The MAK Collection for Occupational Health and Safety

Aniline

MAK Value Documentation, addendum – Translation of the German version from 2018

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Aniline[1)]

MAK Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value) for aniline [62-53-3]. Available publications and unpublished study reports are described in detail. Healthy male and female volunteers showed increased methaemoglobin values in a 6-hour-inhalation-study with exposure to 2 ml aniline/m^3. The median methaemoglobin augmentation was 0.5% from the base level of 0.7% to 1.2% methaemoglobin. Even taking into account the highest observed increase of methaemoglobin, 8 hour-exposure time and the increased respiratory volume at the workplace, a methaemoglobin value of more than 5% would not be expected. Based on this, the MAK value for aniline of 2 ml/m^3 (7.7 mg/m^3) is confirmed. Aniline is still assigned to Peak Limitation Category II, because systemic effects are critical and the excursion factor of 2 is confirmed. Skin contact is expected to contribute significantly to the systemic toxicity. Therefore, the designation with an "H" is confirmed. Aniline continues to be designated with "Sh" and assigned to Carcinogenicity Category 4.

Keywords

aniline; aminobenzene; C. I. 76000; phenylamine; benzenamine; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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1) The substance can occur simultaneously as vapour and aerosol.

2

Aniline[1)]

[62-53-3]

Supplement 2018

MAK value (1983)	**2 ml/m³ (ppm) ≙ 7.7 mg/m³**
Peak limitation (2002)	**Category II, excursion factor 2**
Absorption through the skin (1981)	**H**
Sensitization (2006)	**Sh**
Carcinogenicity (2006)	**Category 4**
Prenatal toxicity (2006)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value (2015)	**500 µg aniline (after hydrolysis)/l urine**
BLW (2015)	**100 µg aniline (released from haemoglobin conjugate)/l blood**
Vapour pressure	0.68 hPa (IFA 2016)
log K_{OW}[2)]	0.9 (IFA 2016)
Solubility	36 g/l water (IFA 2016)
1 ml/m³ (ppm) ≙ 3.864 mg/m³	**1 mg/m³ ≙ 0.259 ml/m³ (ppm)**

There is documentation from 1992 available for aniline (documentation "Aniline" 1993) and supplements for peak limitation (supplement "Aniline" 2010 a), for a re-evaluation (supplement "Aniline" 2010 b) and for prenatal effects (supplement "Anilin" 2012, available in German only).

In 2016, the Commission began using a revised approach for assessing substances with a MAK value based on systemic effects and derived from inhalation studies in animals or studies with volunteers at rest; this new approach takes into account that the respiratory volume at the workplace is higher than under experimental condi-

1) The substance can occur simultaneously as vapour and aerosol.

2) octanol/water partition coefficient.

tions. However, this does not apply to gases or vapour with a blood:air partition coefficient < 5 (see List of MAK and BAT Values, Sections I b and I c). According to the formula of Buist et al. (2012), the blood:air partition coefficient of aniline at a vapour pressure of 0.68 hPa is 13 000. This supplement evaluates whether the MAK value for aniline needs to be re-assessed as a result of the higher respiratory volume at the workplace.

In addition, there is a new volunteer study available with inhalation exposure to aniline concentrations of 2 ml/m^3.

1 Toxic Effects and Mode of Action

Aniline leads to the formation of methaemoglobin in humans and experimental animals.

In an inhalation study in volunteers exposed to aniline concentrations of 2 ml/m^3 for 6 hours, the methaemoglobin concentration in blood reached an average level of 1.2% methaemoglobin (MetHb) and increased on average by 0.5% and a maximum 1.35% in comparison with the control values.

In a study of the developmental toxicity of aniline, increased liver weights and changed haematological parameters were observed in the foetuses of rats given gavage doses of 100 mg/kg body weight and day for 2 weeks.

Aniline can cause contact allergy in humans. The results from in vitro studies and animal experiments indicate a low contact sensitization potential. There are no data available for respiratory sensitization.

Aniline induces tumours in the rat spleen and was found to have mutagenic potential in rats and mice, but no mutagenic effects on germ cells.

2 Mechanism of Action

A detailed presentation of the effects of aniline can be found in the documentation from 1992 (documentation "Aniline" 1993) and the supplement from 2007 (supplement "Aniline" 2010 b).

The effect of aniline manifests itself primarily in the erythrocytes, as the dose-dependent, reversible formation of methaemoglobin (MetHb). Irreversible haemichromes can develop from MetHb and precipitate as Heinz bodies. Secondary effects of the damage to erythrocytes can be observed in the spleen of rats. These include swelling, inflammation, hyperplastic and fibrotic changes of the splenic stroma, extramedullary erythropoiesis, oxidative stress and spleen tumours. Due to physiological differences, effects on the spleen of humans occur to a markedly lesser extent.

