SCOEL/REC/145
4-Aminotoluene
(*p*-Toluidine)

Recommendation from the
Scientific Committee on Occupational Exposure Limits

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Adopted 12 September 2016

EUROPEAN COMMISSION

Directorate-General for Employment, Social Affairs and Inclusion
Directorate B —Employment
Unit B.3 — Health and safety

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2017

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8-hour TWA:	1 ppm (4.46 mg/m^3)
STEL (15 min):	2 ppm (8.92 mg/m^3)
BLV:	None
Additional categorisation:	None
Notation:	"skin"

This evaluation is based on Greim (2004), Henschler (1990), ACGIH (2001), ECB (2000), NLM (1991, 2005, 2006), OECD/SIDS (2005), the references cited in these reviews and additional database search performed in Nov. 2015 and Aug. 2016.

The present Recommendation was adopted by SCOEL on 12 September 2016.

RECOMMENDATION EXECUTIVE SUMMARY

Outcome Considerations

Methaemoglobin (MHb) formation is the critical non-neoplastic effect in animals and humans exposed to 4-aminotoluene (4-AT). Depending on the concentration of MHb, methaemoglobinemia may have serious health effects in humans. Quantitative data on the formation of MHb after inhalation of 4-AT in humans or in experimental animals are not available.

Experimentally, MHb levels reached between 4.2 % and 6.6 % after 3 months of feeding 40 mg/kg/day of 4-AT in rats (the lowest dosed examined) and were only marginally further increased after 6 months (Jodynis-Liebert and Bennasir 2005). By analogy to tolerable levels of CO-Hb in carbon monoxide exposed persons, a MHb level of 4-5 % has been considered tolerable (Bolt *et al* 1985; see also REC-153 for aniline). Thus, 40 mg/kg/day 4-AT may be regarded as the LOAEL concerning MHb induction in rats. Comparison of equimolar intravenous doses of 4-AT and aniline in cats indicates that the ability of 4-AT to induce MHb formation is lower and about half as high as the ability of aniline (McLean *et al* 1969).

4-AT was not mutagenic or genotoxic in most *in vitro* tests with bacterial or eukaryotic test systems including mammalian cells. DNA damage was observed in human lung cells and unscheduled DNA synthesis in rat hepatocytes. The *in vivo* database is very limited. A mutagenic response was obtained in *a Drosophila* test. Strand breaks in liver and kidney of mice and DNA binding in various tissues of rats have been detected. 4-Methylphenylhydroxylamine, an intermediate of 4-AT that is involved in methaemoglobin formation, is mutagenic in bacterial test systems. In summary, a minor genotoxic potential of 4-AT *in vivo* cannot be ruled out.

The database with respect to carcinogenic effects in humans is insufficient. Two cases of bladder papillomas and 6 cases of bladder tumours were identified in an examination of 81 workers with occupational exposure to 4-AT and, most of them, also to 2AT. The latter (*o*-toluidine) is an established human bladder carcinogen (Khlebnikova *et al* 1970).

Several older animal carcinogenicity studies have been performed in the 1970s. Weekly subcutaneous injections of 4-AT over a period of 2 years led to an increase in malignant tumours at the site of application in both males and females and in benign liver tumours in females. No tumours at the site of application occurred after dermal application of a solution of 4-AT to the skin of mice. 4-AT was not carcinogenic in an 18-month feeding study with male rats, but in the same study, feeding of 4-AT caused a slight increase of liver tumours in male and female mice. From the report it appears likely that these were benign (hepatic adenomas). In the same study, the isomer 2AT (o-toluidine) was clearly carcinogenic under similar conditions (Section 7.7.2). Therefore, although the possibility of metabolic formation of genotoxic *N*-oxidation products in humans may raise some concern for a genotoxic potential of 4-AT, there is no experimental or epidemiological proof of carcinogenicity at present. Compared to its structural isomer 2AT (*o*-toluidine), a carcinogenic potential of 4-AT, if such a potential exists, must be distinctly lower.

In essence, modern studies on carcinogenicity of 4-AT are needed. Because the available data are not clear, SCOEL does presently not classify 4-AT as to carcinogenicity.

