months treatment period (approximately 4 - 5 % [protein-low diet], detailed data not given).

In a limited carcinogenicity study (see Chapter 3.1.7; Weisburger et al., 1978) 25 male CD rats per group received doses of 0, 1000 and 2000 ppm p-toluidine in the diet for 18 months (corresponding to 0, 75 and 150 mg/kg bw/day) followed by a 6 months recovery period. A control group of 25 male rats received diet only. Doses were chosen due to preliminary 30-day feeding study followed by a 2-week recovery period (no details given). No mortality and no signs of toxicity are reported. Body weight development seems to correspond to the respective control group because body weight gain in the treated rats 10 % below that of the respective controls should have resulted in a reduction of the dosage. No gross and no histopathological changes were discovered. Other examined parameters were not reported. Thus, under the conditions of this investigation, the NOAEL (systemic toxicity) is 2000 ppm (approximately 150 mg/kg bw/day).

In the analogous study with CD-1 mice of both sexes, animals were initially fed 0, 1000 and 2000 ppm p-toluidine (corresponding to 150 and 300 mg/kg bw/day) for a period of 6 months. Due to significantly decreased body weights (> 10 %, details not given) and increased mortality rate when compared to the concurrent controls doses were reduced to 500 and 1000 ppm (corresponding to 75 and 150 mg/kg bw/day) and given for further 12 months followed by a 3 months recovery period. No other toxic effects or any other examined parameters were reported. With respect to

tumor development see Chapter 3.1.7. Thus under the conditions of this investigation the NOAEL (systemic toxicity) is 500 ppm (approximately 75 mg/kg bw/day; Weisburger et al., 1978).

m-Toluidine (SIAM 11): There has been reported a valid combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD TG 422 with the structurally closely related isomer m-toluidine which has been assessed during OECD-ICCA SIAM 11 in 2001. In this study SD (Crj:CD) rats received m-toluidine by gavage at doses of 0; 30; 100 and 300 mg/kg bw/day. Males were dosed for 42 days and females were dosed from 14 days before mating and throughout pregnancy until day 3 of lactation. Hematological and biochemical analyses were conducted for males only. Compound-related clinical signs were low locomotor activity and pale skin at 300 mg/kg bw/day. Erythrocyte counts, blood hemoglobin concentration and hematocrit were decreased at 100 and 300 mg/kg bw/day in males. Histopathological lesions observed in both sexes were deposit pigmentation and extramedullary hematopoiesis in the liver at 100 and 300 mg/kg bw/day and in the spleen already at 30 mg/kg bw/day. Other histological findings were very slight hepatocyte swelling starting at 100 mg/kg bw/day in males and at 300 mg/kg bw/day in females. Changes in renal tubular epithelium with pigment deposit were observed starting from 100 mg/kg bw/day in both sexes. At the lowest dose of 30 mg/kg bw/day marginal deposit pigmentation and extramedullary hematopoiesis in the spleen were observed, suggesting that a slight hemolysis had occurred. Additionally, there are sufficient evidences that this chemical – like also p-toluidine – induces methemoglobinemia, but methemoglobin content was not determined in this study. Therefore the dose of 30 mg/kg bw/day should be considered to represent an adverse effect level due to suggestive evidence of hemolytic anemia. The LOAEL for repeated dose toxicity of m-toluidine is 30 mg/kg bw/day (lowest dose tested) (MHW Japan, 1995; UNEP, 2003).

In a limited carcinogenicity study (same publication as described above for p-toluidine; Weisburger et al., 1978) treatment of rats and mice with m-toluidine in feed for 18 months resulted in a NOAEL (systemic toxicity) of 8000 ppm in rats (highest dose tested, approximately 467 mg/kg bw/day) and of 4000 ppm (1100 mg/kg bw/day) in male mice based on reduced body weight and/or increased mortality rate and of 16 000 ppm in female mice (highest dose tested, approximately 3067 mg/kg bw/day).

p-Isopropylaniline:

There has been reported a valid combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test according to OECD TG 422 with the structurally closely related **p-isopropylaniline**. In this study SD (Crj:CD) rats received p-isopropylaniline by gavage at doses of 0; 6; 20 and 60 mg/kg bw/day. Males were dosed for 48 days (start at 15 days before mating) and females were dosed from 15 days before mating and throughout pregnancy until day 3 of lactation; males were sacrificed on day 48 and females on day 4 of lactation. Toxic effects were seen at 20 mg/kg bw/day and above consisting of methemoglobinemia and related symptoms (1.2 % methemoglobin at 20 mg/kg bw/day; extramedullary hematopoiesis and pigment deposits in spleen and liver; increase in liver and spleen weight). The NOEL for repeated dose toxicity is 6 mg/kg bw/day (MHW Japan, 1999).

Table 11 Hematotoxicty of p-toluidine, m-toluidine and p-isopropylaniline following repeated application

	Spezies, route, doses (mg/kg bw/day), treatment time	Hematotoxicity	NOEL	Reference
p-Toluidine	Rat, p.o., 0, 40, 80, 160, for 6 months	Dose-related increase of methemoglobin up to 10.5 %	< 40 mg/kg bw/day	Malik-Brys and Senczuk, 1995a, b
m-Toluidine	Rat (male), p.o., 0, 30, 100, 300 for 42 days	Deposite pigmentation, extramedullary hematopoiesis in the spleen	< 30 mg/kg bw/day	UNEP2003
p-Isopropyl-aniline	Rat (m), po., 0, 6, 20, 60 for 48 days	Dose-related effects at 20 mg/kg bw/day and above, statistically sign. at 60 mg/kg bw/day: erythrocytes ↓, hemoglobin ↓, hematocrit ↓, methemoglobin ↑, reticulocytes ↑, spleen weight ↑	6 mg/kg bw/day	MHW, 1999

Conclusion

p-Toluidine: There are no adequate repeated dose toxicity studies available for p-toluidine. There are a number of limited studies sufficient to support a weight of evidence approach. Limitations include documentation of the experiments in general, number of animals under test, treatment time as well as the lack of necessary investigations. Nevertheless, the overall weight of evidence indicates low systemic toxicity with liver and blood as target organs.

Based on increased liver to body weight ratio in the available subacute feeding study a NOAEL of 165 ppm (corresponding to 13.8 mg/kg bw/day) can be derived for rats. In studies over a period of 6 months dose-related (40 - 160 mg/kg bw/day) increases in methemoglobin level up to ≥ 10 % are reported for rats. In addition, it is demonstrated that prolongation of treatment time up to 12 months does not result in further increase in methemoglobin levels in rats. Treatment of rats and mice with p-toluidine in feed for 18 months resulted in a NOAEL (systemic toxicity) of 2000 ppm in rats (highest dose tested, approximately 150 mg/kg bw/day). In mice treated with 500 ppm (approximately 75 mg/kg bw/day) no influence on body weight and/or mortality rate was reported, however hepatomas occurred in males.

m-Toluidine (SIAM 11)

With m-toluidine there has been reported a valid combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD TG 422 on rats with gavage application of the structurally closely related isomer m-toluidine which has been assessed during OECD-ICCA SIAM 11 in 2001. In this study *m-toluidine* leads to deposit pigmentations and extramedullary hematopoiesis in spleen starting already at the lowest dose of 30 mg/kg bw/day

representing the LOAEL. There are sufficient evidences that this chemical induces methemoglobinemia, but methemoglobin content was not determined in this study.

p-Isopropylaniline

With p-isopropylaniline there has been reported a valid combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD TG 422 on rats with gavage application resulting in a NOEL (systemic toxicity) of 6 mg/kg bw/day based on erythrocyte toxicity including secondary effects.

Overall conclusion:

Following repeated dosing both toluidine isomers as well as p-isopropylaniline reveal as main targets the erythrocytes (methemoglobin formation) and liver (increased liver weight/m-toluidine and p-isopropylaniline and slight hepatocyte swelling/p-toluidine in rats; liver tumors in mice/m- and p-toluidine). The NOEL's in rats for all three substances are roughly in the same dose range; main toxic principle of all three substances is the methemoglobin formation with accompanying symptoms.

3.1.6 Mutagenicity

Studies in Animals

In vitro Studies

In 1996 and 1997 JETOC reported standard Ames-test (preincubation methodology) with p-toluidine using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2urA (with and without rat liver S9-mix) and concentrations ranging between 0.0 and 5000 µg/ml with negative results. In 1997 JETOC reported additionally *Salmonella typhimurium* TA102 and TA104 and *Escherichia coli* WP2urA/pKM101 (0 - 5000 µg/ml) yielding also negative results. Positive controls were reported to be functional in both publications. Zeiger et al. (1992) did not find mutagenic activity in concentrations ranging between 0 and 3333 µg/plate using *Salmonella typhimurium* TA97, TA98 and TA1535 without metabolic activation and in the presence of hamster or rat liver S9-mix. *Salmonella typhimurium* TA100 was tested negative without metabolic activation and in the presence of rat liver S9-mix but was positive in the presence of hamster liver S9-mix. Concurrent positive controls were always functional (Zeiger et al., 1992).

p-Toluidine was tested for clastogenicity in Chinese hamster lung cells in the presence and in the absence of an exogen metabolic activation system. Test concentrations ranged from 12.5 µg/ml up to 50 µg/ml (Ishidate, 1988) and up to 1000 µg/ml (Ishidate, Harnois and Sofuni, 1988), respectively. Cytotoxicity was determined in preliminary tests with and without S9-mix, in the presence of S9-mix from 25 µg/ml onward (Ishidate, 1988). In both reports induction of chromosomal aberrations were only observed in the presence of S9-mix (from12.5 µg/ml (Ishidate, 1988) and from 500 µg/ml (Ishidate, Harnois and Sofuni, 1988), respectively) but not in the absence of the metabolic activation system.

In vivo Studies

Single intraperitoneal injection of 35 mg/kg bw into male Swiss mice caused significant increases in DNA-single strand breaks in the nuclei of liver and kidney which were prepared 4 hours after application and measured by alkaline elution technique as compared to the concurrent solvent control. As the dose corresponds to 2/3 of the respective LD_{50} (information given in the publication) it cannot be decided definitely whether the effects occurred due to cytotoxicity or real genotoxic mechanisms (Bolognesi, Cesarone and Santi, 1980; Cesarone, Bolognesi and Santi, 1982).

Conclusion

p-Toluidine does not induce point mutations in the vast majority of in-vitro Ames test. In Chinese hamster lung cells p-toluidine is clastogenic in the presence but not in the absence of S9-mix. In vivo, DNA single strand breaks are detected in liver and kidneys of mice using alkaline-elution technique after single intraperitoneal injection of 2/3 of the respective LD_{50}, (35 mg/kg bw), therefore it cannot be decided definitely whether the effects occurred due to cytotoxicity or real genotoxic mechanisms. Overall, there is some indication for clastogenic activity in vitro and some residual suspicion for such action in vivo.

m-Toluidine (SIAM 11)

m-Toluidine is not genotoxic because of negative results in bacterial experiments (*Salmonella typhimurium* TA98, TA100, TA1535, TA 1537, TA1538, G46, C3076, D3052, *Escherichia coli* WP2 and WP2uvrA with or without an exogenous metabolic activation system) and mammalian in vitro tests according to OECD TG 473 (chromosomal aberration in Chinese hamster lung (CHL) cells) as well as in vivo experiments. The four available in vivo genotoxicity studies could not be adopted as the robust study due to the lack of detailed data. Their types were sister chromatid exchange and inhibition of DNA-synthesis. All results were negative (UNEP, 2003).

p-Isopropylaniline

p-Isopropylaniline was tested in the Ames test using *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and WP2uvrA in the presence and absence of an exogenous metabolic activation system and concentrations up to cytotoxicity yielding positive results only in *Salmonella typhimurium* TA100 and TA1535 in the presence of S9-mix (MHW 1999). Negative results were obtained when clastogenicity was tested with Chinese hamster lung (CHL) cells in the presence and in the absence of S9-mix (MHW, 1999).

Overall conclusion

Both, p- and m-toluidine are not mutagenic to *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and to *Escherichia coli* strain WP2uvrA with and without addition of rat liver S9 mix. p-Toluidine was positive in *Salmonella typhimurium* TA 100 in the presence of hamster liver S9 mix; m-toluidine was inactive under these conditions. p-Isopropylaniline showed mutagenic activity only in *Salmonella typhimuriun* TA100 and TA1535 in the presence of rat S9-mix. In mammalian cell systems (chromosomal aberration) for p-toluidine - but not for m-toluidine - there is some indication for clastogenic activity in vitro whereas p-isopropylaniline did not induce chromosomal aberrations in mammalian cell systems in vitro.

3.1.7 Carcinogenicity

The available studies to evaluate carcinogenicity in rats and mice don’t meet the criteria of today and are only reported in brief.

In vivo Studies in Animals

Dermal

In an older study of limited validity, a drop of a 20 % solution of p-toluidine in dioxan was applied to the shaved backs of 32 white mice, twice weekly for 12 weeks. At the end of the treatment period 27/32 animals had survived and were in satisfactory condition (no further information available). No papillomas or carcinomas of the skin were seen (Boutwell and Bosch, 1959).

Oral

Study with rats

In a limited carcinogenicity study 25 male CD rats/group were given 0, 1000 and 2000 ppm p-toluidine in the diet for 18 months (corresponding to 0, 75 and 150 mg/kg bw/day. For general toxicity see chapter 3.1.5). At the end of an additional observation period of 6 months necropsy was performed and rats were examined for gross and histopathological changes. With respect to tumor formation, p-toluidine was inactive in male rats. Thus, under the limited conditions of the test no tumours were observed at any dose level (Weisburger et al., 1978).

Study with mice

In a study over a period of 21 months 25 male and 25 female CD-1 mice were initially fed 0, 1000 and 2000 ppm p-toluidine hydrochloride (corresponding to 150 and 300 mg/kg bw/day) for a period of 6 months. Due to significantly decreased body weights (> 10 %) and increased mortality rate when compared to the concurrent controls doses were reduced to 0, 500 and 1000 ppm (corresponding to 0, 75 and 150 mg/kg bw/day) and given for further 12 months. After a 3 months post exposure observation period mice were killed and examined for gross and histopathological changes (for general toxicity see also chapter 3.1.5). Male mice at both dose levels exhibited a significant increase in hepatomas: concurrent control -- pooled control versus low dose -- high dose: 3/18 (16.7 %) -- 7/99 (7.1 %) versus 8/17 (47 %) -- 9/18 (50 %). Female mice at high dose level also showed an increase in liver tumors: concurrent control -- pooled control versus low dose -- high dose: 0/20 (0 %) -- 1/102 (0.98 %) versus 2/21 (9.5 %) -- 3/17 (17.6 %) (Weisburger et al., 1978).

Subcutan

In a study of limited validity mainly due to the application route, which does not correspond to the human situation, 30 male and 30 female Sprague-Dawley rats/dose group were once per week for 24 months subcutaneously injected with 0, 25 and 75 mg/kg bw/day p-toluidine dissolved in peanut oil. No death occurred during the treatment time and no clinical signs related to treatment were noted. Dose-related reduced body weight was noted (no other information) and liver cell necrosis was observed in peanut oil controls, untreated controls and in all substance treated rats: 4/60 - 4/60 - 8/60 - 9/60. Slightly increased, but not significant, numbers of malignant tumors at the injection site and benign liver tumors were observed in male and female animals when compared to the concurrent oil control; m//f: untreated - peanut oil - low dose - high dose: tumors at the injection site: 0/30//0/30 - 6/30//1/30 - 9/30//2/30 - 8/30//5/30; liver tumors: 0/30//0/30 - 0/30//1/30 - 0/30//1/30 - 1/30//6/30. Thus the author concluded that p-toluidine causes tumors only under extreme conditions (Bayer AG, 1981).

Studies in Humans

In an early survey it is reported that cytoscopic examination of 75/81 workers revealed two cases of bladder papilloma, one being a 23 year old worker who had been exposed for 1 year and 8 months

only to p-toluidine and the other a 49 year old worker who had been exposed to o- and p-toluidine for 23 years (Khlebnikova et al., 1970).

Conclusion

There are no adequate studies with **p-toluidine** to evaluate carcinogenicity in rats and mice. There are a number of limited studies sufficient to support a weight of evidence approach. The limitations include e.g. only one dose in the dermal study, limited number of animals , treatment time too short and are only reported in brief). Following oral and dermal (one dose only) application to rats no tumors can be identified at any dose level. In mice, hepatomas are identified in males in all dose groups whereas females showed liver tumors only in the high dose group.

In a study with subcutaneous injection of p-toluidine to rats only a slight, not significant increase in the number of tumors at the injection site and in the liver are reported.

m-Toluidine (SIAM 11)

The available studies with **m-toluidine** (taken from the same publication as those studies described for p-toluidine) to evaluate carcinogenicity in rats and mice don't meet the criteria of today (e.g. only limited number of animals, treatment time too short and are only reported in brief). Following oral application via the feed to rats (initial doses of 8000 and 16 000 ppm reduced after 3 month to 4000 and 8000 ppm; reported time average doses being 233 and 467 mg/kg bw/day, respectively) no tumors can be identified at any dose level. In the feeding study with mice (initial doses of 16 000 and 32 000 ppm reduced after 5 month to 4000 and 8000 ppm for males and, 8000 and 16 000 for females; reported time average doses being 1100 and 2200 mg/kg bw/day, respectively, for males, and 1533 and 3067 mg/kg bw/day, respectively, for females, respectively) only hepatic tumors are observed with increased incidence in male mice at the low dose (4/16 versus 1/18 in control mice) but not at high dose mice (1/16 versus 1/18 in control mice) (UNEP, 2003).

Overall conclusion

The available studies evaluating the carcinogenicity of p-toluidine and m-toluidine in rats and in mice don't meet the criteria of today (e.g. only limited number of animals, treatment time too short and are only reported in brief). For both isomers no tumors can be detected in rats. In mice hepatic tumours are observed following treatment with p-toluidine in males at both dose levels (75 and 150 mg/kg bw/day) and in females in the high dose group. Following treatment with m-toluidine hepatic tumours were noted only in male mice at 1100 mg/kg bw but not at higher doses. No tumors were observed in females at any dose level.

In view of the limited validity of the carcinogenicity studies there are two aspects to be emphasized: Both isomers are not tumorigenic to rats and lead to liver tumors in mice.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

p-Toluidine

There are no specific studies available which evaluate the possible potential of p-toluidine to affect fertility.

In a subacute (28 days) feeding study, 10 male rats received 0, 165, 825 and 1650 ppm p-toluidine (corresponding to 0, 13.8, 66.8, 125.7 mg/kg bw/day), which was blended with basal diet freshly

every week. No animal died during the study. At autopsy, no significant gross pathological lesions were found among any of the rats examined. Organ to body weight ratio was calculated from testes and revealed no notable changes (see also chapter 3.1.5; Industrial Bio-Test Laboratories Inc., 1973).

In a limited carcinogenicity study (see Chapter 3.1.5 and Chapter 3.1.7; Weisburger et al., 1978) 25 male CD rats per group received doses of 0, 1000 and 2000 ppm p-toluidine in the diet for 18 months (corresponding to 0, 75 and 150 mg/kg bw/day) followed by a 6 months recovery period. At the end of the study autopsy was carried out. No gross and no histopathological findings of the testes were reported.

In the analogous study with mice of both sexes, animals were initially fed 0, 1000 and 2000 ppm p-toluidine (corresponding to 0, 150 and 300 mg/kg bw/day) for a period of 6 months. Due to significantly decreased body weights (> 10 %, details not given) and increased mortality rate when compared to the concurrent controls doses were reduced to 500 and 1000 ppm (corresponding to 0, 75 and 150 mg/kg bw/day) and given for further 12 months followed by a 3 months recovery period. At the end of the study autopsy was carried out and reproductive organs were examined. No gross and no histopathological findings were reported (Weisburger et al. 1978).

m-Toluidine (SIAM 11):

There has been reported a valid combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test according to OECD TG 422 with the structurally closely related isomer m-toluidine which has been assessed during OECD-ICCA SIAM 11 in 2001. In this study SD (Crj:CD) rats received m-toluidine by gavage at doses of 0; 30; 100 and 300 mg/kg bw/day. Males were dosed for 42 days (14 days before mating until 14 days after mating) and females were dosed from 14 days before mating and throughout pregnancy until day 3 of lactation. The toxic effects are presented in detail in chapter 3.1.5. No compound-related adverse effects were detected with regard to the mating performance at any dose level. However, two of ten pregnant females of the 100 mg/kg bw/day-group and all eleven dams of the 300 mg/kg bw/day-group showed total implantation losses in utero. Therefore the NOEL for reproductive toxicity of m-toluidine is 30 mg/kg bw/day. At this dose there was already some degree of hemolytic anemia present as indicated by deposit pigmentation and extramedullary hematopoiesis in the spleen (MHW Japan, 1995; UNEP, 2003).

p-Isopropylaniline:

There has been reported a valid combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test according to OECD TG 422 with the structurally closely related **p-isopropylaniline**. In this study SD (Crj:CD) rats received p-isopropylaniline by gavage at doses of 0; 6; 20 and 60 mg/kg bw/day. Males were dosed for 48 days (start at 15 days before mating) and females were dosed from 15 days before mating and throughout pregnancy until day 3 of lactation; males were sacrificed on day 48 and females on day 4 of lactation. Toxic effects were seen at 20 mg/kg bw/day and above consisting of methemoglobinemia and related symptoms (1.2 % methemoglobin at 20 mg/kg bw/day; extramedullary hematopoiesis and pigment deposits in spleen and liver; increase in liver and spleen weight). The NOEL for repeated dose toxicity is 6 mg/kg bw/day. There were no indications for an impairment of reproductive ability. Therefore the NOEL for reproductive toxicity of p-isopropylaniline is 60 mg/kg bw/day (highest dose tested) (MHW Japan, 1999).

Developmental Toxicity

p-Toluidine

There are no studies available which evaluate the possible potential of **p-toluidine** to cause teratogenicity or embryotoxicity.

m-Toluidine (SIAM 11):

There has been reported a valid combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test according to OECD TG 422 with the structurally closely related isomer **m-toluidine** which has been assessed during OECD-ICCA SIAM 11 in 2001. In this study SD (Crj:CD) rats received m-toluidine by gavage at doses of 0; 30; 100 and 300 mg/kg bw/day. Males were dosed for 42 days (14 days before mating until 14 days after mating) and females were dosed from 14 days before mating and throughout pregnancy until day 3 of lactation. The toxic effects are presented in detail in chapter 3.1.5. Two of ten pregnant females of the 100 mg/kg bw/day-group and all eleven dams of the 300 mg/kg bw/day-group showed total implantation losses in utero. Two of eleven dams of the 30 mg/kg bw/day-group and three of ten dams of the 100 mg/kg bw/day-group did not show the nursing activity and all or more than 50 % of their pups died after birth, while all live offsprings of the other dams in the 30- and 100 mg/kg bw/day-groups showed normal development until day 4 after birth. Therefore this death of pups is considered as a secondary consequence of maternal toxicity, probably due to anemia. Furthermore, change of pup weights and incidence of morphological abnormalities of pups were not significantly different from controls in the 30- and 100 mg/kg bw/day-groups. The NOEL for developmental toxicity for m-toluidine in rats is therefore considered to be 100 mg/kg bw/day (MHW Japan, 1995; UNEP, 2003).

p-Isopropylaniline:

There has been reported a valid combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test according to OECD TG 422 with the structurally closely related **p-isopropylaniline**. In this study SD (Crj:CD) rats received p-isopropylaniline by gavage at doses of 0; 6; 20 and 60 mg/kg bw/day. Males were dosed for 48 days (start at 15 days before mating) and females were dosed from 15 days before mating and throughout pregnancy until day 3 of lactation; males were sacrificed on day 48 and females on day 4 of lactation. Toxic effects were seen at 20 mg/kg bw/day and above consisting of methemoglobinemia and related symptoms (1.2 % methemoglobin at 20 mg/kg bw/day; extramedullary hematopoiesis and pigment deposits in spleen and liver; increase in liver and spleen weight). The NOEL for repeat dose toxicity was 6 mg/kg bw/day. There were no indications for an impairment of reproductive ability. With regard to effects on neonates body weight of pups and viability on day 4 of lactation were decreased at 60 mg/kg bw/day. The NOEL for developmental toxicity for p-isopropylaniline in rats is therefore considered to be 20 mg/kg bw/day (MHW Japan, 1999).

Conclusion

There are no specific data on toxicity for reproduction for **p-toluidine**, but data from repeated dose toxicity studies give no suspicion for possible effects of p-toluidine on reproductive organs. Developmental toxicity studies with p-toluidine are not available.

m-Toluidine (SIAM 11):

In an OECD TG 422 guideline study with **m-toluidine** on rats it is shown that an impairment of reproductive function as well as adverse effects on development might occur after applying

systemically toxic doses to the parents leading to methemoglobin formation. The NOEL for reproductive toxicity of m-toluidine in rats is 30 mg/kg bw/day. At this dose there is already some degree of hemolytic anemia present as indicated by deposit pigmentation and extramedullary hematopoiesis in the spleen. The NOEL for developmental toxicity for m-toluidine in rats is considered to be 100 mg/kg bw/day.**p-Isopropylaniline:** In an OECD TG 422 guideline study with **p-isopropylaniline** on rats there is no impairment of reproductive ability until the highest dose tested (60 mg/kg bw/day) although indications for methemoglobinemia has been detected already at 20 mg/kg bw/day. The NOEL for developmental toxicity for p-isopropylaniline in rats is considered to be 20 mg/kg bw/day (MHW Japan, 1999).

Overall Conclusion

There are no specific data on toxicity for reproduction for p-toluidine. Data from repeated dose toxicity studies give no evidence for possible effects of p-toluidine on reproductive organs. Developmental toxicity studies with p-toluidine are not available. But taking into account the results from an OECD TG 422 guideline study performed with the structurally closely related isomer **m-toluidine** as well as with the structurally related **p-isopropylaniline** on rats it can be deduced that an impairment of reproductive function as well as adverse effects on development might occur after applying systemically toxic doses to the parents leading to methemoglobin formation. The NOEL's for reproductive toxicity in rats are 30 mg/kg bw/day for m-toluidine and 60 mg/kg bw/day for p-isopropylaniline. At these doses there is already some degree of hemolytic anemia present as indicated by deposit pigmentation and extramedullary hematopoiesis in the spleen. The NOEL's for developmental toxicity for m-toluidine in rats are considered to be 100 mg/kg bw/day for m-toluidine and 20 mg/kg bw/day for p-isopropylaniline.

In view of the fact that m-toluidine is more potent in methemoglobin formation than p-toluidine and taking into account that methemoglobinemia in pregnant rats may be causally linked to developmental toxicity it can be assumed that extrapolation of the results with m-toluidine to p-toluidine would imply a tendency to lead to an overestimation of the developmental toxicity of p-toluidine. Since there is no evidence for adverse effects on reproduction or developmental effects for m-toluidine or p-toluidine through a direct mechanism of action further testing of p-toluidine is not regarded to be necessary.

3.2 Initial Assessment for Human Health

There are no specific studies available which evaluate the possible potential of p-toluidine to affect fertility or to cause developmental toxicity. Information from m-toluidine is used to fill the data gap. Therefore the SIAR contains a short comparison of p-toluidine and m-toluidine for all endpoints.

The isomer m-toluidine was already discussed and concluded in SIAM 11, 2001; the data are published by UNEP in 2003. A comparison of the intrinsic toxicological properties of m-toluidine with these properties of p-toluidine showed that m-toluidine is more potent in methemoglobin forming than the p-isomer. Taking into account that methemoglobinemia in pregnant rats is causally linked to developmental toxicity it can be assumed that extrapolation of the results with m-toluidine to p-toluidine would imply a tendency to lead to an overestimation of the developmental toxicity of p-toluidine. Furthermore developmental toxicity data from the structurally related p-isopropylaniline were included in the assessment. This seems to be justified due to the structural similarity of both substances as both aniline derivatives have substituents in para position of nearly the same influence on the reactivity of the respective molecule. This could be demonstrated with the data on acute toxicity as well as with repeated toxicity data. For all three substances methemoglobinemia and/or erythrocyte toxicity seem to be the most relevant mechanism for systemic toxicity. In

addition, with respect to mutagenicity, the comparison of results of the respective tests with these substances demonstrates the inconsistency, which is typical for aromatic amines.

p-Toluidine is absorbed via gastrointestinal tract and is distributed, metabolized and excreted via urine and feces. The identification of 2-amino-5-methylphenol indicates that the metabolism in rat proceeds through ring hydroxylation with subsequent conjugation. There are no specific toxicokinetic data on absorption via skin and respiratory tract; absorption via these administration routes can be reasonably be predicted due to the molecular size of p-toluidine.

m-Toluidine (SIAM 11) is rapidly absorbed via gastrointestinal tract, via skin and is metabolized by ring hydroxylation. Although 2-amino-4-methyl-phenol and 4-amino-2-methylphenol were identified in the rat urine with a small amount of the parent compound, there is no sufficient information on quantitative metabolism of m-toluidine or on toxicokinetics. **Overall conclusion:** Both isomers, p- and m-toluidine are absorbed via gastrointestinal tract and via skin and distributed. They are metabolized by ring hydroxylation with subsequent conjugation and excreted via urine and feces.

For **p-toluidine**, the LC_{50} (inhalative, rat) is > 0.64 mg/l, and LD_{50} (dermal, rabbit) is 890 mg/kg bw. LD_{50} (oral, rat) was determined 656 mg/kg bw and 620 mg/kg bw. Signs of intoxication include hypoactivity, muscular weakness, convulsions, cyanosis and narcosis. p-Toluidine is a methemoglobin forming chemical in rats. Levels up to 21.7 % following oral application to rats and up to 40 % following dermal application to rats were measured. p-Toluidine is a methemoglobin forming chemical in humans as it produces the same toxic effects as aniline from 22 mg/m³ onwards with less cyanosis but more stranguria and hemoglobinuria.

For **m-toluidine**, LD_{50} values are from 450 to 1430 mg/kg bw by oral route to rats and 3250 mg/kg bw by dermal route to rabbits (no information on study quality available). Severe methemoglobin formation is reported following single exposure to m-toluidine ranging up to 36.4 % in rats after oral application and 40 % in rats after dermal application (these data as well as those given above for p-toluidine are derived from a study which examined the methemoglobin formation of m- and p-toluidine in parallel) and up to 60.2 % in cats (i.v.). For **p-isopropylaniline,** LD_{50} values of 985 mg/kg bw and 757 mg/kg bw were reported of rats following single oral application. Single oral application of 25 mg/kg bw to cats resulted in elevated methemoglobin level and an increase in Heinz bodies. **Overall conclusion:** Based on the available data, p- and m-toluidine are of moderate acute toxicity. Main toxic signs result from the methemoglobin formation in rats as well as in humans. m-Toluidine is considerably more active in methemoglobin formation than p-toluidine when tested at equal dosages and under similar experimental conditions. p-Isopropylaniline led to an increase in methemoglobin after oral application of 25 mg/kg bw to cats (no quantitative data available).

p-Toluidine causes irritation to the eyes of rabbits which recovered within 7 days. No irritational effects were observed when applied to the rabbit's ear for 24 hours under occlusive conditions. **p-Toluidine** is a sensitizer by skin contact as shown in a patch test with guinea pigs. There is no valid human data available.

There are no adequate repeated dose toxicity studies available for **p-toluidine**. There are a number of limited studies sufficient to support a weight of evidence approach. Limitations include documentation of the experiments in general, number of animals under test, treatment time as well as the lack of necessary investigations. Nevertheless, the overall weight of evidence indicates low systemic toxicity with liver and blood as target organs. Based on increased liver to body weight ratio in the available subacute feeding study a NOAEL of 165 ppm (corresponding to 13.8 mg/kg bw/day) can be derived for rats. In studies over a period of 6 months dose-related (40 - 160 mg/kg bw/day) increases in methemoglobin level up to ≥ 10 % are reported for rats. In addition, it is de-

monstrated that prolongation of treatment time up to 12 months does not result in further increase in methemoglobin levels in rats. Treatment of rats and mice with p-toluidine in feed for 18 months resulted in a NOAEL (systemic toxicity) of 2000 ppm in rats (highest dose tested, approximately 150 mg/kg bw/day). In mice treated with 500 ppm (approximately 75 mg/kg bw/day) no influence on body weight and/or mortality rate was reported, however hepatomas occurred in males.

With **m-toluidine** there has been reported a valid combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD TG 422 on rats with gavage application of the structurally closely related isomer m-toluidine which has been assessed during OECD-ICCA SIAM 11 in 2001. In this study m-toluidine leads to deposit pigmentations and extramedullary hematopoiesis in spleen starting already at the lowest dose of 30 mg/kg bw/day representing the LOAEL. There are sufficient evidences that this chemical induces methemoglobinemia, but methemoglobin content was not determined in this study. With **p-isopropylaniline** there has been reported a valid combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test according to OECD TG 422 on rats with gavage application resulting in a NOEL (systemic toxicity) of 6 mg/kg bw/day based on erythrocyte toxicity including secondary effects. **Overall conclusion:** Following repeated dosing both toluidine isomers as well as p-isopropylaniline reveal as main targets the erythrocytes (methemoglobin formation) and liver (increased liver weight/m-toluidine and p-isopropylaniline and slight hepatocyte swelling/p-toluidine in rats; liver tumors in mice/m- and p-toluidine). The NOELs in rats for all three substances are roughly in the same dose range; main toxic principle of all three substances is the methemoglobin formation with accompanying symptoms.

p-Toluidine does not induce point mutations in the vast majority of *in vitro* Ames tests. In Chinese hamster lung cells p-toluidine is clastogenic in the presence but not in the absence of S9-mix. *In vivo*, DNA single strand breaks are detected in liver and kidneys of mice using alkaline-elution technique after single intraperitoneal injection of 2/3 of the respective LD_{50} (35 mg/kg bw), therefore it cannot be decided definitely whether the effects occurred due to cytotoxicity or real genotoxic mechanisms. Overall, there is some indication for clastogenic activity *in vitro* and some residual suspicion for such action *in vivo*.

There are no adequate studies with **p-toluidine** to evaluate carcinogenicity in rats and mice. There are a number of limited studies sufficient to support a weight of evidence approach. The limitations include e.g. only one dose in the dermal study, limited number of animals, treatment time too short and are only reported in brief. Following oral and dermal (one dose only) application to rats no tumors can be identified at any dose level. In mice, hepatomas are identified in males in all dose groups whereas females showed liver tumors only in the high dose group. In a study with subcutaneous injection of p-toluidine to rats only a slight, not significant increase in the number of tumors at the injection site and in the liver are reported.

There are no specific data on toxicity for reproduction for **p-toluidine.** Data from repeated dose toxicity studies give no evidence for possible effects of p-toluidine on reproductive organs. Developmental toxicity studies with p-toluidine are not available.

In an OECD TG 422 guideline study with **m-toluidine** on rats it is shown that an impairment of reproductive function as well as adverse effects on development might occur after applying systemically toxic doses to the parents leading to methemoglobin formation. The NOEL for reproductive toxicity of m-toluidine in rats is 30 mg/kg bw/day. At this dose there is already some degree of hemolytic anemia present as indicated by deposit pigmentation and extramedullary hematopoiesis in the spleen. The NOEL for developmental toxicity for m-toluidine in rats is considered to be 100 mg/kg bw/day. In an OECD TG 422 guideline study with **p-isopropylaniline** on rats there is no impairment of reproductive ability until the highest dose tested (60 mg/kg bw/day) although indications for methemoglobinemia has been detected already at 20 mg/kg bw/day. The

NOEL for developmental toxicity for p-isopropylaniline in rats is considered to be 20 mg/kg bw/day. **Overall Conclusion:** There are no specific data on toxicity for reproduction for p-toluidine. Data from repeated dose toxicity studies give no evidence for possible effects of p-toluidine on reproductive organs. Developmental toxicity studies with p-toluidine are not available. But taking into account the results from an OECD TG 422 guideline study performed with the structurally closely related isomer m-toluidine as well as with the structurally related p-isopropylaniline on rats it can be deduced that an impairment of reproductive function as well as adverse effects on development might occur after applying systemically toxic doses to the parents leading to methemoglobin formation. The NOELs for reproductive toxicity in rats are 30 mg/kg bw/day for m-toluidine and 60 mg/kg bw/day for p-isopropylaniline. At these doses there is already some degree of hemolytic anemia present as indicated by deposit pigmentation and extramedullary hematopoiesis in the spleen. The NOELs for developmental toxicity for m-toluidine in rats are considered to be 100 mg/kg bw/day for m-toluidine and 20 mg/kg bw/day for p-isopropylaniline.

In view of the fact that m-toluidine is more potent in methemoglobin formation than p-toluidine and taking into account that methemoglobinemia in pregnant rats may be causally linked to developmental toxicity it can be assumed that extrapolation of the results with m-toluidine to p-toluidine would imply a tendency to lead to an overestimation of the developmental toxicity of p-toluidine. Since there is no evidence for adverse effects on reproduction or developmental effects for m-toluidine or p-toluidine through a direct mechanism of action further testing of p-toluidine is not regarded to be necessary.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

Concerning the aquatic effects short term toxicity, tests for each trophic level are available. The most sensitive species was *Daphnia magna* followed by algae.

Acute toxicity of p-toluidine was tested with four different fish species (Table 12).

For *Pimephales promelas*, two LC_{50} of 149 and 171 mg/l after 96 h were obtained. The studies were conducted under flow-through regime and similar conditions as in the OECD TG 203. Reported values were corrected for recovery and are related to measured concentrations. No effect concentrations concerning behaviour and mortality, NOEC of 59.5 and 93.2 mg/l were observed after 96 h (Geiger et al., 1986; Geiger, Brooke and Call, 1990).

In an acute test performed with *Danio rerio* according to OECD TG 203 a 96 h-LC_{50} of 115 mg/l was obtained (Hoechst AG, 1990).

For *Cyprinus carpio* an 96-h LC_{50} value of 132 mg/l was obtained in a semistatic test system (Yuan, Lu and Zhao, 2001).

With the species *Poecilia reticulata* a 14 d-LC_{50} of 10.7 mg/l was obtained in a semistatic test in accordance to the method described in 1981 by Koenemann. The test was performed with 8 fish in prepared standard water, at 22 °C (Hermens, Leeuwangh and Musch, 1984).

For the daphnids three publications are available. The tests were carried out according to standard methods or similar procedures. They are described below.

A test on the acute toxicity of p-toluidine to the invertebrate *Daphnia magna* was performed according to the OECD TG 202 in a semistatic test system. For a test period of 48 hours an EC_{50} value of 0.12 mg/l was reported (Pedersen et al., 1998).

Following the test procedure described by Bringmann and Kuehn (1959), comparable to a guideline method, a 48 h-EC_{50} value of 0.6 mg/l was obtained with *Daphnia magna* (static test, 23°C, pH = 7.5, 10 daphnids per vessel).

Abe et al. (2001) determined an EC_{50} of 5 mg/l after 48 hours with the OECD TG 202 for *Daphnia magna*. This is a nominal concentration, as no analytical monitoring was mentioned in the article.