Apart from the process of MetHb formation, the aniline metabolite nitrosobenzene is responsible for the formation of the haemoglobin adduct (Hb adduct) as a result of covalent binding to SH groups of the globin.

In about 50% of Europeans, the activity of *N*-acetyltransferase type 2 is low ("slow acetylators"); in slow acetylators the main route of detoxification, *N*-acetylation of the amino group of aniline, is less efficient. This leads to increased Hb adduct for-

mation, which varies between slow and fast acetylators by a factor of 9. In a study with 9 employees, 2 of whom had a glucose-6-phosphate-dehydrogenase deficiency, it was shown on the other hand that glucose-6-phosphate-dehydrogenase deficiency did not affect the formation of the aniline–Hb adduct. Due to the low number of workers, no unequivocal statement can be made (Lewalter and Korallus 1985; Nebert et al. 2013; supplement "Aniline" 2010 b).

After 4-week inhalation exposure to aniline concentrations of 0, 15 or 45 ml/m^3 or oral administration of 0, 10 or 100 mg/kg body weight to groups of 5 female and 5 male Wistar-(CrI:WI(Han)) rats, weak changes in the plasma metabolome occurred, which were more pronounced after oral administration. The liver and testis were identified as the target organs (Fabian et al. 2016). Effects on the plasma metabolome are attributed to systemic toxicity.

Mechanism of the formation of tumours in the spleen of the rat

Erythrotoxic aniline doses lead to the release of iron in the rat spleen, whereby DNA damage can occur as a result of oxidative stress, which in turn is co-responsible for the formation of tumours (supplement "Aniline" 2010 b).

Studies with groups of 6 male rats given aniline in the drinking water showed that the induced oxidative DNA damage in the spleen was accompanied by increased base excision repair (BER) (see Section 5.6.2; Ma et al. 2008, 2011, 2013).

In addition, the administration of aniline doses of 0.5 mmol/kg body weight and day (about 46.57 mg/kg body weight) in the drinking water led to the activation of transcription factor Ap-1 in the spleen and to the increased phosphorylation of various mitogen-activated protein kinases (MAPK) in nuclear extracts of the spleen (Khan et al. 2006).

Furthermore, after administration of aniline in the drinking water, the increased expression of cyclins and cyclin kinase 1 (CDK1), and a decrease in CDK1 inhibitors were observed. The authors conclude that there is an accelerated G2/M phase transition, which can contribute to the formation of the tumours (Wang et al. 2015).

Groups of 6 male Sprague Dawley rats were given aniline doses of 0 or 1 mmol/kg body weight and day (about 93.13 mg/kg body weight) in the drinking water by gavage for 1, 4 or 7 days. After 4 and 7 days, both the mRNA expression and the protein expression of the enzyme haemoxigenase-1 were significantly increased, mainly in the red pulp of the spleen. This was accompanied by an increase in the iron level (free and total) and in the ferritin concentration, which is indicative of a pro-oxidative mechanism (Wang et al. 2010).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Aniline is taken up readily by inhalation, ingestion and also through the skin from the liquid and gaseous phases, then rapidly absorbed and metabolized.

Aniline vapour was dermally absorbed by naked test persons at the same rate as after inhalation-only exposure at a respiratory volume of 418 l/h under resting conditions. The usual respiratory volume is 10 m^3/8 hours (1250 l/h). If this is taken

into account, absorption of aniline by inhalation is about 3 times higher than after dermal absorption. Wearing work clothes reduced absorption through the skin by 42%. Thus, under working conditions (increased respiratory volume, protective clothing) about 19% (418/1250 × (100%–42%)) is absorbed through the skin. With higher humidity and temperature, dermal absorption is about 20% higher. About 25% of the total absorption thus takes place via the skin (documentation "Aniline" 1993; supplement "Aniline" 2010 b).

Analysis of the aniline in the urine and of the aniline–haemoglobin adducts in the blood of workers in the rubber industry revealed that the amount of aniline absorbed through the skin was higher in persons with erythema on the hand and forearm (see Section 4.2; Korinth et al. 2007).

A comparison of the mathematically derived prediction for the amount of aniline absorbed through the skin with data from in vitro experiments in human skin yielded fluxes of 725.2 ± 213.5 µg/cm² and hour (in vitro; Wellner et al. 2008), 677.9 µg/cm² and hour (Fiserova-Bergerova et al. 1990), 76.6 µg/cm² and hour (Guy and Potts 1993) and 112.8 µg/cm² and hour (Wilschut et al. 1995). The authors of the comparative study note that the mathematical models can both overestimate and underestimate absorption in in vitro experiments; in their opinion, in the case of aniline, the flux value tends to be underestimated (Korinth et al. 2012). From the experimentally determined value, an absorbed amount of 1450 mg is calculated for the exposure of 2000 cm² of skin and an exposure duration of one hour.