Derived Limit Values

For setting an OEL, the key health effect of 4-AT is methaemoglobinaemia. The experimental data in cats of McLean *et al* (1969; Section 7.2.2) show that the 4-AT is by a factor of 2 less potent in methaemoglobin induction than aniline, but there is uncertainty in species extrapolation in this respect. However, this ratio is in accordance with early industrial experience in humans (Smyth 1931, Goldblatt 1955; Section 7.2.1). For aniline, SCOEL [in 2016] has recommended an OEL (8h-TWA) of 2 ppm (SCOEL/REC/153), based on the human experimental study of Käfferlein et al (2014). With an assessment factor of 4 for remaining uncertainties of species extrapolation (*i.e.* cats-humans) and a potency of 4-AT half that of aniline, an *OEL (8h-TWA) of 1 ppm (4.46 mg/m^3) is derived for 4-AT*. This derivation is partly based on human data (on aniline), for which in general preference is given according SCOEL's methodology.

In addition, this OEL is much supported by experimental animal data. As pointed out above, the subchronic study in rats by Jodynis-Liebert and Bennasis (2005) (up to 6 month of daily oral dosing) point to an oral LOAEL of 40 mg/kg b.w. A longer time extrapolation is not required, as the effect did only marginally increase between 3 and 6 months of administration. The dose-effect relationship in this experiment makes an estimated NOAEL of 1/3 of this dose plausible (*i.e.*, a repetitive dose that leads to MHb levels only below 4-5% as a threshold of adversity). Thus, an NOAEL of 13.3 mg/kg b.w. in rats can reasonably be anticipated. As aromatic amines are generally well absorbed from the gut, no correction for limited absorption is required. With a species extrapolation factor of 4, a human no-effect level would be derived of 250 mg/75 kg b.w. With a factor of 5 for remaining uncertainties (uncertainties in species extrapolation; limited human individual differences in MHb response) and considering a ventilation volume for an 8h working shift of 10 m^3, again an OEL (8h-TWA) of about 5 mg/m^3 (or 1 ppm) would result.

As the induction of methaemoglobin by aromatic amines is dependent on metabolic *N*-oxidation, which is a time-dependent enymatic process, it may anticipated that a short-term (15 min) excursion of exposure by a factor of 2 has no practically relevant effect on methaemoglobin formation. A *STEL of 2 ppm can be recommended* for 4-AT to be implemented together with the derived 8h-TWA as described above.

Skin notation

By analogy to the isomeric 2-aminotoluene (see 7.1.3.) significant skin absorption of 4-aminotoluene is very likely. Therefore, a "skin" notation is recommended.

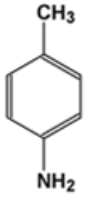
Biological Monitoring

At present, no specific methodology for biological monitoring may be recommended, as no appropriate field studies in exposed humans are available (see 7.1.4.).

RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR 4-AMINOTOLUENE

RECOMMENDATION REPORT

1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

Name:	4-aminotoluene
Synonyms:	*p*-toluidine, 4-toluidine, 4-methylaniline, *p*-methylaniline
Molecular formula:	C_7H_9N
Structural formula:	
EC No.:	203-403-1
CAS No.:	106-49-0 (for *p*-toluidine hydrochloride: 540-23-8)
Molecular weight:	107.15
Conversion factors: (20 °C, 101.3kPa)	1 ppm = 4.46 mg/m^3; 1 mg/m^3 = 0.224 ppm

4-Aminotoluene (4-AT) is a white solid. 4-AT has a melting point of 44 °C and a boiling point of 200 °C. The vapour pressure at 20 °C is 0.26 hPa. 4-AT is slightly soluble in water (11 g/l at 20 °C and pH = 7) and very soluble in alcohol, ether, acetone, oils and dilute acids. A log P_{ow} of 1.39 is reported. The pk_a is 5.1, the density 1.046 g/cm^3 at 20 °C. The substance has a flash point of 87 °C (closed cup) (ACGIH 2001, ECB 2000, NLM 2005).

2. EU HARMONISED CLASSIFICATION AND LABELLING

Information about the EU harmonised classification and labelling for 4-aminotoluene is provided by ECHA (2014a), as summarised in Tables 1 and 2.