Concerning the algal toxicity, Lu, Yuan and Zhao (2001) tested the toxicity of p-toluidine towards *Scenedesmus obliquus* following the OECD TG 201. An EC_{50} of 62.9 mg/l was determined after 48 h for the endpoint growth rate. A test carried out with *Scenedesmus quadricauda* according to the cell multiplication inhibition test designed by the authors (24 °C, continuous illumination) revealed a 96 h-EC_3 of 8.0 mg/l. This value was reported for the endpoint biomass (Bringmann and Kuehn, 1959).

Data for algal toxicity (*S. capricornutum*, 72 h-E_bC_{50}) of m-toluidine (SIAM 11) and o-toluidine (SIAM 19) is 17.7 and 30.9 mg/l, respectively. For *Chlorella pyrenoidosa* the 96 h E_rC_{50} for o-toluidine is 55 mg/l.

Table 12 Tests on acute toxicity of p-toluidine to fish, *Daphnia*, and algae

Species	Test type	Duration/ Endpoint	Effect concentration	Reference	IUCLID
Pimephales promelas (fish)	flow through	96 h-LC_{50}	149 mg/L (m)	Geiger et al., 1986	4.1
Pimephales promelas (fish)	flow through	96 h-LC_{50}	171 mg/L (m)	Geiger, Brooke and Call,1990	4.1
Danio rerio (fish)	Static	96 h-LC_{50}	115 mg/l (m)	HOECHST AG, 1990	4.1
Cyprinus carpio (fish)	Semistatic	96 h-LC_{50}	132 mg/l (n)	Yuan, Lu and Zhao, 2001	4.1
Poecilia reticulata (fish)	Semistatic	14 d-LC_{50}	10.7 mg/l (n)	Hermens, Leeuwangh and Musch 1984	4.1
Daphnia magna (crustacean)	Semistatic	48 h-EC_{50}	0.12 mg/l (m)	Pedersen et al., 1998	4.2
Daphnia magna (crustacean)	Static	48 h-EC_{50}	5 mg/l (n)	Abe et al., 2001	4.2
Daphnia magna (crustacean)	Static	48 h-EC_{50}	0.6 mg/l (n)	Bringmann and Kuehn, 1959	4.2
Scenedesmus obliquus (algae)	Static	48 h-E_rC_{50}	62.9 mg/l (n)	Lu, Yuan and Zhao, 2001	4.3
Scenedesmus quadricauda (algae)	Static	96 h-E_bC_3	8.0 mg/l (n)	Bringmann and Kuehn, 1959	4.3

(n): nominal concentration
(m): measured concentration

Chronic Toxicity Test Results

No chronic tests on the toxicity of p-toluidine towards fish or daphnids are available.

Determination of $PNEC_{aqua}$

As acute test results of p-toluidine for three trophic levels are available, an assessment factor of 1000 was applied for the derivation of the $PNEC_{aqua}$ according to the EU Technical Guidance Document. The lowest of the available $L(E)C_{50}$ values was obtained for *Daphnia magna*, 48 h-EC_{50} = 0.12 mg/l, therefore resulting in a

$PNEC_{aqua}$ = 0.12 µg/l.

Toxicity to Microorganisms

Toxicity of p-toluidine to activated sludge was evaluated by Yoshioka et al. (1986) according to the OECD TG 209. The predominantly domestic sewage obtained an EC_{50} value of 100 mg/l when exposed to p-toluidine for 3 hours.

The toxicity of p-toluidine to *Tetrahymena pyriformis* was tested in a 40 hours test using the population growth impairment as endpoint. The test was performed according to the method described by Schultz (1997). An EC_{50} of 120 mg/l was observed (Schultz, 1999). In another test performed with *Tetrahymena pyriformis* in which the cell multiplication inhibition was the endpoint, a 24 h-EC_{50} of 150 mg/l was obtained (Yoshioka, Ose and Sato, 1985). In a third test with *T. pyriformis* an EC_{50} (60 h) of 143.6 mg/l was obtained (Schultz and Moulton, 1984).

Microbial toxicities of p-toluidine are listed in Table 13.

Table 13 Tests on acute toxicity of p-toluidine to microorganisms (IUCLID 4.4)

Species	Endpoint	Duration/ Endpoint	Effect concentration	Reference
activated sludge predominantly domestic (bacteria)	OECD TG 209	3 h-EC50	100 mg/l (n)	Yoshioka et al., 1986
Tetrahymena pyriformis (protozoa)	Growth impairment	40 h-EC50	120 mg/l (n)	Schultz, 1999
Tetrahymena pyriformis (protozoa)	Cell multiplication	24 h-EC50	150 mg/l (n)	Yoshioka, Ose and Sato, 1985
Tetrahymena pyriformis (protozoa)	Growth impairment	24 h-EC50	143.6 mg/l (n)	Schultz and Moulton, 1984

4.2 Terrestrial Effects

The effect of p-toluidine on the plant Chinese cabbage (*Brassica campestris* var. chinensis) was investigated in a test according to the OECD TG 208. The inhibition of plant root elongation was observed in 15 pretreated seeds growing on filter paper in petri dish containing the test solution. Four replicates were conducted for each concentration level. The test solution was renewed each 12 hours. The test was conducted in the dark, at 25°C. There was control of pH and O_2. A LC_{50} of 102.2 mg/l was reported after 5 days (Feng et al., 1996).

Table 14 Tests on acute toxicity of p-toluidine to microorganisms (IUCLID 4.4)

Species	Endpoint	Duration/ Endpoint	Effect concentration	Reference
Brassica campestris var. Chinensis (Chinese cabbage)	OECD TG 208	5 d-LC50	102.2 mg/l (n)	Feng et al., 1996

4.3 Other Environmental Effects

No data available.

4.4 Initial Assessment for the Environment

p-Toluidine consists of lustrous plates or leaflets with a melting point of 44 °C, and a boiling point of 200.5 °C. The density of the liquid is 0.9619 g/cm^3 at 20 °C. The interpolated vapour pressure at 25 °C is 38.1 Pa. The measured log K_{ow} is 1.39. The solubility in water is 7.4 g/l at 25 °C. The flash point is 87 °C, the auto-ignition temperature 482 °C.

In the atmosphere, p-toluidine is degraded by photochemically produced OH radicals. The half-life is calculated to be ca. 2.9 hours.

With regard to the chemical structure, p-toluidine is not expected to hydrolyze due to the lack of hydrolysable functions.

p-Toluidine is inherently biodegradable (MITI test OECD TG 301 C: > 30 % after 14 days; OECD TG 302 B: 94 % after 8 days (industrial sludge), OECD TG 302 B: 94 % after both 10 and 13 days, OECD TG 302 B: 97.7 % after 5 days (adapted sludge), study similar to OECD TG 301 D: biodegradation 68 % after 20 days (study poorly documented)).

According to the Mackay fugacity model level I, the favorite target compartment of p-toluidine is water with 83.7 %, followed by air with 16.0 %. The calculated Henry's law constant (0.21 - 0.24 Pa m^3/mol at 25 °C) proves a low to moderate potential for volatilization from surface waters.

In a sparsely documented study with fish, bioconcentration factors of < 1.3 were obtained at 100 µg/l and < 13 at 10 µg/l. The bioconcentration factor BCF = 2.35 for p-toluidine, calculated from the octanol-water partition coefficient, indicates that there is a low potential for bioaccumulation of p-toluidine in fish. The available experimental data concerning uptake and elimination of p-toluidine in *Mytilus edulis,* indicates its low potential for bioaccumulation in mussels: 85 % elimination of the steady state body burden after 4 hours.

Experimentally obtained adsorption coefficients (Koc) revealed a low to high sorption potential of p-toluidine. The experimentally achieved K_{oc} values were in the range of 102.2 to 1903.4 depending on soil properties. In addition, K_{oc} values were calculated with PCKOCWIN v. 1.66 (K_{oc} = 72.5) and with the TGD equation for the anilines (K_{oc} = 52). These results indicate a low sorption potential of p-toluidine onto the organic phase of soil or sediments. It can be assumed that at low pH the protonated form of p-toluidine with its electrostatic forces may play an important role in soil sorption processes.

Concerning the toxicity of p-toluidine to aquatic species reliable experimental results of tests with fish, *Daphnia*, and algae are available. The tests were performed according to standard procedures

or similar methods. The lowest effect values from short-term tests, as well as from a prolonged fish toxicity test are:

Danio rerio: 96 h-LC_{50} = 115 mg/l (m)
Poecilia reticulata: 14 d-LC_{50} = 10.7 mg/l (n)
Daphnia magna: 48 h-EC_{50} = 0.12 mg/l (m)
Scenedesmus obliquus: 48 h-E_rC_{50} = 62.9 mg/l(n)
Scenedesmus quadricauda: 96 h-E_bC_3 = 8.0 mg/l (n)

Data for algal toxicity (*S. capricornutum*, 72 h-EbC_{50}) of m-toluidine (SIAM 11) and o-toluidine (SIAM 19) is 17.7 and 30.9 mg/l, respectively. For *Chlorella pyrenoidosa* the 96 h-ErC_{50} for o-toluidine is 55 mg/l.

Tests on chronic toxicity of p-toluidine to aquatic species are not available. Concerning the effects on terrestrial organisms the following data was obtained for plants in a root elongation test with a duration of 5 days:

Brassica campestris: 5 d-LC_{50} = 102.2 mg/l (n)

The lowest toxicity of p-toluidine to microorganisms measured in a test according to OECD TG 209. A 3h-EC_{50} value of 100 mg/l was obtained with predominantly domestic sewage.

As acute test results of p-toluidine for three trophic levels are available, an assessment factor of 1000 was applied for the derivation of the $PNEC_{aqua}$ according to the EU Technical Guidance Document. The lowest of the available $L(E)C_{50}$ values was obtained for *Daphnia magna*, 48 h-EC_{50} = 0.12 mg/l, therefore resulting in a

$PNEC_{aqua}$ = 0.12 µg/l.

5 RECOMMENDATIONS

Human Health:

The chemical possesses properties indicating a hazard for human health (acute and subacute toxicity, methemoglobin formation, skin sensitization, eye irritation, possible genotoxicity and carcinogenicity). Based on the data presented by the Sponsor Country, (relating to production by one producer in one country which accounts for 10 - 50 % of global production and relating to the use pattern in several OECD countries) exposure is controlled in occupational settings, and exposure of consumers appears to be negligible. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country. The substance is currently of low priority for further work.

Environment:

The chemical possesses properties indicating a hazard for the environment (acute aquatic toxicity to *Daphnia magna*). Based on data presented by the Sponsor country (relating to production by one producer in one country which accounts for 10 - 50 % of global production and relating to the use pattern in several OECD countries), exposure to the environment is anticipated to be low. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country. The substance is currently of low priority for further work.

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Soil Adsorption Coefficient with PCKOCWIN v. 1.66, 2000
Soil Adsorption Coefficient according to TGD, 2003
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S I D S

Dossier

Existing Chemical	:	ID: 106-49-0
CAS No.	:	106-49-0
EINECS Name	:	p-toluidine
EC No.	:	203-403-1
TSCA Name	:	Benzenamine, 4-methyl-
Molecular Formula	:	C7H9N

Producer related part

Company	:	Bayer AG
Creation date	:	02.02.1994

Substance related part

Company	:	Bayer AG
Creation date	:	02.02.1994
Status	:	
Memo	:	X Update 1998 AKTUELL EG / ICCA
Printing date	:	15.03.2006
Revision date	:	04.06.1994
Date of last update	:	15.03.2006
Number of pages	:	159
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name : p-toluidine
Smiles Code : Nc1ccc(C)cc1
Molecular formula : C7H9N
Molecular weight : 107.16 g/mol
Petrol class :

Flag : Critical study for SIDS endpoint
15.07.2005

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type : typical for marketed substance
Substance type : organic
Physical status : solid
Purity : >= 99.5 % w/w
Colour :
Odour :

Flag : Critical study for SIDS endpoint
17.03.2004 (1)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1-Amino-4-methylbenzene

4-Amino-1-methylbenzene

4-Aminotoluene

4-Methylaniline

4-Methylbenzenamine

4-Methylphenylamine

4-Toluidine

Benzenamine, 4-methyl-

C.I. 37107

C.I. Azoic Coupling Component 107

p-Aminotoluene

p-Methylaniline

p-Methylbenzenamine

p-Methylphenylamine

p-Tolylamine

1.3 IMPURITIES

Purity : typical for marketed substance
CAS-No : 108-44-1
EC-No : 203-583-1
EINECS-Name : m-toluidine
Molecular formula : C7H9N
Value : < .5 % w/w

Remark : Typical purity of the commercial p-toluidine is ca. 99.5 % minimum, with a maximum of 0.5 % total for all other isomers. Moisture is usually < 0.2 %.
Flag : Critical study for SIDS endpoint
17.03.2004 (1)

Purity : typical for marketed substance
CAS-No : 95-53-4
EC-No : 202-429-0
EINECS-Name : o-toluidine
Molecular formula : C7H9N
Value : < .5 % w/w

Remark : Typical purity of the commercial p-toluidine is ca. 99.5 % minimum, with a

maximum of 0.5 % total for all other isomers. Moisture is usually < 0.2 %.

Flag : Critical study for SIDS endpoint
17.03.2004 (1)

Purity : typical for marketed substance
CAS-No : 7732-18-5
EC-No : 231-791-2
EINECS-Name : water
Molecular formula : H2O
Value : .1 - .2 % w/w

Remark : Typical purity of the commercial p-toluidine is ca. 99.5 % minimum, with a maximum of 0.5 % total for all other isomers. Moisture is usually < 0.2 %.
Flag : Critical study for SIDS endpoint
17.03.2004 (1)

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : 19600 - tonnes produced in 2000

Result : In 2000, the global production volume of p-toluidine is estimated to be 19600 tonnes by 23 producers:
Estimated production volume (tonnes/a)
Western Europe (4 producers) 8000
USA (1 producer) 3000
Japan (1 producer) 1200
South Korea (1 producer) 2400
China (13 producers) 3800
India (2 producers) 1200
In the Sponsor country, there are 3 companies which produce p-toluidine. However, no information on production capacities or volumes is available from these companies
Flag : Critical study for SIDS endpoint
22.09.2005 (2)

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Specific limits :
Symbols : T, N, ,
Nota : C, ,
R-Phrases : (23/24/25) Toxic by inhalation, in contact with skin and if swallowed
(36) Irritating to eyes
(40) Limited evidence of a carcinogenic effect
(43) May cause sensitization by skin contact
(50) Very toxic to aquatic organisms
S-Phrases : (28) After contact with skin, wash immediately with plenty of water
(36/37) Wear suitable protective clothing and gloves
(45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
(61) Avoid release to the environment. Refer to special instructions/Safety data sets

22.06.2004

1.6.2 CLASSIFICATION

Classified : as in Directive 67/548/EEC
Class of danger : carcinogenic, category 3
R-Phrases : (R40)
Specific limits :

19.03.2004

Classified : as in Directive 67/548/EEC
Class of danger : dangerous for the environment
R-Phrases : (50) Very toxic to aquatic organisms
Specific limits :

28.03.2000

Classified : as in Directive 67/548/EEC
Class of danger : irritating
R-Phrases : (R36)
Specific limits :

19.03.2004

Classified : as in Directive 67/548/EEC
Class of danger : sensitizing
R-Phrases : (R43)
Specific limits :

19.03.2004

Classified : as in Directive 67/548/EEC
Class of danger : toxic
R-Phrases : (23/24/25) Toxic by inhalation, in contact with skin and if swallowed
Specific limits :

19.03.2004

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : type
Category : Use in closed system

Flag : Critical study for SIDS endpoint
22.09.2005 (1)

Type of use : industrial
Category : Chemical industry: used in synthesis

Flag : Critical study for SIDS endpoint
22.09.2005 (1)

Type of use : use
Category : Intermediates

Result : p-Toluidine is used exclusively as an intermediate in chemical processes e.g. for the synthesis of precursurs of · 4B acid (4-toluidine-3-sulphonic acid, an intermediate for pigment production)
· m-Nitro-p-toluidine, acetoacetate-p-toluidine, di-p-toluidinoterephthalic acid, which all are intermediates in the production of pigments
· Dehydro-p-toluidine, an intermediate in the production of dyestuff
· Pesticides and pharmaceutical intermediates, and others intermediates
Flag : Critical study for SIDS endpoint
22.09.2005 (3)

Type of use : use
Category : Intermediates

Result : p-Toluidine is used exclusively as an intermediate in chemical processes. The largest subsequent product of p-toluidine is 4B acid (4-toluidine-3-sulphonic acid, an intermediate for pigment production) which amounts to about 2/3 of world p-toluidine demand. p-Toluidine is also used in minor amounts for the manufacturing of
· m-Nitro-p-toluidine, acetoacetate-p-toluidine, di-p-toluidinoterephthalic acid, which all are intermediates in the production of pigments
· Dehydro-p-toluidine, an intermediate in the production of dyestuff
· Pesticides and pharmaceutical intermediates, and others intermediates.
In Western Europe the total demand of p-toluidine (5700 tonnes/a) is exclusively used as an intermediate in chemical synthesis. Its use pattern is well-known:
· For the production of different azo-pigments,quinacridone-pigments and paper dyes 4100 tonnes/a p-toluidine are processed by multi step synthesis followed by purification procedures
· About 1000 tonnes/a of p-toluidine is used as an intermediate for pesticides, e.g. for the insecticide fipronil and the fungicide tolylfluanid
· Another group of valuable chemical intermediates with an amount of about 600 tonnes/a is synthesised by substitution of the amino group of p-toluidine. The most important substances of this group are p-fluorotoluene, p-fluorobenz-aldehyde, p-fluorobenzylchloride and p-bromo-toluene
Flag : Critical study for SIDS endpoint
15.03.2006 (2)

Type of use : use
Category : Intermediates

Remark : Historic data. It is assumed that these data are not relevant for today situation.
Result : The anthraquinone color Acid Violett 43 (CI 60730), which is safe for use in hair dye formulations, may contain traces of p-toluidine (less than 0.1 %). According to the US Food and Drug Administration, in the early 1980s there were 31 cosmetic products containing Acid Violett 43 in the USA. In 1998, it was used in 1 out of 1478 hair dyes, in 1 out of 32 coloring hair rinses, and (in violation of the US Food, Drug and Cosmetics Act) in 1 out of 241 underarm deodorants. In the EU and Japan, Acid Violett 43 is approved only for limited uses in cosmetics. In US hair colouring formulations Acid Violett 43 was used at concentrations of less than 0.1 %

(one exception [out of 31] with 0.1-1 %) in the early 1980s (Fiume, 2001). In the EU, toluidines and their salts and halogenated and sulphonated derivatives are not permitted for use in cosmetic products (EU, 1999).

Flag : Critical study for SIDS endpoint
22.09.2005 (4) (5)

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : MAK (DE)
Limit value :

Result : p-Toluidine has been classified on the MAK 3B list as a substance for which a carcinogenic potential is suspected form in vitro or animal experiments. Therefore no MAK (maximum admissible concentration) is set.
Flag : Critical study for SIDS endpoint
09.05.2005 (6)

Type of limit : TRK (DE)
Limit value : 1 mg/m3

Remark : In Germany for occupational settings, a German threshold limit value concentration (TRK = Technische Richtkonzentration) in the workplace air of 1.0 mg/m3 was set for p-toluidine. This value was authoritative for manufacturers and users of p-toluidine in the Sponsor country (TRGS, 900). It was abolished on January 1, 2005.
Result : maximum admissible concentration in the workplace air set by the AGS: 1 mg/m3 = 0.2 ml/m3
- Cancer Category 3 (TRGS 905)
- Danger of skin absorption (TRGS 900)

04.05.2005 (7)

Type of limit : TLV (US)
Limit value : 2 other: ppm

Remark : TWA value; Notations: skin; A3; BEI(M)
TLV basis - critical effect(s): anoxia, kidney

A3: Confirmed animal carcinogen with unknown relevance to humans
BEI(M): Biological exposure indice; methemoglobin inducer
Flag : Critical study for SIDS endpoint
10.05.2005 (8)

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of danger : 2 (water polluting)

Remark : No. 693 in catalogue
13.05.2004

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation : Stoerfallverordnung (DE)
Substance listed : yes
No. in Seveso directive :

Remark : - Appendix II, No. 4 c
- Appendix III, Part 2, No. 2
- Appendix IV, No. 2
21.03.2004 (9)

1.8.5 AIR POLLUTION

Classified by : TA-Luft (DE)
Labelled by : other: Hoechst AG
Number : 3.1.7 (organic substances)
Class of danger : I

Remark : New classification: Organic substances according to class 5.2.5.
21.03.2004 (10)

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

Memo : Transport (additional information for derogation statement)

Result : The transported goods are classified and labeled according to the relevant national and international transport regulations:
- UN-no. 1708
- GGVSee/IMDG-code 6.1
- ADNR 6.1
- RID/ADR 6.1

22.06.2004 (9)

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered : 1
Date of search : 27.08.2003

01.06.2004

Type of search : Internal and External
Chapters covered : 2
Date of search : 27.08.2003

01.06.2004

Type of search : Internal and External
Chapters covered : 3, 4
Date of search : 27.08.2003

01.06.2004

Type of search : Internal and External
Chapters covered : 5
Date of search : 02.01.2004

01.06.2004

Type of search : External
Chapters covered : 2
Date of search : 01.03.2004

Remark : Search by BUA
01.06.2004

Type of search : External
Chapters covered : 3, 4
Date of search : 01.03.2004

Remark : Search by BUA
01.06.2004

Type of search : External
Chapters covered : 5
Date of search : 04.04.2004

Remark : Search by BUA
01.06.2004

1.13 REVIEWS

2.1 MELTING POINT

Value : 44 °C
Sublimation :
Method : other: not specified
Year : 2002
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
24.05.2004 (1)

Value : 37 - 47 °C
Sublimation :
Method : other: not specified
Year : 2003
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Remark : Pressure reported in at [1 at = 981 hPa] and atm [1 atm = 1013 hPa] was converted to hPa
Result : Beilstein reports melting point values from several original literature sources:

Solvent*	Melting point (°C)
water, ethanol	45.1
hexane	45.5
ethanol	43.5
water	43.5
water-ethanol mixture	43-44
petroleum ether	43-44

Pressure (hPa)	Melting point (°C)
980-954000	43.75-67
736000-2700000	61.6-105.9

*Solvent used for clean-up

Furthermore values in the range of 37 to 47 °C are available without specifying the dependent variable.
Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (11)

Value : 45 °C
Sublimation :
Method : other: not specified
Year : 1999
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (12)

Value : 43.7 °C

Sublimation :
Method : other: not specified
Year : 1995
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (13)

Value : 44 - 45 °C
Sublimation :
Method : other: not specified
Year : 2001
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (14)

Value : 44.5 °C
Sublimation :
Method : other: not specified
Year : 1979
GLP : no
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (15)

Value : 43.8 °C
Sublimation :
Method : other: not specified
Year : 1986
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (16)

Value : 43.5 - 43.8 °C
Sublimation :
Method : other: measured with the apparatus designed by Pouyet et al. (1965)
Year : 1969
GLP : no
Test substance : other TS: p-Touidine, in several purity phases

Method : Pouyet R, Gillet R, and Méallier P (1965). Bull.Soc.Chim. 6, 1784.
Result : The melting point was reported to be between 43.5-43.70 °C during the process of purification by distillation.
One value was taken from the literature for comparison: 43.75 °C.
Depending on the amount of water contained in the purified sample, the melting point varied between 40.10 - 43.70 °C (amount of water: 17.84 - 0 g/l, respectively)
Reliability : (2) valid with restrictions
Basic data given
24.05.2004 (17)

Value : 45 °C
Sublimation :
Method : other: not specified
Year : 1996
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (4) not assignable
Data from non-peer-reviewed handbook or collection of data
24.05.2004 (18)

2.2 BOILING POINT

Value : 200.5 °C at 1013 hPa
Decomposition :
Method : other: not specified
Year : 2002
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
24.05.2004 (1)

Value : 200.4 - 200.6 °C at 1013 hPa
Decomposition :
Method : other: not specified
Year : 2003
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Remark : Pressure is given in mmHg
Result : Beilstein reports several boiling point values from several different sources:

Pressure (hPa)	Boiling point (°C)
1.3	40.27, 46.9
2.7	61.5
4	70-75
5.3	69.5-71.5
13.3	82.2
17.3	84, 115-116
20	89.7
24	79.5
27	95.6
33	100.2, 100-101
40	103-104
67	115.8
133.3	133.7, 133.2
200	145.6
266.6	154.7
400	166.9
533.3	176.9
667	184.6
800	191.1
933	196.9
981	200.4

1010.2	199.9-199.95
1013	200.4, 200.5, 200.55
19612	368
n.d.	202.5-203
n.d.	200.3
n.d.	200-201
n.d.	200
n.d.	198

n.d. = no data

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (11)

Value : 200 °C at
Decomposition :
Method : other: not specified
Year : 1999
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (12)

Value : 200 - 201 °C at
Decomposition :
Method : other: not specified
Year : 2001
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (14)

Value : 200.4 °C at
Decomposition :
Method : other: not specified
Year : 1995
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (13)

Value : 200.4 °C at
Decomposition :
Method : other: not specified
Year : 1979
GLP : no
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (15)

Value : 200.6 °C at 1013 hPa
Decomposition :
Method : other: not specified
Year : 1986
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (16)

Value : 200.3 °C at
Decomposition :
Method : other: not specified
Year : 1996
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (4) not assignable
Data from non-peer-reviewed handbook or collection of data
24.05.2004 (18)

2.3 DENSITY

Type : density
Value : .9619 g/cm³ at 20 °C
Method : other: not specified
Year : 2002
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
24.05.2004 (1)

Type : density
Value : g/cm³ at °C
Method : other: not specified
Year : 2003
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Result : Beilstein reports several density values from several different sources:

Temperature (°C)	Density (g/cm3)
n.d.	1.046
n.d.	1.058
45	0.9658
50	0.9614, 0.9619
55	0.975
60	0.9532
65	0.991
70	0.9449, 0.9444
78.9	0.9339
90	0.9276
120	0.902
135.6-190	0.889-0.8354

n.d. = no data
Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (11)

Type : density
Value : .9619 g/cm³ at 20 °C
Method : other: not specified
Year : 1995
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (13)

Type : density
Value : .9659 g/cm³ at 45 °C
Method : other: not specified
Year : 1986
GLP : no data
Test substance : other TS: p-Toluidin, purity not specified

Remark : The density at 50°C is specified with 0.96155 g/cm3
Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (16)

Type : relative density
Value : at °C
Method : other: not specified
Year : 2003
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Result : Beilstein reports several relative density values from several different sources:

Temp. (°C)	Ref. Temp. (°C)	Rel. Density
20	4	1.1
39.9-175	4	0.9703-0.8502
44	4	0.9663
45	4	0.96589
50	4	0.96155
50	50	0.973
50-85	4	0.9613-0.9332
54	4	0.958
55	4	0.9593-0.95766
58	4	0.954
59	4	0.9546
59.1	4	0.9538
60	60	0.9692
60	4	0.95384
70	70	0.967
172	4	0.857

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (11)

Type : relative density

Value : 1.046 at 20 °C
Method : other: not specified
Year : 1999
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Result : Relative density given as the ratio of the density of the test substance at 20°C and the density of water at 4°C
Reliability : (2) valid with restrictions
Data from handbook or collection of data
18.06.2004 (12)

Type : relative density
Value : 1.046 at 20 °C
Method : other: not specified
Year : 2001
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Result : Relative density given as the ratio of the density of the test substance at 20 °C and the density of water at 4 °C
Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (14)

Type : relative density
Value : 1.046 at 20 °C
Method : other: not specified
Year : 1979
GLP : no
Test substance : other TS: p-Toluidine, purity not specified

Remark : Relative density given as the ratio of the density of the test substance at 20 °C and the density of water at 4 °C.
Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (15)

Type : relative density
Value : 1.046 at 20 °C
Method : other: not specified
Year : 1996
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Result : Relative density given as the ratio of the density of the test substance at 20 °C and the density of water at 4 °C
Reliability : (4) not assignable
Data from non-peer-reviewed handbook or collection of data
24.05.2004 (18)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : .381 hPa at 25 °C
Decomposition :
Method : other (calculated): application of the Cox vapor pressure equation
Year : 1983
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Method : Approx. 97 vapor pressure values on p-toluidine were collected and analyzed.
Collected vapour pressure values from other publications were either experimental values or calculations from a regressed correlation based on experimental data.
Evaluated values were weighted and combined to fit in a Cox vapor pressure equation: logP = (1-D/T) x 10 E(A+BT+CTE2) by the least squares method.
T: temperature in K.
p: pressure in atm (1 atm = 101.325 kPa)

The coefficients derived for p-toluidine were:
A = 0.915691
B = -6.57014 E-04
C = 5.11261 E-07
D = 473.445

Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
24.05.2004 (19)

Value : .29 hPa at 25 °C
Decomposition :
Method : other (calculated): with MPBPWIN v1.41
Year : 2004
GLP :
Test substance :

Remark : modified Grain Method using MP: 43.7°C; BP: 200.4°C
Reliability : (2) valid with restrictions
Accepted calculation method
24.05.2004 (20)

Value : .45 hPa at 25 °C
Decomposition :
Method : other (measured): not specified whether measured or calculated
Year : 1986
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (16)

Value : 1.3 hPa at 42 °C
Decomposition :
Method : other (measured): not specified whether measured or calculated
Year : 2002
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Result : Other reported value: 80 hPa at 140 °C
Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (1)

Value : 1.72375 hPa at 42.9 °C
Decomposition :
Method : other (measured)
Year : 1994
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Result : A curve is given of the pressure (psia) results in relation to the temperature (F). From this curve a pressure of 0.025 psia at a temperature of 109.2 F (42.89 °C) can be read. (1 psia=68.95 hPa)
Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (21)

Value : 1.33 hPa at 42 °C
Decomposition :
Method : other (measured): not specified whether measured or calculated
Year : 1979
GLP : no
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (15)

Value : 1.3 hPa at 42 °C
Decomposition :
Method : other (measured): not specified whether measured or calculated
Year : 1996
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Reliability : (4) not assignable
Data from non-peer-reviewed handbook or collection of data
24.05.2004 (18)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : 1.39 - 1.44 at °C
pH value :
Method : other (measured)
Year : 1995
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Remark : Three values are given: 1.39, 1.39, and 1.44 from 3 different sources. log Pow 1.39 was signed as preferred value for the neutral form.
Reliability : (2) valid with restrictions
Data from handbook or collection of data

Flag : Critical study for SIDS endpoint
24.05.2004 (22)

Partition coefficient : octanol-water
Log pow : 1.62 at °C
pH value :
Method : other (calculated): with KOWWIN v1.67, 2000
Year : 2004
GLP :
Test substance :

Reliability : (2) valid with restrictions
Accepted calculation method
13.02.2004 (20)

Partition coefficient : octanol-water
Log pow : .979 at 25 °C
pH value :
Method : other (measured): estimation according to OECD Chemicals Testing Programme Ecotoxicology Group (1979)
Year : 1982
GLP : no data
Test substance : other TS: p-toluidine, purity of analytical grade

Method : The test substance was dissolved in distilled water or n-octanol (each 100 mg/l); the aqueous test solution was shaken with n-octanol in a separatory funnel for 2 hours (100 ml of each test solution). Following 2 hours without shaking, 100 ml n-octanol test solution was shaken with 100 ml water. The 2 phases were separated and the concentration of the test substance was determined by gas liquid chromatography. The partition coefficient (P) is defined as the ratio of the equilibrium concentration (C) of a dissolved substance in a two-phases system.

$$P = \frac{C_{n\text{-}octanol}}{C_{water}}$$

Result : Original value reported: Pow = 9.53
Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles
24.05.2004 (23)

Partition coefficient : octanol-water
Log pow : 1.39 at °C
pH value :
Method : other (calculated)
Year : 2000
GLP :
Test substance :

Remark : The value of the partition coefficient was calculated from the ClogP for Windows software (Biobyte Corp.). Partition coefficient values for the several pH values (6.0,7.8, and 9.0) tested in the study were calculated according to the following equation

log D = log P - log (1+10^(pKa-pH))

in which D is the apparent partition coefficient or

distribution coefficient.

Result : The following calculated apparent partition coefficient values were given:

pH	log D
6.0	1.35
7.8	1.39
9.0	1.39

Reliability : (2) valid with restrictions
Accepted calculation method

11.05.2004 (24)

Partition coefficient : octanol-water
Log pow : 1.39 - 1.41 at °C
pH value :
Method : other (measured)
Year : 1996
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Result : Two different octanol-water partition coefficient values are given for p-toluidine: 1.39 and 1.41 but the origin of the values is not specified. A third value of 1.6 is given as calculated.
Reliability : (4) not assignable
Data from non-peer-reviewed handbook or collection of data

24.05.2004 (18)

Partition coefficient : octanol-water
Log pow : 1.39 at °C
pH value :
Method : other (calculated)
Year : 2003
GLP :
Test substance :

Remark : The value of the partition coefficient was computer calculated from the ClogP for Windows software (Vers. 3.55, Biobyte, Claremont, CA, USA).
Reliability : (4) not assignable
Documentation insufficient for assessment

25.02.2004 (25)

Partition coefficient : octanol-water
Log pow : 1.39 at °C
pH value :
Method : other (measured)
Year : 1999
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Remark : The value of the octanol-water partition coefficient for p-toluidine is indicated as a measured value but its origin is not specified.
Reliability : (4) not assignable
Documentation insufficient for assessment

24.05.2004 (26)

Partition coefficient : octanol-water
Log pow : 1.54 at °C
pH value :
Method : other (calculated)

Year : 1984
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Remark : Calculation according to Rekker RF (1977). The Hydrophobic Fragmental Constant. Elsevier, Amsterdam.
Reliability : (4) not assignable
Documentation insufficient for assessment
24.05.2004 (27)

Partition coefficient : octanol-water
Log pow : 1.39 at °C
pH value :
Method : other (measured)
Year : 1989
GLP : no data
Test substance : other TS: p-Toluidin, purity not given

Remark : The Log Kow values were experimentally measured or computer calculated by the fragment method. In either case the values were taken from the CLOGP Version 3.34 program.
Reliability : (4) not assignable
Documentation insufficient for assessment
24.05.2004 (28)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : 7.4 g/l at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: not specified
Year : 2001
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
24.05.2004 (14)

Solubility in : Water
Value : 7.225 g/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: SRC WSKOW v1.41

Year : 2004
GLP :
Test substance :

Reliability : (2) valid with restrictions
Accepted calculation method
11.05.2004 (20)

Solubility in : Water
Value : 9.6 g/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: interferometric method
Year : 1975
GLP : no
Test substance : other TS: p-toluidine, purity not specified

Remark : Two measured values are given, both were 0.09 mol/l (= 9.6 g/l) at 25°C. A calculated value of 0.1 mol/l was reported corresponding to 10.7 g/l.
Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (29)

Solubility in : Water
Value : 7.39 g/l at 20.8 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: not specified
Year : 2003
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Result : Beilstein reports several water solubility values from several different sources:

Temperature (°C)	Solubility (g/l)
11.5	3.51*
13	5.56
15	6.54
16	5.81
20	6.23
20.8	7.39
22	7.76*
23.7	7.13
26.7	9.5
31.7	11.42
44	17.73*

69 23.6*

* These values are given in parts of substance/parts of water. The respective g/l values were calculated considering that the density of water is 1g/cm3.

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
24.05.2004 (11)

Solubility in : Water
Value : 6.6 at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: not specified
Year : 1984
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Method : Concentration of p-toluidine was measured in saturated solutions (double distilled water) by spectrophotometry (284 nm)
Result : Solubility reported: 6.2e-2 mol/l corresponding to 6.6 g/l
Reliability : (4) not assignable
Documentation insufficient for assessment
24.05.2004 (30)

Solubility in : Water
Value : 7.4 g/l at 21 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: not specified
Year : 1996
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Result : Solubility at 60 °C reported as 24 g/l
Reliability : (4) not assignable
Data from non-peer-reviewed handbook or collection of data
24.05.2004 (18)

Solubility in : Water
Value : 73.5 g/l at 20.8 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C

Description :
Stable :
Deg. product :
Method : other: not specified
Year : 1986
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Reliability : (4) not assignable
Data from handbook or collection of data. However as other available values are 10-fold smaller at the same temperature range, it seems this is due to an edp (Electronic Data Processing) error

24.05.2004 (16)

2.6.2 SURFACE TENSION

Test type :
Value : 36.06 mN/m at 45 °C
Concentration :
Method : other: not specified
Year : 1986
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Remark : The surface tension at 60°C is specified with 34.10 mN/m.
Reliability : (2) valid with restrictions
Data from handbook or collection of data

24.05.2004 (16)

2.7 FLASH POINT

Value : 87 °C
Type : closed cup
Method : other: not specified
Year : 2002
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
24.05.2004 (1)

Value : 86 °C
Type : closed cup
Method : other: not specified
Year : 2001
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data

24.05.2004 (14)

Value : 87 °C
Type : closed cup
Method : other: not specified

Year : 1986
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (16)

2.8 AUTO FLAMMABILITY

Value : 482 °C at
Method : other: not specified
Year : 2002
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Remark : Auto-ignition temperature
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
24.05.2004 (1)

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

Acid-base constant : 4.98
Method : other: calculated
Year : 2003
GLP :
Test substance :

Remark : The value of the ionization constant was calculated from the Micro quantitative structure-activity relationships (QSARs) software (Vers. 2.0, Hunter System, Washington, DC).
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
25.02.2004 (25)

Method : other: not specified
Year : 2003
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Result : Beilstein reports several dissociation constant values from different sources.
Solvent Temperature Dissociation constant

		(°C)	(pK)
no data		20	5.08
no data		25	5.07
ethanol /water		25	4.34
methanol / water		25	4.99
water		18	5.15
water		19.9	5.07
water		20	9
water		23	5.26
water		25	*
water		29.9	4.8 / 4.94
water / dioxan		29.9	4.76 / 4.8 / 5.12 / 6.24
water / HCl		25	3.07

* 5.03 / 5.05 / 5.07 / 5.08/5.1 / 5.11 / 5.15 / 9.07 / 9.35

Reliability : (2) valid with restrictions
Data from handbook or collection of data
24.05.2004 (11)

Acid-base constant : 5.1
Method : other: not specified
Year : 1999
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Reliability : (4) not assignable
Documentation insufficient for assessment
24.05.2004 (31)

Acid-base constant : 4.98
Method : other: not specified
Year : 2000
GLP : no data
Test substance : other TS: p-toluidine, purity not specified

Reliability : (4) not assignable
Documentation insufficient for assessment
11.05.2004 (24)

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	500000 molecule/cm³
Rate constant	:	= .000000000132 cm³/(molecule*sec)
Degradation	:	= 50 % after 2.9 hour(s)
Deg. product	:	
Method	:	other (calculated): AOPWIN v1.91
Year	:	2000
GLP	:	
Test substance	:	other TS: p-Toluidine
Remark	:	The calculated half-life is based on a mean OH radical concentration of 5E+05 OH radicals/cm3 as a 24 h average.
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

13.03.2006 (20)

Type	:	Air
Light source	:	
Light spectrum	:	Nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	
Year	:	1969
GLP	:	
Test substance	:	other TS: p-Toluidin, high purity (distilled)
Remark	:	No information on the test conditions is reported.
Result	:	UV absorption was measured between 220 and 320 nm in ethyl alcohol at room temperature. Their absorptivity coefficients (e) were: e = 8770 (at 236 nm) e = 1930 (at 289 nm) It is reported that two bands of maximal absorption were determined also in ethanol in preceeding literature.
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint

18.06.2004 (17)

Type	:	other: buffered medium
Light source	:	other: mercury arc lamp
Light spectrum	:	> 300 nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	other: Riboflavin
Conc. of sensitizer	:	
Rate constant	:	cm³/(molecule*sec)
Degradation	:	50 % after .7 minute(s)
Deg. product	:	not measured
Method	:	other (measured): see Test conditions

Year : 1989
GLP : no
Test substance : other TS: p-Toluidin , Purity not given

Remark : The unit µm for concentration is not explained but assumed to be µmol/l (= µM).
Result : -p-Toluidine was virtually inert to direct photolysis.
-In the presence of riboflavin it was rapidly photodecomposed: t 1/2 = 0.7 min.
-The rate constants of all reactions were normalised to that of a standard reaction, the photodecomposition of valerophenone (k = 0.058/min).
Test condition : -Experiments were carried out in 0.02 M phosphate buffer at pH 7.
-Changes in oxygen concentration were not monitored.
-Concentrations of both sensitizer and substrate were 5 µm.
-Reactions were carried out in 10 ml Kimax screw-capped tubes.
-The light source was a Pyrex-filtered, water-cooled 200 W medium pressure mercury arc lamp (merry-go-round photoreactor, Ace Glass).
-The principal emitted lines are 313 and 365 nm.
-Disappearance of the test substance was followed by HPLC using a varialbe wave-length absorbance detector.
Reliability : (2) valid with restrictions
Study well documented

18.06.2004 (32)

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C

Result : p-Toluidine is not expected to undergo hydrolysis in the environment due to the lack of hydrolysable functional groups
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
14.03.2006 (33)

3.1.3 STABILITY IN SOIL

Type : laboratory
Radiolabel : yes
Concentration :
Soil temperature : °C
Soil humidity :
Soil classification :
Year :
Deg. product :
Method : other: radiotracer experiment
Year : 1985
GLP : no data
Test substance : other TS: p-Toluidine
Deg. products : 124-38-9 204-696-9 carbon dioxide

Method : Surface samples (0-15 cm) of silty loam soils from distinct areas were air-dried, and ground to particles lee than 2mm; experiments were performed with 5 g oven-dried soil added to 125 ml flasks containing aqueous

solutions of p-toluidine (4.7 µmol) plus water to adjust the soil to -0.033 MPa water potential; 14C activity of p-toluidine added to soil were 0.4 Bq/µmol; initial activity was 4.0 TBq/kg; the flasks were sealed and incubated for 63 days; the sealed flasks were opened every third day for aeration; exposure temperature was 23°C in the dark.