3.2 Metabolism

In the documentation from 1992 (documentation "Aniline" 1993) and the supplement from 2007 (supplement "Aniline" 2010 b) it was shown in detail that aniline is metabolized by ring hydroxylation and *N*-hydroxylation as well as by *N*-acetylation.

Humans

In urine samples from 31 persons not occupationally exposed to aniline, the metabolites *N*-acetyl-4-aminophenol (median value 80 µg/l) and *N*-acetyl-2-aminophenol (median value 2071 µg/l) were detected, but not the metabolite acetanilide. In the urine of 6 workers occupationally exposed to aniline, all three metabolites were found with median values of 5720 µg *N*-acetyl-4-aminophenol/l, 918 µg *N*-acetyl-2-aminophenol/l and 78.7 µg acetanilide/l. The occupational exposure concentration for these 6 persons was below the MAK value of 2 ml/m³ (no other details). From these data the authors conclude that the detection of *N*-acetyl-4-aminophenol and *N*-acetyl-2-aminophenol in urine is not necessarily an indicator of exposure to aniline (Dierkes et al. 2014).

In the plasma of a female patient, 11 hours after the ingestion of an unknown amount of aniline, concentrations of aniline of 0.13 mg/l and of the metabolites acetanilide and acetaminophen of 0.79 mg/l and 2.3 mg/l, respectively, were found. In her urine, levels were detected of 3.2 mg/l for aniline, 4.3 mg/l for acetanilide, 106 mg/l for acetaminophen and 315 mg/l for acetaminophen conjugates (Iwersen-Bergmann and Schmoldt 2000).

Rats

In primary hepatocytes from female SD rats, incubation with 1 mM aniline for half an hour led to *p*-aminophenol concentrations of 300 nM/10^6 cells as well as 2 to 10 times higher concentrations of the metabolites *N*-acetyl-4-aminophenol, acetanilide, 4-aminophenol-glucuronide and phenylhydroxylamine sulfate. Only traces of the metabolite *N*-acetyl-4-aminophenol-glucuronide were found (Noguchi et al. 1996). Detailed information on the incubation conditions, which would be required for quantification of the metabolite concentrations, is lacking.

4 Effects in Humans

A cross-sectional study with 1004 volunteers who had been asked to participate by the Bavarian health offices, yielded a mean urinary aniline concentration of 5.44 µg/l (range 0.1–384.04 µg/l; median value 3.05 µg/l; 95th percentile 14.5 µg/l). There were differences in the urinary aniline concentrations between women (4.22 µg/l) and men (6.4 µg/l), although there were practically no differences between smokers (4.76 µg/l) and non-smokers (5.16 µg/l). Aniline was found in 93.9% of the urine samples. The detection limit was 0.1 µg/l (Kütting et al. 2009). From this study, a reference value of 14.5 µg aniline/l urine was derived for non-smoking adults (no other details; Umweltbundesamt 2011).

In earlier population studies, the median aniline values were between 0.8 and 3.7 µg/l urine. A major portion (75%–86%) of the aniline ingested is eliminated in the urine as acetoaminophen (Modick et al. 2014).

4.1 Single exposures

In the documentation from 1992 (documentation "Aniline" 1993) cases of acute intoxication were described in which the symptoms that occurred could be attributed to methaemoglobinaemia.

After intoxication by an unknown amount of aniline (a maximum 4 ml in a soft drink, consumed by two persons together), one person collapsed 15 minutes after the intake; the MetHb level later determined was 66.7%. The MetHb level in the other person determined 45 minutes after the intake of aniline was 49.5% (no other details; Kusin et al. 2012).

In a case of intoxication following the intake of an unknown amount of aniline the female patient's MetHb level after 3.5 hours was 35%, and Heinz bodies (2 per 1000 erythrocytes) were found in her blood. The patient collapsed, and suffered from a headache and cyanosis. The plasma aniline level 11 hours after ingestion was 0.13 mg/l and the concentrations of the aniline metabolites acetanilide and acetaminophen were 0.79 mg/l and 2.3 mg/l, respectively. The levels found in urine were 32 mg aniline/l, 4.3 mg acetanilide/l, 106 mg acetaminophen/l and 315 mg acetaminophen conjugates/l. The metabolite phenylhydroxylamine, which is responsible for the formation of MetHb, could not be detected (Iwersen-Bergmann and Schmoldt 2000).