Table 1: 4-Aminotoluene: Classification according to part 3 of Annex VI, table 3.1 (list of harmonised classification and labelling of hazardous substances of Regulation (EC)

Index no.	International Chemical Identification	EC no.	CAS no.	Classification		Labelling			Spec. Conc. Limits, M-factors	Notes
				Hazard Class& Category Code (s)	Hazard statement code (s)	Picto-gram Signal Word Code (s)	Hazard statement code (s)	Suppl. Hazard statement code (s)		
612-160-00-4	p-toluidine/ 4-aminotoluene	203-403-1	106-49-0	Acute Tox. 3 Acute Tox. 3 Skin Sens. 1 Eye Irrit. 2 Acute Tox. 3 Carc. 2 Aquatic Acute 1	H311 H317 H319 H331 H351 H400	GHS06 GHS09 GHS08 Dgr	H311 H317 H319 H331 H351 H400			

Table 2: 4-Aminotoluene. Classification according to part 3 of Annex VI, table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC of Regulation (EC) No1272/2008; Source: ECHA inventory database http://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/cl-inventory/view-notification-summary/22403

Classification	Risk Phrases	Safety Phrases	Indication of danger	Concentration Limits	
				Concentration	Classification
Carc. Cat. 3; R40 T; R23/24/25 Xi; R36 R43 N; R50	23/24/25 36 40 43 50	(1/2) 28 36/37 45 61	T N	-	

3. CHEMICAL AGENT AND SCOPE OF LEGISLATION

4-Aminotoluene is a hazardous chemical agent in accordance with Article 2 (b) of Directive 98/24/EC and falls within the scope of this legislation.

4-Aminotoluene is not a carcinogen or mutagen for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC.

4. EXISTING OCCUPATIONAL EXPOSURE LIMITS

Occupational exposure limits for 4-aminotoluene exist in a number of countries, as shown in the table below. The values presented below represent examples and are not an exhaustive listing of all limit values within the EU and other countries.

Table 3: Existing OELs for 4-aminotoluene; adopted from the GESTIS database (GESTIS, 2015)

EU-countries	TWA (8 hrs)		STEL (15 min)		
	ppm	mg/m³	ppm	mg/m³	References
Austria	0.2	1	0.8	4	GKV (2011)
Belgium	2	8.9			Royal Decision (2014)
Denmark	2	9	4	18	BEK (2011)
Hungary		1		4	MHSFA (2000)
Ireland	0.2	0.9			HSA (2011)
Latvia		0.5		1	GESTIS (2015)
Poland		8			GESTIS (2015)
Spain	2	8.9			INSHT(2011)
Non EU-countries	ppm	mg/m³	ppm	mg/m³	
Australia	2	8.8			Safe Work Australia (2011)
Canada (Ontario)	2				Ontario Ministry of Labour (2013)
Canada (Québec)	2	8.8			IRSST(2010)
New Zealand	2	8.8			HS (2013)
Singapore	2	8.8			GESTIS (2015)
South Korea	2	9			GESTIS (2015)
Switzerland	0.2				SUVA (2015)

5. OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE

4-AT is used as an intermediate in the synthesis of dyes and other organic chemicals, in the preparation of ion exchange resins and as a reagent for the detection of lignin, nitriles and phloroglucinol (ACGIH 2001, NLM 2005).

5.1. Occurrence and use

According to (OECD, 2005) 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 may be formed during pyrolysis and during the combustion of plastics.

p-Toluidine was detected in the river Rhine in 1979, with the highest p-toluidine concentration of 1 µg/l, whereas, in 1991, p-toluidine was not detected in several rivers in North Rhine-Westfalia in Germany (detection limit: 0.1 - 1 µg/l) (OECD, 2005).

p-Toluidine occurs in tobacco smoke (Pailer et al 1966; Neurath 1969; Schmeltz and Hoffmann 1977; Patrianakos and Hoffmann 1979) and high levels of p-toluidine in indoor atmospheres due to smoking were measured by Luceri et al (1993) and Palmioto et al (2001). Based on such information, (OECD 2005) suggested that general population can be exposed to 4-aminotoluene via inhalation of tobacco smoke.

For 4-aminotoluene no consumer use is known; it is exclusively used as an intermediate in chemical processes (OECD 2005).