Amine concentrations were determined in a Liquid Scintillation Counter after performance of a sequentially extraction of the soils as follows
a) with 60:40 (v/v) ethylacetate:methanol (EtAc-MeOH) to remove soluble and weakly bound amines
b) with1 M ammonium acetate (NH4OAc) (pH 7) to recover amines bound to soil colloids by electrostatic forces
c) with 0.5 M sodium hydroxide (NaOH) to solubilize soil organic matter and associated covalently bound amines.
The CO2 trapping solution was changed at 7-d intervals and radioactivity was determined as described.

Result : Extracted amines at day zero:

a)EtAc-MeOH		67%
b)NH4OAc		12.3%
c)NaOH		8.4%
Sum:	87.7%	

Extracted amines after 63 d incubation period:

EtAc-MeOH		13.0% +/- 4.5%
NH4OAc		3.1% +/-0.4%
NaOH		31.8% +/-2.5%
Sum:	47.9%	

Decomposition of p-toluidine was low (ca. 15% CO2 evolution of added conc.)

The extraction at day zero indicates that p-toluidine was initially loosely associated with clay and organic matter through electrostatic interactions, hydrophobic bonding or reversible imine linkages with humate carbonyls (reported soil pH of approx. 5 resulted in protonation of p-toluidine).
The increase of p-toluidine in the NaOH fraction until day 63 suggests that the amine is increasingly covalently linked to humic components in soil.

Test substance : labeled p-toluidine: uniformly 14C-ring-labeled
unlabeled p-toluidine: Sigma Technical Grade; initial concentration was 0.19 M

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

Flag : Critical study for SIDS endpoint

18.06.2004 (34)

Type : laboratory
Radiolabel :
Concentration :
Soil temperature : °C
Soil humidity :
Soil classification :
Year :
Deg. product :
Method : other
Year : 1986
GLP :
Test substance : other TS:p-Toluidine, uniformly ring-labeled (4.5 Tbq/kg); unlabeled p-toluidine: Sigma Technical Grade

Method : Surface soils (0-15 cm depth) samples were air dried and ground to <2 mm.
Aqueous solutions of 9.33 µmol of p-toluidine (7.9 Bq/14Cmmol) were added to 100 g soil to reach a final soil concentration of 10 mg/kg. Soils were adjusted to -0.033 Mpa water potential by adding distilled water. The flasks were than mixed and connected to a closed aeration apparatus and incubated in the dark at 23°C for approx. one year. Humidified air (CO2-free) was passed at 0.48 l/h over the soil; CO2 was absorbed in 25 ml of 1 M KOH. KOH traps solutions were changed periodically and analyzed colorimetric by titration. Further samples were analyzed by Liquid Scintillation Counting after acidification of the samples and collecting the evolving CO2.

Result : 19-35% of added p-toluidine was evolved as CO2 in 308 days:

	Recovery of evolved 14CO2	recovery of soil residuals	total
Soil 1:	21.2%	62.4%	83.6%
Soil 2:	18.9%	72.8%	91.7%
Soil 3:	27.5%	65.8%	93.3%
Soil 4:	28.7%	74.4%	103.1%
Soil 5:	20.7%	78.4%	99.1%
Soil 6:	35.0%	59.1%	94.1%

A preliminary experiment indicated that < 1% of p-toluidine was lost through volatilization. Therefore, the authors concluded that the evolved 14C was CO2 from decomposition of p-toluidine.

Test condition : Soil texture:

Soil 1, sand: 76.6 % sand, 21.3 % silt, 2.1 % clay
Soil 2, sand: 83.2 % sand, 12.7 % silt, 4.1 % clay
Soil 3, silt loam: 18.4 % sand, 69.2 % silt, 12.4 % clay
Soil 4, silt loam: 17.5 % sand, 64.3 % silt, 18.2 % clay
Soil 5, silty clay loam: 4.3 % sand, 58.7 % silt, 37 % clay
Soil 6, loam: 48.3 % sand, 41.6 % silt, 10.1 % clay

Other soil properties:

Soil 1: pH 4.7; OC 1.91 %; wc: 123; CEC: 16.9
Soil 2: pH 5.2; OC 1.04 %; wc: 114; CEC: 10.2
Soil 3: pH 5.4; OC 0.98 %; wc: 244; CEC: 14.7
Soil 4: pH 5.4; OC 2.08 %; wc: 185; CEC: 25.0
Soil 5: pH 6.4; OC 2.71 %; wc: 372; CEC: 45.4
Soil 6: pH 7.0; OC 1.90 %; wc: 189; CEC: 12.8

OC = Organic carbon
wc =water content at -0.033 Mpa in g water/kg soil
CEC = cationic exchange capacity in cmol(+)/kg

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

Flag : Critical study for SIDS endpoint

23.06.2004 (35)

Type : laboratory
Radiolabel : no
Concentration : 500 mg/kg
Soil temperature : 19 °C
Soil humidity : 30 other: % from absolutely dry soil
Soil classification :
Year :
Deg. product : not measured
Method : other: see Test conditions
Year : 1981

GLP	:	no
Test substance	:	other TS: p-Toluidin, Purity not given
Method	:	The study has been carried out to evaluate the possibility of utilising industrial sewage from coke industry plants as nitrogen fertilizer during the nonvegetative period by sewage irrigation.
Remark	:	Translated from Russian. First published in Pochvovedenie.
Result	:	-p-Toluidine had a life time ["duration of existence"] of 9 days. -Degradation products persisted for over 90 days.
Test condition	:	- Slightly eroded, average-humus, lightly grained chernozem on hard carbonaceous woody loam was used. -Humus content: 5.05-5.09%, hydrolysed nitrogen: 6.8, mobile phosphorus: 1.0, mobile calcium: 34.9 mg/100g soil. -The amount of dry residue in an aqueous extraction of soil was 0.09-0.102%. -The pH of the aqueous soil extraction was 7.1-7.5. -The test substance dissolved in ether was spread on the surface of a thin layer of soil. -A qualitative analysis of the soil for content of the test substance and their transformation products was conducted in 24 h using thin layer chromatography.
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles

18.06.2004 (36)

Type	:	laboratory
Radiolabel	:	
Concentration	:	
Soil temperature	:	°C
Soil humidity	:	
Soil classification	:	
Year	:	
Deg. product	:	
Method	:	other: see Test conditions
Year	:	1980
GLP	:	no
Test substance	:	other TS: p-Toluidine, purity: technical grade
Method	:	Reactions of several ring-substituted anilines with humates (characterized by infrared spectroscopy) was studied in aqueous solution.
Remark	:	Investigations are not focused on p-toluidine (4-methylaniline).
Result	:	The primary amines were found to bind to humate in two phases. It was supposed that the initial rapid reversible equilibrium may represent formation of imine linkages with the humate carbonyls. A following slow reaction was thought to represent 1,4 addition to quinone rings followed by tautomerization and oxidation resulting in an amino-substituted quinone. Investigations concerning the effect of ortho-substitution were performed with 2-methyl- and 4-methylaniline, respectively as well as with 2-chloroaniline and 4-chloroaniline. 34% of the 4-methylaniline was recovered while 85% of the 2-methylaniline was recovered indicating, that ortho substituents inhibit binding of the aromatic amines. The reactivity of various amines with quinones are in the order of 4-methylaniline > aniline > 4-chloroaniline > 3,4-dichloraaniline > N-methylaniline >> 2-chloroaniline > 2,5 dichloroaniline.
Test condition	:	Binding and release experiments were performed in closed test tubes. The test compounds (mixtures of 3-5 compounds) were added in methanol solution (shaken; stored at 21-23°C or kept in water bath at 30°C. Extraction was performed by repetitive centrifugation when methanol was the solvent. When water was used as solvent, extraction was achieved with ethyl acetate.

In kinetic experiments with humates, aliquots of the reaction mixture were periodically, extracted, concentrated, and analysed. To achieve higher precision in recoveries 2-chloronitrobenzene was used as internal standard. A gas chromatograph with nitrogen-phosphorus detector was used to determine aromatic amines.
Kinetic experiments with model compounds (aqueous methanol reaction mixtures) were directly injected into the gas chromatograph. Linear first-order rate plots were obtained for each substituted aniline in the reaction with benzoquinone over more than 90% of the reaction.

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

19.03.2004 (37)

Type : laboratory
Radiolabel :
Concentration :
Soil temperature : °C
Soil humidity :
Soil classification :
Year :
Deg. product :
Method :
Year : 1985
GLP :
Test substance :

Remark : The basic and neutral components of a tar obtained from a condensate of a high-Btu coal gasification pilot plant were analysed by capillary column gas chromatography and gas chromatography/mass spectroscopy. Methylaniline (Toluidine) was identified in the basic fraction of the low-temperature reactor tar at following concentrations: 14.8 mg/g at 30.0 min. retention time, 19.6 mg/g at 30.6 min. retention time, and 46.3 mg/g at 31.2 min. retention time. The basic compounds dissolved in methylene chloride were exposed to a 20 ppm Fe3+ solution (4h) and a 200 ppm Fe3+ solution for 18 hours. Methylaniline was transported from the organic to the aqueous solution of about 13-27% when exposed to 20 ppm Fe3+, whereas 78-84% decrease of methylaniline concentration was observed in the organic phase when exposed to 200 ppm Fe3+ for 18 hours.

Reliability : (4) not assignable
Not assignable
Isomers are not mentioned

19.03.2004 (38)

Type :
Radiolabel :
Concentration :
Soil temperature : °C
Soil humidity :
Soil classification :
Year : 1984

Remark : The oxidative coupling reaction in binding to soil may be enzymatically-mediated.

Reliability : (4) not assignable
Documentation insufficient for assessment

02.03.2004 (39)

Deg. product :
Method :
Year : 1985

GLP :
Test substance : other TS: p-Toluidine, purity not given

Remark : Soil- and clay catalysed free radical oxidation of organic chemicals were discussed considering their physicochemical and structural relationship. p-Toluidine was judged to be potentially oxidizable due to following characteristics:
-1) The ring substituent fragments were classified as electron donating (Hammett sigma constant for the para position < 0
-2) The redox potential of the soil must be greater than that of the chemical. Highly oxidized soils showed a redox potential of 0.8 V. The half-wave potential E1/2 of p-toluidine obtained from literature are (direct current polarography results in a wave, where the half-wave potential is one-half of the limiting current):
0.92 V at pH 0.9; 0.85 V at pH 2.5; 0.76 V at pH 4.0; 0.66 V at pH 7.4, and 0.53 V at pH 11.5.
-3) As clay minerals are hydrophilic, low water solubility will limit adsorption. Reported water solubilities (S) of p-toluidine were: log S = 5.38 ppm at 22°C and 3.86 ppm at 21°C, respectively. These values correspond to 240 g/l at 22°C and 7.2 g/l at 21°C.
Reliability : (4) not assignable
Secondary literature

19.03.2004 (40)

3.2.1 MONITORING DATA

Type of measurement : other: natural occurrence
Media : food
Concentration :
Method : GC quantification, MS identification

Result : Toluidine (isomers not specified, but p-toluidine likely to be present) occurs in vegetables like cabbage (Lactuca sativa), carrots (Daucus carota), celery (Apium graveolens), and peas (Pisum sativum).
Test condition : - About 20 vegetables and several other food products were examined
- GC quantification after derivatisation with trifluoroacetic acid anhydride
- MS identification
- Determination limit depending on sample clean-up, not explicitely reported for p-toluidine but for isomer: 0.1 mg o-toluidine/kg fruit
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
18.06.2004 (41)

Type of measurement : other: natural occurence
Media : biota
Concentration :
Method : GC/MS

Result : The filamentous fungus Penicillium viridicatum evolved p-toluidine and other volatile organic compounds during growth on malt extract agar and under several conditions mimicing colonization of automobile air conditioning systems. p-Toluidine was also released from a bacterial biofilm of Methylobacterium mesophilicum interlaced with Penicillium viridicatum.
Test condition : - Stock cultures of Methylobacterium mesophilicum and Penicillium viridicatum were maintained in R2A and malt extract agar (MEA; both from Difco Laboratories), respectively

- 5-7 d sporulating Penicillium viridicatum were streaked onto agar (amended with 1 % dextrose), incubated for 2-7 d, and placed into 250 ml purge and trap jars
- Methylobacterium mesophilicum were streaked onto R2A, incubated for 2 d, and placed into purge and trap jars
- Air conditioning equipment (unused evaporator) was cut into of sections, inoculated with a suspension of Methylobacterium mesophilicum, sprayed with sterile water, placed into purge and trap jars, and incuabated at alternating temperatures (4 °C and 25 °C) for 4 days
- Other air conditioning equipment (e.g. foam insulation) was cut into pieces, inoculated with conidia of Penicillium viridicatum, incubated for 14 - 60 days, transferred to purge and trap vessels for VOC analysis
- VOC analysis of headspace by GS/MS

Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
23.06.2004 (42)

Type of measurement : concentration at contaminated site
Media : ground water
Concentration :
Method : reverse phase HPLC

Method : Study to elucidate the role of the manganese peroxidase (MnP) from white-rot fungi (species not reported).
An abiotic system consisting of Mn(III) in oxalate buffer
under aerobic conditions (Mn(II)/oxalate/O2) was used to
transform 2-amino-4,6-dinitrotoluene and several other munition site contaminants (including p-nitrotoluene and p-toluidine)
Remark : Situation at former munitions sites is briefly described
Result : In the environment p-toluidine is formed by reduction of p-nitrotoluene, e.g. at former munitions sites. p-Toluidine was degraded much faster than its precursor, p-nitrotoluene (conversions: 77.5 +/- 5.3 % for p-toluidine and 42.8 +/- 5.2 % for p-nitrotoluene)
Test condition : - 50 µM (5.35 mg/l) of the test substance were incubated for 96 h at 20 °C in a system containing oxalate and Mn(III), under pure oxygen
- The reaction mixture was sterilized
- pH rose from 4.5 to 7.5-8.0 over the time of the experiment
- Quantitative determination of nitroaromatic compounds by reverse phase HPLC

Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
18.06.2004 (43)

Type of measurement : other: laboratory measurement to elucidate abiotic formation from p-nitrotoluene
Media : other: aqueous deaerated TiO2/Pt suspension
Concentration :
Method : HPLC

Result : p-Toluidine can be formed photochemically from p-nitrotoluene in the presence of titanium dioxide or other photocatalyst in deaerated medium
Test condition : - TiO2 (Anatase), with a specific surface of 17.3 m2/g, was used, Pt added
- 2 g TiO2/500 ml
- HPLC for analysis of aromatics
- Acetic acid, formic acid, ammonium, nitrate analyzed by ion chromatography

Reliability : (2) valid with restrictions
Basic data given

19.03.2004 (44)

Type of measurement : other: concentration in fuel
Media : other: coal oil
Concentration :
Method : GC/MS

Method : - Acidic extraction
- Gel chromatography for purification
- Derivatisation with trifluoroacetic anhydride
- GC/MS
Result : Toluidine (isomers not specified, but p-toluidine likely to be present) was detected as a component of coal oil at a concentration of 135 mg/kg
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
18.03.2004 (45)

Type of measurement : other: concentration in fuel
Media : other: liquid fuels
Concentration :
Method : GC/FID

Result : o-Toluidine and/or p-toluidine (not specified which isomer) are present in the water soluble fractions of two liquid fuels, regular gasoline with 87 octane (0.8 mg/l) and gasohol, an ethanol containing liquid fuel (0.19 mg/l). They were not detected in 5 other liquid fuels.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
18.06.2004 (46)

Type of measurement : other: concentration in fuel
Media : other: gasoline
Concentration :
Method : HPLC

Result : p-Toluidine is present in gasolines and their aqueous extracts
Test condition : - Regular and premium grade gasolines from various suppliers were extracted for at least 4 h
- Quantification HPLC
- Identification HPLC/MS
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
18.03.2004 (47)

Type of measurement : background concentration
Media : surface water
Concentration : < .02 - 1 µg/l
Method : GC, photometry

Method : - GC according to 1980 publication of the authors
- Colorimetric determination of total amines content as azo compounds by coupling with N-(1-naphthyl)-ethylenediamine. Absorbance was read at 555 nm
- Detection limit: 0.02 µg/l (GC) and 0.5 µg/l (photometry)
- Sampling in 1979, water including sediments
Result : In 1979, several aromatic amines were found in surface waters of the Netherlands. In 46 water samples (containing sediments) of the river Rhine from Lobith (kilometre 865), the mean p-toluidine concentration was 0.17

µg/l (26 samples above the determination limit of 0.02 µg/l, maximum 1.0 µg/l). In the tributaries of the Rhine, Boven Merwede and Issel, the mean p-toluidine concentration was 0.07 µg/l (5 samples of 12 above detection limit, maximum 0.35 µg/l) and 0.08 µg/l (6 samples of 13 above detection limit, maximum 0.39 µg/l), respectively

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

18.06.2004 (48)

Type of measurement : concentration at contaminated site
Media : ground water
Concentration :
Method : GC/MS

Method : - Samples taken 15 months after underground gasification was terminated
- Water samples extracted with CH2Cl2 and fractionated into acidic, basic, and neutral fractions
- Direct injection of fractions concentrate into GC
- GC (Hewlett-Packard 5880, SP2100-fused silica column, flame ionization detector)
- Identification of peaks by GC/MS (Hewlett-Packard 5985)

Result : 3 ground water samples from the vicinity of an US underground coal gasification site, contained toluidine in concentrations of up to 9.2 µg/l (sum of o- and p-isomers: 0.06, 1.4, 9.2 µg/l)

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

18.06.2004 (49)

Type of measurement : other: contaminated and uncontaminated sites
Media : other: wastewater and surface water
Concentration :
Method : GC/MS

Remark : Graphs have been omitted or tables are refered to as graphs. Note of graph 5 refers to wrong graph (table).

Result : p-Toluidine is reported to occur in 6 out of 19 water samples with a range of 0.7-18 µg/l (limit of determination 0.1 µg/l).
Since samples of wastewater and surface water(s) [including the river Main in Germany] are reported as one result, it is not clear where p-toluidine occurred.

Reliability : (4) not assignable
Documentation insufficient for assessment

18.06.2004 (50)

Type of measurement : background concentration
Media : surface water
Concentration :
Method :

Method : In 1991, p-toluidine and other organic compounds were monitored in several rivers in North Rhine-Westfalia in Germany

Result : p-Toluidine was neither detected in the Rhine (3 sampling sites) nor in any of 6 of its tributaries with a detection limit of 1 µg/l (detection limit in the Wupper 0.1 µg/l).

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

18.03.2004 (51)

Type of measurement : background concentration
Media : surface water
Concentration :
Method : solid phase extraction with GC/MS after derivatization with benzoyl choride

Result : With a limit of detection of 23 ng/l, p-toluidine could not be detected in samples of drinking water of Jabalpur (India), river water and treated paper mill effluent
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
18.06.2004 (52)

Type of measurement : concentration at contaminated site
Media : other: tobacco smoke
Concentration :
Method : GC/MS of trifluoroacetyl derivatives

Result : p-Toluidine and several other amines occur in tobacco smoke
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
18.06.2004 (53)

Type of measurement : concentration at contaminated site
Media : other: tobacco smoke
Concentration :
Method :

Result : p-Toluidine occurs in tobacco smoke. The ring-substituted aromatic amines of tobacco smoke are most likely formed during pyrolysis. Thus, o-toluidine is formed in severals sources where pyrolysis of nitrogen-containing fuels occurs.
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
19.03.2004 (54)

Type of measurement : concentration at contaminated site
Media : other: tobacco smoke
Concentration :
Method : GC of trifluoroacetyl derivatives

Result : p-Toluidine occurs in tobacco smoke. Formation may be due to pyrolysis. On the other hand, nonenzymatic browning reactions occur which lead to the formation of nitrogen heterocycles (e.g. pyrrazols) from sugars and amino acids. These products may be transferred into the smoke.
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
18.06.2004 (55)

Type of measurement : concentration at contaminated site
Media : other: tobacco smoke
Concentration :
Method : GC with ECD

Result : High levels of aromatic amines were found in tobacco smoke. The p-toluidine load of the main stream smoke (primary smoke [which is inhaled

by the smoker]) was 7-59 ng/cigarette depending on the protein and nitrate content of the cigarettes. The side stream smoke (secondary smoke [which is also inhaled by the non-smoker]) contained 1-2 orders of magnitude more p-toluidine (1,730 ng/cigarette). The authors concluded that aromatic amines like p-toluidine are formed by pyrolysis.

Test condition : - A 20 channel automatic smoker (Borgwaldt, Hamburg) used
- Smoke of 200 cigarettes collected in 5 % HCl
- After making basic with NaOH, extracted with ether
- Derivatisation with pentafluoropropionic anhydride
- Clean-up by 2 sequential LC runs on Florisil columns
- GC (equipped with ECD) of pentafluoropropionyl derivatives

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

18.06.2004 (56)

Type of measurement : concentration at contaminated site
Media : other: tobacco smoke
Concentration :
Method : GC/MS

Method : - GC (Hewlett-Packard 5890 series II and MSD 5971A, Superox II column from Biorad)
- Smoking machine with aspiration of 21 ml/s main stream (one 2 sec puff per minute) and 138 ml/s side stream
- Air sampling: pump 33 ml/s (DuPont P4000 with automatically adjusted flow), duration 8.33 h
- Adsorbtion of cigarette smoke in acidic solution
- Extraction separatedly with diethyl ether and hexane, alkalinization
- Washing on Florisil column
- Eluate directly injected into GC/MS

Result : Both the main stream smoke of cigarettes, (which is inhaled by the smoker) and the side stream smoke of cigarettes (which is also inhaled by the non smoker) contain significant amounts of all toluidine isomers and other aromatic amines. Depending on the brand, the p-toluidine content is 14-42 ng/cigarette in the main-stream smoke, and 10-100 times more in the side-stream smoke (562-2,390 ng/cigarette).
In air, there are several aromatic amines (tracers of cigarette smoke). There is a strong correlation of o-toluidine levels (ng/m3) in indoor air with the smoking status of the inhabitants:
- Office of a non smoker with smokers in contiguous room 3.7
- Office of a non smoker with smokers in contiguous room after overnight ventilation 0.5
- Office with 1 smoker 2.9
- Office with 2 smokers 6.3
- Club room 11.3
- Non-smoking train compartment 1.1
- Hair-dresser saloon 4.8

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

18.06.2004 (57)

Type of measurement : other: background concentration and concetration at contaminated site
Media : air
Concentration :
Method : GC/MS

Result : These observations were confirmed by an examination of 10 aromatic amines in air in several Italian sites. In the most heavily polluted outdoor air

of the cities examined (air of the centre of Brindisi), the p-toluidine concentration was approximately 20 ng/m3. In air from a smokers room the p-toluidine concentration was approximately 8 ng/m3 (city not reported)

Test condition : - Air sampling with constant flow pumps; 1 m3 (8 h)
- Amines trapped in 5 % HCl
- Trapping solution washed with diethylether, made basic with NaOH, extracted with hexane
- Derivatisation with pentafluoropropionic anhydride
- GC/MS

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

19.03.2004 (58)

Type of measurement : other: foundries
Media : air
Concentration : .001 - .77 µg/l
Method : Liquid chromatography (LC) for isocyanates, GC for sum of isocyanates and amines; amines from difference GC-LC

Remark : Although the authors attributed the traces of o-toluidine and p-toluidine found in the air of 2 foundries to the thermal decomposition of plastics, they did neither check air from outside the foundaries nor did they eliminate other sources like fuel combustion or release from metal melts, e.g. during heating of metal.

Result : About 40 air samples from modern iron foundry:
0.001 - 0.037 µg/l (sum of o- and p-toluidine)
4 air samples from aluminium foundry:
0.05 - 0.77 µg/l (sum of o- and p-toluidine)
In slightly decomposed core material (except from binder, core material not specified) from grey iron casting at 1350 °C p-toluidine was detected in a concentration of 0.6-0.9 mg/kg. p-Toluidine was not detectable in unused (intact) core material and in totally decomposed core material.

Reliability : (3) invalid
Significant methodological deficiencies

18.06.2004 (59)

Type of measurement : other: production facility
Media : other: raw wastewater
Concentration : 1 g/l
Method :

Remark : Raw wastewater situation not relevant for environmental monitoring because p-toluidine is virtually completely eliminated from wastewater

Result : In raw wastewater from 3-chloro-4-methylaniline manufacturing, p-toluidine was present at approximately 1 g/l. This p-toluidine was derived from the hydrogenation feedstock containing several percent of p-nitrotoluene. The authors developed a membrane extractor which decreased the p-toluidine concentration by more than 99 % during treatment. Additionally, a biodegradation of essentially 100 % is reported.

Reliability : (2) valid with restrictions
Basic data given

19.03.2004 (60)

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : adsorption
Media : other
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: OECD guideline 106 (modified)
Year : 1998

Method : Soil adsorption batch experiments were performed with the European reference soil set (EUROSOILS); 4.5 g soil were equilibrated with 22 ml 0.01 M CaCl2 by shaking for 12 h. The clear solution obtained by centrifugation (5 min. at 2500 rpm) was decanted; 4 TS concentrations in the range of 0.2 - 10 mg/l in 0.01 M CaCl2 were incubated for 24 h (shaken); after centrifugation 2.5 ml of the resulting clear solution were analysed for the concentration of the TS by means of RP-HPLC/UV. Adsorption coefficient (KD) was calculated as:

KD= [X/m]/Ce, with

X= test substance adsorbed on soil (g) at equilibrium
m= mass of dry soil (g)
Ce= equilibrium concentration in solution (g/ml)

Freundlich isotherm was determined by plotting log(x/m) versus log(Ce) for various initial concentrations

Result : Soil characteristics and determined adsorption coefficients:

Soil; texture	clay [%]	Corg [%]	pH	Koc
Eurosoil 1, clay	75.0	1.3	5.1	1903.4
Eurosoil 2, silt loam	22.6	3.7	7.4	102.2
Eurosoil 3, loam	17.0	3.45	5.2	200.2
Eurosoil 4, silt	20.3	1.55	6.5	121.4

Test substance : p-Toulidine; purity 99.9%
Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions
Flag : Critical study for SIDS endpoint
18.06.2004 (61)

Type : adsorption
Media : water - soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: QSAR Estimation Method: PCKOCWIN v1.66
Year : 2004

Method : PCKOCWIN uses first order molecular connectivity index and a series of group contribution factors (based on Kow and water solubility) to predict Koc.
Result : Koc = 72.5
Reliability : (2) valid with restrictions

Accepted calculation method
Flag : Critical study for SIDS endpoint
25.02.2004 (20)

Type : adsorption
Media : water - soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: according to Graveel JG, Sommers LE, and Nelson DW (1986). J. Environ. Qual. 15(1), 53-59.
Year : 1986

Method : Surface soils (0-15 cm depth) samples were air dried and ground to <2 mm. 14C-p-toluidine (4.5 Tbq/kg); unlabeled p-toluidine was of technical grade. 4 g soil was equilibrated with 40 ml 0.01 M Ca[NO3]2 at 25°C for 24 hours in a shaking water bath. Initial concentrations ranged from 5 mg/l to 100 mg/l; after centrifugation initial and final concentrations in the solution phases were determined using a Liquid Scintillation Counter (LSC). The amount of absorbed amine was calculated by difference between initial and equilibrium concentration.
Desorption from soils equilibrated with amines was determined by adding 40 ml of 0.01 M Ca[NO3]2 and shaking in a water bath for 24 h. After centrifugation radioactivity was measured in the supernatants by LSC. The amount of p-toluidine was calculated from the weight of solution in the pellet and the amine concentration.
All values are averages of two replicates and expressed on an oven-dry soil basis.

Result : Soil properties:

Soil 1: pH 4.7; Organic carbon 1.91%; 76.6% sand, 21.3% silt, 2.1% clay
Soil 2: pH 5.2, Organic carbon 1.04%; 83.2% sand, 12.7% silt, 4.1% clay
Soil 3. pH 6.4, Organic carbon 2.71%; 4.3% sand, 58.7% silt, 37% clay

Sorption of p-toluidine by soils yielded isotherms that could be described by the Freundlich equation

Soil 1: equilibrium pH 4; Koc 323; K = 5.97
Soil 2: equilibrium pH 4.3; Koc 496; K = 5.36
Soil 3: equilibrium pH 5.9; Koc 508; K = 13.21

The K were correlated with clay content (r=0.997). Since for p-toluidine a pKa of 5.08 is given, appreciable concentrations of protonated and neutral species will be presented in the three soil types. p-toluidine probably was retained by clay minerals and organic matter through cation exchange. Desorption of sorbed p-toluidine was similar in the three soils varying from 11.3 to 15.8%.

Reliability : (2) valid with restrictions

Study meets generally accepted scientific principles
Flag : Critical study for SIDS endpoint
18.03.2004 (35)

Type : adsorption
Media : water - soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: application of TGD Koc-formula for anilines
Year : 2004

Remark : Using a log Kow of 1.39 and the TGD equation for anilines:
log Koc = 0.62 log Kow + 0.85 = 1.71
a Koc = 52 can be calculated.
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
25.02.2004 (20)

Type : adsorption
Media : water - soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: see below
Year : 1985

Method : Soil samples of silty loam from distinct areas were air-dried, and ground to particles lee than 2mm; experiments were performed with clay fractions < 2µm of the calcium-saturated clay minerals: montmorillonita and kaolinite; saturation was achieved by washing a 2% (w/v) soil suspension with 1 M CaCl2 for four times. Excess salt was removed by repeated washing with water.
Adsorption experiments were conducted using 1 g clay and 10 ml 14C-labeled p-toluidine (uniformly ring-labeled). The initial concentration was 0.19 M; samples were equilibrated in glass centrifuge tubes shaken for 8 h at 25°C.
Amine concentrations were determined via Liquid Scintillation Counter.
Sequentially extraction of the clays were performed
a) with 60:40 (v/v) ethylactate:methanol (EtAc-MeOH) to remove soluble and weakly bound amines
b) with1 M ammonium acetate (NH4OAc) (pH 7) to recover amines bound to soil colloids by electrostatic forces
c) with 0.5 M sodium hydroxide (NaOH) to solubilize soil organic matter and associated covalently bound amines.
Result : Result:

	clay mineral Montmorillonite	Kaolinite
-Equilibrium solution	57.8%	70.2%
- sorbed	42.2%	29.8%

Adsorbed amine extracted:

a)EtAc-MeOH	30.1%	23.3%	
b)NH4OAc	45.3%	34.9%	
c)NaOH	24.5%	41.8%	

Evolution of carbon dioxide (14.5 %) indicates decomposition during the 63 d incubation period

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

21.06.2004 (34)

Type : adsorption
Media : water - soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: see below
Year : 1981

Method : Soils were air-dried and ground to pass a 2-mm sieve. Organic carbon (OC) was determined according to the Walkley-Black method (correction factor 1.3). OC was converted to organic matter by multiplying the OC content by 1.724.

Four soil series from distinct areas were used for the experiment. The soil texture was silt loam.

	pH	OC (%)
Soil no. 1	7.5	1.09
Soil no. 2	6.7	2.51
Soil no. 3	6.1	3.53
Soil no. 4	6.2	4.25

Adsorption was measured at four initial concentrations: 20, 15, 10, and 5 ppm at 20 +/- 2°C.

10 ml of chemical solution and 1 g soil were shaken for 2 hours in 0.01 m CaCl2 in 40 ml glass centrifuge tubes with glass stoppers. After centrifugation for 10 minutes, the concentration of the test substance in the supernatants was measured by using UV spectroscopy at appropriate wavelength.

Result : A logKom of 1.66 is reported as mean of the four soils. By using the multiplication factor of 1.724, the Kom value is converted to Koc, resulting in a mean Koc value of 78.8.
Test substance : p-Toluidine, analytical samples
Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles
Flag : Critical study for SIDS endpoint
19.03.2004 (62)

Type : adsorption
Media : other: montmorillonite-phosphate crosslinked compounds-water
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: see below

Year : 1999

Method : Adsorption experiments were performed in order to evaluate the potential use of montmorillonite-(Cerium or Zirconium) phosphate (5Ce-sample and 5Zr-sample) crosslinked compounds in removing organic pollutants such as p-toluidine 0.1 g of each adsorbent was placed in 100 ml dark conical flasks with 50 ml amine solution in distilled water. The initial concentrations ranged from 1.5 xE-3 to 6.5E-2 cmol/l for the 5Ce-sample and from 1.6 xE-4 to 3.4E-2 cmol/l for the 5Zr-sample. All flasks were incubated in a thermostatic shaker bath at the selected temperature (288 or 308K). Time to reach equilibrium was 72 h for p-toluidine. Samples were centrifuged to give clear supernatants (determined pH 3.7 with 5Ce and pH 3.9 with 5Zr). Thereafter, pH was adjusted to pH 7 and absorbance was measured spectrophotometrically at a wavelength of 232.2 nm for p-toluidine.
X-ray diffraction patterns as well as the Fourier-transformed infrared spectra were determined for the corresponding pellets.

Result : 5Ce samples showed high affinity to p-toluidine, whereas the 5Zr-samples revealed mid affinity. The Fourier-transformed infrared spectroscopy indicated that at the pH generated by the adsorbents the protonated species plays an important role in the adsorption process, which coincides with the results of the X-ray diffraction analysis showing that the aromatic amines have intercalated into the adsorbance. The pKa value reported for p-toluidine is 5.1.

Test substance : p-Toluidine, purity: 99%

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

19.03.2004 (31)

Type : volatility
Media : water - air
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: see below
Year : 1992

Remark : Henry's Constants of p-toluidine was determined as function of composition of methanol-water mixed solvents by using a gas-liquid equilibration method.
The final concentration of the toluidines in the liquid phase was checked. p-toluidine was extracted from the gas phase by passing through methanol. Concentrations were determined spectrophotometrically at 286 nm.

Reported log Henry Constants for p-toluidine in water at 25°C are:

conc. in liquid phase	log H
0.603 mM:	-4.06
2.053 mM	-4.06
5.017 mM	-4.04

According to the SRC EPI Database conversion of the dimensionless Henry Constant corresponds to H= 2.02E-6 atm*m³/mol (=0.2047 Pa m³/mol)

Test condition : pH value of the test solutions ca. 7; temperature: 25°C
Test substance : p-Toluidine purchased from Aldrich or Pfaltz & Bauer used as received
Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles
Flag : Critical study for SIDS endpoint
19.03.2004 (63)

Type : volatility
Media : water - air
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: QSAR Estimation Method: HENRYWIN v3.10
Year : 2004

Result : Experimental value cited in SRC EPIWIN: 0.2047 Pa*m³/mol (Jayasinghe, DS et al., 1992)

Henry Law Constant (H):
1) Bond method: H = 0.2128 Pa*m³/mol
2) Group method: H = 0.2371 Pa*m³/mol

All results at 25 °C
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
19.03.2004 (20)

Type : volatility
Media : water - air
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: application of the TGD HLC-formula
Year : 2004

Remark : Using the characteristic vapour pressure and solubility of o-toluidine at 25 °C, and applying the HLC formula (vapour pressure/water solubility) a Henry´s law constant of 0.52 Pa×m3/mol is obtained. Vapour pressure = 38.1 Pa; Solubility = 7.4 g/l
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
25.02.2004 (20)

3.3.2 DISTRIBUTION

Media : other: air - water - sediment(s) - soil - biota - aerosol
Method : Calculation according Mackay, Level I
Year : 2004

Method : Chemical data used in the calculation:
Temperature (°C) = 25
Molar Mass (g/mol) = 107.16
Vapour Pressure (Pa) = 38.13 Pa
Water Solubility (g/l) = 7.4 g/l
log Pow = 1.39
Melting Point = 44°C

Phase properties and composition of the compartments:

	Volume (m3)	Density (kg/m3)	Composition
Air:	6.0 E+09	1.185	
Water:	7.0 E+06	1000	
Soil:	4.5 E+04	1500	2% (Organic Carbon, OC)
Sediment:	2.1 E+04	1300	5% (OC)
Susp. Sed.:	3.5 E+01	1500	16.7% (OC)
Aerosol:	1.2 E-01	1500	
Aquatic Biota:	7.0 E+00	1000	5% (lipid)

Calculation was performed according to the model described in the first publication of Mackay (1991). Phase properties and composition of the compartments were modified as suggested by the German Federal Environmental Agency (UBA, Germany).