5.2. Production and use information

4-Aminotoluene is commercially manufactured by reduction of p-nitrotoluene. According to Bowers 2002) early commercial production of toluidines involved the nitration of toluene followed by a dissolving metal reduction, usually with iron and hydrochloric acid, to give a mixture of toluidine isomers. These early mixed toluidines were commercially important
as dye intermediates. Today the isomers are separated by fractional distillation at the nitrotoluene stage, and the individual compounds typically reduced by catalytic hydrogenation.

In 2000, the global production volume of 4-aminotoluene was estimated to be 19.600 tonnes by 23 producers (Srour 2002) with the following worldwide distribution:

- Western Europe: 8.000 tonnes/a (4 producers),
- USA :3.000 tonnes/a (1 producer),
- Japan: 1.200 tonnes/a (1 producer),
- South Korea: 2.400 tonnes/a (1 producer),
- China: 3.800 tonnes/a (13 producers), and
- India: 1.200 tonnes/a (2 producers).

According to (Bowers, 2002), p-toluidines find considerable application in the dye and pigment industries, as well as in the manufacture of triarylmethane dyes. Two compounds derived from m- and p-toludine, *N,N*-dimethyl-m-toluidine and *N,N*-dimethyl-p-toluidine, have found use as accelerators for peroxide-cured epoxy and unsaturated polyester resins.

According to (OECD, 2005) in Western Europe the total demand of 4-aminotoluene (5700 tons/year) is exclusively used as an intermediate in chemical synthesis. 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).

5.3. Occupational exposure

4-AT is a chemical intermediate for dyes. It is used for organic synthesis and as a test reagent (NTP 2015). No consumer use is known for 4-AT (OECD/SIDS 2005).

5.4. Routes of exposure and uptake

The routes of exposure for 4-aminotoluene include inhalation, skin absorption, ingestion, skin and or eye contact (NIOSH 2011). However, occupational exposure to 4-aminotoluene is most likely to occur through inhalation and dermal contact. The general population may be exposed to 4-aminotoluene via inhalation of tobacco smoke (OECD 2005).

6. MONITORING EXPOSURE

4-Aminotoluene can be monitored in the air of the workplace by applying the following methods (NIOSH, 2011):

- OSHA, Method No.73, 1988
- NIOSH method 2002

In both methods 4-aminotoluene is sampled from the air in the workplace by adsorption onto a solid sorbent or absorption into solution, followed by extraction of 4-aminotoluene with an organic solvent. The 4-aminotoluene-containing extract can then be analysed by gas chromatography (GC), using flame ionisation detection (FID), a nitrogen-specific detector (NSD), or an electron capture detector (ECD), as shown in Table 4.

Table 4: Overview of sampling and analytical methods for monitoring 4-aminotoluene in the workplace

Method	Sorbent	Desorption solution	Analysis	Recovery (%)	LOQ	Precision (%)	References
OSHA No.73	Acid-treated filter	Sodium hydroxide	GC- ECD	93	0.55 $\mu g/m^3$	11.2 (including additional 5% for sampling error)	OSHA 1988
NIOSH method 2002	Silica gel	Ethanol	GC-FID	n.s*	n.s*	n.s*	NIOSH 1994

n.s: not specified.

The OSHA No.73 (OSHA, 1988) method has been completely evaluated based on the established evaluation procedures of the organic methods evaluation branch.

The NIOSH method 2002 (NIOSH, 1994) has been partially evaluated for 4-aminotoluene and states that use of a nitrogen-specific detector instead of a flame ionisation detector will greatly increase sensitivity. However, the text of the method does not provide any data specific to 4-aminotoluene for the recovery in (%), LOQ and precision in (%).

4-Aminotoluene can be monitored in the plasma or urine by applying the following methods:

- MAK 1993
- MAK 2000

Table 5: Overview of sampling and analytical methods for monitoring *p*-toluidine in biological samples (blood and urine)

Method	Application	Analysis	Standard deviation (rel)(*Sw*)*	Prognostic range(*u*)*	Recovery (%)	Detection limit	Refs
MAK 1993	Determination of p-toluidine in urine, plasma and erythrocytes	GC/MS	u: 12.0 and 9.8% p: 8.3 and 7.1% H: 6.1 and 8.0%	u:25.1 and 20.4% p:17.4 and 14.9% H:12.8 and 16.7%	u: 85-114 p: 90-115 H: 89-110	1.0 µg/L blood/urine or plasma	DFG 1993
MAK 2000	Determination of the adducts of p-toluidine released from haemoglobin	GC/MS with negative chemical ionisation	6.9%	15.3 %	114%	1.0 ng/L blood	DFG 2000

In essence, there are no measuring difficulties (air monitoring and biological monitoring) at the proposed OEL levels.

7. HEALTH EFFECTS

7.1. Toxicokinetics (absporption, distribution, metabolism, excretion)

2-AT is absorbed easily via the gastrointestinal tract and is distributed, metabolised and excreted as metabolites via urine and faeces. 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. However, absorption *via* these administration routes can be reasonably predicted due to the molecular similarity to p-toluidine (OECD/SIDS 2005).

7.1.1. Human data

There were no data available.

7.1.2. Animal data

Data regarding toxicokinetics following inhalation or dermal uptake were not available.

Seventy-two hours after oral (gavage) administration of 500 mg/kg ^{14}C-4-AT in male rats, the radioactivity was detectable in all organs with the highest concentrations occurring in fat, liver, skin, kidneys and blood. The lowest concentrations were found in brain, testes, bone marrow and muscle. The level of DNA binding was about 1.2-fold higher for 4-AT than for 2-aminotoluene (2-AT). Similar, but smaller differences were seen for binding to RNA and protein. The area under the plasma concentration curve for 4-AT was about 1.8-fold lower than that for 2-AT. Both isomers were eliminated from plasma with a half-life of 12–14 hours (Brock *et al* 1990).

4-AT caused a decrease in aryl hydrocarbon hydroxylase activity, aminopyrine demethylase activity and cytochrome P450 content in the liver of Wistar rats after i.p. administration of 75 mg/kg per day on 3 consecutive days. Microsomal epoxide hydrolase and cytosolic GSH-transferase activity were increased. No significant effects were seen in lung and kidneys (Henschler 1990).

2-Amino-5-methylphenol was identified as a urinary metabolite of 4-AT in rats. Only small amounts of unchanged 4-AT appear in urine. After a single oral administration of 500 mg/kg, excretion amounted to 2.5 % in 24-hour urine of male rats (Cheever *et al* 1980). Similar results were observed in a subchronic study with male rats receiving 40, 80 and 160 mg/kg bw per day with the diet (Jodynis-Liebert and Bennasir 2005, see Section 7.3.2). The excretion of 4-AT in 24-hour urine as determined on one day at weeks 1–4 and every second week thereafter showed a dose-dependent increase of the absolute amount and was about 2–6 %, 2.3–4.3 % and 1.3–3.6 % of the administered dose levels (as read from figures). At each dose, there was a tendency for an increase of excretion during the first weeks.

7.1.3. In vitro data

The structural analogue 2-aminotoluene (2-AT, *o*-toluidine) was demonstrated to rapidly penetrate the human skin *in vitro* (Luersen *et al* 2006).

Incubations of fresh full-thickness human skin samples with 4-AT in vitro resulted in formation of the N-acetylated metabolite (Manevski et al 2014).

4-Hydroxymethylaniline and 4-aminobenzaldehyde were identified as metabolites of 4-AT in microsomal preparations from rabbit liver. Binding of 4-AT or its corresponding nitroso metabolite to haemoglobin (Hb) was observed in female rats after oral treatment with 0.6 mmol/kg (64 mg/kg) (Henschler 1990).

7.1.4. Toxicokinetic modelling

No publication on toxicokinetic modelling was retrieved.

7.1.5. Biological monitoring

4-AT was detected in blood and urine of non-occupationally exposed smokers and non-smokers. No differences in urinary 4-AT concentration could be detected between non-smokers and smokers. The mean level of Hb adducts of 4-AT in blood of male cigarette smokers was - depending on the type of tobacco smoked - 50–100 % higher than in that of non-smokers (Henschler 1990). In theory, the induction of methaemoglobinaemia might be used for biological monitoring. However, this requires a measurement immediately after blood sampling. As the MHb-reductase is active in erythrocytes, measurement results of MHb will rapidly change upon sample storage.

A general means of biological monitoring of aromatic amines is the determination of haemoglobin adducts. Analytical methods for quantification of haemoglobin adducts have been validated (DFG 2000; see also chapter 6). However, no data from human field studies are available so far to suggest a BLV or BGV.

7.2. Acute toxicity

The main symptom of acute toxicity is methaemoglobinaemia (MHb formation).