Result : Water: 83.69 %
Air: 15.98 %
Soil: 0.16 %
Sediment: 0.16 %
Susp. Sediment: <0.01 %
Biota (fish): <0.01 %
Aerosol: <0.01 %

Reliability : (2) valid with restrictions
Accepted calculation method

Flag : Critical study for SIDS endpoint
30.06.2004 (20)

Media : other: air - water - soil - sediment(s) - biota - suspended sediment
Method : other (calculation): non-steady-state equilibrium model
Year : 1983

Method : -Mass and concentration distribution fraction, mean residence time, and concentration-time profile at the non-steady-state from physicochemical properties and first-order rate constants of transformation and advection processes can be calculated.
-As hypothetical closed system the OECD Generic Environment is used as model environment. The advective flow of air and water is not considered and characteristics of the environment (e.g. compartment volume, pH, temperature) are fixed.
-It is assumed that the input flow rate for the chemical was 100 g/day.

Result : Data used in the calculation:
-Temperature(°C): not defined
-Molar Mass (g/mol): 107.2
-Water solubility (mg/l): 7400
-Vapour pressure (Pa): 45.3
-log Pow: 1.50
-Henry´s law constant (calculated): 0.00026
-Koc (calculated): 156
-BCF (calculated): 0.8

-Properties of the compartments were not defined

Mass distribution fractions (%):
Air: 26.52
Water: 71.06
Soil: 0.43
Sediment: 1.99
Biota: 0.000029
Susp. Sed.: 0.0022

Reliability : (2) valid with restrictions
Basic data given

18.06.2004 (64)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge, industrial
Contact time :
Degradation : = 94 (±) % after 8 day(s)
Result :
Deg. product :
Method : OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year : 1990
GLP : no
Test substance : other TS: p-toluidine, purity is not specified

Method : Initial test substance concentration: 50-400 mg/l DOC
Remark : Acclimatization period: 3 days; approx. 10 % of the total elimination caused by physical mechanisms
Result : 79 % removal during the log phase (4 days)
Reliability : (2) valid with restrictions
Guideline study without detailed documentation
Flag : Critical study for SIDS endpoint
22.03.2004 (65)

Type : aerobic
Inoculum : activated sludge, adapted
Concentration : 200 mg/l related to COD (Chemical Oxygen Demand) related to
Contact time :
Degradation : = 97.7 (±) % after 5 day(s)
Result :
Deg. product :
Method : other: batch system (comparable to Zahn-Wellens Test OECD TG 302B)
Year : 1976
GLP : no
Test substance : other TS: p-toluidine, purity is not specified

Method : Test compound as sole source of carbon; gradual increase of TS concentration during 20 days adaptation period up to 200 mg/l related to COD.
Result : Degradation result based on COD removal; degradation rate: 20.0 mg COD/g/h
Test condition : Duration of the test: 120 h; inoculum was adapted for 20

days. Inoculum concentration applied was 100 mg/l dry matter; the tested substance was the sole carbon source; temperature = 20+/-3°C; pH = 7.2; mineral medium; dark; continuously stirred

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

Flag : Critical study for SIDS endpoint

19.06.2004 (66)

Type : aerobic
Inoculum : activated sludge
Contact time :
Degradation : = 94 (±) % after 13 day(s)
Result : inherently biodegradable
Control substance : Diethylene glycol
Kinetic : 6 day(s) ca. 50 %
8 day(s) ca. 77 %
Deg. product : not measured
Method : OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year : 1986
GLP : no
Test substance : other TS: p-toluidine, purity is not specified

Remark : Missing information concerning origin and adaptation of inoculum. Furthermore the degradation of reference compound did not reach the 14 days pass level of >70 % as prescribed by the OECD guideline.

Result : Test concentration: 189.9 mg/l (149 mg/l DOC)
---
17 % after 1 day
19 % after 3 days
90 % after 6 days
94 % after 10 days

Test concentration: 383.6 mg/l (300.97 mg/l DOC)
---
15 % after 1 day
50 % after 6 days
77 % after 8 days
94 % after 13 days

Approx. 3 days of acclimatization before exponential growth phase started; elimination curve indicative for biotic transformation.

Reliability : (2) valid with restrictions
Guideline study without detailed documentation

Flag : Critical study for SIDS endpoint

19.06.2004 (67)

Type : aerobic
Inoculum : activated sludge
Concentration : 100 mg/l related to Test substance
related to
Contact time : 14 day(s)
Degradation : > 30 (±) % after 14 day(s)
Result :
Control substance : Aniline
Kinetic : %
%

Deg. product :
Method : other: comparable to MITI-test (OECD Guideline 301 C)
Year : 1978
GLP : no
Test substance : other TS: p-toluidine, purity is not specified

Method : Ratio of test substance to activated sludge 100 ppm:30 ppm;
test temperature: 25 +/- 2°C; pH of the supernatant of
activated sludge is 7.0 +/-1
Remark : If %-age biodegradation from the oxygen consumption exceeds
30% after 2 weeks from the beginning of the test and the
result of a direct analysis is at least this value, the test substance is judged
as "well-biodegradable" according to the criteria used at that time.
Result : 4-methylaniline was confirmed to be well biodegradable
Reliability : (2) valid with restrictions
Data collection approved by MITI
Flag : Critical study for SIDS endpoint
13.03.2006 (68)

Type : aerobic
Inoculum : activated sludge
Concentration : 3 mg/l related to Test substance
related to
Contact time :
Degradation : 68 (±) % after 20 day(s)
Result :
Kinetic of testsubst. : 5 day(s) 0 %
10 day(s) 60 %
20 day(s) 68 %
%
%
Deg. product : not measured
Method : other: similar to OECD TG 301D
Year : 1974
GLP : no
Test substance : other TS: p-Toluidine, purity not specified

Remark : p-Toluidine was emulgated.
COD: 2 470 mg/g of stock solution (1000 mg/l)
BOD after 20 days calculated for the stock solution: 1670 mg/l
Reliability : (4) not assignable
Documentation insufficient for assessment
Flag : Critical study for SIDS endpoint
15.07.2004 (69)

Type : aerobic
Inoculum : activated sludge
Concentration : 100 mg/l related to Test substance
related to
Contact time : 28 day(s)
Degradation : (±) % after
Result :
Deg. product :
Method : other: MITI-I (OECD TG 301C)
Year : 2002
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Result : Direct analysis: TOC: 1 %, 6 %, 98 %
HPLC: 1 %, 2 %, 100 %

Indirect analysis: BOD (NH3) 0 %, 0 %, 97 %

Substance was assessed as non-biodegradable

Test condition : Concentration of activated sludge: 30 mg/l
Reliability : (4) not assignable
Documentation insufficient for assessment

14.03.2006 (70)

Type : aerobic
Inoculum : other: activated sludge, aniline-acclimated
Concentration : 500 mg/l related to Test substance
related to
Contact time :
Degradation : ca. 60 (±) % after 192 hour(s)
Result :
Deg. product :
Method : other: Respirometer test
Year : 1960
GLP : no
Test substance : other TS: p-toluidine, analytical grade

Method : Test in a Warburg respirometer; content of active sludge solids: 2500 mg/l; results corrected for endogenous respiration
Result : Oxidation was recorded as mg O2 uptake per liter of the mixture in the flask. Results were presented in a graph (O2 uptake (mg/l) with the length of Warburg run (h)). From this graph a degradation percentage could be determined. Air oxidation and volatility of the substrates were determined by a 24 h Warburg run in the absence of microorganisms. Results of this run were extrapolated to cover time periods up to 192 hours.
An oxygen uptake of 1560 mg/l was recorded after 192 hours. From this and a COD of 2540 mg/g substance, a degradation of about 60 % can be calculated.
Test condition : - The solution of mineral salts used to prepare the substrate solutions and the activated sludge suspensions for the Warburg runs had the following composition: 500 mg/l K2HPO4, 325 mg/l (NH4)2HPO4, 50 mg/l NaCl, 50 mg/l CaCl2, 25 mg/l MgSO4 and 5 mg/l FeCl3. The solvent was tap water.
- Simulated sewage was prepared by mixing in tap water an aqueous solution of glucose and Difco nutrient broth and concentrated mixture of the same salts employed in the diluent.
- Acclimatization of the activated sludge to aniline as sole source of carbon and energy was carried out in 1500 ml aeration tubes by the batch-feed method.
- Original source of microorganisms was mixed liquor from the aeration tank of a municipal treatment plant.
- The microflora was fed and aerated at least 1 h before use in the Warburg respirometer.
- Incubation was carried out at 20 °C for 120 to 192 hours.
Each flask was set up to contain 2500 mg/l activated sludge solids and 500 mg/l test compound (substrate) in a total volume of 20 ml.
Reliability : (2) valid with restrictions
Basic data given

22.06.2004 (71)

Type	:	
Inoculum	:	domestic sewage
Deg. product	:	
Method	:	other: see below
Year	:	1983
GLP	:	no
Test substance	:	other TS: 4-toluidine "of highest purity available"
Method	:	- Primary effluent of raw municipal sewage from the Ithaca, N.Y., sewage treatment plant was amended with 10 µg of the test compound per ml. - The test series were incubated at 29°C in the dark (aerobic, anaerobic conditions, control: sterilized sewage). - Samples were taken at 0, 2, 7 days, and thereafter at weekly intervals. - Test substance concentration was determined by spectrophotometry (260-320 nm). Metabolites were identified by gas chromatography.
Result	:	Degradation of p-toluidine in sewage was investigated under aerobic and anaerobic conditions. 4-toluidine vanished from aerated non-sterile sewage (decrease of initial absorbance to 0% after approx. 15 days) but not from sterile sewage or sewage in the absence of oxygen. 4-methylformanilide and 4-methylacetanilide were metabolites of 4-toluidine detected by gas chromatography and identified by mass spectroscopy.
Reliability	:	(2) valid with restrictions Minor deficiency in description of methods and result concerning p-toluidine, however results indicative of biodegradation of p-toluidine in sewage effluent.

25.02.2004 (72)

Type	:	aerobic
Inoculum	:	other: suspension of Niagara silt loam
Concentration	:	30 mg/l related to Test substance related to
Contact time	:	
Degradation	:	100 (±) % after 4 day(s)
Result	:	
Deg. product	:	
Method	:	other: photometrical measurement of ring-cleavage; method according to Alexander M & Aleem MIH (1961). J. Agr. Food Chem. 9, 44.
Year	:	1966
GLP	:	no
Test substance	:	other TS: p-toluidine, purity is not specified
Remark	:	Study design is suitable to derive some general conclusions on the biodegradability but not to examine the biodegradability of individual compounds in detail.
Test condition	:	Nutrient solution contained inorganic nutrients and test substance as the sole carbon source 1 ml of an 1 % suspension of Niagara silt loam was added to closed bottle containing 40 ml of nutrient solution. Bottles were incubated in the dark at 25 °C. Contact time was up to 64 days including adaptation period. Ring cleavage was checked by decrease of absorbance at 285 nm, measured after centrifugation in the supernatant. Precipitates and supernatants were returned to the appropriate reaction bottles. Control tests were performed with identical samples except that 8 mg of HgCl2 and 5E-07 M Tween 80 were added to each bottle. Tests for toxicity of the test substances to microorganisms were done on identical samples however using glucose as an

additional source of carbon.
Reliability : (2) valid with restrictions
Basic data given
25.02.2004 (73)

Type : aerobic
Inoculum : other bacteria: enriched culture
Contact time :
Degradation : (±) % after
Result : other: biodegradable
Deg. product :
Method :
Year : 2000
GLP : no
Test substance : other TS: p-toluidine, purity not specified

Method : The development of an extractive membrane bioreactor (EMB) is described in this paper. Dense phase membranes are use for the extraction of pollutants into a biomedium, an interesting method in regard to the treatment of industrial effluents containing specific compounds instead of complex mixture of pollutants. First, a microbial culture able to degrade 3-chloro-4-methylaniline (3C4MA) was developed in a continuous enrichment reactor. This culture was than inoculated in a lab-scale EMB unit and adapted to the conditions of industrial waste water containing ca. 2 g/l methanol, 3C4MA (ca. 2 g/l), and p-toluidine (ca. 1 g/l; PT). The waste water was pumped into the bioreactor at flow rate increasing over time from 25 to 80 l/d. Monitoring of reactor performance was conducted of measuring TOC, GC, and toxicity in inlet waste water, outlet waste water and biomedium, and ammonia and phosphate concentrations in the biomedium.
Result : More than 99% of 3C4MA and PT were extracted from the wastewater into the bioreactor treating 30 g/d p-toluidine and 60 g/d 3C4MA.
Results for biodegradation were focused on 3C4MA. The only result presented concerning biodegradation of PT was for lab-scale EMB indicating biodegradation of PT of about 90% (steady state was reached approx. at the tenth day).
Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles
25.02.2004 (60)

Type : anaerobic
Inoculum : other: aquifer slurry
Contact time :
Degradation : (±) % after
Result : under test conditions no biodegradation observed
Deg. product :
Method : other: according to Kuhn and Suflita. Haz. Waste Haz. Mat. 6(2), 121-133.
Year : 1989
GLP : no data
Test substance : other TS: p-toluidine, analytical grade or highest purity available (Aldrich Chemical Co., Milwaukee, WI)

Method : Biodegradation of chemicals (including p-toluidine) was tested in aquifer slurries from a sulfate reducing and a methanogenic site. Aquifer samples were taken from two sites adjacent to the municipal landfill. p-Toluidine dissolved in water was added to aquifer

slurries at initial concentration of ca. 0.2 mM. Tests were performed in duplicate and autoclaved aquifer slurries served as control. Incubation was performed at room temperature in the dark for 10 months.
Samples were taken immediately after addition of p-toluidine and thereafter periodically (1 ml removed by syringe).
Analysis was performed with HPLC/UV. Detection limit was </= 10 µM

Result : About 27-35 % of p-toluidine already disappeared in the sterile controls monitored over a 10 months period. Therefore, the reported data were corrected for this abiotic loss.
p-Toluidine revealed no biotic transformation, neither under sulfate reducing nor under methanogenic conditions. (Aniline was degraded under sulfate reducing conditions by about 40 % within 10 months, but not under methanogenic conditions).

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

19.06.2004 (74)

Type : anaerobic
Inoculum : other: Desulfobacula toluolica (strain Tol2); bacteria
Deg. product :
Method :
Year : 1998
GLP : no
Test substance : other TS: p-toluidine, purity: "of highest purity available"

Method : The strictly anaerobic sulfate-reducing bacterium Desulfobacula toluolica (strain Tol2) was investigated in dense cell suspension for its ability to co-metabolite p-toluidine while using toluene as the primary source of carbon as well as for its ability to metabolite p-toluidine as the sole source of carbon : Cells pre-grown on toluene were harvested in the late exponential growth phase (about 1800 mg cell dry mass/l) in an anoxic chamber under an atmosphere of N2:H2 (90:10). Cell density was adjusted to an optical density of 4.0 at 580 nm. Toluene and p-toluidine were added at distinct concentrations and incubated.
Samples were identified by HPLC/MS and GC/MS methods.
Sulfate was analyzed by precipitation test with barium chloride and sulfide was analyzed photometrically.

Result : This organism was also shown to metabolite toluidine in cell dense suspension when added as sole source of carbon. Identified metabolites by HPLC/MS were a biphenyl-like compound as well as phenylacetic acid. The probable conversion of p-toluidine to p-aminophenylacetic acid and phenylacetic acid as dead end products suggested that p-toluidine degradation is initiated by the carboxylation of the methyl group.

Concentrations of 3.5 mM p-toluidine completely inhibited the bacterial growth. Degradation of p-toluidine (80%) was observed when added to the cell dense suspension (1 mM p-toluidine and 4 mM toluene as additional electron donor; incubation time 550 h; degradation of control: 20%)
1 mM p-toluidine added to dense cell suspension was completely degraded after an incubation time of 575 h.

Reliability : (2) valid with restrictions
Scientifically acceptable

25.02.2004 (75)

Type :

Inoculum : other bacteria
Deg. product :
Method :
Year : 2001
GLP : no
Test substance : other TS: toluidine isomers of highest purity commercially available

Remark : Achromobacter xylosoxidans T7, a rod shaped Gram-negative bacteria was isolated and characterized. The enriched bacteria culture were shown to grow on all three toluidine isomers as sole source of carbon (as single substrate or a mixture). Optimum condition for degradation of toluidine isomers was at concentration of 2.4 mM at pH 5.5 and 30°C resulting in complete degradation within 4 days.
An equimolar toluidine mixture of the isomers of 0.8 mM was mineralized within 3-7 days. Experiments indicated the metabolization of the toluidines via the respective methylcatechols as intermediates. No accumulation was observed of any intermediates via HPLC-analysis.

Reliability : (2) valid with restrictions
Scientifically acceptable, basic data given

22.06.2004 (76)

Type : aerobic
Inoculum :
Concentration : 5.35 mg/l related to Test substance
related to
Contact time :
Degradation : 77.5 (±5.3) % after 96 hour(s)
Result :
Deg. product :
Method : other
Year : 2002
GLP : no
Test substance : other TS: p-toluidine, Sigma (purity > 98%, determined by HPLC)

Method : An abiotic system consisting of Mn(III) in oxalate buffer under aerobic conditions (Mn(II)/oxalate/O2) was used to transform 2-amino-4,6-dinitrotoluene and its derivatives (including p-toluidine). Study elucidated the role of the manganese peroxidase (MnP) from white-rot fungi.

Result : 77.5 +/-5.3 % of the initial concentration of p-toluidine were transformed presumably by superoxide radicals formed during the reaction of cleavage of oxalate to -COO-radicals. These radicals reacted with oxygen to yield superoxide radicals which in water become protonated to effective -HOO radicals.

Test condition : 50 µM (5.35 mg/l) of the test substance were incubated for 96 hours at 20 °C in a system containing oxalate and Mn(III), under aerobic conditions. The reaction mixture was sterilized. pH measured in the mixtures rose from 4.5 to 7.5-8.0 over the time of the experiment. Quantitative determination of nitroaromatic compounds was performed by reversed phase HPLC.

Reliability : (3) invalid
Unsuitable test system

25.02.2004 (43)

Type : aerobic
Inoculum : other: Water of river Songhua, China
Concentration : 2 mg/l related to COD (Chemical Oxygen Demand)

related to

Contact time :
Degradation : 46 (±) % after 5 day(s)
Result : other: biodegradable
Deg. product :
Method : other: Determination of biodegradation rate constant
Year : 2001
GLP : no
Test substance : other TS: p-toluidine, reagent grade

Method : The test substance was added to 250 ml biochemical oxygen demand (BOD) bottles. The bottles were then filled to capacity with the water sample, sealed and incubated for 5 days at 20+/-1 °C.- Two replicates were conducted for each chemical and each control (inoculum only). The dissolved oxygen concentrations were determined by iodometric titration method.
Remark : It is not clear in which study the measurements were done, and which study cites the other.
Result : A biodegradation rate constant of 0.84 (1/d) was determined for p-toluidine.
Test condition : Water samples were gathered from the Jilin Province section in the Songhua river. No large industry enterprises or new pollutant sources are presented in the vicinity of this section. Temperature of the original water samples ranged between 15 and 20 °C, the concentration of dissolved oxygen ranged between 7.8 and 9.0 mg/l, and the pH was between 6.8 and 7.0. The bacteria counts were determined by standard plate count techniques and were about 1200 to 3000 colony forming units/ml. Medium was composed of 3 g of beef extract, 10 g of peptone, 20 g of agar and 1 l of distilled water. The pH of the culture medium was adjusted to 7.6 and the culture was sterilized for 20 min. at 121 °C. 1 ml of diluted water sample was cultivated in 15 ml of the above medium at 31 °C for 24 h.- The added concentration of chemicals was approximately 2 mg/l on the basis of their theoretical oxygen demand and residual dissolved oxygen of at least 1 mg/l at the final day.
Reliability : (4) not assignable
Documentation insufficient for assessment

22.06.2004 (77) (78) (25)

Type : aerobic
Inoculum :
Deg. product :
Method : other: calculated by QSAR models
Year : 2001
GLP :
Test substance : other TS: p-toluidine

Remark : Multiple linear regression (MLR) and artificial neural network (ANN) models were presented to predict the biodegradability. The biodegradation data of a diverse set of 241 molecules were divided into a training set of 172 chemicals for developing the MLR and ANN models and into test sets of 12 and 57 chemicals for evaluating the predictive ability of these models. Parameters used for establishing the models were molecular connectivity (1 parameter) and 14 atom-type E-stat indices. The linear model revealed a square correlation coefficient (r^2) of 0.76 for the training set and a r^2 of 0.68

for the test set. Better predictions were achieved for the artificial neural network resulting in a square correlation coefficient of 0.84 for the training set and 0.76 for the test set, respectively.
Both models predicted a fast biodegradation of p-toluidine belonging to the second test set. This result was confirmed by the observed biodegradability of p-toluidine reported in this paper as "biodegrades fast" (inherently).

Reliability : (4) not assignable
Development of QSAR correlation: correlation coefficient < 0.9; observed results are second quotations not assignable to the origin

22.06.2004 (79)

Type : aerobic
Inoculum : aerobic microorganisms
Deg. product :
Method : other: Respirometer Test
Year : 1978
GLP :
Test substance :

Method : Biodegradation test of chemical substance by microorganisms etc. stipulated in the Order Prescibing the Items of the Test Relating to the New Chemical Substance (1974), Order of the Prime Minister, the Minister of Health and Welfare, the MITI No.1).
This guideline corresponds to 301C, Ready Biodegradability: Modified MITI Test I stipulated in the OECD Guidelines for Testing of Chemicals (May 12, 1981).

Result : BODT after 14 days:
- 48.9 % (end product NO2)
- 59.6 % (end product NH3)

Test condition : -Test concentration: 100 mg/l
-Sludge concentration: 30 mg/l

Reliability : (4) not assignable
Original reference not yet available

03.03.2004 (80)

Type : aerobic
Inoculum : Aerobacter sp. (Bacteria)

Remark : -Aerobacter is able to disrupt the ring of the substance at a concentration of 500 mg/l at 30 °C in 48 hours.
-Aerobacter mutant is able to disrupt the ring of the substance at a concentration of 500 mg/l at 30 °C in 3 hours.

Reliability : (4) not assignable
Documentation insufficient for assessment

27.02.2004 (81)

3.6 BOD5, COD OR BOD5/COD RATIO

BOD5
Method :
Year : 1968
Concentration : related to
BOD5 : 1440 mg/l
GLP : no
COD
Method :
Year : 1968
COD : 2540 mg/g substance

GLP : no
RATIO BOD5 / COD
BOD5/COD : .57

Reliability : (4) not assignable
Documentation insufficient for assessment
17.02.2004 (82)

BOD5
Method :
Year :
Concentration : related to Test substance
BOD5 : mg/l
GLP :
COD
Method :
Year : 1955
COD : mg/g substance
GLP : no

Remark : The BOD values are expressed as grams per gram of chemical tested at 20°C. The standard dilution method used sewage as seed (the test sample is diluted with plant solution and left sealed for 5 days at 20°C. The difference in dissolved oxygen before and after is compared).
Result : Two BOD5 values are reported: 1.63 and 1.44 g/g
Test substance : p-toluidine, purity not specified
Reliability : (4) not assignable
Secondary literature
19.02.2004 (83)

BOD5
Method :
Year : 1971
Concentration : related to
BOD5 : mg/l
GLP : no

Remark : The BOD values are expressed as grams per gram of chemical. The standard dilution method used sewage as seed (unacclimated waste seed).
Result : The BOD5 values are between 1.44 and 1.63 g/g
Test substance : p-toluidine, purity not specified
Reliability : (4) not assignable
Documentation insufficient for assessment
02.03.2004 (84)

BOD5
Method :
Year : 1973
Concentration : related to
BOD5 : mg/l
GLP : no

Remark : -A BOD5 of 57 % and a COD of 90 % related to TOD is reported.
Reliability : (4) not assignable
Documentation insufficient for assessment
26.02.2004 (85)

COD

Method :
Year : 1971
COD : mg/g substance
GLP :

Remark : - Concentration tested: 2.5 mg/l
- Results expressed in lb (pounds)
Result : - ThOD = 3.14 lb/lb (stoichiometric oxygen demand to CO2, H2O and HNO3)
- BOD5 = 1.6 lb/lb (standard dilution method)
- Degradation rate after 5 days ca. 51 %
Reliability : (4) not assignable
Documentation insufficient for assessment
07.10.2004 (86)

3.7 BIOACCUMULATION

Species : Cyprinus carpio (Fish, fresh water)
Exposure period : 28 day(s) at °C
Concentration :
Elimination :
Method : other: Bioconcentration test
Year : 2002
GLP : no data
Test substance : other TS: p-Toluidine, purity not specified

Result : BCF: <1.3 <13
Test concentration: 100 µg/l 10 µg/l
Reliability : (4) not assignable
Documentation insufficient for assessment
Flag : Critical study for SIDS endpoint
14.03.2006 (70)

Species : other: Mytilus edulis
Exposure period : at °C
Concentration :
Elimination : yes
Method : other: see below
Year : 1988
GLP :
Test substance : other TS: p-toluidine, purity not specified

Result : No BCF was determined for steady state.
Rapid elimination was observed and >/= 85% of the tissue residues were depurated within 4 h.
Mussels converted 17.5% of their steady state body burdens to the corresponding N-acetyl derivatives as the only metabolite.
Test condition : - The uptake of 14C-labeled p-toluidine was determined by placing the mussels in 2x10E-5 M solutions for 4 h to achieve steady state conditions.
- Elimination rates were measured by transferring the mussels to clean water and monitoring for depurated radioactivity.
- Metabolism was determined by analysis of tissue residues and depurated metabolites (HPLC; GC/MS).
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint

25.02.2004 (87)

BCF	:	= 2.35
Elimination	:	
Method	:	other: QSAR Estimation Method: BCFWIN v2.15 (2000)
Year	:	2004
GLP	:	
Test substance	:	
Remark	:	Calculation was based on a log Pow of 1.39
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

31.01.2004 (20)

3.8 ADDITIONAL REMARKS

Memo	:	Determination of aniline catabolic plasmid pTDN1 in adapted Pseudomonas putida
Result	:	The aniline catabolic plasmid pTDN1 was discovered after the adaption of Pseudomonas putida mt-2 (ATCC 33015) to growth on aniline m-, and p-toluidine. The nucleotide sequence of this plasmide was determined.
Reliability	:	(2) valid with restrictions Scientifically acceptable

25.02.2004 (88)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	flow through
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	59.5
LC0	:	59.5
LC50	:	149
EC50	:	137
Limit test	:	no
Analytical monitoring	:	yes
Method	:	other: see below
Year	:	1986
GLP	:	no
Test substance	:	other TS: p-toluidine; purity 99%
Method	:	Fish (31 d old; mean length: 19.2 mm; mean weight: 0.098 g) exposed in Lake Superior water; 5 TS concentrations in the range of 61.2 - 343 mg/l tested (plus control); number of dead fish recorded every 24 h; observations of fish behaviour and body morphology at regular intervals; TS analysis by GLC LC50 and EC50 values as well as the confidence intervals were calculated using the corrected average of the analysed tank concentration and the Trimmed Spearman-Karber Method. The EC50' were based upon loss of equilibrium. The mean toxicant concentrations used in the calculations were corrected for analytical recoveries of spiked river water samples.
Remark	:	The pH of the stock solution was adjusted to that of lake water with HCL. Increased alkalinity values were due to a reaction between the titrant, causing unusually high measurements.
Result	:	Confidence limits (95 %): LC50 = 135 - 163 mg/l EC50 = 124 - 150 mg/l Affected fish lost schooling behaviour and were hyperactive; they were overreactive to external stimuli, had increased respiration and edema, were darkly coloured and lost equilibrium prior to death.
Test condition	:	25°C; pH 7.75; dissolved oxygen: 8.0 mg/l; hardness: 48.1 mg CaCO3/l; alkalinity: 89.7 mg CaCO3/l; tank volume: 2.0 l
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag	:	Critical study for SIDS endpoint

16.06.2004 (89)

Type	:	flow through
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	93.2
LC0	:	93.2
LC50	:	171

EC50	:	171
Limit test	:	no
Analytical monitoring	:	yes
Method	:	other: see below
Year	:	1990
GLP	:	no
Test substance	:	other TS: p-toluidine; purity: 99%
Method	:	Fish (30 d old; mean length: 20.1 mm; mean weight: 0.115 g) exposed in Lake Superior water; 5 TS concentrations in the range of 37.6 - 210 mg/l tested (plus control); number of dead fish recorded every 24 h; observations of fish behaviour and body morphology at regular intervals; TS analysis by HPLC LC50 and EC50 values as well as the confidence intervals were calculated using the corrected average of the analysed tank concentration and the Trimmed Spearman-Karber Method. The EC50' were based upon loss of equilibrium. The mean toxicant concentrations used in the calculations were corrected for analytical recoveries of spiked river water samples.
Result	:	LC50 95% confidence interval: 138-213 mg/l EC50 95% confidence interval: 137-213 mg/l Affected fish were hyperactive and overreactive to external stimuli, had increased respiration, convulsions and were hemorrhaging. Equilibrium loss was observed prior to death.
Test condition	:	24.8°C; pH 7.9; dissolved oxygen: 7.0 mg/l; hardness: 45.2 mg CaCO3/l; alkalinity: 43.8 mg CaCO3/l; tank volume: 2.0 l
Reliability	:	(2) valid with restrictions Test procedure comparable to standard method and in accordance with generally accepted scientific standards; detailed documentation of test procedure and test conditions
Flag	:	Critical study for SIDS endpoint

16.06.2004 (90) (28)

Type	:	semistatic
Species	:	Cyprinus carpio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	132
Limit test	:	
Analytical monitoring	:	no data
Method	:	other: see below
Year	:	2001
GLP	:	no
Test substance	:	other TS: p-toluidine; purity: 99%
Method	:	Carps (average length 11.6 +-2.3 cm, average weight 23.8 +/-6.4 g; one year old) were acclimatized under laboratory condition for two weeks after they were sterilized in 5% (w/v) salt water. Test water was dechlorinated tap water with 21.45 mg/l chlorine; temperature of the test water: 15-18 °C; dissolved oxygen: 6.35 mg/l; pH: 7.0-7.5; solvent: acetone 0.05-0.1 % (v/v). 60 l glass tanks containing 20 l test water were loaded with ten randomly selected fish. Test water was replaced twice a day (10 l each time); solvent control with ten fish.

The energy of the lowest unoccupied molecular orbital (ELUMO) was calculated by the quantum chemical method MOPAC6.0-AM1. QSARs using ELUMO and log P were developed for carp; algae, and Photobacterium phosphoreum.

Result : Experimental value carp LC50 96-h: 132 mg/l

Calculated values obtained by QSARs:
Carp: LC50 (96h): 56 mg/l
Algae: EC50 (72 h): 288 mg/l
Bacteria: EC50 (15 min.): 199 mg/l

The correlation coefficient R is up to 0.80, 0.81 and 0.98 between carp and P. phosphoreum, carp and algae, and P. phosphoreum and algae respectively.

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

16.06.2004 (91)

Type : static
Species : Brachydanio rerio (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
NOEC : < 50
LC0 : 50
LC50 : 115
LC100 : 220
Limit test : no
Analytical monitoring : yes
Method : OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year : 1990
GLP : yes
Test substance : other TS: p-toluidine; purity >/= 99.9 %

Method : Fish (length: 2.7-3.4 cm) exposed to TS concentrations of 50, 100 and 220 mg/l (plus control) in reconstituted water (ISO/DIS 7346/1); 10 fish per concentration; fish loading </= 1 g/l; TS analysis by HPLC/UV

Result : In all concentrations tested, fish showed adverse effects on swimming behaviour, respiration, and appearance.
Dead fish had either lighter or darker coloration than normal; they were convulsed and showed red gills.

No loss of TS concentration during 96 h exposure was observed.

In the report the LC50 is given in a range between 100 - 220 mg/l. However, the LC50 value can be interpolated using probit analysis with the calculation program TOXRAT (inhibitions lower equal 0% or greater equal 100% were replaced according to settings ["Fudging"]). Based on the effect concentrations given in the report: LC50 = 115 mg/l.

Test condition : 21.2-22.8°C; pH 7.8-8.3; oxygen content: 7.5-8.5 mg/l; 12 h daily illumination

Reliability : (2) valid with restrictions
Guideline study with acceptable modification

Flag : Critical study for SIDS endpoint

17.06.2004 (92)

Type : semistatic
Species : Poecilia reticulata (Fish, fresh water)
Exposure period : 14 day(s)

Unit	:	mg/l
LC50	:	= 10.7
Limit test	:	
Analytical monitoring	:	no data
Method	:	other: 14 day test acc. to Koenemann (1981)
Year	:	1984
GLP	:	no
Test substance	:	other TS: p-toluidine; purity not given
Method	:	Koenemann H (1981). Toxicology 19, 209-238.
Remark	:	TS predissolved in 2-propanol
Test condition	:	- 22+/-1°C - oxygen content >/= 5 mg/l - hardness: 25 mg CaCO3/l
Reliability	:	(2) valid with restrictions Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
Flag	:	Critical study for SIDS endpoint

25.02.2004 (27)

Type	:	static
Species	:	Cyprinodon variegatus (Fish, estuary, marine)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	60
Limit test	:	no
Analytical monitoring	:	yes
Method	:	EPA OTS 797.1400
Year	:	1985
GLP	:	yes
Test substance	:	other TS: p-Toluidine, 99.5 % purity
Test condition	:	GLP Guideline study. Test material analysis not done under GLP.
Reliability	:	(4) not assignable Original reference not yet available

30.06.2004 (93)

Type	:	static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	>= 100
Limit test	:	
Analytical monitoring	:	no
Method	:	other: Letale Wirkung beim Zebrabaerbling, UBA-Verfahrensvorschlag, Mai 1984, Letale Wirkung beim Zebrabaerbling Brachydanio rerio LC0, LC50, LC100, 48-96h
Year	:	1985
GLP	:	no
Test substance	:	other TS: p-Toluidine, Purity not given
Test condition	:	-10 fish per test concentration in 5 l water were applied -Solvent for preparation of test substance in water: ethyl alcohol 1:1 -Concentrations tested: 1, 10, 100 mg/l -Temperature: 22.4-24.1 -pH: 5.6-7.1
Reliability	:	(4) not assignable Documentation insufficient for assessment

03.03.2004 (94)

Type : static
Species : Leuciscus idus (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC0 : 42.2
LC100 : 100
Limit test :
Analytical monitoring : no
Method : other: see test conditions
Year : 1985
GLP : no
Test substance : other TS: p-Toluidine, Purity not given

Test condition : -10 fish per test concentration in 5 l water were applied
-Solvent for preparation of test substance in water: ethyl alcohol 1:1
-Concentrations tested: 42.2, 56.2, 75, 100 mg/l
-Temperature: 19.2-19.7
-pH: 5.9-6.8
Reliability : (4) not assignable
Documentation insufficient for assessment

03.03.2004 (95)

Type : static
Species : Oryzias latipes (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l
LC50 : = 42
Limit test :
Analytical monitoring : no data
Method : other: Method according to ' Testing Methods for Industrial Wastewater, JIS K0102, Japanese Industrial Standards Committee, p. 154 (1971)
Year : 1982
GLP : no
Test substance : other TS: p-toluidine, analytical grade

Method : 10 fish per trial (length: 2 cm; weight: 0.2 g) were acclimatised for ten days; test substances were dissolved in water and neutralized if necessary. Fish were exposed in 2 l of test solution; mercuric chloride as reference compound.
Result : 24 h LC50 = 60 mg/l
Test condition : 25°C; deionized water
Reliability : (3) invalid
Deficiency in the description of material and method: Holding water is reported as deionised water; no information on the reconstitution of the water

25.02.2004 (23)

Type : static
Species : Poecilia reticulata (Fish, fresh water)
Exposure period : 14 day(s)
Unit : mg/l
Method : other: calculated with QSAR
Year : 1989
GLP :
Test substance : other TS: p-toluidine

Remark : The gathered data are based on examinations performed by Könemann (1981), Hermens et al. (1984), and Deneer et al. (1987). The use of log P and molecular connectivity indices to predict the acute toxicity by means of multiple

regression analysis was compared.
It was shown that QSARs based on chi(2)v or a combination of chi(0)v, chi(0), and a dummy variable for the presence of a benzene ring were equivalent or sometimes even better to those based on log P values.
Experimental values for 4-methylaniline were obtained from Hermens, J. et al., Ecotoxicol. Environ. Saf. 8, 388-394 (1984).

Result : Calculated results obtained for p-toluidine:
using logLC50 (Hermens et al. 1984): 2.0 (corresponding to LC50 = 10.7 mg/l)
using log P: 1.54
using chi(0): 5.98
using chi(0)v: 4.89
using chi(2)v: 1.91

Reliability : (4) not assignable
Development of QSAR correlation. Currently, not commonly used calculation method

16.06.2004 (96)

Type :
Species : Oryzias latipes (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l
LC50 : = 43
Limit test :
Analytical monitoring : no data
Method : other: not specified
Year : 1986
GLP : no
Test substance : other TS: p-toluidine

Remark : QSAR analysis of 48-h LC50 values of Oryzias latipes obtained from literature using log Pow, MW, organic and inorganic characters and molecular connectivity indices were performed in order to find the most useful parameter and combination. Regression analysis revealed that connectivity indices fit best for estimation of the LC50 value.
Reported parameters used in the calculation concerning p-toluidine: MW = 107; log P = 0.98; O* = 140, I*= 85; 3XP = 2.31, log LC50 = 2.59 (corresponding to LC50 = 42 mg/l). A LC50 of 43 mg/l was used in the other two publications of Yoshioka in 1986.

Reliability : (4) not assignable
Secondary literature; original reference not available

16.06.2004 (97) (98) (99)

Type :
Species : Poecilia reticulata (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
Method : other: calculated with QSAR
Year : 2002
GLP :
Test substance : other TS: p-toluidine

Remark : - Method:
Toxicity and molecular descriptors were secured for 127 chemicals (P. reticulata, LC50 96 h; T. pyriformis, IGC50 40 h (impairment on growth)). Relationships were generated
using log 1/IGC50 as the dependent variable and log 1/LC50 as the independent variable. Modelling was performed by

using least squares regression. Fit was quantified with the coefficient of determination r² and the root of the mean square for error s. Outlier were identified by the 95% model confidence interval.

- Results:
For the calculation used toxicity and molecular descriptors for Poecilia and Tetrahymena concerning 4-methylniline were:
Poecilia log 1/LC50 = 0.72 mM (corresponding to a LC50 = 20 mg/l)
Tetrahymena: log 1/IGC50 = -0.05 mM
mode of action: non-covalent bioreactivity

The result fits for anilines (r² = 0.43) and nitroaromatics (r² = 0.68) were not well related between endpoints for these chemicals (anilines: n=27; s= 0.46)

Reliability : (4) not assignable
Development of QSAR correlation. Currently, not commonly used calculation method

16.06.2004 (100)

Type :
Species : Poecilia reticulata (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
Method : other: calculated with QSAR
Year : 2003
GLP :
Test substance : other TS: p-Toluidine

Remark : - Method:
QSAR models were developed with three E-state structure descriptors and one molecular connectivity chi valence index. Statistics of the model revealed that the model may be used for estimation of pLC50 values of similar structure (r²= 0.87; s= 0.25 and q² = 0.85 leave-one-out (LOO)).