7.2.1. Human data

Smyth (1931) noted that toluidine (isomer not specified) causes strangury, haemoglobinuria and anaemia with symptoms similar to aniline poisoning, but with less pronounced methaemoglobinemia. lt is also reported, but without supporting details, that 40 ppm toluidines (176 mg/m^3, all isomers, no detailed data) will cause severe intoxication within 60 minutes and that 10 ppm (44 mg/m^3) may lead to symptoms of illness "if exposure continues for more than a short time" (Goldblatt 1955).

7.2.2. Animal data

Valid data on the inhalation toxicity of 4-AT were not available.

For oral administration (no details available), LD_{50} values of 620–794 mg/kg, 330–794 mg/kg and 270 mg/kg are reported for rats, mice or rabbits, respectively. For 4-AT hydrochloride, rat LD_{50} values of 1 285 mg/kg and 2 951 mg/kg are reported (ECB 2000). An LD_{50} of 890 mg/kg is reported for dermal application in rabbits (ACGIH 2001).

As with other anilines and similar aromatic amines, methaemoglobinaemia has been observed following administration of 4-AT. Oral (gavage) administration of 200 mg/kg

caused a MHb level of 21.7 % within one hour in rats; MHb levels of up to 40 % were observed 2–6 h after dermal application of 0.25–1.25 % 4-AT (ECB 2000).

The MHb forming ability of a series of aniline derivatives was compared in cats. At single equimolar intravenous doses (0.25 mmol/kg), 4-AT caused a mean MHb level of 39.6 % and was by a factor of 2 less potent than aniline (72.3 % MHb) (McLean *et al* 1969). MHb formation was slow in anaesthetised dogs after i.v. administration of 0.77 mmol/kg AT hydrochloride (111 mg/kg) and reached a MHb level of about 13 % after 8 hours (Kiese 1963).

7.3. Specific Target Organ Toxicity/Repeated Exposure

7.3.1. Human data

Methaemoglobinaemia has been observed in occupationally exposed workers (Section 7.7).

7.3.2. Animal data

7.3.2.1. Inhalation

No data are available.

7.3.2.2. Oral exposure

In a sub-acute feeding study, 10 male rats/group were fed diets containing 0, 165, 825 or 1650 ppm 4-AT (0, 13.8, 66.8, 125.7 mg/kg/day). There were no mortality and no clinical signs of 4-AT poisoning. Body weight gain was reduced at the highest dose and the relative liver weight was increased in mid- and high-dose animals. No gross lesions were observed at necropsy (Industrial Bio-Test Laboratories 1973). In a further study, male rats received 4-AT at doses of 0, 40, 80 and 160 mg/kg bw/day in two kinds of diet with 4 % or 14 % fat for 1 or 3 months (Jodynis-Liebert and Bennasir 2005). After 3 months, body weight gain was significantly and markedly lower at the highest dose in both diet groups and at the middle dose in the high-fat group. The MHb level in blood was between 1.2 and 1.5 % in controls and significantly increased at all dose levels in all groups after 1 and 3 months; MHb reached 3.7 and 3.6 % after one and 6.6 % and 4.2 % after 3 months at the lowest dose. In another experiment of the same working group (Malik-Brys and Senczuk 1995), a MHb-level of 7.5 % was reached at the same 4-AT doses after 6 months. The concentration of reduced glutathione in the liver significantly increased at all dose levels in all groups after 1 and 3 months. In parallel, hepatic lipid peroxidation increased compared to controls; the increase was lower at the highest dose. Alanine aminotransferase was slightly (< 1.8-fold) increased, especially after 3 months of high-fat diet. 4-AT had no effect on blood urea nitrogen (BUN), serum aspartate aminotransferase and sorbitol dehydrogenase. Other parameters were not investigated. No consistent differences between 4-AT and 2AT on the assessed parameters were evident except that 2AT but not 4-AT caused an increase in BUN. Only selected parameters were investigated in these studies, and morphology was not included.

According to OECD/SIDS (2005), there were no adequate repeated dose toxicity studies available for p-toluidine. 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) may be derived for rats. In studies over a period of 6 months dose-related (40 - 160 mg/kg bw/day) increases in methaemoglobin 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 methaemoglobin 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 (OECD/SIDS 2005).

7.3.2.3. Dermal exposure

Liver cell necrosis was observed in rats in a carcinogenicity study with subcutaneous application of 4-AT (Steinhoff and Dycka 1981, see Section 7.7.2).

7.3.3. In vitro data

No data is available.

7.4. Irritancy and corrosivity

7.4.1. Human data

4-AT has an aromatic, "wine-like" odour (NLM 2005). A value of 0.33 ppm (1.5 mg/m^3) is reported as olfactory threshold, without any further details (Falcy and Malard 2005).

7.4.2. Animal data

No data were available regarding respiratory irritation.

7.4.2.1. Skin

lt is reported that 4-AT caused no irritation requiring labelling in a standard test according to OECD guideline 404 (ECB 2000).

7.4.2.2. Eyes

In a standard test according to OECD guideline 405, 4-AT was irritating to the eyes of rabbits (ECB 2000).

7.4.3. In vitro data

No data is available.

7.5. Sensitisation

7.5.1. Human data

No data were available regarding sensitisation to 4-AT. However, cross-reactivity to 4-AT has been observed in epicutaneous tests with patients showing sensitisation to *p*-phenylenediamine (Kleniewska 1975).

7.5.2. Animal data

4-AT was tested in an occlusive epicutaneous test with guinea pigs. Induction was carried out with 2 % 4-AT in vaseline without adjuvant every second day for a total of four times. For the challenge reaction, 10 animals/group were treated with 0.1, 0.5, 1 and 2 % 4-AT in vaseline. Sensitisation (slight erythema) was observed in 0, 4, 6 and 8 of the animals. Further testing revealed cross-reactivity in animals sensitised to *p*-phenylenediamine (Kleniewska and Maibach 1980).

7.5.3. In vitro data

No data are available.

7.6. Genotoxicity

7.6.1. Human data

There were no data available.

7.6.2. Animal data

4-AT gave a positive response in a Drosophila "wing spot"- test at the highest feeding dose (5 mM) (ECB 2000). An increase in DNA strand breaks was observed in liver and kidney of male mice after i.p. administration of 35 mg/kg (Henschler 1990).

7.6.3. In vitro

4-AT or its hydrochloride did not induce mutations in the vast majority of tests with *Salmonella typhimurium* strains G46, TA98, TA100, TA1535, TA1537 and TA1538 and in *Escherichia coli* strains WP2, WP2 uvrA, C3706 and D3052 in the presence or absence of exogenous metabolic activation system. A positive response with 4-AT hydrochloride was observed in one study with *S. typhimurium* strain TA100 in the presence of S9 mix from induced hamster liver. 4-AT did not induce DNA repair in *E. coli* pol A. No mitotic crossing-over was induced in *Saccharomyces cerevisiae* D3, no mitotic gene conversion in *S. cerevisiae* D4 and no strand breaks in V79 Chinese hamster fibroblasts. 4-AT caused DNA damage in human lung cells and unscheduled DNA synthesis in rat hepatocytes (NLM 2005, 2006, Henschler 1990, ECB 2000).

4-Methylphenylhydroxylamine, a probable metabolite of 4-AT *in vivo,* was mutagenic in *S. typhimurium* strain TA98 with S9 mix and without S9 mix in TA100 in a fluctuation test in *E. coli* WP2 uvrA. Also, 4-methylphenylhydroxylamine induced mitotic crossing over in *S. cerevisiae* D4 (Henschler 1990).

According to OECD/SIDS (2005), 4-AT does not induce point mutations in the vast majority of Ames tests *in vitro*. In Chinese hamster lung cells 4-AT 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. OECD/SIDS (2005) summarised "some indication" for clastogenic activity *in vitro* and "some residual suspicion for such action" *in vivo*.

According to a note of NTP (2016), genetic toxicology testing in *Salmonella* has been completed, with negative results.