- Results:
Results obtained concerning 4-methylaniline:
pLC50 = -logLC50 (observed): = 3.72
pLC50 (calculated): = 3.45

(unit of LC50 values is not reported; assuming that values are given in µmol/l, experimental LC50 value would correspond to 20 mg/l and calculated value to 38 mg/l, respectively)

Reliability : (2) valid with restrictions
Development of QSAR correlation. Currently, not commonly used calculation method

16.06.2004 (101)

Type :
Species : Rutilus rutilus (Fish, fresh water)
Exposure period : 3 day(s)
Unit : mg/l
LOEC : 50
Method : other: description of the method is not given
Year : 1958
GLP : no
Test substance : other TS: p-Toluidin, Purity not given

Result : -The test criteria are described in damage of the fish.
-A damage of the fish occurred in 3-4 days.
-Further, at a concentration of 20 mg/l a tainting (by taste) of fish flesh is reported.
Reliability : (4) not assignable
Documentation insufficient for assessment
27.02.2004 (102)

Type :
Species : Scardinius erythrophthalmus (Fish, fresh water)
Exposure period :
Unit :
Method : other: description of the method is not given
Year : 1971
GLP : no
Test substance : other TS: p-Toluidin, Purity not given

Remark : -At a concentration of 20 mg/l a tainting of fish flesh is reported (by taste, rendering the fish useless as a food source).
Reliability : (4) not assignable
Secondary literature
02.03.2004 (84)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : semistatic
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : .12
Limit Test : no
Analytical monitoring : yes
Method : OECD Guide-line 202
Year : 1998
GLP : yes
Test substance : other TS: p-toluidine, purity >99%

Method : Young daphnids (<24 hours old) were exposed to the test substance in a concentration range of 0.02 . 1.6 mg/l.
Immobilisation was recorded after 0, 24 h and 48 h.
The sensitivity of the test animals was check regularly with K2Cr2O7 as reference substance.
The test substance was dissolved in ISO-medium (pH 7.8 +/- 0.1, hardness: 250 +/- 25 mg/l CaO3), ultrasonicated for 5 minutes and stirring for 22 h. Test concentration analyses were performed from control, from the lowest, medium and highest test concentration at the beginning of the test and after 24 h as well as at 24 h and 48 hour after renewal of the test substance; four replicates/concentration; 5 animals/replicate;after preparation of samples analysis by external laboratory (analysis probably with gas chromatography, raw data are not available); EC50 values were calculated by using Probit analyses.
Result : Nominal values:
EC10 (24 h): 0.497 mg/l (0.32-0.64 mg/l)
EC50 (24 h): 1 mg/l (0.85-1.2 mg/l)
EC90 (24 h): 1.5 mg/l (1.28-1.6 mg/l)

EC10 (48 h): 0.073 mg/l (0.031-0.10 mg/l)
EC50 (48 h): 0.18 mg/l (0.15-0.23 mg/l)
EC90 (48 h): 0.293 mg/l (0.24-0.39 mg/l)

Measured values:
EC50 (24 h): 0.67 mg/l (0.57-0.81 mg/l)
EC50 (48 h): 0.12 mg/l (0.10-0.16 mg/l)

Test condition : temperature: 20 +/- 1 °C; 16 h light - 8 h darkness; test were run in 250 ml glass vessels containing 150 ml test solution; the vessels were sealed (plastic sheets); pH value was in the range of 7.8-8.1; O2-contents (given as % of saturation) was in the range of 95-99%.

Reliability : (1) valid without restriction
Guideline study, basic data given

Flag : Critical study for SIDS endpoint

16.06.2004 (103)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : 5
Limit Test : no
Analytical monitoring : no data
Method : OECD Guide-line 202
Year : 2001
GLP : no data
Test substance : other TS: p-Toluidine, purity is not specified

Remark : It is assumed that due to an edp (Electronic Data Processing) error the authors reported the values of vitamins B12 and biotin in the test medium to be 1.0 g and 0.75 g respectively, however, the correct data according to the standards are expected to be 1 µg vitamin B12 and 0.75 µg biotin in 1 litre.
Furthermore an embryo development inhibition assay was performed. The development time was recorded for every hatched young animal. In addition, gross morphological abnormalities of hatched animals were inspected under a low-magnification microscope. This experiment was carried out for 3 days under static exposure conditions.
In this assay a 72h-EC50 of 0.065 mg/l was observed.

Test condition : The test was performed under the following conditions:
- Daphnids were previously acclimated at 20 °C under a 16/8-h light/darkness cycle (less than 600 lux).
- The test medium contained 293.8 mg CaCl2x2H2O, 123.3 mg MgSO4x7H2O, 5.8 mg KCl, 64.8 mg NaHCO3, 10 mg Na2SiO3x9H2O, 0.274 mg NaNO3, 0.143 mg KH2PO4, 0.184 mg K2HPO4, 2.86 mg H3BO3, 0.996 mg FeSO4x7H2O, 0.361 mg MnCl2x4H2O, 0.306 mg LiCl, 0.071 mg RbCl, 0.152 mg SrCl2x6H2O, 0.0168 mg CuCl2x2H2O, 0.013 mg ZnCl2, 0.010 CoCl2x6H2O, 3.25 µg KI, 2.19 g Na2SeO3, 0.575 g NH4CO3, 2.50 mg Na2EDTAx2H2O, 75 µg Thiamine HCl, 1.0 µg Vitamin B12 and 0.75 µg Biotin.
- Young female juveniles, aged less than 24 h were used and 20 animals were exposed to the test solution. The surface of the test water was covered with teflon sheet to minimize evaporation of the culture medium and test substance.
- Temperature, dissolved oxygen and pH in the test solutions for testing period were 20 °C, 8.0-9.1 mg/l and 7.5-8.5, respectively.

- The total number of immobilized juveniles was determined after 24 and 48 h.

Reliability : (2) valid with restrictions
Guideline study without detailed documentation
Flag : Critical study for SIDS endpoint
16.06.2004 (104)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : .6
Analytical monitoring : no
Method : other: according to Bringmann and Kühn (1959). Ges. Ing. 80(4), 115-120.
Year : 1959
GLP : no
Test substance : other TS: p-toluidine, purity not specified

Method : Static test in beta-mesosaprobic to mesotrophic river water; 10 daphnids (max. 24 h-old animals) per vessel; test parameter: reaction of exposed daphnia to electro-acoustic irradiation (50 Hz).
Remark : Test cultures of the daphnids were regarded as affected in the case that >/= 50 animals out of hundred were affected.
Test condition : Temperature = 23 °C; pH = 7.5
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
16.06.2004 (105) (106)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC0 : .0002
EC100 : 50
Limit Test : no
Analytical monitoring : no data
Method : other: DIN 38412, Part 11 (Daphnia short-term test)
Year : 1989
GLP : no
Test substance : other TS: p-toluidine, purity not specified

Method : - 20 daphnids (6-24 h old) per concentration
- loading: 1 daphnia/2 ml medium
- duplicate samples
- 3-4 concentration levels were tested.
- EC0 and EC100 values were taken from the results obtained for the test concentrations.

Result : EC50 values could not be calculated from the specific values.
Test condition : Incubation temperature: 20°C; composition of dilution water: acid capacity: K54.3 of 0.8 mmol/l; total hardness of 2.4 mmol/l; calcium to magnesium ratio = 4:1; Na to K ratio = 10:1; initial pH = 8.0+/-0.2
Reliability : (2) valid with restrictions
Test procedure in accordance with national standard method and described in sufficient detail
16.06.2004 (107)

Type	:	static
Species	:	Mysidopsis bahia (Crustacea)
Exposure period	:	96 hour(s)
Unit	:	mg/l
EC50	:	1.5
NOEC	:	.63
Limit Test	:	no
Analytical monitoring	:	yes
Method	:	EPA OTS 797.1930
Year	:	1985
GLP	:	yes
Test substance	:	other TS: p-Toluidine, 99.5 % purity
Test condition	:	GLP Guideline study. Test material analysis not done under GLP.
Reliability	:	(4) not assignable Original reference not yet available

30.06.2004 (108)

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
Method	:	other: not specified
Year	:	2000
GLP	:	
Test substance	:	other TS: p-toluidine, analytical grade
Method	:	The study assessed the toxicity of 13 anilines and 11 phenols to Daphnia magna at pH values of 6.0, 7.8 and 9.0.
Result	:	The results were considered valid if dissolved oxygen measured at the end of the test was at least 60 % of saturation and if the percentage of immobilization observed for the controls was zero. Based on control experiments it is known that Daphnia can survive only between pH 6.0 and 9.0 in water, at pH values greater than 9.0 and less than 6.0, mortality was observed. Results are given as log (1/EC50), where EC50 is given in mol/l. pH=6.0: log(1/EC50) = 4.37 (EC50 = 4.6 mg/l) pH=7.8: log(1/EC50) = 4.52 (EC50 = 3.2 mg/l) pH=9.0: log(1/EC50) = 4.67 (EC50 = 2.3 mg/l)
Test condition	:	Daphnia magna were cultured parthenogenetically in an environmental chamber at a temperature of 22+/-2 °C, with a photoperiod of 14 h daylight / 10 h darkness; 6-24 h old Daphnids were used for the toxicity tests; they were fed with a diet of green algae; acute toxicity tests were conducted with 10 animals in 25ml of test water; at each pH, 6 concentrations of the test substance were tried; 3 determinations were performed each time; 3 different pH were tested: 6.0, 7.8 and 9
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles

16.06.2004 (24)

Type	:	
Species	:	other aquatic worm: Tubifex (Annelida, Clitellata)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	= 25
Analytical monitoring	:	no data

Method	:	other: see below
Year	:	1986
GLP	:	no data
Test substance	:	other TS: p-toluidin, purity not specified
Method	:	Tubifex of 30-50 mm in length were exposed to chemicals in order to determine the LC50 for 24 hours and 48 hours exposure period at 20 °C.
Remark	:	Results obtained were compared with EC20 values of activated sludge inhibition test, LC50 Oryzias latipes and EC50 of Tetrahymena pyriformis proliferation inhibition test (see other chapters). Regression analysis showed good correspondence with a sensitivity of the Tubifex test lying between those of the activated sludge and O. latipes test.
Result	:	LC50 (24 h) Tubifex: 64 mg/l LC50 (48 h) Tubifex: 25 mg/l
Reliability	:	(4) not assignable Japanese reference with short abstract in English

16.06.2004 (99)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	other algae: Scenedesmus obliquus
Endpoint	:	growth rate
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	62.9
Limit test	:	no
Analytical monitoring	:	no data
Method	:	other: OECD 201 algae inhibition test, 1981
Year	:	2001
GLP	:	no
Test substance	:	other TS: p-toluidine, purity not specified
Method	:	The algae were cultured in a liquid medium; pH was adjusted at pH 7.2 +/- 0.2; 5 concentrations were tested for each test compound (2 replicates per concentration and for control); algae in the logarithmic growing period were inoculated in erlenmayer flasks (250 ml), amounting to 60 ml of the culture medium, the compound and the algae; the initial cell concentration was ca. 1 x 10E4 cells/ml; incubation was performed at 20+/-1 °C, continuous light and an average illumination intensity of about 4000 lux. Growth was monitored by microscope (400 times). Data were handled according to the following formulas:

$$\mu = \ln(Nt/N0)/(t-t0)$$

μ = average specific growth rate
N0 = initial cell concentration
Nt = cell concentration after 48h
t-t0 = experimental period (48 h)

$$I = [\mu(b) - \mu(tox)]/\mu(b) \times 100\%$$

I = inhibition rate
μ(b) = average specific growth rate of control
μ(tox) = average specific growth rate of the toxic compound

		The EC50 values were determined by one variable linear regression analysis.
Remark	:	For anilines and phenols, Kow contributes most to the QSAR and E(LUMO) very little. E(LUMO): 0.173 eV (calculated by the quantum yield chemical method MOPAC6.0-AM1) log Kow: 1.39 (obtained from literature) By using E(LUMO) and the log Kow the quantitative structure activity relationship model was developed: log1/EC50 = 0.272 log Kow - 0.659 E(LUMO) + 2.54 (r^2= 0.793,S.E.= 0.316, F = 71.07, n=40). Calculated log 1/EC50 was 2.80 mol/l (QSAR) (corresponds to and EC50 of 169.8 mg/l).
Result	:	The experimental result is given as log 1/EC50: 3.19 mol/l (corresponding to an EC50 of 62.9 mg/l)
Reliability	:	(2) valid with restrictions Guideline study
Flag	:	Critical study for SIDS endpoint
26.02.2004		(109)

Species	:	Scenedesmus quadricauda (Algae)
Endpoint	:	biomass
Exposure period	:	96 hour(s)
Unit	:	mg/l
EC3	:	= 8
Limit test	:	
Analytical monitoring	:	no
Method	:	other: cell multiplication inhibition test
Year	:	1959
GLP	:	no
Test substance	:	other TS: p-toluidine, purity not specified
Remark	:	Reported TT (toxicity threshold) refers to nominal concentration and is comparable to EC3
Test condition	:	Stock cultures of algae were kept in municipal wastewater at 24 °C and daylight. Wastewater was enriched with 570 mg/l KNO3, 200 mg/l CaSO4, 140 mg/l KH2PO4, 90 mg/l MgSO4, and 3 mg/l FeCl3. The culture medium was renewed every 2 months. As the stock cultures were not free of bacteria, only sterile equipment was used in order to avoid contamination by other algae. One week prior to test 100 ml of culture medium was inoculated with 10 ml of stock culture. The inoculum were grown for one week at 24 °C and continuous illumination (Osram HNI 40 Watt and Osram HNT 40 Watt). Photoelectric measurement of scattering of cell suspension at end of test.
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint
14.03.2006		(105) (106)

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	growth rate
Exposure period	:	7 day(s)
Unit	:	mg/l
EC10	:	= 1.1
EC50	:	= 22.5
Limit test	:	
Analytical monitoring	:	no
Method	:	other: cell multiplication inhibition test according to Bringmann, G. & Kuehn, R., Vom Wasser 50, 45-60 (1978)

Year : 1978
GLP : no
Test substance : other TS: p-toluidine, purity not specified

Method : Kuehn, R., Vom Wasser 50, 45-60 (1978)
Test condition : - Static test
- Incubation of 10 ml test solution (algae in defined mineral medium with appropriate TS concentration)
- Turbidity measurement
- Values base on the area under the curve according to OECD-method.
Reliability : (3) invalid
It is unclear whether the algae are within the exponential growth throughout the whole exposure period of 7 days
25.02.2004 (110) (111)

Species : Scenedesmus subspicatus (Algae)
Endpoint : other: fluorescence inhibition
Exposure period : 3 hour(s)
Unit : mg/l
EC10 : = .43
EC50 : = 14.5
Limit test :
Analytical monitoring : no
Method : other: see below
Year : 1989
GLP : no
Test substance : other TS: p-toluidine, purity not specified

Method : Fluorescence inhibition by the TS was determined in a flow-through-cuvette after one light pulse of 0.5 sec (685 nm); IC50 defined as the lowest, reproducible effective concentration.
Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles
26.02.2004 (111)

Species : Selenastrum capricornutum (Algae)
Endpoint : growth rate
Exposure period : 14 day(s)
Unit : mg/l
EC10 : .067
EC50 : .203
EC90 : .617
Limit test : no
Analytical monitoring : no
Method : other: see below
Year : 1988
GLP : no
Test substance : other TS: p-toluidine, purity not specified

Method : Growth rate was determined spectrocolorimetrically as adsorbance of the test solutions at 665 nm. The inhibition concentrations (10%; 50%; 90%) were determined by probit analysis.
Reliability : (3) invalid
It is unclear whether the algae are within the exponential growth throughout the whole exposure period
25.02.2004 (112)

Species : other algae: Chlorella autotrophica (green alga)

Endpoint : other: radius of growth inhibition
Exposure period :
Unit :
Limit test :
Analytical monitoring : no
Method : other: see below
Year : 1977
GLP :
Test substance : other TS: p-toluidine, purity not specified

Method : Response of algal lawns to TS concentrations in the range of 1-10,000 ug/disk was examined; lawns initially seeded (1+/-0.2 x 10E5 cells/ml) in 1 % agarized (Difco 0140) medium; TS in absolute ethanol was absorbed on antibiotic sensitivity disks, which were placed directly on the agar surface; the sealed petri dish cultures were incubated for 3-7 days at 28°C to 30°C; radius of growth inhibition around the disk was determined visually and microscopically.
Result : No growth inhibition of p-toluidine on Chlorella occurred at concentrations of up to and including 500 µg/plate. Partial inhibition was observed at a concentration of 1000 µg/plate. Growth of Chlorella was completely inhibited on petridishes treated with 2,000 or 10,000 µg p-toluidine/plate. No inhibition was seen in ethanol controls.
Reliability : (3) invalid
Unsuitable test system

25.02.2004 (113)

Species : other algae: Cylindrotheca spec. (diatom); Chlorella autotrophica (green alga)
Endpoint : other: radius of growth inhibition
Exposure period :
Unit :
Limit test :
Analytical monitoring : no
Method : other: see below
Year : 1978
GLP : no
Test substance : other TS: p-toluidine, purity not specified

Method : Response of algal lawns of two algae to TS concentrations in the range of 0.1-500 ug/disk was examined; lawns initially seeded (1+/-0.2 x 10E5 cells/ml) in 1 % agarized (Difco 0140) medium; TS in absolute ethanol was absorbed on antibiotic sensitivity disks, which were placed directly on the agar surface; the sealed petri dish cultures were incubated for 3-7 days at 28°C to 30°C; radius of growth inhibition around the disk was determined visually and microscopically.
Result : Growth inhibition (0 = no inhibition; pi = partial inhibition; ci = complete inhibition):

Organism	TS concentration [ug/disk] 0.1	1	10	100	500
Cylindrotheca spec., strain N	0	n.t.	n.t.	n.t.	pi
Chlorella autotrophica, strain 580	0	n.t.	n.t.	n.t.	o

n.t.

No inhibition seen in ethanol controls
Test condition : 28-30°C; continuous illumination
Reliability : (3) invalid
Unsuitable test system
26.02.2004 (114)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : aquatic
Species : activated sludge of a predominantly domestic sewage
Exposure period : 3 hour(s)
Unit : mg/l
EC50 : = 100
Analytical monitoring : no
Method : OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year : 1986
GLP : no
Test substance : no data

Method : TS predissolved in a vehicle consisting of dimethylsulfoxide and HCO-40 (surfactant; Nikko Chemicals) at a ratio of 4:1; concentration of the vehicle: 2000 mg/l at which the effect on respiration was negligible.
Synthetic sewage fed was dissolved in 1 l of distilled water: 16 g peptone, 11 g of meat extract, 3 g of urea, 0.7 g NaCl, 0.4 g CaCl2.2H20, 0.2 g MgSo4.7H20, and 2.8 g K2HPO4.
If sludge was not used at the same day of collection, then 50 ml of synthetic sewage fed was added to each liter and aerated overnight. Sludge was washed with distilled water (3x) and suspended in distilled water to obtain the level of a mixed liquor suspended solids of 4 g/l.
5 concentrations tested; controls without substances at the start and at the end of the test series; reference substance: 3,5-dichlorophenol.

Synthetic sewage fed (16 ml) and adequate amount of stock solution were mixed and made up to 300 ml with distilled water. 200 ml activated sludge was added. Aeration rate of the mixture was about 1 liter/min at 20°C. After 3 hours exposure period test vessels were sealed and connected to an oxygen electrode in order to measure the oxygen consumption over 10 minutes. Respiration rate was calculated as follows:

$$\text{Percentage inhibition} = (1 - 2Rs/(Rc1 + Rc2)) \times 100$$

Rc1, Rc2, and Rs are respiration rates control 1, of control 2, and at the tested concentration of the test chemical, respectively.
The concentration at which percentage inhibition showed 50% was derived from plotting the percentage inhibition against concentration on log-normal paper.

Result : In the publication of Yoshioka, Ose, and Sato (1986) it is reported a 3 h-EC50 > 100 mg/l, presumably due to a Electronic Data Processing error (edp).
Reliability : (2) valid with restrictions
Reliable with restrictions
Flag : Critical study for SIDS endpoint
08.03.2004 (98) (99)

Type	:	aquatic
Species	:	Tetrahymena pyriformis (Protozoa)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC50	:	= 150
Analytical monitoring	:	no
Method	:	other: cell multiplication inhibition test
Year	:	1985
GLP	:	no
Test substance	:	other TS: p-toluidine, analytical grade
Method	:	2 different counting methods were used. One used a microscope with a specially prepared glass slide which contained a depression (20x50 mm) that could hold 20 cells. A quantity of cultured medium was dropped onto the glass slide and an adequate amount of 3.7 % formaline and 0.7 % CaCl2 was added to kill the cells. The count was repeated 3 times and the mean value of the number of cells was recorded. The other method used a Coulter counter (Model Zb: Nikkaki). The samples were diluted to 50 % with Isotone. The count was repeated twice and the mean value recorded.
Test condition	:	Tetrahymena pyriformis was preserved in a sterile medium (of 2 % proteose peptone at a temperature of 20 °C) which was renewed at 2-4 week intervals. Tetrahymena pyriformis was pre-cultured at a temperature of 30 °C for 24 h. Stock solution of test substance was added to the sterile medium to provide a concentration ratio of 1.8 in 10 ml of 2 % proteose peptone. The solutions were then inoculated with 0.2 ml of the pre-cultured T. pyriformis and cultivated at a temperature of 30 °C for 24 h without agitation.
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles
Flag	:	Critical study for SIDS endpoint

08.03.2004 (98) (115) (99)

Type	:	aquatic
Species	:	Tetrahymena pyriformis (Protozoa)
Exposure period	:	40 hour(s)
Unit	:	mg/l
EC50	:	ca. 120
Analytical monitoring	:	no
Method	:	other: Population growth impairment assay
Year	:	1999
GLP	:	no
Test substance	:	other TS: p-toluidine, purity > 95 %
Method	:	Test was performed according to the method described by Schultz TW (1997). 200 substances were tested to derive QSAR. TETRATOX: Tetrahymena pyriformis population growth impairment endpoint. A surrogate for fish lethality. Toxicol. Methods 7, 289-309. The test was conducted in foam-stoppered 250 ml Erlenmeyer flasks containing 50 ml of sterile, semidefined proteose-peptone-based medium. Test culture was inoculated with log-growth-phase culture. Initial density varied from 1000 to 5000 cells/ml. The temperature was maintained at 27+/-1 °C. Medium was buffered to pH 7.4 prior to sterilization. The assay was conducted as a 40 h static test.
Result	:	Result was given as log 1/IGC50 = -0.05, IGC50 in mM, IGC50

= 50 % growth inhibition concentration

Test condition : Test was performed using the freshwater ciliate Tetrahymena pyriformis (Strain GL-C). The test conditions were as follows: non-neutralised, allow for 8-9 cell cycles in control cultures. The pH of the test media was 7.3 and was not controlled during the test. Prior to testing in duplicate for three replicates, the compound was tested in a range finding test. Test replicates consisted of 6 to 8 concentrations with duplicate flasks of each concentration. The endpoint population density was measured spectrophotometrically at 540 nm.

Test substance : The stock solution was presumably dissolved in < 7.5 ml/l DMSO (dimethlysulfoxide).

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

08.03.2004 (26) (116) (117)

Type : aquatic
Species : Tetrahymena pyriformis (Protozoa)
Exposure period : 60 hour(s)
Unit : mg/l
EC50 : 143.6
Method : other: see below
Year : 1984
GLP : no data
Test substance : other TS: p-toluidine, purity is not specified

Result : Result is expressed in the article as IGC50 in mmol/L = 1.34 (IGC50 = inhibition growth concentration)

Test condition : - Static conditions
- Temperature: 28 °C
- Culture medium: proteose pepton
- Endpoint: population growth
- Measured parameter: optical density
- Five concentrations tested
- 2 replicates
Stock solution were prepared in dimethyl sulfonxide (DMSO) and aliquots of stock solutions max. 300 ul were added in 50 ml freshwater with 0.2 ml culture medium.

Test substance : The stock solution was prepared in a non-defined amount of DMSO.

Reliability : (2) valid with restrictions
Basic data given

09.03.2004 (118)

Type : aquatic
Species : other protozoa: Spirostomum ambiguum
Exposure period : 24 hour(s)
Unit : mg/l
EC50 : 192.9
LC50 : 307.5
Analytical monitoring : no
Method : other: Spirotox test
Year : 1999
GLP : no
Test substance : other TS: p-Toluidine, purity is not specified

Result : Results were given in mmol/l after 24 and 48 h.
For the deformation differences:
24 h and 48 h-EC50= 1.80+/-0.41 mmol/l and 0.93 +/- 0.01

mmol/l, respectively = 192.9+/-43.9 mg/l and 99.7 +/- 1.07 mg/l, respectively

For lethality: 24 h and 48 h-EC50= 2.87+/-0.55 mmol/l and 1.52 +/- 0.26, respectively = 307.5 +/- 58.9 mg/l and 162.9 +/- 27.9 mg/l

Test condition : Test organism: Spirostomum ambiguum, one of the biggest protozoans (2-3 mm long); Diluent: Tyrod solution: 125 mg NaCl, 3.1 mg KCl, 3.1 mgCaCl2, 1.55 mg MgCl2, 15.6 mg NaHCO3 and 0.78 mg NaH2PO4 per liter of deionised water. Total hardness = 2.8 mg CaCO3/land pH = 7.4 +/- 0.2. Incubation took place in darkness at 25 °C.- 2 kinds of test responses were observed: a) different deformations and b) lethal response.

Reliability : (2) valid with restrictions
Basic data given

08.03.2004 (119)

Type : other: broth medium
Species : other bacteria: Cyanobacteria
Exposure period :
Unit :
Analytical monitoring : no
Method : other: Bacterial lawn assay with 8 species of cyanobacteria
Year : 1978
GLP : no
Test substance : other TS: p-toluidine, purity not specified

Method : Response of bacterial lawns of 8 cyanobacteria and two bacteria to TS concentrations in the range of 0.1-500 ug/disk was examined; lawns initially seeded (1+/-0.2 x 10E5 cells/ml) in 1 % agarized (Difco 0140) medium; TS in absolute ethanol was absorbed on antibiotic sensitivity disks, which were placed directly on the agar surface; the sealed petri dish cultures were incubated for 3-7 days at 28°C to 30°C; radius of growth inhibition around the disk was determined visually and microscopically.

Result : Growth inhibition (0 = no inhibition; pi = partial inhibition; ci = complete inhibition):

Organism	TS concentration [ug/disk] 0.1	1	10	100	500
Coccochloris elabens, strain 17a	0	pi	ci	ci	ci
Eucapsis sp.	0	pi	ci	ci	ci
Agmenellum quadruplicatum, strain PR6	0	pi	ci	ci	ci
Oscillatoria williamsii strain Mev	0	0	ci	ci	ci
Anabaena sp.	0	0	0	ci	ci
Fisherella sp.	0	0	0	pi	ci
Nostoc sp.	0	0	0	0	ci
Microcoleus chthonoplastes	0	0	0	0	ci
Escherichia coli strain 786	0	0	0	0	n.t.
Staphylococcus epidermidis (strain 673)	0	0	0	0	n.t.

n.t., however no inhibition was observed at 1000 ug/disk

No inhibition seen in ethanol controls
Test condition : 28-30°C; continuous illumination
Reliability : (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
08.03.2004 (114)

Type : aquatic
Species : Escherichia coli (Bacteria)
Exposure period : 6 hour(s)
Unit : mg/l
EC0 : >= 1000
Analytical monitoring : no
Method : other
Year : 1959
GLP : no
Test substance : other TS: p-toluidine, purity not specified

Method : River water was used as dilution water (havel: acidification capacity: 2.6 ml n/10 HCL per 100 ml; 12° dH (German water hardness); pH was adjusted to 7.5; incubation temperature 27°C; peptone (10 gamma/ml); added glucose: 10 mg/ml

endpoint: effect of TS on the acid production of E. coli, determined by pH differences of the test preparations compared to the control; pH value was determined by colorimetric indicator.
Result : No inhibition was observed even at the highest TS concentration of 1000 mg/l
Reliability : (3) invalid
Unsuitable test system
08.03.2004 (105)

Type : aquatic
Species : Pseudomonas fluorescens (Bacteria)
Exposure period :
Unit : mg/l
EC3 : > 200
Analytical monitoring : no
Method : other
Year : 1960
GLP : no
Test substance : other TS: p-toluidine, purity not specified

Method : River water was used as dilution water (Havel: pH-value 7.5 - 7.8; acidification capacity: 2.7 ml n/10 HCl per 100 ml; pH was adjusted to 7.5; incubation temperature 27°C; peptone (10 gamma/ml); added glucose: 10 mg/ml; exposure period: 16-19 hours

endpoint: effect of TS on the acid production of E. coli, determined by pH differences of the test preparations compared to the control; pH value was determined by colorimetric indicator.
Result : TT (Toxicity threshold) reported, comparable to EC3; value refers to nominal TS concentration
Reliability : (3) invalid
Unsuitable test system

08.03.2004 (120)

Type	:	aquatic
Species	:	other protozoa: Microregma heterostoma
Exposure period	:	28 hour(s)
Unit	:	mg/l
EC0	:	< 40
Analytical monitoring	:	no
Method	:	other: according to Bringmann and Kuehn. Ges. Ing. 80, 239-242
Year	:	1959
GLP	:	no
Test substance	:	other TS: p-toluidine, purity not specified
Remark	:	Microregma heterostoma was exposed to dilution series of p-toluidine in pasteurised river water for 28 h at 27°C. Toxicological threshold of p-toluidine on Microregma was recorded as starting inhibition of food (added E.coli) uptake determined as change of the turbidity of the test solutions.
Reliability	:	(3) invalid Unsuitable test system

08.03.2004 (106)

Type	:	aquatic
Species	:	Tetrahymena pyriformis (Protozoa)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	101.63
Analytical monitoring	:	no
Method	:	other: Population growth
Year	:	1989
GLP	:	no
Test substance	:	other TS: p-Toluidin, Purity not given
Result	:	The result was expressed in log BR in mmol/l. BR was defined as 50% population growth concentration.
Test condition	:	The inverse of the population growth concentration was determined using a static design at 27°C. Axenic cultures were reared in 250 ml Erlenmeyer flask containing 50 ml of medium supplemented with varying amounts of the test substance. Optical density at 540 nm was used to estimate population levels. Probit analysis of the control-normalized absorbance versus concentration was used to calculate relative toxicity. Percent loss of the test substance was measured as the difference between the t=0 and t=48 concentration.
Reliability	:	(4) not assignable Documentation insufficient for assessment

08.03.2004 (28)

Type	:	aquatic
Species	:	activated sludge
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC0	:	= 250
EC50	:	= 500
Analytical monitoring	:	no
Method	:	ETAD Fermentation tube method "Determination of damage to effluent bacteria by the Fermentation Tube Method"
Year	:	1986
GLP	:	no
Test substance	:	other TS: p-toluidine, purity not specified

Remark	:	Values refer to saturated solution (10 g p-toluidine dissolved in 1 l water; stirred for 12 hours at 20°C, pH 7; content ca. 7.2 g/l
Test condition	:	20°C; pH 7
Reliability	:	(4) not assignable Documentation insufficient for assessment

08.03.2004 (121)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

Species	:	Brassica campestris var. chinensis (Dicotyledon)
Endpoint	:	growth
Exposure period	:	5 day(s)
Unit	:	mg/l
LC50	:	102.2
Method	:	OECD Guide-line 208 "Terrestrial Plants, Growth Test"
Year	:	1996
GLP	:	no data
Test substance	:	other TS: p-Toluidine, purity >/= 95 %
Test condition	:	- Plant root elongation method according to OECD TG 208 - 15 pretreated seeds on filter paper in petri dish containing test solution - semi-static exposure (renewal each 12 hours); pH 6.85-7.12; in the dark; at 25 °C; four replicates - pH and O2 control - 6 concentrations tested; stock solution was prepared with deionized water
Reliability	:	(1) valid without restriction Guideline study
Flag	:	Critical study for SIDS endpoint

17.06.2004 (122)

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo : In vivo
Type : Distribution
Species : rat
Number of animals
Males : 4
Females :
Doses
Males : 500 mg/kg bw in corn oil/methanol (8:2)
Females :
Vehicle : other: corn oil/methanol (8:2)
Route of administration : other: single application by gavage
Exposure time : 72 hour(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st: 12-15 hours
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other: see freetext TC
Year : 1990
GLP : no data
Test substance : other TS: p-[ring-U-14C]toluidine, radiochemical purity >99 %

Result : Peak blood levels were observed for the para-isomer at 24 and 12 h respectively with determination of the AUC for p-toluidine (AUC = 1.6 mg hr/ml).
As half-life time of plasma elimination 12 to 15 hours was derived
TISSUE AND ORGAN CONCENTRATIONS
Mean concentration values in [µg Eq/g tissue] 72 h after treatment: whole blood 10.3, subcutaneous abdominal fat 26.4, liver 18.8, abdominal skin 18.2, kidneys 15.5, spleen 8.9, bladder 7.7, lungs 5.1, gastrointestinal tract 4.3, heart 2.9, bone marrow 1.4, muscle 1.1, brain 0.9, testes 0.9
Test condition : Pharmacokinetics and tissue distribution:
4 Crl: CD BR-rats were dosed orally with 500 mg/kg bw p-14C-toluidine, formulated in corn oil/methanol = 8:2 (dosing volume: 2 ml), and housed individually and immediately after dosing in glass metabolism units.
Blood samples were drawn from each of the 4 rats via jugular-vein cannula at 30 min and 2, 6, 12, 24, 36, 48 and 72 h after dosing.
Areas under the plasma concentration-time curves (AUC) were determined.
Rats were sacrificed 72h after dosing and selected organs and tissues were removed and assayed for radioactivity by tissue combustion and scintillation counting.
Reliability : (2) valid with restrictions
Time course of tissue distribution not recorded
Flag : Critical study for SIDS endpoint
04.06.2004 (123)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : rat
Number of animals
Males : 4
Females :

Doses
Males : 0, 500 mg/kg bw
Females :
Vehicle : other: corn oil
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other: see freetext ME
Year : 1980
GLP : no data
Test substance : other TS: p-toluidine, purity: 99.5 %

Method : TEST ORGANISMS:
- Animals: adult male Sprague-Dawley rats
- Weight at study initiation: 380-440g

ADMINISTRATION and URINE EXAMINATIONS:
- 4 animals were administered with a single dose of 500 mg non-labelled p-toluidine and 24h urine was collected.

- 12 rats were administered with 1 ml/kg corn oil for 24h control urine

EXAMINATIONS:
determination of urine volume
determination of unchanged p-toluidine and metabolites by gas-liquid chromatography and mass spectra

STATISTICAL ANALYSIS:
Statistical differences between groups were determined using Student`s t-test

Result : 2.5% of the administered p-toluidine appeared unchanged in the 24-hour urine
2-amino-5-methylphenol as metabolite from p-toluidine was identified; quantification was not given
Reliability : (2) valid with restrictions
Only males included and no quantification of the metabolites
Flag : Critical study for SIDS endpoint
04.06.2004 (124)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : dog
Number of animals
Males : 4
Females :
Doses
Males : 0.77 mmol (approx. 111.1 mg/kg bw)
Females :
Vehicle : water
Route of administration : i.v.
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :

Adverse effects on prolonged exposure :
Half-lives : 1st: 1 hour
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other: see freetext ME
Year : 1963
GLP : no
Test substance : other TS: p-toluidine hydrochloride, no data on purity

Method : 4 dogs, older than one year, received i.v. injections of p-toluidine hydrochloride. The concentration of p-toluidine in blood was observed for a period of 6 hours by measuring according to Brodie and Axelrod (1948): J. Pharmacol. exp. Ther. 94, 22
Products from N-oxidation were extracted from blood with carbon tetrachloride and determined with the method of Herr and Kiese (1959), Naunyn-Schmiedeberg's Arch.exp. Path. Pharm. 235, 351
Hemoglobine was estimated by measuring the increase of the extinction at 550 mμ that was caused by adding cyanide to a blood solution of pH=6.8
Result : Results were only reported as graphics:

1) Half-life time of p-toluidine was: approximately one hour. 7 hours post application approximately 12 µg p-toluidine per ml blood was found.

2) Hemoglobin content increased with increasing time from application, and reached a plateau 6 hours post application, value seems to be only one sixth of o-toluidine

3) Carbon tetrachloride extracts contain p-nitrosotoluene
Reliability : (2) valid with restrictions
Data of the results were only shown as graphics, no data on the purity of the TS
Flag : Critical study for SIDS endpoint
04.06.2004 (125)

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species : rat
Number of animals
Males :
Females :
Doses
Males :
Females : 0, 40, 80, 160 mg/kg bw/day
Vehicle :
Route of administration : oral feed
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other: see freetext ME
Year : 1995
GLP : no data
Test substance : other TS: p-toluidine, no data on purity

Method : groups of female Wistar rats (n=8) received p-toluidine in feed with

a) protein content 8 % for 6 months (0, 40, 80, 160 mg/kg bw/day) and for 12 months (160 mg/kg bw/day)

b) protein content 24 % for 6 months (40, 80, 160 mg/kg bw/day) and 12 months (0, 160 mg/kg bw/day)

Determination of p-toluidin concentration in blood, urine and methemoglobin levels

Remark : see also chapter 5.4

Result : a) protein content 8 % for
---------6 months:
--blood content: dose related increase (graphic only)
--urine content: dose related increase (graphic only)
---------12 months:
--blood content (160 mg): lower than the respective value after 6 months of treatment (graphic only)
--urine content (160 mg): lower than the respective value after 6 months of treatment(graphic only)
methemoglobin levels (see chapter 5.4)

b) protein content 24 %
---------6 months:
--blood content: dose related increase (graphic only)
--urine content: dose related increase (graphic only)
---------12 months:
--blood content (160 mg): slightly elevated when compared with the respective value after 6 months of treatment (graphic only)
--urine content (160 mg): lower than the respective value after 6 months of treatment (graphic only)
methemoglobin levels (see chapter 5.4)

Reliability : (2) valid with restrictions
Provides additional information although reported in brief

Flag : Critical study for SIDS endpoint

04.06.2004 (126) (127)

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species : rat
Number of animals
Males : 4
Females :
Doses
Males : 500 mg/kg bw in corn oil
Females :
Vehicle : other: corn oil
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st.:
2nd.:
3rd.:
Toxic behaviour :
Deg. product :
Method : other: see freetext TC
Year : 1990

GLP : no data
Test substance : other TS: p-[ring-U-14C]toluidine, radiochemical purity >99 %

Remark : DNA, RNA and protein binding in rats
Result : Binding levels to DNA, RNA and total protein binding were low and appeared to plateau by 24 and 48 h after administration.
level of DNA binding (24 hrs):
approx. 9.8 pmoles (10exp-1)/µg DNA
level of RNA binding (peak at 12 hrs):
approx. 2.3 pmoles (10exp-1)/µg RNA
level of hepatic protein binding (24 hour max.)
approx. 28 pmoles (10exp-1)/µg protein
Test condition : 4, 8, 12, 24 and 48 hours following single application by gavage rats (4-5 rats per timepoint) were sacrificed. Livers were immediately removed and homogenized.

Hepatic DNA, RNA binding were determined according Cooper (1977) and Burton (1956).
Total protein binding was determined by method as described Hughes (1986)
Reliability : (2) valid with restrictions
study meets general acceptable principles
04.06.2004 (123)

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species : rat
Number of animals
Males : 6
Females :
Doses
Males : 0, 75 mg/kg bw in sunflower oil
Females :
Vehicle : other: sunflower oil
Route of administration : i.p.
Exposure time : 3 day(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st.:
2nd.:
3rd.:
Toxic behaviour :
Deg. product :
Method : other: see freetext ME
Year : 1984
GLP : no data
Test substance : other TS: p-toluidine, purity: 98 %

Method : TEST ORGANISMS:
- Animals: male Wistar rats
- body weight: 200 - 250 g
- Number of animals: 6 per group
ADMINISTRATION / EXPOSURE
- Duration of test/exposure: 3 days
- Type of exposure: i.p.
- Vehicle/control: sunflower oil
Rats were fasted for 12h after the last administration before being killed. Rats were decapitated on the fourth day, livers, kidneys and lungs were immediately excised, weighed and homogenized.

PARAMETERS INVESTIGATED:
Cytochrome P450, Cytochrome b5, NADPH cytochrome c reductase, Aryl hydrocarbon hydrolase (AHH), Aminopyrine demethylase, Epoxide hydrolase, Glutathione-S-transferase,
Ratio of Glutathione-S-transferase to AHH activities and Ratio of Epoxide Hydrolase to AHH activities

STATISTICS:
Analysis were performed (method not mentioned); differences were assumed to be significant when p<0.05

Remark : Determination of metabolizing enzymes in liver, kidneys and lung
Result : Effects on enzym-activities by organ (significant changes versus resp. controls):
LIVER
--Cytochrome P-450:
0.865 versus 1.044 nmol x mg protein[exp.-1]
--AHH:
186 versus 295 pmol x mg protein[exp-1] x min[exp-1]
--Aminopyrine demethylase:
0.626 versus 0.834 nmol x mg protein[exp.-1] x min[exp-1]
--Epoxide hydrolase
2.69 versus 0.99 nmol x mg protein[exp.-1] x min[exp-1]
--Gluthatione S-transferase
1791 versus 1171 nmol x mg protein[exp.-1] x min[exp-1]

KIDNEYS
no significant changes

LUNG
no significant changes
Reliability : (2) valid with restrictions
Changes in organ weights were not reported
04.06.2004 (128)

In Vitro/in vivo : In vitro
Type : Metabolism
Species : rabbit
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :

Remark : liver microsomes of rabbits:
p-toluidine is not a substrate for arylhydroxylation, but instead underwent side-chain oxidation to form 4-hydroxymethylaniline, which was further oxidized to aldehyde
Reliability : (4) not assignable
Documentation insufficient for assessment because concerning p-toluidine report is too short
04.06.2004 (129)

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : 656 mg/kg bw
Species : rat

Strain : no data
Sex : male
Number of animals : 5
Vehicle : other: corn oil
Doses : 316, 464, 681, 1000 mg/kg bw suspended in corn oil
Method : other: 5 male rats/dose, single application of TS, suspended in corn oil, by gavage, post exposure observation period: 14 days, observation for clinical signs, gross autopsy of survivors and decedents
Year : 1973
GLP : no data
Test substance : other TS: p-toluidine; no data on purity, M.P. 44.5°C

Result : LD 50: 95% confidence limits: 543-791 mg/kg bw

Dosage (mg/kg bw): onset of symptons // cumul. mortality // recovery of survivors
316: 5/5 within 0-4 hrs // 0/5 //at day 1
464: 5/5 within 0-4 hrs // 0/5// at day 2
681: 5/5 within 0-4 hrs // 3/5 within 3 days// at day 4
1000: 5/5 within 0-4 hrs // 5/5 within 3 days

Signs of intoxications:
hypoactivity, cyanosis, anorexia, death

gross pathology:
survivors, decedents: no significant findings

Reliability : (2) valid with restrictions
No information of strain used, no information on statistical evaluation
Flag : Critical study for SIDS endpoint
04.06.2004 (130)

Type : LD50
Value : = 620 mg/kg bw
Species : rat
Strain : Wistar
Sex : male
Number of animals : 10
Vehicle : other: Lutrol
Doses : 100, 500, 600, 650, 700, 900 mg/kg bw
Method : other: single oral application by gavage, TS dissolved in lutrol, observation time: 14 days, calculation of LD50 value: Fink, Arzneim.-Forschg: 15, 624, 1965
Year : 1978
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : dose (mg/kg bw): time of deaths//no. of dead rats/ no. of rats with signs of intoxication/ no. of rats used:

100 mg/kg bw : no deaths // 0/10/10
500 mg/kg bw: 2-3 days // 2/10/10
600 mg/kg bw: 3 hrs-5 days // 4/10/10
650 mg/kg bw: 2-3 hrs // 4/10/10
700 mg/kg bw: 2-3 days// 9/10/10
900 mg/kg bw: 3 hrs-3 days // 10/10/10

signs of intoxication:
poor reflexes, increased excretion of urine, emaciation, eye bloody, narcosis, cyanosis

Reliability : (2) valid with restrictions

No gross and/or microscopic pathology
Flag : Critical study for SIDS endpoint
04.06.2004 (131)

Type : other: methemoglobinemia
Value : 200 mg/kg bw
Species : rat
Strain : Wistar
Sex : female
Number of animals :
Vehicle : no data
Doses : 200 mg/kg bw
Method : other: single application by gavage, blood taken from heart or tail vein, immediately examination for methemoglobin according to the method of Everlyn -Malloy
Year : 1984
GLP : no
Test substance : other TS: p-toluidine, no data on purity

Remark : Single oral application of 200 mg/kg bw p-toluidine resulted in a methemoglobin level (max) of 21.7 % two hours post application.
Reliability : (2) valid with restrictions
No data on number of animals, no data on purity of the substance, no data on GLP, standard deviation not given
Flag : Critical study for SIDS endpoint
08.06.2004 (132)

Type : LD50
Value : = 1285 mg/kg bw
Species : rat
Strain :
Sex : no data
Number of animals :
Vehicle : no data
Doses :
Method : other: no data
Year : 1973
GLP : no data
Test substance : other TS: p-toluidine hydrichloride, no data on purity

Reliability : (4) not assignable
Secondary literature
04.06.2004 (133)

Type : LD50
Value : = 760 mg/kg bw
Species : rat
Strain :
Sex : no data
Number of animals :
Vehicle : no data
Doses :
Method : other: no data
Year : 1981
GLP : no data
Test substance : other TS: p-toluidine, no data on purity

Reliability : (4) not assignable
Documentation insufficient for assessment
04.06.2004 (134)

Type	:	LD50
Value	:	= 1285 mg/kg bw
Species	:	rat
Strain	:	Osborne-Mendel
Sex	:	male
Number of animals	:	10
Vehicle	:	water
Doses	:	see freetext TC
Method	:	other: single dose by stomach tube, 14-day observation period, calculation of LD50 with the Bliss probit method
Year	:	1969
GLP	:	no
Test substance	:	other TS: p-toluidine hydrochloride, no data on purity
Test condition	:	TEST ORGANISMS: - Animals: Osborne-Mendel male rats - Weight at study initiation: 250 g ADMINISTRATION: - Route: gavage - Doses: dosages in a series of 3 levels at 10 antilog unit intervals with 10 animals at each level - Doses per time period: single dose - Post dose observation period: 14 days
Reliability	:	(4) not assignable Documentation insufficient for assessment

04.06.2004 (135)

Type	:	LD50
Value	:	= 794 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	no data
Number of animals	:	
Vehicle	:	other: olive oil
Doses	:	
Method	:	other: no data
Year	:	1978
GLP	:	no data
Test substance	:	no data
Reliability	:	(4) not assignable Documentation insufficient for assessment

04.06.2004 (136)

Type	:	other: LD50 of 4-Isopropylaniline (CAS No. 99-88-7)
Value	:	ca. 985 mg/kg bw
Species	:	rat
Strain	:	Crj: CD(SD)
Sex	:	male/female
Number of animals	:	5
Vehicle	:	other: corn oil
Doses	:	700, 910, 1183, 1538, 2000 mg/kg bw
Method	:	other: OECD Guide-line 401 (in Japanese), see also freetext: Method
Year	:	1999
GLP	:	yes
Test substance	:	other TS: 4-isopropylaniline (CAS-No: 99-88-7), purity: 99.27 %
Method	:	5 weeks old rats (Crj:CD(SD)IGS-SPF) with the initial weight of 127-135 g

for males, and 105-111 g for females were used. Animals had free access to pellet food till 16-18 hours before dosing and after dosing. 5 animals were used per sex and dose.
water: free take
ADMINISTRATION
vehicle: 1% (w/v) Carboxymethylcellulose
route: 10 ml/kg bw by gavage
post dose observation: up to 14 days after administration
OBSERVATION
daily: general appearance
day 0, 1, 3, 5, 7, 10, 14: body weight
day 14: autopsy and histopathology on liver, kidneys, spleen, heart, lung, brain, stomach, intestine, ovary, testis and epididymides.
LD50 value estimated by Probit method

Remark : guideline study reported in Japanese , only sunnary tables and abstract available

Result : Mortality:

Dose [mg/kg bw]	m / f
700	0 of 5 / 0 of 5
910	2 of 5 / 2 of 5
1183	4 of 5 / 4 of 5
1538	5 of 5 / 5 of 5
2000	5 of 5 / 5 of 5

Death of both sexes occurred in the 910 mg/kg and higher groups. In animals in all the groups abnormal gait, decreased spontaneous motor activity and salivation were observed in both sexes. Lacrymation and adoption of a prone, lateral position and/or hunched back position were observed in both sexes receiving 910 mg/kg bw or more. Moreove, hair soiling and abdominal distention were observed in some groups.

LD50 (male, female): 985 mg/kg bw

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
13.01.2006 (137)

Type : other: approximate lethal dose
Value : 1000 mg/kg bw
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : other: peanut oil containing 15 % acetone
Doses : increasing amounts (no further information given
Method : other: according to Deichmann anf leblanc,J. Ind. Hyg. and Tox. 25, 415 (1943)
Year : 1949
GLP : no
Test substance : other TS: no data on purity

Method : Acute oral toxicity was tested by determining the appropriate lethal dose (ALD) for rats: single doses of increasing amounts were given to a sseries of rats by stomach tube. the minimum dose which killed was considered as ALD

Result : the ALD was 1000 mg/kg bw. the material caused pain, weakness, cyanosis and death within 44 hours. Pathologic examination indicated damage to the liver and kidneys.

Reliability : (4) not assignable
Insufficient documented method which doesn't meet the criteria of today
21.06.2004 (138)

Type : LD50
Value : = 330 mg/kg bw
Species : mouse
Strain :
Sex : no data
Number of animals :
Vehicle : no data
Doses :
Method : other: no data
Year : 1981
GLP : no data
Test substance : other TS: p-toluidine, no data on purity

Reliability : (4) not assignable
Documentation insufficient for assessment
04.06.2004 (134)

Type : LD50
Value : = 794 mg/kg bw
Species : mouse
Strain :
Sex : no data
Number of animals :
Vehicle : no data
Doses :
Method : other: keine Daten
Year : 1973
GLP : no data
Test substance : other TS: p-toluidine, no data

Reliability : (4) not assignable
Secondary literature
04.06.2004 (133)

Type : LD50
Value : = 270 mg/kg bw
Species : rabbit
Strain :
Sex : no data
Number of animals :
Vehicle : no data
Doses :
Method : other: no data
Year : 1977
GLP : no data
Test substance : other TS: p-toluidine, no data on purity

Reliability : (3) invalid
No data on source
04.06.2004 (139)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC50

Value	:	> .64 mg/l
Species	:	rat
Strain	:	no data
Sex	:	male
Number of animals	:	6
Vehicle	:	other: air
Doses	:	0.64 mg/l
Exposure time	:	1 hour(s)
Method	:	other: administration as vapor at room temperature, total air flow 10 litre/min, exposure time: 1 hr, observation time: up to 14 days, record of signs of intoxication, gross autopsy. Male rats: bodyweight 188-260 g
Year	:	1973
GLP	:	no data
Test substance	:	other TS: p-toluidine, no data on purity: M.P.: 44.5°C
Result	:	no rat died during and post exposure; male rat body weight: 188-260 g Signs of intoxication started within 0-4 hours and included generalized inactivity, rhinitis and lacrimation, and ceased within one day. Gross autopsy revealed no significant findings.
Reliability	:	(2) valid with restrictions No information about the strain used exposure time 1 hr only, only one concentration
Flag	:	Critical study for SIDS endpoint

08.06.2004 (130)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	= 890 mg/kg bw
Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	5
Vehicle	:	water
Doses	:	464, 691, 1000, 1470 mg/kg bw
Method	:	other: 5 rabbits per dose, TS moistened with sufficient water to make a paste, no data on exposure duration, post exposure observation: up to 14 days, record of smptoms, gross autopsy of survivors and decedents
Year	:	1973
GLP	:	no data
Test substance	:	other TS: p-toluidine, no data on purity, M.P.: 44.5 °C
Result	:	LD50: 95% confidence interval: 622-1272 mg/kg bw 464 mg/kg bw: no symptoms, mortality: 1/5 at day 4 691 mg/kg bw: onset of symptoms 4-12 hours post application, mortality: 1/5 day 4, survivors recovered one day post exposure 1000 mg/kg bw: onset of symptoms 0-4 hours post application, mortalitiy: 3/5 12-24 hours and day 4 post exposure, respectively; survivors recovered one day post exposure 1470 mg/kg bw: onset of symptoms 0-4 hours post application, mortalitiy: 5/5 12-24 hours and day 4 post exposure, respectively Signs of intoxication: hypoactivity, muscular weakness, convulsions and vocalisation just prior to death dermal irritation: moderate to severe erythema, mild edema, focal chemical burns, subdermal hemorrhages

Gross autopsy:
survivors: no significant findings
decedents: granular livers

Reliability : (2) valid with restrictions
No information about the strain used, statistical evaluation not given

Flag : Critical study for SIDS endpoint

26.05.2004 (130)

Type : other: methemoglobinemia
Value :
Species : rat
Strain : Wistar
Sex : female
Number of animals :
Vehicle : no data
Doses : 0.5, 0.75, 1, and 1.25 % solution of p-toluidine (taken from graphic)
Method : other: single dermal applicationf exposure time: 2-6 hours, immediately afterwards methemoglobin determination according to Evelyn-Malloy
Year : 1984
GLP : no
Test substance : other TS: p-toluidine, no data on purity

Remark : 1. Time course measurements on methemoglobinemia following single dermal application:
----Single dermal application resulted in methemoglobin
----level up to approximately 20 %, value returned to ----normal within 48 hours.

2. Dose-response relation measurements on methemoglobin content following single dermal application of different doses:
----Dermal application (0.5, 0.75, 1, and 1.25 % solution ----of p-toluidine) resulted in dose-related increase in ----methemoglobinemia up to 40 %;

Methemoglobin level increased also with duration of exposure (no futher information).

Reliability : (2) valid with restrictions
No data on number of animals, no data on purity of the substance, no data on GLP, standard deviation not given

Flag : Critical study for SIDS endpoint

26.01.2006 (140)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type : LD50
Value : = 50 mg/kg bw
Species : mouse
Strain :
Sex : male
Number of animals :
Vehicle : no data
Doses :
Route of admin. : i.p.
Exposure time :
Method : other: no data
Year : 1969
GLP : no data
Test substance : no data

29.01.2004 (141)

Type	:	LD50
Value	:	= 1012 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	female
Number of animals	:	
Vehicle	:	peanut oil
Doses	:	
Route of admin.	:	s.c.
Exposure time	:	
Method	:	other: dose-finding for a cancerogenicity study see TC
Year	:	1981
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	LD50 = 1012 mg/kg body weight 95 % confidence limit: 840 - 1170 mg/kg bw
Test condition	:	TEST ORGANISMS: - Animals: female Sprague-Dawley rats - Age: 6 weeks ADMINISTRATION: - Route: subcutan - Vehicle: peanut oil - Doses per time period: single dose - Post dose observation period: 3 weeks
Reliability	:	(2) valid with restrictions Insufficient documentation; investigated for dose-finding only

19.03.2004 (142)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	500 mg
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	2
Vehicle	:	water
PDII	:	
Result	:	slightly irritating
Classification	:	
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1986
GLP	:	yes
Test substance	:	other TS: no data on purity
Remark	:	no further data available
Reliability	:	(4) not assignable No details given, secondary literature

18.06.2004 (143)

Species	:	rabbit
Concentration	:	500 mg
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	2
Vehicle	:	water
PDII	:	

Result : not irritating
Classification :
Method : other: moistened with water, inner surface of the ear. fixed with plaster, after exposure washing with soap and plant oil, observation time: 7 days
Year : 1979
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
Limited documentation, only 2 animals
Flag : Critical study for SIDS endpoint
25.05.2004 (144)

Species : rabbit
Concentration : 500 mg
Exposure : no data
Exposure time : no data
Number of animals : 6
Vehicle : other: none
PDII :
Result : irritating
Classification :
Method : other: 500 mg dry powder, 6 rabbits, abraded and intact skin (no further information), reading: 24 and 72 hours post application: erythema and edema, scoring according to Draize
Year : 1973
GLP : no
Test substance : other TS: p-toluidine, no data on purity, M.P.: 44.5 °C

Result : INTACT SKIN:
Erythema
24 hours: 4/6 rabbits score: 4; 2/6 rabbits score: 3
72 hours: 5/6 rabbits score: 4; 1/6 rabbits score: 0
Edema
24 hours: 4/6 rabbits Score: 4; 2/6 rabbits score: 3
72 hours: 5/6 rabbits score: 4; 1/6 rabbits score: 0
ABRADED SKIN:
Erythema
24 hours: 3/6 rabbits score 4; 2/6 rabbits score 3; 1/6 rabbits: score 2
72 hours: 6/6 rabbits score: 4
Edema
24 hours:4/6 rabbits score: 4; 1/6 rabbits score: 3; 1/6 rabbits score: 2
72 hours: 6/6 rabbits score: 4

no information wether recovery occurred

summary irritation score: 7.21/8.00
Reliability : (4) not assignable
Limited documentation; no information on exposure time and conditions
25.01.2006 (130)

Species : rabbit
Concentration : 500 mg
Exposure : Occlusive
Exposure time : 4 hour(s)
Number of animals : 6
Vehicle : water
PDII :
Result : not irritating
Classification :

Method	:	EPA OTS 798.4470
Year	:	1997
GLP	:	no data
Test substance	:	other TS: p-toluidine, purity: 99.8 %
Method	:	p-toluidine was moistened with water and applied to the shaved back of 2 males + 4 females, then subst. removed with water, examination for signs of dermal irritation: 30-60 min, 24, 48, 72 hrs post removal of the wrapping
Result	:	No signs of corrosivity 30-60 min scoring : very slight to well-defined erythema and very slight edema by 72 hour scoring: no rabbit exhibited any signs of dermal irritation primary irritation score was calculated to be 0.15
Reliability	:	(2) valid with restrictions Guideline study, but individual animal data not given

09.05.2005 (145)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	irritating
Classification	:	
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1986
GLP	:	yes
Test substance	:	other TS: p-toluidine, no data on purity
Remark	:	no further data available, secondary literature
Reliability	:	(4) not assignable No details given, secondary literature

21.06.2004 (146)

Species	:	rabbit
Concentration	:	50 mg
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	2
Vehicle	:	none
Result	:	slightly irritating
Classification	:	
Method	:	other: application of TS into the conjunctival sac of one eye of each of the 2 rabbits , observation time: 7 days
Year	:	1979
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	cornea and iris were not impaired conjunctiva : redness (score 1/3) in the eyes of both rabbits over 24 hours, swelling (score 1/4) in the eye of one rabbit: recovery within 24 hours lacrimation immediately after application of TS: recovery within 24 hours at the end of the observation period: no signs of irritation

Reliability	:	(2) valid with restrictions No information on rinsing of the eyes, only 2 animals, short documentation
Flag	:	Critical study for SIDS endpoint
26.05.2004		(144)
Species	:	rabbit
Concentration	:	100 mg
Dose	:	
Exposure time	:	unspecified
Comment	:	no data
Number of animals	:	6
Vehicle	:	none
Result	:	irritating
Classification	:	
Method	:	other: undissolved TS , time of reading: 24, 48 and 72 hours
Year	:	1973
GLP	:	no
Test substance	:	other TS: p-toluidine, no data on purity, M.P.: 44.5°C
Result	:	Reading time: mean score 24 hours: mean score(cornea, iris, conjunctivae): 56.2/110 48 hours: mean score(cornea, iris, conjunctivae): 52.0/110 72 hours: mean score(cornea, iris, conjunctivae): 43.3/110 summary mean score: 56.7/110 no information on recovery
Reliability	:	(2) valid with restrictions Limited documentation; observation time should be longer to evaluate reversibility
Flag	:	Critical study for SIDS endpoint
19.03.2004		(130)
Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 other: g
Exposure time	:	24 hour(s)
Comment	:	rinsed after (see exposure time)
Number of animals	:	6
Vehicle	:	other: none
Result	:	not irritating
Classification	:	
Method	:	EPA OTS 798.4500
Year	:	1997
GLP	:	no data
Test substance	:	other TS: p-toluidine, putity > 98 %
Method	:	Administration of TS into the right conjunctival sac of 6 females, left eye served as control, scoring vor irritation at 1, 24, 48, 72 hrs, 7, 14 days: FHSA scoring
Result	:	Cornea: at 24 hour scoring: corneal opacity in 5/6, in 4/6 at the 48 and 72 hour reading Iris: iridial irritation in 1-3/6 rabbits at the 24 hour-, 48 hour-, 72 hour- and 7 day-reading interval. Conjunctiva: erythema, chemosis, discharge in 6/6 rabbitsat 1 hour and 24 hour-reading; 7 day-reading: 2/6 conjunctival erythema, 1/6 chemosis and discharge

14 days following treatment all rabbits recovered completely from all signs of ocular irritation.

FHSA-scoring:
A maximum primary eye irritation score of 27.8/max.110 was observed at the 24 hour interval.
After 72 hours, the mean scores of corneal opacity, iris lesions, conjunctival erythema and chemosis were 0.7, 0.4, 1.7 and 1.8, respectively, and therefore considered as a nonirritant.

Reliability : (1) valid without restriction
Guideline study, but individual animal data not shown

09.05.2005 (147)

5.3 SENSITIZATION

Type	:	Patch-Test
Species	:	guinea pig
Concentration	:	1st: Induction 2 % occlusive epicutaneous 2nd: Challenge occlusive epicutaneous 3rd: other: see also ME
Number of animals	:	10
Vehicle	:	petrolatum
Result	:	sensitizing
Classification	:	
Method	:	other: see freetext ME
Year	:	1980
GLP	:	no
Test substance	:	other TS: p-toluidine, purified by recrystalisation

Method : 10 albino Hartley strain guinea pigs were used per challenge dose
Application area:
flanc over the scapula was clipped and shaved
Induction:
2 % in petrolatum, four times for 24 hours each, occlussive patches (plastic tape) on alternate days secured with a rubber dressing wound around the trunk

14 days later:
Challenge:
4 concentrations on the opposite flank with a closed technique: Finn chamber, secured with plastic tape and rubber dressing: 2%, 1%, 0.5%, 0.25%
Reading:
24, 48, and 72 hours after removal; maximum responses were at 48 hours
Evaluation: 4 point scale
0=no vilible reaction
1=slight erythema
2=moderate erythema
3=intense erythema and swelling
Statistical method:
Analysis of variance

Result : Challenge concentration // No of animals responding // mean score: p-toluidine (pT) versus p-phenylene-diamine (ppd)

2 % pT // 8/10 // 1.4 versus 2 % ppd // 10/10 // 2.2
1 % pT // 6/10 // 0.8 versus 1 % ppd // 10/10 // 2.1
0.5 % pT // 4/10 // 0.4 versus 0.5 % ppd // 10/10 // 1.5
0.25% pT // 0/10 // 0 versus 0.25% ppd // 4/10 // 0.5

The reaction intensity of ppd as positive control was significant from pT

Reliability : (2) valid with restrictions
No information on GLP and no exact information on purity

Flag : Critical study for SIDS endpoint

19.03.2004 (148)

Type : Patch-Test
Species : human
Concentration : 1st: 2 % occlusive epicutaneous
2nd:
3rd:
Number of animals :
Vehicle : other: yellow paraffin
Result :
Classification :
Method : other: see freetext ME
Year : 1975
GLP : no
Test substance : other TS: p-Toluidine, chromatographically pure

Method : For patch test filter paper was used 10 mm in diameter and was applied to the lateral aspect of the arm and covered with celophane extending 5 mm beyond the patch and fixed with adhesive tape.
The results were read after 48 and 96 hours.
Erythema and infiltration were recorded as positive result even if present only during the first reading.

Remark : 58 patients, known to be hypersensitive to p-phenylene-diamine, were patch tested with 2% p-toluidine in yellow paraffin.
63.8 % of the patients showed positive reactions.

Reliability : (4) not assignable
Only patients with dermatitis included in the test

Flag : Critical study for SIDS endpoint

25.05.2004 (149)

5.4 REPEATED DOSE TOXICITY

Type : Sub-acute
Species : rat
Sex : male
Strain : no data
Route of admin. : oral feed
Exposure period : 28 days
Frequency of treatm. : daily
Post exposure period : no data
Doses : 0, 165, 825, 1650 ppm (approx. 0, 13.8, 66.8, 125.7 mg/kg bw/day, calculated from food consumption)
Control group : yes, concurrent no treatment
NOAEL : 165 ppm
Method : other: see freetext ME
Year : 1973
GLP : no data
Test substance : other TS: p-toluidine, no data on purity,M.P.: 44.5°C

Method : Dry material was blended with the basal diet to provide the desired levels; diets were prepared fresh weekly

record of survival, food and TS consumption, body weight weekly, pathology: organ weights (liver, kidneys, adrenals and testes) gross examination

Remark : see also chapter 5.8.3
Result : --No deaths or signs of intoxication
were noted among any of the animals during the experimental period.
--Terminal body weight:
1650 ppm significantly reduced whem compared to control:
292 g versus 343 g
--Organ-body weight ratios (%)
liver, 825 and 1650 ppm: significantly increased when compared to control:
6.42 and 7.71 versus 5.10
--At autopsy, no significant gross pathologic lesions were found among any of the rats examined.
Reliability : (2) valid with restrictions
Only very limited information given, not all parameters necessary investigated
Flag : Critical study for SIDS endpoint
17.06.2004 (130)

Type : Sub-chronic
Species : rat
Sex : female
Strain : Wistar
Route of admin. : oral feed
Exposure period : 6 and 12 months
Frequency of treatm. : daily
Post exposure period : no data
Doses : 0, 40, 80, 160 mg/kg bw/day
Control group : yes, concurrent no treatment
Method : other: see freetext ME
Year : 1995
GLP : no data
Test substance : other TS: p-toluidine: no data on purity

Method : groups of female Wistar rats (n=8) received p-toluidine in feed with

a) protein content 8 % for 6 months (0, 40, 80, 160 mg/kg bw/day) and for 12 months (160 mg/kg bw/day)

b) protein content 24 % for 6 months (40, 80, 160 mg/kg bw/day) and 12 months (0, 160 mg/kg bw/day)

Determination of p-toluidin concentration in blood, urine and methemoglobin levels
Remark : see also chapter 5.0
Result : a) protein content 8 % for
---------6 months:
--blood content: dose related increase (graphic only)
--urine content: dose related increase (graphic only)
--methemoglobin level: control data not given, (graphic only < 2 %) 2.2 %, 6.7 %, 10.5 %
---------12 months:
--blood content (160 mg): lower than the respective value after 6 months of treatment (graphic only)
--urine content (160 mg): lower than the respective value after 6 months of treatment(graphic only)
--methemoglobin level (160 mg): lower than the respective value after 6 months of treatment (graphic only: approx. 4-5%)

b) protein content 24 %
---------6 months:
--blood content: dose related increase (graphic only)

--urine content: dose related increase (graphic only)
--methemoglobin level: dose related increase (graphic only) approx 2-8%
---------12 months:
--blood content (160 mg): slightly elevated when compared with the respective value after 6 months of treatment (graphic only)
--urine content (160 mg): lower than the respective value after 6 months of treatment (graphic only)
--methemoglobin level (160 mg): lower than the respective value after 6 months of treatment (graphic only) approx. 2 %

Reliability : (2) valid with restrictions
Provides new information although reported in brief, not all parameters necessary investigated

Flag : Critical study for SIDS endpoint

08.06.2004 (126) (127)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male
Strain	:	other: CD
Route of admin.	:	oral feed
Exposure period	:	18 months
Frequency of treatm.	:	daily
Post exposure period	:	6 months
Doses	:	0, 1000, 2000 ppm (approx. 0,. 75, 150 mg/kg bw)
Control group	:	yes, concurrent no treatment
NOAEL	:	ca. 2000 ppm
Method	:	other: see freetext ME
Year	:	1978
GLP	:	no
Test substance	:	other TS: p-toluidine, no data on purity

Method :
TEST ORGANISMS
- Age: 6-8 weeks
Acclimation period: 2 weeks
- Number of animals: 25 per group
ADMINISTRATION /EXPOSURE
- Diet: purina certified rodent diet
- Doses:
Doses were chosen based on preliminary 30-day feeding study followed by a 2-week recovery period (no further information)
OBSERVATIONS:
body weights
NECROPSY:
Animals which died during the first 6 month of treatment were discarded without necropsy.
A complete gross necropsy was done on all animals which died after 6 month on test or were killed at the end of the study.
Tissues were fixed, sectioned, and stained by hematoxylin and eosin.
HISTOPATHOLOGY
Histopathological examinations were done on all grossly abnormal organs, tumor masses, lung, liver, spleen, kidney, adrenal, heart, bladder, stomach, intestines, reproductive organs, and pituitaries.
STATISTICS
Statistical analysis of tumors found was performed using the Fisher exact test with Bonferroni correction.

Remark : see also chapter 5.7
see also chapter 5.8.3

Result : no mortality and no signs of toxicity are reported. Body weight development seems to correspond to the respective control group because body weight gain in the treated rats 10 % below that of the respective controls should

result in a reduction of the dosage. No gross and no histopathological findings are reported.
Thus, under the condition of this investigation, the NOAEL(systemic toxicity) is 2000 ppm (approximately 150 mg/kg bw/day)

Reliability : (2) valid with restrictions
Study doesn't meet the criteria of today and is reported in brief, not all parameters necessary investigated

Flag : Critical study for SIDS endpoint

17.06.2004 (150)

Type	:	Sub-chronic
Species	:	mouse
Sex	:	male/female
Strain	:	CD-1
Route of admin.	:	oral feed
Exposure period	:	18 months
Frequency of treatm.	:	daily
Post exposure period	:	3 months
Doses	:	6 months: 0, 1000, 2000 ppm (approx. 0, 150, 300 mg/kg bw), 12 months: 0, 500, 1000 ppm (approx. 0, 75, 150 ppm)
Control group	:	yes, concurrent no treatment
NOAEL	:	500 ppm
LOAEL	:	ca.
Method	:	other: see freetext ME
Year	:	1978
GLP	:	no
Test substance	:	other TS: p-toluidine, no data on purity

Method :

TEST ORGANISMS
- Age: 6-8 weeks
- Acclimatisation period: 2 weeks
- Number of animals: 25 per group

ADMINISTRATION /EXPOSURE
- diet: purina certified rodent diet
- Doses:

Doses were chosen based on prelimminary 30-day feeding study followed by a 2-week recovery period (no further information)
---Initially 1000, 2000 ppm (approximately 150, 300 mg/kg bw/day) over feeding period of 6 months,
---Reduction of doses after 6 months because weight gain was by 10 % below that observed in the concurrent controls:
500 and 1000 ppm ppm (approximately 75, 150 mg/kg bw/day)

OBSERVATIONS:
body weights
NECROPSY:
Animals which died during the first 6 month of treatment were discarded without necropsy.
A complete gross necropsy was done on all animals which died after 6 month on test or were killed at the end of the study.
Tissues were fixed, sectioned, and stained by hematoxylin and eosin.
HISTOPATHOLOGY
Histopathological examinations were done on all grossly abnormal organs, tumor masses, lung, liver, spleen, kidney, adrenal, heart, bladder, stomach, intestines, reproductive organs
STATISTICS
Statistical analysis of tumors found was performed using the Fisher exact test with Bonferoni correction.

Remark : see also chapter 5.7
see also chapter 5.8.3

Result	:	1000 ppm, 2000 ppm: body weight reduction: > 10 % (data not given) survivors: m: 18/25 (control)--17/25 (low dose)-18/25 (high dose; f: 20/25 (control)--21/25 (low dose)-17/25 (high dose) consequence: reduction of testsubstance: 500 ppm, 1000 ppm 500 ppm, male, female: no signs of toxicity were reported
Reliability	:	(2) valid with restrictions Study doesn't meet the criteria of today and is reported in brief, not all parameters necessary investigated
Flag	:	Critical study for SIDS endpoint

17.06.2004 (150)

Type	:	Sub-acute
Species	:	rat
Sex	:	no data
Strain	:	no data
Route of admin.	:	gavage
Exposure period	:	12 days
Frequency of treatm.	:	once daily
Post exposure period	:	1-2 weeks
Doses	:	200 mg/kg bw/day as 6% solution in peanut oil containing 15 % acetone
Control group	:	no data specified
Method	:	other: vsee freetext ME
Year	:	1949
GLP	:	no
Test substance	:	other TS: no data on purity
Method	:	Substance was given to 6 rats by administering orallyapproximately 1/5 of the ALD, 5 times a week for 2 weeks, so that the total of twice the lethal dose was administered. the rats were checked for change in weight and any unusual clinical symptoms. Following the final treatment they were observed for a period of one or two weeks prior being sacrificed. Tissues of all rats were examined for gross and micropathology.
Result	:	the rats became pale and weak after 6 treatments but regained normal strength and color a week after treatment ended. the rats showed marked loss of weight until the fifth treatment followed by a slow gain until the last week of observation when they began to gain rapidly. They were sacrificed 12 days after the final treatment and showed evidence of damage to the spleen, kidneys and liver.
Reliability	:	(4) not assignable Doesn't meet the criteria of today: no individual animal data available, no data on purity of test substance, limited number of animals under test, and reported only as summary

21.06.2004 (138)

Type	:	Sub-acute
Species	:	rat
Sex	:	male/female
Strain	:	Crj: CD(SD)
Route of admin.	:	gavage
Exposure period	:	male; 46 days (including 14days before mating) female: more than 37 days (from 14 days before mating to Day 3 of parturition)
Frequency of treatm.	:	once daily
Post exposure period	:	no
Doses	:	0, 6, 20, 60 mg/kg bw/day dissolved in corn oil
Control group	:	yes, concurrent vehicle

NOAEL : ca. 6 mg/kg bw
Method : other: OECD combined repeat dose and reproductive/developmental toxicity screening test (see freetext Method)
Year : 1999
GLP : yes
Test substance : other TS: 4-Isopropylaniline (CAS-No. 88-99-7): purity: 99.27 %

Method : TEST ORGANISMS
age: 8 weeks old for males and females
weight at initiation: 350-402 g for male, 195-257 g for female
number of animals: 12 per sex per dose
pellet food and water: free access
ADMINISTRATION
vehicle: 1%(w/v) corn oil
type of administration: gavage, once a day
duration of administration:
male; 46 days (including 14days before mating)
female: more than 37 days (from 14days before mating to Day 3 of parturition)
MATING PROCEDURE
one by one in each cage
CLINICAL OBSERVATIONS AND FREQUENCY
clinical signs and mortality: every day
body weight:
male; Day 1, 2, 5, 7, 10, 14, 21, 28, 35, 42, 46
female: before mating Day 1, 2, 5, 7, 10, 14
during gestation Day 0, 1, 3, 5, 7, 10, 14, 17, 20
after parturition Day 0, 1, 4
food consumption: at every body weight check (24h consumption), except Day 0 of gestation and Day 0 of parturition for female
water consumption: not checked
HISTOPATHOLOGICAL OBSERVATIONS
urinalysis: by all males at Day 43-44; pH, protein, sugar, ketones, urobilinogen, bilirubin, occult blood, specific gravity, deposit and appearance
hematology: by all males at Day 46; erythrocyte count, MCV, platelet count, leukocyte count, hemoglobin, hematocrit, MCH, mean corpuscular hemoglobin (MCHC), defferential leukocyte count, prothrombin time and ATPP
blood biochemical: Same sample as hematology was used.; total protain, albumin, alubmin/globulin (A/G) ratio, GOT, GPT, alkaline phosphotase (ALP), lactate dehydrogenase (LDH), cholin esterase (Ch-E), gamma-GTP, total bilirubin, gulucose, total cholesterol, triglyceride, phospholipids, urea nitrogen, creatinine, sodium, potassium, chlorine, calcium and inorganic phosphorus
organs: by all males after extraction of blood, and by all females at Day 4 after (estimated) parturition;
for weight check; brain, lung, heart, liver, kidneys, spleen, adrenal, pituitary gland, thymus, thyroids, testis, epididymides and ovaries
for observation; above mentioned organs plus other organs, and number of implants and corpora lutea
for histopathological findings; lung, cecum, liver, kidney, testis, epididymis, prostate, spleen, mediastinal lymph node, renal lymph node, lumbar lymph node, pituitary gland, adrenal and skin
Remark : guideline study reported in Japanese , only sunnary tables and abstract available
Result : Results from repeated dose toxicity study part:

1 female was found dead in the 60 mg/kg group at day 25 of gestation. Anemic eyeballs and salivation were observed in the 20 mg/kg or more

groups in both sexes; palor in the 60 mg/kg group was noted in females during gestaion period.
Body weight gain (graphics only) showed a tendency for decrease in the 20 mg/kg or more groups in males and in the 60 mg/kg group in females during gestation period.
Food consumption (graphics only) was decreased in the 60 mg/kg groups in males during the early administration period.