7.7. Carcinogenicity

7.7.1. Human data

Among 81 persons (62 men and 19 women, aged 22–55 years) employed in production of 2AT and 4-AT were 4 cases of bladder papilloma. Thirty-five of the workers were in production, 18 were fitters and 10 were cleaning personnel (no other details given); 9 persons had been exposed for less than 1 year, 31 between 1 and 5 years, 20 between 6 and 10 years, and 21 for more than 10 years. Concentrations of 4-AT in the air were not given; for 2AT air levels were 0.7–28.6 mg/m^3, 6–9 mg/m^3 in most samples [about 1–2 ppm]. Cystoscopic examination of 75 of the 81 workers revealed 2 cases of bladder papilloma, one being a 23-year-old worker who had been exposed for 1 year and 8 months only to 4-AT, and the other was a 49-year-old worker exposed to both substances for 23 years. Methaemoglobinaemia (6–19 %) was diagnosed in 20 persons. Of 16 employees who had been exposed for between 12 and 17 years, 6 had developed bladder tumours (4 carcinomas, 1 papilloma, 1 multiple papilloma) (Khlebnikova *et al* 1970). The problem of the study is the co-exposure with the known carcinogen 2AT and the lack of specific exposure data on 4-AT. Therefore, it is impossible to draw any specific conclusions on 4-AT from this study.

7.7.2. Animal data

Carcinogenicity studies with inhalation exposure were not available.

4-AT hydrochloride was fed to 25 male CD rats/group at concentrations of 1 000 and 2 000 ppm in the diet for 18 months. The higher dose is reported to represent the maximum tolerated dose (MTD). A number of other aromatic amines and nitro compounds were also tested in this study and for every 5 test substances a control group of 100 animals was used. There were no signs of toxicity and no increase in the incidence of any tumour (Weisburger *et al* 1978).

In the same study, male and female CD-1 mice (25/ sex and group) were fed diets containing 4-AT hydrochloride at either 1 000 ppm for 6 months followed by 500 ppm for 12 months or at 2 000 ppm for 6 months followed by 1 000 ppm for 12 months. The dose was adjusted since the MTD had been exceeded. Mice (n = 25) of each sex served as matched controls and groups of 99 males and 102 females as pooled controls. All animals were observed for 21 months. There was a significant increase in hepatic adenomas in males at both dose levels (low dose: 8/17, high dose: 9/19) and in females (unspecified "liver tumours") at the higher dose (3/17) (Weisburger *et al* 1978).

In the same study, the isomeric 2AT (*o*-toluidine) was clearly carcinogenic in male rats (subcutaneous fibromas and fibrosarcomas, bladder carcinomas, multiple tumours, pituitary and adrenal adenomas) and in male and female mice (haemangiosarcomas and haemangiomas). No clear effect was seen for 3AT (*m*-toluidine; Weisburger *et al* 1978).

In a further unpublished study, Sprague-Dawley rats were treated with 0, 25 and 75 mg/kg of 4-AT by subcutaneous injection in peanut oil once a week for 24 months. 4-AT treatment caused a decrease in body weight gain but no decrease in survival time. The number of malignant tumours at the site of injection was slightly increased at both dose levels in males and females. Also, the incidence of benign liver tumours was increased at the high dose (especially in females) (Steinhoff and Dycka 1981).

4-AT caused no papillomas or carcinomas at the site of application after treatment of female mice with one drop of a 20 % solution of 4-AT in dioxane on the skin of the back twice a week for 12 weeks (Henschler 1990).

7.8. Reproductive toxicity

7.8.1. Human data

No data were available. It may be anticipated that the formation of methaemoglobin by 4-AT exposures that are consistently higher than the proposed OEL could lead to secondary developmental toxicity.

7.8.2. Animal data

Oral administration of 200 mg/kg/day is reported to inhibit DNA synthesis in mouse testicular tissue (ACGIH 2001). Further data were not available.

According to OECD/SIDS (2005), 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.

7.9. Mode of action and adverse outcome pathway considerations

A comparison by OECD/SIDS (2005) of the intrinsic toxicological properties of m-toluidine with these properties of 4-AT (p-toluidine) showed that m-toluidine is more potent in methaemoglobin forming than the p-isomer. Taking into account that methaemoglobinemia 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 isomeric substances methaemoglobinemia 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 an inconsistency that is typical for aromatic amines.

7.10. Lack of specific scientific information

The toxicological database for 4-AT is limited. There are no epidemiological studies on exposed industrial cohorts, and biomonitoring studies on exposed cohorts are lacking as well. There is also only limited information on carcinogenicity, and almost no information on reproductive toxicity.

8. GROUPS AT EXTRA RISK

There is no specific information regarding groups at extra risk.

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