Hematology of males revealed methemoglobin increase in the 20 mg/kg or more groups (1.2 % or 2.5% versus 0.7% in controls)
Furthermore, in the 60 mg/kg male group,
---Decrease:
HCT (40.7% versus 44.7% in controls),
HGB (13.4g/dl versus 15.4 g/dl in controls,
RBC (6.71 x10[exp.6]/mm³ versus 8.21 x10[exp.6]/mm³ in controls)
MCHC (32.9% versus 34.4% in controls)
---Increase:
MCV (60.8µm³ versus 54.5µm³ in controls
MCH (20.0 pg versus 18.7pg)
PLT (1281 x10[exp.6]/mm³ versus 1092 x10[exp.6]/mm³ in controls)
RC (110% versus 28% in controls)

Increases in spleen weights in
- males: in the 60 mg/kg group (absolut/relative): 1.22g/0.683g% versus 0.76g/0.142g% in controls
- females: in the 20 mg/kg or more (absolut/relative):
0.71g/0.231g%, 1.05g/0.351g% versus 0.51g/0.169g% in controls;

Increases in liver weights
- males given 20 mg/kg bw or more (absolut/relative):
15.82g/3.083g%, 16.39g/3.223g% versus 15.12g/2.815g% in controls
- females given 60 mg/kg bw (absolut/relative):
14.43g/4.832g% versus 12.85g/4.285g% in controls

As gross necropsy findings, blackening and enlargement of the spleen were observed in 20 mg/kg or more groups in both sexes.
As histological findings, increases in hematopoiesis in bone marrow, congestion, deposites of pigment and extramedullary hematopoiesis in the spleen were observed in 20 mg/kg or more groups in both sexes. In the liver, extramedullary hematopoiesis was observed in 60 mg/kg males and in the 20 mg/kg or more groups in females. Deposites of pigment and hypertrophy of hepatocytes were observed in both sexes receiving 60 mg/kg bw/day.

NOEL(systemic toxicity male, female): 6 mg/kg bw/day

Results from reproductive and developmental toxicity study part:

As for reproductive ability of parent animals, no adverse effects of the substance were observed in either sex:
with respect to estrous cycle length, copulation index, fertility index, implantation index, gestation index and duration of gestation period, delivery index.
NOEL(parental toxicity): 60 mg/kg bw/day

With regard to the effects on neonates,
no effects on live birth index
no effeccts on sex ratio
60 mg/kg bw-group:
body weight of pups in both sexes decreased (no data)
viability on day 4 of lactation decreased in males:

males: 85.7 % versus 96.4% in controls
females: 97,2% versus 95.1 % in controls
NOEL(developmental toxicity) 20 mg/kg bw/day

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
13.01.2006 (137)

Type :
Species : other: deer mouse
Sex : no data
Strain : other: Peromyscus maniculatus
Route of admin. : oral feed
Exposure period : 3 days
Frequency of treatm. : daily
Post exposure period :
Doses : 1025 mg/kg bw/day
Control group : no data specified
Method : other: keine Daten
Year : 1985
GLP : no data
Test substance : other TS: p-toluidine, no further data

Result : more than 50% of the animals died
Reliability : (4) not assignable
Documentation insufficient for assessment
14.06.2004 (151)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA102, TA104
Escherichia coli WP2urA, WP2urA/pKM101
Test concentration : +/-S9-mix: 1) 0.0763, 0.305, 1.22, 4.88, 19.5, 78.1, 313, 1250, 5000 µg/plate, 2) 78.1, 156, 313, 625, 1250, 2500, 5000 µg/plate, 3) -S9-mix, TA102, TA104: 19.5, 39.1 µg/plate
Cycotoxic concentr. : from 625 µg/ml
Metabolic activation : with and without
Result : negative
Method : other: preincubation method according to Ames, Mutat. Res. 31,347(1975); Maron, Mutat. Res.113,173(1983); highest doses used: cytotoxic, positive controls, solvent (DMSO) control (see also freetext ME)
Year : 1997
GLP : no data
Test substance : other TS: p-toluidine, purity >= 99 %

Method : -------positive controls:
---without S9-mix:
2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (Salmonella typhimurium TA100, TA98, Escherichia coli WP2uvrA, WP2uvrA/pKM101)
Sodium azide (Salmonella typhimurium TA1535)
4-Nitroquinoline-N-oxide (Salmonella typhimurium TA1538)
9-Aminoacridine (Salmonella typhimurium TA1538)
Bleomycin (Salmonella typhimurium TA102)
Pyruvic aldehyde (Salmonella typhimurium TA104)
---with S9-mix
2-Aminoanthracene (for all strains)
-------negative control:
solvent (DMSO) control
-------Preparation of S9 Fraction:

Male Sprague-Dawley rats were used for the preparation of liver fractions. Sodium phenobarbital and 5,6-benzofravone were used as an inducer of the rat metabolic activation system. Sodium phenobarbital was injected intraperitoneally into the rats 4 days before killing and 1, 2 and 3 days before killing 5,6-benzoflavone was injected intraperitonally. From these rats liver S9 fraction was prepared according to Ames et al. (1975), Methods for detecting carcinogens and mutagens in the Salmonella /mammalian microsome mutagenicity test, Mutat. Res. 31, 347-364. S9 was dispensed into freezing ampules and stored at -80°C. Once the stock S9 had been thawed, remained S9 was not reused.

Evaluation criteria:
Twohold rule was used for data evaluation. the chemicals are considered to be mutagenic when dose-related increase in revertant colony count is observed and the number of revertant colonies per plate with the test substance is more than twice that of the negative control (solvent control) and when a reproducibility of test result is observed.

Result : The positive controls were functional.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
25.05.2004 (152)

Type : Ames test
System of testing : Salmonella typhimurium TA98, TA100, TA1535, TA1537, Escherichia coli WP2uvrA
Test concentration : +/-S9-mix: 1) 0, 20, 39, 78, 156, 313, 625, 1250, 2500, 5000 µg/ml; 2) 0, 78, 156, 313, 625, 1250, 2500, 5000 µg/ml;
3) +S9-mix: 0, 78, 156, 313, 625, 1250, 2500, 5000 µg/ml
Cycotoxic concentr. : from 2500 µg/ml
Metabolic activation : with and without
Result : negative
Method : other: preincubation method according to Ames, Mutat. Res. 31, 347 (1975); Maron, Mutat. Res.113,173 (1983); highest doses used: cytotoxic, positive controls, solvent (DMSO) control (see also freetext ME)
Year : 1996
GLP : no data
Test substance : other TS: p-toluidine, purity : 99 %

Method : -------positive controls:
---without S9-mix:
2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (Salmonella typhimurium TA100, TA98, Escherichia coli WP2uvrA, WP2uvrA/pKM101)
Sodium azide (Salmonella typhimurium TA1535)
4-Nitroquinoline-N-oxide (Salmonella typhimurium TA1538)
9-Aminoacridine (Salmonella typhimurium TA1538)
Bleomycin (Salmonella typhimurium TA102)
Pyruvic aldehyde (Salmonella typhimurium TA104)
---with S9-mix
2-Aminoanthracene (for all strains)
-------negative control:
solvent (DMSO) control
-------Preparation of S9 Fraction:
Male Sprague-Dawley rats were used for the preparation of liver fractions. Sodium phenobarbital and 5,6-benzofravone were used as an inducer of the rat metabolic activation system. Sodium phenobarbital was injected intraperitoneally into the rats 4 days before killing and 1, 2 and 3 days before killing 5,6-benzoflavone was injected intraperitonally. From these rats liver S9 fraction was prepared according to Ames et al. (1975), Methods for detecting carcinogens and mutagens in the Salmonella /mammalian microsome mutagenicity test, Mutat. Res. 31, 347-364. S9

was dispensed into freezing ampules and stored at -80°C. Once the stock S9 had been thawed, remained S9 was not reused.

Evaluation criteria:
Twohold rule was used for data evaluation. the chemicals are considered to be mutagenic when dose-related increase in revertant colony count is observed and the number of revertant colonies per plate with the test substance is more than twice that of the negative control (solvent control) and when a reproducibility of test result is observed.

Result : The positive controls were functional.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
19.03.2004 (153)

Type : Ames test
System of testing : Salmonella typhimurium TA97, TA98, TA100, TA1535
Test concentration : 0, 33, 100, 333, 1000, 2000, 3333 µg/plate in water
Cycotoxic concentr. : cytotoxicity was determined in preliminary experiments (no further information)
Metabolic activation : with and without
Result :
Method : other: preincubation protocol
Year : 1992
GLP : no data
Test substance : other TS: p-toluidine hydrochlorid, purity: 95.7 %

Method : -----Preincubation procedure:
incubation time with TS: 20 min
TS was testes with and without S9-mix
-----Metabolic activation systems:
S9-mix was prepared from Aroclor 1254-induced male Sprague-Dawley rats (RLI) and males Syrian Hamster (HLI) in 10 % and 30 % concentrations.
-------Controls:
Positive controls were used, but the name of the substances were not mentioned.
negative controls: solvent: DMSO
-----Evaluation of the results
A chemical was judged mutagenic or weakly mutagenic if it produced a reproducible dose-related response over the solvent control.
Result : Negative results were noted in all strains with and without metabolic activation except TA100 in the presence of hamster liver S9-mix.
The positive controls were functional.
Overall conclusion: weak positive
Reliability : (2) valid with restrictions
Only 4 strains used, no cytotox. concentration given, no information on GLP
Flag : Critical study for SIDS endpoint
19.06.2004 (154)

Type : Chromosomal aberration test
System of testing : Chinese hamster lung (CHL) cells
Test concentration : 0.05, 0.025, 0.0125 mg/ml in DMSO
Cycotoxic concentr. : In preliminary screening determination of the concentration at which cell growth was inhibited, +S9-mix >= 0.025 mg/ml; -S9-mix: no further data
Metabolic activation : with and without
Result : positive
Method : other: see freetext ME
Year : 1988
GLP : no data

Test substance	:	other TS: p-toluidine, no data on purity
Method	:	--Incubation time with the TS was 3 hours in the presence and in the absence of S9-mix and after being centrifuged again cultured for additional 21 hours. --To arrest cells in metaphase, colcemid was added to all cultures 2 hours before harvest. --up to 100 metaphases were counted --solvent treated cells served as controls. --Positive controls were not reported. --metabolic activation system: S9-mix was prepared from Wistar or Fisher rat liver intraperitoneally injected with 500 mg/kg PCB 5 days before sacrifice.
Result	:	p-toluidine induced an increased rate of aberrations only in the presence of the metabolic activation system
Reliability	:	(2) valid with restrictions No data of purity and GLP
Flag	:	Critical study for SIDS endpoint

16.06.2004 (155)

Type	:	Chromosomal aberration test
System of testing	:	Chinese hamster lung (CHL) cells
Test concentration	:	up to 1000 µg/ml
Cycotoxic concentr.	:	no data
Metabolic activation	:	with and without
Result	:	positive
Method	:	other: see freetext ME
Year	:	1988
GLP	:	no data
Test substance	:	other TS: p-toluidine, no data on purity
Method	:	Chinese hamster lung cells were used Metabolic activation system was prepared from rat liver according to standard method. Treatment schedule: Treatment time was 3 hours, followed by a recovery period of 21 hours before sampöing and evaluation
Result	:	absence of S9-mix: no chromosomal aberrations up to the highest dose of 1000 µg/ml in the presence of S9-mix: positive from 0.5 mg/ml onwards
Reliability	:	(2) valid with restrictions Although only reported in a review together with 950 other chemicals, there is sufficient information
Flag	:	Critical study for SIDS endpoint

16.06.2004 (156)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA98, TA100
Test concentration	:	data not shown
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: according to Maron et al., Mutat. Res. 113, 173 (1983)
Year	:	1989
GLP	:	no data
Test substance	:	other TS: p-toluidine, no data on purity
Remark	:	test done in presence of norharman
Reliability	:	(4) not assignable Special study, insufficient documentation

25.05.2004 (157)

Type : Ames test
System of testing : Salmonella typhimurium TA97, TA98, TA100, TA104
Test concentration : (1) no data (2) 50, 250, 500, 2500, 5000 µg/plate
Cycotoxic concentr. : no data
Metabolic activation : with and without
Result :
Method : other: (1) Spot test (2) according to Maron et al., Mutat. Res. 113, 173 (1983), plate incorporation methodology, DMSO as neg. contr., pos. contr: 4-nitroquinoline-N-oxide,2-aminofluorene
Year : 1986
GLP : no data
Test substance : other TS: p-toluidine, no data on purity

Remark : positive in TA100
Result : (1) Spot test: ambiguous; (2) Ames test, plate incorporation methodology: negative
Reliability : (4) not assignable
Details of the results were not reported, no data on purity of TS and no information about GLP

15.07.2004 (158) (159)

Type : Ames test
System of testing : Salmonella typhimurium TA98
Test concentration : 0, 40, 120, 200 µg/plate
Cycotoxic concentr. : no data
Metabolic activation : with
Result : negative
Method : other: Mutat. Res. 48, 121 (1977)
Year : 1982
GLP : no data
Test substance : other TS: no data on purity

Method : The test was done only with Salmonella typhimurium in the presence of S9-mix
a) with Norharman
b) without Norharman
Result : p-toluidine was negative with and without the addition of norharman
Reliability : (4) not assignable
Special study, insufficient documentation

15.07.2004 (160)

Type : Ames test
System of testing : Salmonella typhimurium TA100
Test concentration : no data
Cycotoxic concentr. : 30 µmol/plate
Metabolic activation : with and without
Result : negative
Method : other: according to Ames et al., Mutat. Res. 31, 347 (1975)
Year : 1980
GLP : no data
Test substance : other TS: p-toluidine, no data on purity

Reliability : (4) not assignable
Documentation insufficient for assessment

15.07.2004 (161)

Type : Ames test
System of testing : Salmonella typhimurium TA98, TA100

Test concentration : 5-50 nmoles/plate
Cycotoxic concentr. : no data
Metabolic activation : with and without
Result : positive
Method : other: according to Ames et al., Mutat. Res. 31, 347 (1975) with slight modifications
Year : 1984
GLP : no data
Test substance : other TS: p-toluidine, no data on purity

Result : p-toluidine was positive only in Salmonella typhimurium TA100 in the presence of S9-mix.
Reliability : (4) not assignable
documentation insufficient for assessment and only 2 strains used
15.07.2004 (162)

Type : Ames test
System of testing : Salmonella typhimurium TA1538
Test concentration : 0, 50, 100 mg/plate in DMSO
Cycotoxic concentr. : no data
Metabolic activation : with and without
Result : negative
Method : other: according to Ames et al., Mutat. Res. 31, 347 (1975), pos. control: acetylaminofluorene
Year : 1977
GLP : no data
Test substance : other TS: p-toluidine, no data on purity

Reliability : (4) not assignable
Insufficient documentation, one strain only, cytotoxicity not given
15.07.2004 (163)

Type : Ames test
System of testing : Salmonella typhimurium TA100
Test concentration : no data
Cycotoxic concentr. : no data
Metabolic activation : with and without
Result : negative
Method : other: according to Ames, Mutation Res. 31, 347-364 (1975)
Year : 1980
GLP : no data
Test substance : other TS: p-toluidine, purity: 97-99 %

Reliability : (4) not assignable
Documentation insufficient for assessment
15.07.2004 (164)

Type : Ames test
System of testing : Salmonella typhimurium TA98, TA100, TA1535, TA1537,TA1538
Test concentration : 1000 µg/plate (highest concentration tested)
Cycotoxic concentr. : no data
Metabolic activation : with and without
Result : negative
Method : other: according to Ames. Mutat. Res. 31, 347 (1975), McCann et al., Proc.Natl. Sci USA 72, 979 (1975), no further details reported
Year : 1979
GLP : no data
Test substance : other TS: p-toluidine, no data on purity

Reliability : (4) not assignable

Documentation insufficient for assessment
15.07.2004 (165) (166)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA102
Test concentration	:	in general up to 5000 µg/ml (no details)
Cycotoxic concentr.	:	limitation: data not given
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: according to OECD Guide-line 471, but specified for TA102 by D. Levine Proc. Natl. Acad. Sci (USA) 79, 7445
Year	:	1988
GLP	:	yes
Test substance	:	other TS: p-toluidine, highest purity available
Method	:	A collaborative study of 3 laboratories: Controls: negative control: solvent: Ethanol or DMSO or DMSO/ethanol-mixture positive controls Mitomycin C, 2-Aminoanthracene metabolic activation system: Aroclor 1254-induced livers of Sprague-Dawley rats Result evaluation: The compound was judged positive if a reproducable dose-dependent increase in the number of revertants was observed. no statistical evaluation
Result	:	the positive controls were functional
Reliability	:	(4) not assignable Special study, only one strain used

15.07.2004 (167) (168)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538, G46, C3076, D3052
Test concentration	:	no data
Cycotoxic concentr.	:	no data
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: modified Ames test according to Cline and McMahon, 1977, Res. Commun Chem Pathol Pharmacol 16, 523-533; positive controls: Streptozotocin, 2-AAf
Year	:	1983
GLP	:	no data
Test substance	:	other TS: p-toluidine, no data on purity
Remark	:	positive controls were functional
Reliability	:	(4) not assignable Documentation insufficient for assessment

15.07.2004 (169)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA1535, TA1538
Test concentration	:	0, 2.5, 5, 10, 15, 20, 25, 50, 100, 150, 200, 250 µg/plate
Cycotoxic concentr.	:	no data
Metabolic activation	:	with and without
Result	:	negative

Method : other: plate incrporation procedure, positive controls: ethylmethane sulfonate or BPL, 2-nitrofluorene,
Year : 1979
GLP : no data
Test substance : other TS: p-toluidine, no data on purity

Reliability : (4) not assignable
documentation insufficient for assessment: results only reported as survyey, and only 2 tester strains used

15.07.2004 (170)

Type : Bacterial gene mutation assay
System of testing : Escherichia coli WP2 uvrA
Test concentration : 5-10 mg/plate
Cycotoxic concentr. : no data
Metabolic activation : without
Result : negative
Method : other: according Green and Muriel (1976),Mutation Res. 38, 3-32
Year : 1978
GLP : no data
Test substance : other TS: p-toluidine, no data on purity

Method : The compound was placed directly on the centre of the plates, which were then inverted and incubated for 48 hours at 37°C, after which they were scored for colonies.
Reliability : (4) not assignable
Documentation insufficient for assessment

15.07.2004 (171)

Type : Bacterial gene mutation assay
System of testing : Escherichia coli WP2, WP2uvrA-
Test concentration : maximum compound concentrations of 1000 µg/ml agar
Cycotoxic concentr. : no data
Metabolic activation : with and without
Result : negative
Method : other: according to Cline and McMahon, 1977, Res. Commun Chem Pathol Pharmacol 16,523-533: positive controls: Streptozotocin, 2-AAf
Year : 1983
GLP : no data
Test substance : other TS: p.toluidine, no data on purity

Remark : The positive controls were functional
Reliability : (4) not assignable
Documentation insufficient for assessment

15.07.2004 (169)

Type : Gene mutation in Saccharomyces cerevisiae
System of testing : Saccharomyces cerevisiae
Test concentration : max concentration: 1 mg/ml dissolved in DMSO
Cycotoxic concentr. : >1 mg/l
Metabolic activation : without
Result : negative
Method : other: mitotic Conversion
Year : 1970
GLP : no data
Test substance : other TS: p-toluidine, no data on purity

Reliability : (4) not assignable
Documentation insufficient for assessment

15.07.2004 (172)

Type	:	Gene mutation in Saccharomyces cerevisiae
System of testing	:	Saccharomyces cerevisiae strain D3
Test concentration	:	1 mg/ml
Cycotoxic concentr.	:	no data
Metabolic activation	:	no data
Result	:	positive
Method	:	other: see freetext ME
Year	:	1974
GLP	:	no data
Test substance	:	other TS: Hydrochlorid

Method : Cells were cultivated in senisynthetic complete medium for 72 hours at 30°C to achieve a confluent lawn of growth. Cells were then suspended in reaction mixture (hydroxylation medium) and p-toluidine was added.
2 samples were prepared:
1) Oxygen was bubbled through one sample
2) Nitrogen was bubbled through the other
Evaluation was performed 0,15, 30, 45, 60 min later.

Remark : mitotic crossing over

Result : p-Toluidine induced an increase in the frequency of colonies in the hydroxylation medium only when oxygen was bubbled through the mixture.

Reliability : (4) not assignable
Special study

15.07.2004 (173) (174) (175)

Type	:	Gene mutation in Saccharomyces cerevisiae
System of testing	:	Saccharomyces cereviiae D3
Test concentration	:	0.5 % (highest dose tested)
Cycotoxic concentr.	:	> 0.5 %
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: see freetext ME
Year	:	1979
GLP	:	no data
Test substance	:	other TS: p-toluidine, no data on purity

Method : Method:
A suspension of S. cerevisiae D3 was incubated was incubated with p-toluidine for 4 hours at 30°C on a roller drum
S9-mix
was prepared from rat livers pretreated with Aroclor 1254

appropriate positive and negative controls were included (no further information)

Reliability : (4) not assignable
Survey of 101 substances

15.07.2004 (165) (176) (177)

Type	:	DNA damage and repair assay
System of testing	:	Escherichia coli polA+/polA-
Test concentration	:	250 µg/plate
Cycotoxic concentr.	:	no data
Metabolic activation	:	no data
Result	:	negative
Method	:	other: see freetext ME
Year	:	1979
GLP	:	no data
Test substance	:	other TS: p-toluidine, no data on purity

Method : Filter discs with known amounts of the test agent were deposited onto the surface of the agar plate after they had dried. Following incubation at 37°C in the dark for 7-12 hours, the diameter zones of growth inhibition were determined.
positive control: methane sulfonate and chloramphenicol
Reliability : (4) not assignable
Documentation insufficient for assessment
15.07.2004 (165) (170)

Type : other: DNA damage
System of testing : Escherichia coli PolA-/PolA+
Test concentration : no data
Cycotoxic concentr. : no data
Metabolic activation : with and without
Result : negative
Method : other: plate incorporation methodology
Year : 1987
GLP : no data
Test substance : other TS: p-toluidineno data

Reliability : (4) not assignable
Documentation insufficient for assessment
15.07.2004 (178)

Type : other: DNA-adduct formation in Salmonella typhimurium TA98 in the presence of norharman
System of testing : Salmonella typhimurium TA98
Test concentration : 4 mg testsubstance in 2 ml DMSO and 20 ml S9 mix
Cycotoxic concentr. : no data
Metabolic activation : with
Result : negative
Method : other: 32 P-post labelling method
Year : 1996
GLP : no data
Test substance : other TS: p-toluidine, no data on purity

Method : 32P-post-labelling analysis:
Salmonell typhimurium TA98 (4 ml) overnight culture was incubated with 8 mg norharman and 4 mg toluidine in the presence of 20 ml S9-mix for 6 hours at 37°C. 3 adduct spots were detected at a Relative Adduct Labelling (RAL) of 3.74/10(exp.8) nucleotides.
Neither Norharman nor p-toluidine themselve gave any evidence of adduct.
Reliability : (4) not assignable
Special study
15.07.2004 (179)

Type : other: Fluktuationstest
System of testing : Escherichia coli WP2uvrA
Test concentration : 0, 0.125, 0.25, 0.5 mM dissolved in ethanol abs.
Cycotoxic concentr. : no data
Metabolic activation : without
Result : negative
Method : other: according to green et al (1976), Mutation Res. 38, 33-42
Year : 1985
GLP : no data
Test substance : other TS: p-toluidine, no data on purity

Reliability : (4) not assignable
Documentation insufficient for assessment (e.g. no positive controls mentioned)

15.07.2004 (180)

Type	:	Unscheduled DNA synthesis
System of testing	:	primary rat hepatocytes
Test concentration	:	8 doses with the range of 1000 - 0.5 nmole/ml
Cycotoxic concentr.	:	presumably > 100 nmol/ml
Metabolic activation	:	no data
Result	:	positive
Method	:	other: preparation of hepatocytes: according to Williams et al. 1977, In Vitro 13, 809-817; autoradiographic assay according to Probst et al. 1981, Environ. Mutagen 3, 11-32
Year	:	1983
GLP	:	no data
Test substance	:	other TS: p-toluidine, no data on purity
Method	:	solvent: DMSO
Result	:	positive at 50-500 nmol/ml
Reliability	:	(4) not assignable Documentation insufficient for assessment

15.07.2004 (169)

Type	:	other: DNA damage
System of testing	:	human lung fibroblasts
Test concentration	:	68 µmol
Cycotoxic concentr.	:	no data
Metabolic activation	:	no data
Result	:	positive
Method	:	other: alkaline elution technique according to Becker et al., 1989, Environm. Health 26, 469-483; Kohn et al., 1976, Biochemistry 15, 4629-4637
Year	:	1990
GLP	:	no data
Test substance	:	other TS: p-toludidine, purity 95-99.5 %
Reliability	:	(4) not assignable Documentation insufficient for assessment, only one concentration tested

15.07.2004 (181)

Type	:	other: DNA damage test
System of testing	:	Chinese hamster lung (V79) cells
Test concentration	:	0.3, 1.0, 3.0, 10.0mM in DMSO
Cycotoxic concentr.	:	no data
Metabolic activation	:	with
Result	:	negative
Method	:	other: alkaline elution method according to Swenberg et al., 1976, Biochem Biophys Res Commun 72, 732
Year	:	1980
GLP	:	no data
Test substance	:	other TS: p-toluidine: purity: 97-99 %
Test condition	:	Incubation time: 2 hours METABOLIC ACTIVATION: S9 mix liver homogenates from Aroclor 1254 induced rats Solvent: DMSO Controls no data of positive and negative controls
Reliability	:	(4) not assignable No data on positive controls, only tested in the presence of S9-mix

15.07.2004 (164)

Type : other: DNA binding
System of testing : granulocytes (human)
Test concentration : 5, 10 µmol
Cycotoxic concentr. : no data
Metabolic activation : with and without
Result : positive
Method : other: see freetext ME
Year : 1988
GLP : no data
Test substance : other TS: p-toluidine, no data on purity, radiochemical purity >=99.5 %

Method : Isolated DNA and RNA from human granulocytes were incubated with radiolabelled p-toluidine of different concentrations with different incubation time and with and without activation. For stimulation phorbol myristate acetat was used:
1. 5 µmol p-toluidine for 30 min
2. 10 µmol p-toluidine for 0, 10 and 30 min
Remark : positive following stimulation with phorbol myristate acetate
Reliability : (4) not assignable
Special study

15.07.2004 (182)

Type : other: Inhibition of cell growth
System of testing : Ascites sarcoma BP8 cells
Test concentration : 1, 0.1, 0.01, 0.001 mM as DMSO solution
Cycotoxic concentr. : no data
Metabolic activation : without
Result : negative
Method : other: cells were incubated with Ts for 48 hours, cell density was determined according to Piloti, Toxicology 5, 49 (1975)
Year : 1980
GLP : no data
Test substance : other TS: p-toluidine, no data on purity

Reliability : (4) not assignable
Special study

15.07.2004 (183) (184)

Type : other: Membrane damage
System of testing : Human diploid embryonic lung fibroblasts (line MRC 5)
Test concentration : 25 mM
Cycotoxic concentr. : no data
Metabolic activation : without
Result : negative
Method : other: radio-labelled cells were incubated with Ts for 30 min.the released radioactivity was measured.
Year : 1980
GLP : no data
Test substance : other TS: p-toluidene, purity: 97 %

Reliability : (4) not assignable
Special study

15.07.2004 (183) (185)

Type : other: inhibition of oxidative metabolism
System of testing : brown fat cells, hamster
Test concentration : 1mM dissolved in DMSO
Cycotoxic concentr. : no data

Metabolic activation	:	without
Result	:	negative
Method	:	other: measureing the inhibation of noradrenaline induced respiration of isolated hamster brown fat cells
Year	:	1980
GLP	:	no data
Test substance	:	other TS: p-toluidine, no data on purity
Reliability	:	(4) not assignable Special study

15.07.2004 (183) (186)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 100, TA1535, TA98, TA1537, Escherichia coli WP2uvrA
Test concentration	:	-S9-mix, 2 trials: 46.9, 93.8, 188,375, 750,1500 µg/plate; +S9-mix: (1) 23.4, 46.9, 93.8, 188, 375, 750, 1500 µg/plate; +S9-mix: (2) 5.86, 11.7, 23.4, 46.9, 93.8, 188, 375, 750, 1500 µg/plate
Cycotoxic concentr.	:	-S9-mix: TA100, TA1535, TA98, TA1537: >=750 µg/plate; WP2uvrA: 1500 µg/plate +S9-mix: all 5 strains: 1500 µg/plate
Metabolic activation	:	with and without
Result	:	positive
Method	:	other: Guidelines for Screening toxicity testing of Chemicals (Japan) and OECD test Guideline 471
Year	:	1999
GLP	:	yes
Test substance	:	other TS: 4-isopropylaniniline (CAS-No.88-99-7): purity:99.27 %
Method	:	Test procedure: - Preincubation method 3 plates per test and 2 replicates - Solvent: acetone - Controls negative control: acetone positive controls --- without S9-mix: S. typhimurium TA98, TA100, E. coli WP2uvrA: -----2-(2-Furfuryl)-3-(5-nitro-2-furyl)acrylamide S. typhimurium TA 1535: Sodium azide S. typhimurium TA 1537: 9-Aminoanthracene --- with S9-mix: all strains: 2-aminopanthracene - Metabolic activation system: S9-mix, prepared from rat liver induced with phenobarbital and 5,6-benzoflavone Interpretation of results: the test substance is considered to be positive for mutagenic activity when assay plates with the test substance show significant increase in revertant colony count as compared with that on negative control plates and when this effect is reasonably reproducible or dose dependent.
Remark	:	guideline study reported in Japanese , only sunnary tables and abstract available
Result	:	4-Isopropylaniline was mutagenic in Salmonella typhimurium TA100 and TA 1535 with an exogenous activation system.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

13.01.2006 (137)

Type	:	Chromosomal aberration test
System of testing	:	Chinese hamster lung (CHL/IU) cells
Test concentration	:	-S9-mix: 0.050, 0.10, 0.20, 0.40 mg/ml (1) 24 h; (2) 48 h; -S9-mix: 0.063, 0.13, 0.25, 0.50, 1.0 mg/ml 6-(18)h +S9-mix: 0.075, 0.15, 0.30, 0.60 mg/ml 6-(18)h
Cycotoxic concentr.	:	-S9-mix (24 h): 0.40 mg/ml; (48 h): 0.40 mg/ml; 6-(18)h: >=0.50 mg/ml +S9-mix 6-(18)h: 0.60 mg/ml
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: Guidelines for Screening mutagenicity Testing of Chemicals (Japan) and OECD test Guideline 473
Year	:	1999
GLP	:	yes
Test substance	:	other TS: 4-Isopropylaniline (CAS-No. 88-99-7): purity: 99.27 %
Method	:	SYSTEM OF TESTING - Cell type used: Chinese Hamster Lung (CHL) cells - Metabolic activation system: rat liver induced with phenobarbital and 5,6-benzoflavone - No. of metaphases analyzed: 200 ADMINISTRATION: - Number of replicates: 2 plates/test - Application: ----24 and 48 hours treatment only without metabolic activation; ----6 hours short-term treatment with and without metabolic activation; CONTROLS: - Positive and negative control groups: ----negative control: solvent Acetone ----positive control: -S9mix: Mitomycin C; +S9mix: Cyclophosphamide CRITERIA FOR EVALUATING RESULTS: positive: significantly different from solvent control at p<0.01 Fisher's exact probability test
Remark	:	guideline study reported in Japanese , only sunnary tables and abstract available
Result	:	4-Isopropylaniline did not induce structural chromosomal aberrations and polyploidy up to the highest dose for which it was possible to analyse chromosomes an continuous treatment and on short term treatment with and without an exogemous metabolic activation system.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

13.01.2006 (137)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	other: DNA Single-strand break
Species	:	mouse
Sex	:	male
Strain	:	other: Swiss CD-1
Route of admin.	:	i.p.
Exposure period	:	once
Doses	:	0, 35 mg/kg bw
Result	:	positive
Method	:	other: alkaline elution according to Cesarone et al., 1979, Anal. Biochem.100, 188-197
Year	:	1980
GLP	:	no data
Test substance	:	other TS: p-toluidine, no data on purity

Method	:	Single i.p. injection of p-toluidine into male Swiss mice. 4 hours after application isolation of nuclei from liver and kidneys and lysis on a membrane filter. DNA is eluted using alkaline buffer as function of molecular weight. As negative control: solvent
Result	:	Single strand-breaks were observed in DNA of liver and kidney nuclei.
Reliability	:	(2) valid with restrictions No data on purity of TS, no data on GLP and only one dose used
Flag	:	Critical study for SIDS endpoint

14.06.2004 (187) (188)

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	CD-1
Route of admin.	:	i.p.
Exposure period	:	once
Doses	:	43.75, 87.50, 175 mg/kg bw
Result	:	negative
Method	:	OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year	:	1997
GLP	:	yes
Test substance	:	other TS: p-toluidine, purity: 99.8 %

Method	:	Priliminary dose selection study: 3 CD-1 mice/sex/dose group received single intraperitoneal injections of 50.0, 163, 275, 388, 500 mg/kg bw dissolved in corn oil and were then observerd for 3 days. Due to clinical signs of toxicity and and mortality occurring at all doses above 163 mg/kg bw this dose was estimated as maximum tolerated dose (MTD). Micronucleus test: 5 mice/sex/dose group and harvest timepoint testsubstance was dissolved in corn oil Controls: negative control: vehicle control. positive control was available, substance not mentioned Observation of all animals for clinical signs and mortality. Test animals were sacrificed 24, 24 and 72 hours post treatment Control animals were sacrificed 24 hours post treatment Evaluation: 100 immature erythrocytes were scored per animal instead of 2000
Result	:	---mortality: significant mortality in the 175 mg/kg bw groups: all males died during 48 and 72 hours post dosing ---signs of toxicity were observed at all dose levels ---PCE:NCE ratio was not changed indicating that there was no cytotoxicity.
Reliability	:	(4) not assignable Guideline study which is available only as abstract

15.07.2005 (189)

Type	:	other: DNA, RNA and protein binding
Species	:	rat
Sex	:	male
Strain	:	no data
Route of admin.	:	gavage
Exposure period	:	once
Doses	:	500 mg/kg bw radiolabelled in cornoil
Result	:	

Method	:	other: see freetext ME
Year	:	1990
GLP	:	no data
Test substance	:	other TS: p-[ring-U-14C]toluidine, radiochemical purity > 99 %
Method	:	4,8, 12, 24 and 48 hours following single application by gavage rats (4-5 rats per time point) were sacrificed. Livers were immediately removed and homogenized. Hepatic DNA, RNA binding was determined according to Cooper (1977) abd Burton (1956) total protein binding was determined by a method as described by Hughes (1986)
Result	:	Binding levels to DNA, RNA and total protein binding were low and apeared to plateau by 12 to 48 hour after administration data in graphics only ---level of DNA binding (24 hrs): approx. 9.8(10exp-1) pmoles/µg DNA ---level of RNA binding (peak at 12 hrs): approx. 2.3(10exp-1) pmoles/µg RNA ---level of hepatic protein binding (24 hrs max): approx. 28(10exp-1) pmoles/µg protein
Reliability	:	(4) not assignable No test according guidelines to examine genetic toxicity in vivo

19.06.2004 (123)

Type	:	other: inhibition of testicular DNA synthesis
Species	:	mouse
Sex	:	no data
Strain	:	no data
Route of admin.	:	oral unspecified
Exposure period	:	
Doses	:	0, 200 mg/kg bw
Result	:	positive
Method	:	other: according to Friedman and Staub, 1976, Mutation Res. 37, 67-76, see also freetext TC
Year	:	1977
GLP	:	no data
Test substance	:	other TS: p-toluidine, no data on purity
Result	:	Incorporation of the tritiated thymidine = 77.7 % of concurrent controls.
Test condition	:	Measurement of incorporation of [3H]thymidine into testicular DNA (expressed as cpm per µg DNA). The mean values were then tested for statistically significant deviations from the concurrent controls by simplified t-test. Method evaluation
Reliability	:	(4) not assignable Method evaluation, only one dose tested, individual data not reported

14.06.2004 (190)

5.7 CARCINOGENICITY

Species	:	mouse
Sex	:	no data
Strain	:	no data
Route of admin.	:	dermal
Exposure period	:	12 weeks
Frequency of treatm.	:	twice weekly
Post exposure period	:	no
Doses	:	20% solution in dioxane

Result	:	negative
Control group	:	no
Method	:	other: see freetext ME
Year	:	1959
GLP	:	no
Test substance	:	other TS: p-toluidine, no data on purity
Method	:	about 1 week prior to first application of the test substance, the fur was shaved from the test area of the back of the mice with electric clipper. The solution to be tested was applied as a single drop to the mid-dorsal region of each mouse at the times specified. The mice were inspected tor tumors weekly. Water and diet at libitum air conditioned rooms: 74°F Age at beginn of the treatment: 2-3 months In addition to gross observations body weight curves and survival was recorded
Result	:	--survival: 27/32 --the condition of the mice was satisfactory (no further information) --no skin papillomas or skin carcinomas were observed
Reliability	:	(4) not assignable Study does not meet the criteria of today e.g. with respect to the strain of animals used, treatment time, only one concentration used, and study reporting in general
Flag	:	Critical study for SIDS endpoint

25.05.2004 (191)

Species	:	rat
Sex	:	male
Strain	:	other: CD
Route of admin.	:	oral feed
Exposure period	:	18 month
Frequency of treatm.	:	daily
Post exposure period	:	6 months
Doses	:	0, 1000, 2000 ppm (approx. 0,. 75, 150 mg/kg bw)
Result	:	negative
Control group	:	yes, concurrent no treatment
Method	:	other: see freetext TC
Year	:	1978
GLP	:	no data
Test substance	:	other TS: p-toluidine hydrochloride, purified by treatment with charcoal, purity controlled by thin layer chromatography (no further data)
Remark	:	see also chapter 5.4
Test condition	:	TEST ORGANISMS - Age: 6-8 weeks Acclimation period: 2 weeks - Number of animals: 25 per group ADMINISTRATION /EXPOSURE - Diet: purina certified rodent diet - Doses: Doses were chosen based on preliminary 30-day feeding study followed by a 2-week recovery period (no further information) OBSERVATIONS: body weights NECROPSY: Animals which died during the first 6 month of treatment were discarded without necropsy. A complete gross necropsy was done on all animals which died after 6 month on test or were killed at the end of the study. Tissues were fixed, sectioned, and stained by hematoxylin and eosin.

HISTOPATHOLOGY
Histopathological examinations were done on all grossly abnormal organs, tumor masses, lung, liver, spleen, kidney, adrenal, heart, bladder, stomach, intestines, reproductive organs, and pituitaries.
STATISTICS
Statistical analysis of tumors found was performed using the Fisher exact test with Bonferroni correction.

Reliability : (2) valid with restrictions
Study doesn't meet the criteria of today and is reported in brief: limited number of animals , no data on purity of TS, treatment time too short, no individual animal data given

Flag : Critical study for SIDS endpoint

21.06.2004 (192) (193) (150)

Species : mouse
Sex : male/female
Strain : CD-1
Route of admin. : oral feed
Exposure period : 18 months
Frequency of treatm. : daily
Post exposure period : 3 months
Doses : 6 months: 0, 1000, 2000 ppm (approx. 0, 150, 300 mg/kg bw), 12 months: 0, 500, 1000 ppm (approx. 0, 75, 150 ppm)
Result : positive
Control group : yes, concurrent no treatment
Method : other: see freetext TC
Year : 1978
GLP : no data
Test substance : other TS: p-toluidine hydrochloride, purified by treatment with charcoal, purity controlled by thin layer chromatography (no further data)

Remark : see also chapter 5.4
Result : CONCURRENT CONTROL--LOW DOSE- HIGH DOSE--POOLED CONTROL
liver tumours:
--- male: hepatomas female: liver tumours
m: 3/18--8/17-9/18--7/99; f: 0/20--2/21-3/17--1/102

Test condition : TEST ORGANISMS
- Age: 6-8 weeks
- Acclimatisation period: 2 weeks
- Number of animals: 25 per group
ADMINISTRATION /EXPOSURE
- diet: purina certified rodent diet
- Doses:
Doses were chosen based on prelimminary 30-day feeding study followed by a 2-week recovery period (no further information)
---Initially 1000, 2000 ppm (approximately 150, 300 mg/kg bw/day) over feeding period of 3 months,
---Reduction of doses after 3 months because weight gain was by 10 % below that observed in the concurrent controls:
500 and 1000 ppm ppm (approximately 75, 150 mg/kg bw/day)

OBSERVATIONS:
body weights
NECROPSY:
Animals which died during the first 6 month of treatment were discarded without necropsy.
A complete gross necropsy was done on all animals which died after 6 month on test or were killed at the end of the study.
Tissues were fixed, sectioned, and stained by hematoxylin and eosin.

HISTOPATHOLOGY
Histopathological examinations were done on all grossly abnormal organs, tumor masses, lung, liver, spleen, kidney, adrenal, heart, bladder, stomach, intestines, reproductive organs
STATISTICS
Statistical analysis of tumors found was performed using the Fisher exact test with Bonferoni correction.

Reliability : (2) valid with restrictions
Study doesn't meet the criteria of today and is reported in brief: limited number of animals , no data on purity of TS, treatment time too short, no individual animal data given

Flag : Critical study for SIDS endpoint

21.06.2004 (192) (193) (150)

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	s.c.
Exposure period	:	24 months
Frequency of treatm.	:	once/week
Post exposure period	:	no
Doses	:	0, 25, 75 mg/kg bw in peanut oil
Result	:	negative
Control group	:	yes, concurrent vehicle
Method	:	other: carcinogenicity: see freetext TC
Year	:	1981
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Result : MORTALITY: no death occurred; positive controls: significantly reduced surviving time probably due to early appearance of malignant tumours

CLINICAL SIGNS:
no differences to negative controls
BODY WEIGHT, m, f: dose related reduced body weights when compared to the negative controls; positive controls showed significantly reduced body weights

HISTOPATHOLOGY: NON-NEOPLASTIC LESIONS:
LIVER-CELL-NECROSIS: 8/60 low dose-, 9/60 high dose-rats
Comparison to controls:
untreated controls: 4/60
Peanut oil controls: 4/60
Benzidine-controls, (low-mid-high dose): 5/60-23/60-33/60

TUMOUR INCIDENCES:
Slightly increased number of malignant tumors at the injection site and benign liver tumors were observed in male and female animals when compared to the concurrent oil control.
Malignant tumors at the injection site per 30 animals:
sex : untreated // peanut oil // low dose (25mg/kg) // high dose (75 mg/kg):
male: 0 // 6 // 9 // 8
female: 0 // 1 // 2 // 5
Benign liver tumors per 30 animals:
Male: 0 // 0 // 0 // 1
Female: 0 // 1 // 1 // 6

Tumorincidence of malignant tumors at the injection site (all dose groups)
untreated // peanut oil // p-toluidine
0% // 12% // 20%

Overall, considering the total number of animals with malignant tumours, no statistically significant differences were observed in male and female animals when compared to the concurrent oil control

Test condition : TEST ORGANISMS
- Age: 6 weeks
- Number of animals: 30 rats/sex/group including negative controls and positive control groups

ADMINISTRATION / EXPOSURE
- Type of exposure: subcutan
- Vehicle: peanut oil
- Application volume: 1 ml/kg bw
-dose selection based on determination of LD50-values
- controls:
----negative control: peanut oil treated rats and
---------- untreated rats
----positive control: benzidin treated rats (0.93, 8.33, 25 mg/kg bw/day)

CLINICAL OBSERVATIONS AND FREQUENCY
- Body weight: no data on frequency
- Clinical signs: no data on frequency
- Mortality: no data on frequency

HISTOPATHOLOGY
all organs and tissues suspected tumour-bearing
area of injection, liver, lungs, spleen, urinary bladder, brain

Statistical evaluation:
as described in IARC Monographs Suppl. 2, 1980:
Death rate method,
Trend test,
Test for heterogenicity,
'Prevalence-rate' method

Conclusion : The author concluded: p-toluidine causes tumours only under extrem conditiones.

Reliability : (2) valid with restrictions
study doesn't meet the criteria of today:number of animals to low, application route and procedure not typical for human situation, only 2 dosages, no GLP, no individual animal data given

Flag : Critical study for SIDS endpoint

14.06.2004 (142)

5.8.1 TOXICITY TO FERTILITY

Type : Fertility
Species : rat
Sex : male/female
Strain : Crj: CD(SD)
Route of admin. : gavage
Exposure period : males 48 days; females 15 days before mating, throughout pregnancy until day 3 of lactation
Frequency of treatm. : once daily
Premating exposure period
Male : 15 days
Female : 15 days
Duration of test : 54 days
No. of generation studies :
Doses : 0, 6, 20, 60 mg/kg bw/day dissolved in corn oil

Control group : yes, concurrent vehicle
NOAEL parental : ca. 60 mg/kg bw
NOAEL F1 offspring : ca. 20 mg/kg bw
other: : ca. 6 mg/kg bw
NOAEL(systemic toxicity)
Result : see freetext: Result
Method : OECD Guide-line 422
Year : 1999
GLP : yes
Test substance : other TS: 4-Isopropylaniline (CAS-No. 88-99-7) purity: 99.27 %

Method : TEST ORGANISMS
age: 8 weeks old for males and females
weight at initiation: 350-402 g for male, 195-257 g for female
number of animals: 12 per sex per dose
pellet food and water: free access
ADMINISTRATION
vehicle: 1%(w/v) corn oil
type of administration: gavage, once a day
duration of administration:
male; 46 days (including 14days before mating)
female: more than 37 days (from 14days before mating to Day 3 of parturition)
MATING PROCEDURE
one by one in each cage
CLINICAL OBSERVATIONS AND FREQUENCY
clinical signs and mortality: every day
body weight:
male; Day 1, 2, 5, 7, 10, 14, 21, 28, 35, 42, 46
female: before mating Day 1, 2, 5, 7, 10, 14
during gestation Day 0, 1, 3, 5, 7, 10, 14, 17, 20
after parturition Day 0, 1, 4
food consumption: at every body weight check (24h consumption), except Day 0 of gestation and Day 0 of parturition for female
water consumption: not checked
HISTOPATHOLOGICAL OBSERVATIONS
urinalysis: by all males at Day 43-44; pH, protein, sugar, ketones, urobilinogen, bilirubin, occult blood, specific gravity, deposit and appearance
hematology: by all males at Day 46; erythrocyte count, MCV, platelet count, leukocyte count, hemoglobin, hematocrit, MCH, mean corpuscular hemoglobin (MCHC), defferential leukocyte count, prothrombin time and ATPP
blood biochemical: Same sample as hematology was used.; total protain, albumin, alubmin/globulin (A/G) ratio, GOT, GPT, alkaline phosphotase (ALP), lactate dehydrogenase (LDH), cholin esterase (Ch-E), gamma-GTP, total bilirubin, gulucose, total cholesterol, triglyceride, phospholipids, urea nitrogen, creatinine, sodium, potassium, chlorine, calcium and inorganic phosphorus
organs: by all males after extraction of blood, and by all females at Day 4 after (estimated) parturition;
for weight check; brain, lung, heart, liver, kidneys, spleen, adrenal, pituitary gland, thymus, thyroids, testis, epididymides and ovaries
for observation; above mentioned organs plus other organs, and number of implants and corpora lutea
for histopathological findings; lung, cecum, liver, kidney, testis, epididymis, prostate, spleen, mediastinal lymph node, renal lymph node, lumbar lymph node, pituitary gland, adrenal and skin
Remark : guideline study reported in Japanese , only sunnary tables and abstract

available

Result : Results from repeated dose toxicity study part:

1 female was found dead in the 60 mg/kg group at day 25 of gestation.
Anemic eyeballs and salivation were observed in the 20 mg/kg or more groups in both sexes; palor in the 60 mg/kg group was noted in females during gestaion period.
Body weight gain (graphics only) showed a tendency for decrease in the 20 mg/kg or more groups in males and in the 60 mg/kg group in females during gestation period.
Food consumption (graphics only) was decreased in the 60 mg/kg groups in males during the early administration period.

Hematology of males revealed methemoglobin increase in the 20 mg/kg or more groups (1.2 % or 2.5% versus 0.7% in controls)
Furthermore, in the 60 mg/kg male group,
---Decrease:
HCT (40.7% versus 44.7% in controls),
HGB (13.4g/dl versus 15.4 g/dl in controls,
RBC (6.71 x10[exp.6]/mm³ versus 8.21 x10[exp.6]/mm³ in controls)
MCHC (32.9% versus 34.4% in controls)
---Increase:
MCV (60.8µm³ versus 54.5µm³ in controls
MCH (20.0 pg versus 18.7pg)
PLT (1281 x10[exp.6]/mm³ versus 1092 x10[exp.6]/mm³ in controls)
RC (110% versus 28% in controls)

Increases in spleen weights in
- males: in the 60 mg/kg group (absolut/relative): 1.22g/0.683g% versus 0.76g/0.142g% in controls
- females: in the 20 mg/kg or more (absolut/relative):
0.71g/0.231g%, 1.05g/0.351g% versus 0.51g/0.169g% in controls;

Increases in liver weights
- males given 20 mg/kg bw or more (absolut/relative):
15.82g/3.083g%, 16.39g/3.223g% versus 15.12g/2.815g% in controls
- females given 60 mg/kg bw (absolut/relative):
14.43g/4.832g% versus 12.85g/4.285g% in controls

As gross necropsy findings, blackening and enlargement of the spleen were observed in 20 mg/kg or more groups in both sexes.
As histological findings, increases in hematopoiesis in bone marrow, congestion, deposites of pigment and extramedullary hematopoiesis in the spleen were observed in 20 mg/kg or more groups in both sexes. In the liver, extramedullary hematopoiesis was observed in 60 mg/kg males and in the 20 mg/kg or more groups in females. Deposites of pigment and hypertrophy of hepatocytes were observed in both sexes receiving 60 mg/kg bw/day.

NOEL(systemic toxicity male, female): 6 mg/kg bw/day

Results from reproductive and developmental toxicity study part:

As for reproductive ability of parent animals, no adverse effects of the substance were observed in either sex:
with respect to estrous cycle length, copulation index, fertility index, implantation index, gestation index and duration of gestation period, delivery index.

NOEL(parental toxicity): 60 mg/kg bw/day

With regard to the effects on neonates,
no effects on live birth index
no effeccts on sex ratio
60 mg/kg bw-group:
body weight of pups in both sexes decreased (no data)
viability on day 4 of lactation decreased in males:
males: 85.7 % versus 96.4% in controls
females: 97,2% versus 95.1 % in controls

NOEL(developmental toxicity) 20 mg/kg bw/day

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
13.01.2006 (137)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	male/female
Strain	:	Crj: CD(SD)
Route of admin.	:	gavage
Exposure period	:	males 48 days; females 15 days before mating, throughout pregnancy until day 3 of lactation
Frequency of treatm.	:	once daily
Duration of test	:	54 days
Doses	:	0, 6, 20, 60 mg/kg bw/day dissolved in corn oil
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	ca. 60 mg/kg bw
NOAEL teratogen.	:	ca. 20 mg/kg bw
Result	:	see freetext: Result
Method	:	other: OECD Guide-line 422 (see freetext method)
Year	:	1999
GLP	:	yes
Test substance	:	other TS: 4-Isopropylaniline (CAS-No. 88-99-7): Purity: 99.27 %

Method :

TEST ORGANISMS
age: 8 weeks old for males and females
weight at initiation: 350-402 g for male, 195-257 g for female
number of animals: 12 per sex per dose
pellet food and water: free access
ADMINISTRATION
vehicle: 1%(w/v) corn oil
type of administration: gavage, once a day
duration of administration:
male; 46 days (including 14days before mating)
female: more than 37 days (from 14days before mating to Day 3 of parturition)
MATING PROCEDURE
one by one in each cage
CLINICAL OBSERVATIONS AND FREQUENCY
clinical signs and mortality: every day
body weight:
male; Day 1, 2, 5, 7, 10, 14, 21, 28, 35, 42, 46
female: before mating Day 1, 2, 5, 7, 10, 14
during gestation Day 0, 1, 3, 5, 7, 10, 14, 17, 20
after parturition Day 0, 1, 4
food consumption: at every body weight check (24h consumption), except Day 0 of gestation and Day 0 of parturition for female
water consumption: not checked
HISTOPATHOLOGICAL OBSERVATIONS

urinalysis: by all males at Day 43-44; pH, protein, sugar, ketones, urobilinogen, bilirubin, occult blood, specific gravity, deposit and appearance
hematology: by all males at Day 46; erythrocyte count, MCV, platelet count, leukocyte count, hemoglobin, hematocrit, MCH, mean corpuscular hemoglobin (MCHC), defferential leukocyte count, prothrombin time and ATPP
blood biochemical: Same sample as hematology was used.; total protain, albumin, alubmin/globulin (A/G) ratio, GOT, GPT, alkaline phosphotase (ALP), lactate dehydrogenase (LDH), cholin esterase (Ch-E), gamma-GTP, total bilirubin, gulucose, total cholesterol, triglyceride, phospholipids, urea nitrogen, creatinine, sodium, potassium, chlorine, calcium and inorganic phosphorus
organs: by all males after extraction of blood, and by all females at Day 4 after (estimated) parturition;
for weight check; brain, lung, heart, liver, kidneys, spleen, adrenal, pituitary gland, thymus, thyroids, testis, epididymides and ovaries
for observation; above mentioned organs plus other organs, and number of implants and corpora lutea
for histopathological findings; lung, cecum, liver, kidney, testis, epididymis, prostate, spleen, mediastinal lymph node, renal lymph node, lumbar lymph node, pituitary gland, adrenal and skin

Remark : guideline study reported in Japanese , only sunnary tables and abstract available

Result : Results from repeated dose toxicity study part:

1 female was found dead in the 60 mg/kg group at day 25 of gestation.
Anemic eyeballs and salivation were observed in the 20 mg/kg or more groups in both sexes; palor in the 60 mg/kg group was noted in females during gestaion period.
Body weight gain (graphics only) showed a tendency for decrease in the 20 mg/kg or more groups in males and in the 60 mg/kg group in females during gestation period.
Food consumption (graphics only) was decreased in the 60 mg/kg groups in males during the early administration period.

Hematology of males revealed methemoglobin increase in the 20 mg/kg or more groups (1.2 % or 2.5% versus 0.7% in controls)
Furthermore, in the 60 mg/kg male group,
---Decrease:
HCT (40.7% versus 44.7% in controls),
HGB (13.4g/dl versus 15.4 g/dl in controls,
RBC (6.71 x10[exp.6]/mm³ versus 8.21 x10[exp.6]/mm³ in controls)
MCHC (32.9% versus 34.4% in controls)
---Increase:
MCV (60.8µm³ versus 54.5µm³ in controls
MCH (20.0 pg versus 18.7pg)
PLT (1281 x10[exp.6]/mm³ versus 1092 x10[exp.6]/mm³ in controls)
RC (110% versus 28% in controls)

Increases in spleen weights in
- males: in the 60 mg/kg group (absolut/relative): 1.22g/0.683g% versus 0.76g/0.142g% in controls
- females: in the 20 mg/kg or more (absolut/relative):
0.71g/0.231g%, 1.05g/0.351g% versus 0.51g/0.169g% in controls;

Increases in liver weights
- males given 20 mg/kg bw or more (absolut/relative):
15.82g/3.083g%, 16.39g/3.223g% versus 15.12g/2.815g% in controls
- females given 60 mg/kg bw (absolut/relative):
14.43g/4.832g% versus 12.85g/4.285g% in controls

As gross necropsy findings, blackening and enlargement of the spleen were observed in 20 mg/kg or more groups in both sexes.
As histological findings, increases in hematopoiesis in bone marrow, congestion, deposites of pigment and extramedullary hematopoiesis in the spleen were observed in 20 mg/kg or more groups in both sexes. In the liver, extramedullary hematopoiesis was observed in 60 mg/kg males and in the 20 mg/kg or more groups in females. Deposites of pigment and hypertrophy of hepatocytes were observed in both sexes receiving 60 mg/kg bw/day.

NOEL(systemic toxicity male, female): 6 mg/kg bw/day

Results from reproductive and developmental toxicity study part:

As for reproductive ability of parent animals, no adverse effects of the substance were observed in either sex:
with respect to estrous cycle length, copulation index, fertility index, implantation index, gestation index and duration of gestation period, delivery index.

NOEL(parental toxicity): 60 mg/kg bw/day

With regard to the effects on neonates,
no effects on live birth index
no effeccts on sex ratio
60 mg/kg bw-group:
body weight of pups in both sexes decreased (no data)
viability on day 4 of lactation decreased in males:
males: 85.7 % versus 96.4% in controls
females: 97,2% versus 95.1 % in controls

NOEL(developmental toxicity) 20 mg/kg bw/day

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
13.01.2006 (137)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

Type : other
In vitro/in vivo : In vivo
Species : rat
Sex : male
Strain : no data
Route of admin. : oral feed
Exposure period : 28 days
Frequency of treatm. : daily
Duration of test :
Doses : 0, 165, 825, 1650 ppm (approx. 0, 13.8, 66.8, 125.7 mg/kg bw/day, calculated from food consumption)
Control group : yes, concurrent no treatment
Result : other: see freetext RS
Method : other: see freetext ME
Year : 1973
GLP : no
Test substance : other TS: p-toluidine, no data on purity,M.P.: 44.5°C

Method : Dry material was blended with the basal diet to provide the desired levels; diets were prepared fresh weekly

record of survival, food and TS consumption, body weight weekly, pathology: organ weights (liver, kidneys, adrenals and testes) gross examination

Remark : see also chapter 5.4

Result : --No deaths or signs of intoxication
were noted among any of the animals during the experimental period.
--Terminal body weight:
1650 ppm significantly reduced whem compared to control:
292 g versus 343 g
--Organ-body weight ratios (%)
testes: there were no notable changes when compared to control:
low-mid-high vers. contr. [%]: 0.88-0.88-1.1 vers. 0.92
--At autopsy, no significant gross pathologic lesions were found among any of the rats examined.

Reliability : (2) valid with restrictions
Only very limited information given, not all parameters necessary investigated

Flag : Critical study for SIDS endpoint

17.06.2004 (130)

Type : other
In vitro/in vivo : In vivo
Species : rat
Sex : male
Strain : other: CD
Route of admin. :
Exposure period : 18 months
Frequency of treatm. : daily
Duration of test : 24 months
Doses : 0, 1000, 2000 ppm (approx. 0,. 75, 150 mg/kg bw)
Control group : yes, concurrent no treatment
Result : other: see freetext RS
Method : other: see freetext ME
Year : 1978
GLP : no
Test substance : other TS: p-toluidine, no data on purity

Method : TEST ORGANISMS
- Age: 6-8 weeks
Acclimation period: 2 weeks
- Number of animals: 25 per group
ADMINISTRATION /EXPOSURE
- Diet: purina certified rodent diet
- Doses:
Doses were chosen based on preliminary 30-day feeding study followed by a 2-week recovery period (no further information)
OBSERVATIONS:
body weights
NECROPSY:
Animals which died during the first 6 month of treatment were discarded without necropsy.
A complete gross necropsy was done on all animals which died after 6 month on test or were killed at the end of the study.
Tissues were fixed, sectioned, and stained by hematoxylin and eosin.
HISTOPATHOLOGY
Histopathological examinations were done on all grossly abnormal organs, tumor masses, lung, liver, spleen, kidney, adrenal, heart, bladder, stomach, intestines, reproductive organs, and pituitaries.
STATISTICS

Statistical analysis of tumors found was performed using the Fisher exact test with Bonferroni correction.

Remark : see also chapter 5.4
see also chapter 5.7

Result : no mortality and no signs of toxicity are reported.
Body weight development seems to correspond to the respective control group because body weight gain in the treated rats 10 % below that of the respective controls should result in a reduction of the dosage.
No gross and no histopathological findings are reported.

Reliability : (2) valid with restrictions
Study doesn't meet the criteria of today and is reported in brief, not all parameters necessary investigated

Flag : Critical study for SIDS endpoint

17.06.2004 (150)

Type : other
In vitro/in vivo : In vivo
Species : mouse
Sex : male/female
Strain : CD-1
Route of admin. : oral feed
Exposure period : 18 months
Frequency of treatm. : daily
Duration of test : 21 months
Doses : 6 months: 0, 1000, 2000 ppm (approx. 0, 150, 300 mg/kg bw), 12 months: 0, 500, 1000 ppm (approx. 0, 75, 150 ppm)
Control group : yes, concurrent no treatment
Result : other: see freetext RS
Method : other: see freetext ME
Year : 1978
GLP : no
Test substance : other TS: p-toluidine, no data on purity

Method : TEST ORGANISMS
- Age: 6-8 weeks
- Acclimatisation period: 2 weeks
- Number of animals: 25 per group
ADMINISTRATION /EXPOSURE
- diet: purina certified rodent diet
- Doses:
Doses were chosen based on prelimminary 30-day feeding study followed by a 2-week recovery period (no further information)
---Initially 1000, 2000 ppm (approximately 150, 300 mg/kg bw/day) over feeding period of 6 months,
---Reduction of doses after 6 months because weight gain was by 10 % below that observed in the concurrent controls:
500 and 1000 ppm ppm (approximately 75, 150 mg/kg bw/day)

OBSERVATIONS:
body weights
NECROPSY:
Animals which died during the first 6 month of treatment were discarded without necropsy.
A complete gross necropsy was done on all animals which died after 6 month on test or were killed at the end of the study.
Tissues were fixed, sectioned, and stained by hematoxylin and eosin.
HISTOPATHOLOGY
Histopathological examinations were done on all grossly abnormal organs, tumor masses, lung, liver, spleen, kidney, adrenal, heart, bladder, stomach, intestines, reproductive organs

STATISTICS
Statistical analysis of tumors found was performed using the Fisher exact test with Bonferoni correction.

Remark : see also chapter 5.4
see also chapter 5.7

Result : 1000 ppm, 2000 ppm:
body weight reduction: > 10 % (data not given)
survivors:
m: 18/25 (control)--17/25 (low dose)-18/25 (high dose;
f: 20/25 (control)--21/25 (low dose)-17/25 (high dose)
consequence:
reduction of testsubstance:
500 ppm, 1000 ppm:
reproductive organs: no gross and histopathological findings were reported.

Reliability : (2) valid with restrictions
Study doesn't meet the criteria of today and is reported in brief, not all parameters necessary investigated

Flag : Critical study for SIDS endpoint
17.06.2004 (150)

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Type of experience : Health records from industry

Remark : Toluidines (isomer not specified) produce the same symptomes as does aniline, with less cyanosis but more strangury and hemoglobinuria.

Reliability : (4) not assignable
Review article

Flag : Critical study for SIDS endpoint
15.03.2004 (194)

Type of experience : Health records from industry

Remark : concentrations of 40 ppm (176 mg/m3) toluidine in the atmosphere for more than 60 minutes caused severe toxic effects in persons, 10 ppm (44 mg/m3) lead to symptoms of illness and concentration in the atmosphere greater than 5 ppm (22 mg/m3) indicate unsatisfactory conditions.

Test substance : o-, m-, p-toluidine, isomer not specified

Reliability : (2) valid with restrictions
Exposure against a mixture of toluidine isomeres

Flag : Critical study for SIDS endpoint
25.05.2004 (195)

Type of experience : Health records from industry

Remark : Cytoscopic examination of 75/81 revealed two cases of bladder papilloma, one being a 23 year old worker who had been exposed for 1 year and 8 months only to p-toluidine and the other a 49 year old worker who had been exposed to o- and p-toluidine for 23 years

Reliability : (4) not assignable
Exposure concentration not given

Flag : Critical study for SIDS endpoint
15.03.2004 (196)

Type of experience : other: Human exposure and biological monitoring in smokers and non-smokers (blood)

Remark : Method evaluation for routinely monitoring of HB adducts in humans
Result : Hemoglobin adducts of 15 aromatic amines were determined in non-smokers and smokers living in Turin, Italy.
Blood samples from 25 non-smokers and 61 smokers were examined.
There was an increase of p-toluidine-HB adducts in smokers 306 pg/g HB (blond tabaco), 415 pg/g Hb (black tobacco) versus 209 pg/g in non-smokers.
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
08.06.2004 (197) (198) (199)

Type of experience : other: Biological monitoring (urine)

Remark : The levels of aniline and toluidines were determined in human urine. p-Toluidine was found in 2 out of 11 smokers (1.8 - 4.4 µg) and in 4 out of 9 non-smokers (1.7 - 8.3 µg). It was concluded that diet as a source other than cigarette smoke, may contribute significantly to urinary p-toluidine
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
08.06.2004 (200)

Type of experience : other: Biological monitoring (blood)

Result : A trend to higher hemoglobin-adduct levels in smokers was observed for p-toluidine.
In the Boston cohort, the p-toluidine hemoglobine adduct level was 0.18 - 0.42 ng/g hemoglobin for different groups of smokers, and 0.09 ng/g hemoglobin for non-smokers. In the Turin cohort, the average p-toluidine hemoglobine adduct level was 0.31 ng/g hemoglobin in 40 smokers, and 0.21 ng/g hemoglobin in 25 non-smokers.
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
08.06.2004 (201)

Type of experience : other: Analytical method

Remark : p-Toluidine can be determined simultaneously with numerous other arylamines.
Reliability : (4) not assignable
Discussion of a new method
08.06.2004 (202)

Type of experience : other: Biological monitoring (blood)

Remark : No correlation could be found between increasing urinary cotinine levels indicating increasing exposure to environmental tobacco smoke and hemoglobin adducts of p-toluidine in nonsmoking pregnant women.
Reliability : (4) not assignable
Insufficient documentation, abstract only
08.06.2004 (203)

Type of experience : other: Biological monitoring (urine)

Result : p-Toluidine was detected in the urine of nonsmoking subjects who were not occupationally exposed to arylamines
Reliability : (2) valid with restrictions
Basic data given
08.06.2004 (204) (205)

Type of experience : other: Biological monitoring (blood)

Remark : The amount of Hb-adducts of p-toluidine in the blood of exposed workers can be quantified by GC-MS. The method is discussed.
Result : Hemoglobin adducts of p-toluidine were detected in an exposed worker but, unfortunately, neither the results nor the exposure to tobacco smoke or other hazardous substances were detailed by the Sabbioni and Beyerbach (1955)
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
08.06.2004 (206)

Type of experience : other: Biological monitoring (blood)

Remark : Hb adducts form aromatic amines in children were strongly influenced by site of residence, whereas environmental tabacco smoke exposure did not significantly increase the adduct level.
Result : Hb adducts form aromatic amines in children were strongly influenced by site of residence (three different-sized Bavarian towns. The highest mean adduct level was observed in the largest town), whereas environmental tobacco smoke exposure (determined by interview), did not significantly increase the adduct level.
Reliability : (2) valid with restrictions
Meets scientifically accepted criteria
Flag : Critical study for SIDS endpoint
08.06.2004 (207)

Type of experience : other: Biological monitoring (urine)

Result : In the general population (84 adults from Western Germany), the level of p-toluidine in urine was 1.2 µg/l (median, 0 - 27 µg/l). For 34 males, the median was 3.1 µg/l, and for 50 females, the median was 0.69 µg/l.
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
08.06.2004 (208)

Type of experience : other: Biological monitoring (urine)

Method : Occupationally exposed workers from 3 chemical plants (presumably in Germany) were examined.
Result : There were no significant differences in renal excretion of p-toluidine between occupationally exposed and non exposed smokers and nonsmokers.
The urinary p-toluidine concentrations were similar in occupationally exposed smokers (n = 22) and non-smokers (n = 21), 2.1 µg/l and 2.4 µg/l, respectively (difference not significant). The level was independent from the acetylator status of the workers (2.1 and 2.2 µg/l for fast and slow acetylators, respectively). However, there was a 2/3 increase in the urinary p-toluidine levels in unexposed smokers (mean 2.2 µg/l, n = 8), compared to unexposed non-smokers (1.3 µg/l, n = 8).
Reliability : (2) valid with restrictions

Basic data given
Flag : Critical study for SIDS endpoint
08.06.2004 (204)

Type of experience : other: Biological monitoring (human milk)

Result : In human milk from 7 smokers and 24 non-smokers, DeBruin, Pawliszyn, and Josephy (1999) found several aromatic amines of cigarette smoke, but they did not detect p-toluidine with a detection limit of 0.01 ppb.
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
08.06.2004 (209)

Type of experience : other: Hemoglobin adduct background level of toluidines

Result : The hemoglobin adduct background level of toluidine (no isomer specified) is 1 - 10 µg/l for the general population due to tobacco smoke.
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
01.06.2004 (210)

Type of experience : other: Biological monitoring (blood)

Result : The p-toluidine hemoglobine adduct level was doubled in smokers (0.13 ng/g hemoglobin, n = 12), compared to non-smokers (0.07 ng/g hemoglobin, n = 10).
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
08.06.2004 (211)

5.11 ADDITIONAL REMARKS

Type : Excretion

Remark : p-Toluidine and its glucuronide was prepared. It was dissolved in 0.2m phosphate buffer pH=7.4 and incubated at 37°C to determine the magnitude of its hydrolyzability. In order to determine urinary excretion p-toluidine was injected subcunateously into rabbits the urinary excreation was great and paralleled the hydrolyzability of the glucuronide (no further details available).
Reliability : (4) not assignable
Abstract only
14.06.2004 (212)

Type : Metabolism

Remark : Male Wistar rats rats were fed with p-toluidine and rat liver preparations were made: N-arylformamide und N-arylacetamide im cytosol was detected.
Reliability : (4) not assignable
Special study, insufficient documentation
05.03.2004 (213)

Type : other

Remark : Dermal application on the skin of mouse tail caused no change in respiration rate or motor activity during the 6 hour exposure period.
Reliability : (4) not assignable
Abstract only
14.06.2004 (214)

Type : other

Remark : Covalent binding of p-toluidine to hemoglobin was studied in female Wistar rats (gavage application) and hemoglobin binding index was determined: 0.6 mmol/kg bw (ca.= 64.2 mg/kg bw) in 1,2-Propandiol; hemoglobin binding index: 4.3 (mmol/mol Hb/Dosis (mmol/kg)
Reliability : (2) valid with restrictions
Meets general accepted scientific criteria, but rat is less susceptible than man
14.06.2004 (215) (216)

Type : other

Remark : Substitution of methyl-groups to the aromatic ring lowered the effects to the muscles of rats.
Reliability : (4) not assignable
Documentation insufficient for assessment
04.03.2004 (217)

Type : other

Remark : In an investigation of nephrotoxicity of substituted anilines in the rat, 4-methylation (p-toluidine hydrochloride) was found to prevent renal damage and to produce instead centilobular liver necrosis.
Reliability : (4) not assignable
Abstract only
14.06.2004 (218)

Type : other

Remark : In the model created by Pott and Guy (1992, human skin in vitro) p-toluidine was absorbed through skin.
Reliability : (4) not assignable
Special study, predictive model
14.06.2004 (219)

Type : other

Remark : Single oral treatment of female Wistar rats with 0.5 mmol (ca.= 54 mg/kg bw) and sacrifice 24 hours later yielded a hemoglobin binding index (HBI): 4.3 (aniline: 22)
Reliability : (2) valid with restrictions
Meets scientifically accepted criteria
14.06.2004 (220)

Type : other

Remark : In rats dermal absorption of p-toluidine from 1 % water solution or 5 % ointment was faster through the skin of the tail than through the dorsal skin. The absorption was faster from water solution than from ointment. Linear positive correlation was found between exposed skin area and absorption rate.
Reliability : (4) not assignable

Only English abstract available
14.06.2004 (221)

Type : other

Remark : in vitro: hepatic microsomes of rats and mice oxidize p-toluidine to p-aminobenzoic acid
Reliability : (4) not assignable
Special study
14.06.2004 (222)

Type : other

Remark : Investigation on permeation mechanisms through artificial lipoidal membranes
p-toluidine served as nodel substance
Reliability : (4) not assignable
Method evaluation
04.03.2004 (223) (224) (225) (226) (227) (228)

Type : other

Remark : In vitro, metabolism of p-toluidine by rat liver microsomal fractions resulted not in the formation of cytochrome P450 metabolic intermediate complex.
Reliability : (4) not assignable
Special study
14.06.2004 (229)

Type : other

Remark : The acute toxicities of 24 substituted anilines in terms of 50%-inhibition-concentrations (I50) for viability of cells and their adenosine triphosphate (ADP) content were measured with monolayer cultures of Balb/3T3 cells: I50 (50 % inhibition concentration for viability) for p-toluidine in Balb/3T3 is 0.201 mM
Reliability : (4) not assignable
Special study
14.06.2004 (230)

Type : other

Remark : p-Toluidin is no inhibitor of mammary tumour inhibiting aromatase.
Reliability : (4) not assignable
Special study
14.06.2004 (231)

Type : other

Remark : Reaction of p-toluidine with normal and 18-O-labeled H2O2 in presence of chloroperoxidase and pea seed peroxygenase was found to give quantitative incorporation of 18-O into the nitroso metabolite.
Reliability : (4) not assignable
Special study
04.03.2004 (232)

Type : other

Remark : The N-hydroxilation of p-toluidine which forms the nitroso

derivate of the aromatic amine is paralleled by methemoglobin production in the cat.

Reliability : (4) not assignable
Secondary literature; survey
14.06.2004 (233)

Type : other

Remark : review on toxicity
Reliability : (4) not assignable
04.03.2004 (234)

Type : other

Remark : review on toxicity
08.03.2004 (235)

Type : other

Remark : review on toxicity
06.03.1998 (236)

Type : other

Remark : in vitro: N-acetylation of arylamines by recombinant human NAT1 and NAT2:
p-Toluidine was N-acetylated by recombinant human NAT1 and polymorphic NAT2 acetyltransferases.

Reliability : (4) not assignable
Special study
14.06.2004 (237)

Type : other

Remark : After i.v.-administration of 0.025 mM p-toluidine or its corresponding N-hydroxy derivate to rabbits p-toluidine produced much smaller amounts of MetHb than the corresponding hydroxylamin (2.5 versus 30 % of total Hb) within 10 min.

Reliability : (4) not assignable
Special study
14.06.2004 (238)

Type : other

Remark : In vitro:
Calf thymus DNA was modified in vitro by reaction with activated N-hydroxyarylamine-derivate of p-toluidine.
In vivo:
Female Wistar rats (n=2) were given a single doses of p-toluidine and its analogous nitroderivate by oral gavage and 24 hours later sacrificed.

Hepatic DNA and in vitro modified DNA were hydrolyzed enzymatically to individual 2'-deoxyribonucleonucleosides. Adducts were determined using HPLC/MS/MS by comparison to synthesized standards.

In vitro:
p-toluidine formed adducts to 2'-deoxyguanosine and to 2'-deoxyadenosine after in vitro reaction to DNA.
in vivo:

No DNA adducts could be detected in rats dosed with p-toluidine

Reliability : (4) not assignable
Method evaluation

19.06.2004 (239)

Type : other

Remark : A conformational analysis of C8-arylanine nucleoside and nucleotide was done:
the non-phosphorylated adducts show anti conformation of the glycosidic link, while the corresponding 5'-phosphorylated adducts have syn conformation. All adducts exhibita predominant D2'-endo conformation of the sugar ring and gg conformation of the exocyclic bond.

Reliability : (4) not assignable
Although basic information available no additional information with respect to toxicological property

19.06.2004 (240) (241)

Type : other:

Remark : p-toluidine was evaluated with the Ocular and Dermal Irritection tests method.
The Ocular Irritection test evaluated p-toluidine as noderate irritant; the Dermal Irritection test evaluated p-toluidne ans non-irritant.

Reliability : (3) invalid
No validated test system

21.06.2004 (242)

Type : other: in vitro: MetHb formation

Remark : Assessment of MetHb formation of aniline derivates;
in vitro method using rat blood and hepatic metabolic activation system.
The study showed MetHb forming potency of p-substituted anilines was linearly dependent on the properties of substituents, such as hydrophobicity, steric effect and hydrogenbonding potency.
(english abstract from japanese paper only).

Reliability : (4) not assignable
Special study

25.05.2004 (243)

Type : other: Drug Metabolism

Remark : There are indications that the side-chain hydroxylation of p-toluidine is decreased by more than 80 % in Vitamin C deficient liver microsomal cytochrome p450 of guinea pigs.

Reliability : (4) not assignable
Special study, only abstract available

04.03.2004 (244)

Type : other: Hematotoxicity

Remark : Nine adult cats (older then 24 weeks) were administered with 0.25 mmol/kg bw (approx. 27 mg/kg bw) p-toluidine for a single i.v. injection.
Methemoglobin determinations 1, 2, 3, 4, 5 hours after injection: 28.1 34.3, 32.7, 33.2, 32.1 % methemoglobin, respectively. Mean 32.1 and mean max. 39.6 % methemoglobin

Reliability : (2) valid with restrictions
Application route not suitable to the human situation

19.03.2004 (245) (246)

Type : other: Hematotoxicity

Remark : Single i.p. admininistration of 0.5 mM/kg bw into mice resulted in 6.9 % methb within 10 min, 5 % methb within 30 min and 1.0 % within 90 min and 0.2 % within 150 min after administration (neg. control mice: 0.8 % methb).

Reliability : (4) not assignable
Administration route is not suitable to the human situation (English abstract from Japanese paper only)

25.05.2004 (247)

Type : other: microsomal metabolism

Remark : The metabolisation of p-toluidine by hepatic microsomes of male Wistar rats changed with the increased number of chlorine substituents: increasing number of chlorine substituents cause a significant increased importance of side-chain C-hydroxylation.

Reliability : (4) not assignable
Special study

05.03.2004 (248)

Type : other: microsomal metabolism

Remark : The N-hydroxylation of aromatic amines by rabbit liver microsomesis mediated by cytochrome P450 (details concerning p-toluidine are not reported).

Reliability : (4) not assignable
Documentation insufficient for assessment

14.06.2004 (249)

Type : other: microsomal metabolism

Remark : The N-oxidation of p-toluidine by hepatic microsomes is different in guinea pig, rabbit, mouse, or rat.

Reliability : (4) not assignable
Literature review

04.03.2004 (250)

Type : other: microsomal metabolism

Remark : Addition of pyruvate to p-toluidine caused a decrease of 15 % in acetylation rate by rat liver homogenate.

Reliability : (4) not assignable
Documentation insufficient for assessment

04.03.2004 (251) (252)

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- Soil Adsorption Coefficient with PCKOCWIN v. 1.66, 2000
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