The uptake of an unknown amount of aniline from a shoe polish by a 69-year-old woman led to signs of cyanosis, but not to dyspnoea. The MetHb level in blood was 33.5% and even after repeated administration of methylene blue decreased only slightly to 21.7%. The activity of MetHb reductase was 3.3 IU/g Hb (background range: 2.5–5.3 IU/g Hb) and that of glucose-6-phosphate dehydrogenase 12.6 U/g Hb (maximum 10 U/g Hb) (ECHA 2016).

After inhalation of aniline, a female student's MetHb level was 38.3%, and cyanosis, a headache, dizziness and sinus tachycardia occurred. One day later, after the administration of 1.7 mg methylene blue/kg body weight, the MetHb level in her blood was down to merely 0.5%. The *p*-aminophenol level in the urine was 2.16 mg/l and decreased to 0.77 mg/l within 3 days (ECHA 2016).

In a volunteer study, 19 persons were exposed to aniline concentrations of 2 ml/m^3 for a total of 6 hours, in intervals of 2 hours with 15-minute breaks. During the exposure, they exercised on a bicycle ergometer three times for 20 minutes each at a respiratory volume of 30 l/min (median value 33 l/min, 22–39 l/min). The aniline concentration in the exposure chambers was monitored at two-second intervals using a mass spectrometer. During the exposure, the methaemoglobin level in blood was determined every two hours, and 2, 4, 6, 18 and 42 hours after the end of exposure. The aniline concentrations in urine were also determined every two hours during the exposure and 2, 4, 6, 14, 18, 42 and 66 hours after the end of exposure during the follow-up period. The group of volunteers consisted of 10 male (age: 26–59 years) and 9 female (age: 23–53 years) persons. The 19 volunteers comprised 15 slow and 4 fast acetylators. The MetHb levels determined at 5 sampling times within 5 days in 4 male and 4 female persons not exposed served as controls. The MetHb levels and urinary aniline concentrations are presented in Table 1. In the main study, the exposure to aniline led to an average increase in the blood MetHb level from 0.72% ± 0.19% to 1.21% ± 0.29%. The individual peak value was 2.07% MetHb. After the exposure, the MetHb level in blood decreased with a half-life (presumably terminal) of about 18 hours. With regard to MetHb formation, there was no difference between male and female volunteers, or between fast and slow acetylators. The half-life for the elimination of aniline in urine was 5 hours. Table 1 also shows the data from a preliminary study, in which 2 male and 2 female volunteers (slow acetylators) were exposed to aniline concentrations of 2 ml/m^3 for 8 hours, in intervals of 2 hours with breaks of 15 minutes. The follow-up period in the preliminary study was 24 hours. The preliminary study showed that after exposure for 6 hours a plateau was reached and no further increase in the formation of MetHb could be observed. The authors suggested as an explanation a steady-state between MetHb formation and the degradation of MetHb by the MetHb reductase in erythrocytes. All volunteers were non-smokers. No adverse effects on health such as skin, eye and airway irritation or cyanosis were observed in any of the volunteers (Käfferlein et al. 2014 a, b).

In the main study, taking into consideration the mean base level of 0.72% MetHb, a maximum value of 1.35% (2.07% – 0.72% = 1.35%) for the increase in MetHb induced by aniline was obtained. The peak aniline concentration in urine was 418.3 µg/l and thus below the BAT (biological tolerance) value of 500 µg/l urine (Drexler and Hartwig 2017; Käfferlein et al. 2014 b).

Unlike in the preliminary study, no plateau was observed for the increase in the MetHb level caused by the exposure, so that linear extrapolation from the 6-hour exposure in the experiment to an 8-hour exposure at the workplace is required. The MetHb levels extrapolated to 8 hours are about 1.4% (mean value) and about 2.52% (maximum value). The maximum value expected for the aniline-induced increase in MetHb after 8 hours is therefore 1.35% × 8/6 = 1.80%.

4.2 Repeated exposure

In a cohort of 51 workers from three plants of a supplier to the automotive industry who were exposed to aniline and *o*-toluidine, an investigation was carried out as to whether skin lesions are responsible for increased absorption of aromatic amines. Of the workers, 41 (82%) had visible erythema and/or scaling on both hands and/or forearms. Determination of the exposure by personal air sampling according to the NIOSH method No. 2017 yielded mean values in non-smokers of 6.6 µg aniline/m³ (range 1.0–37.4 µg/m³, median value 2.5 µg/m³) and in smokers of 6.7 µg aniline/m³ (range 0.3–48.3 µg/m³, median value 3.3 µg/m³). The aniline levels were on average 12.7 and 11.8 µg/l urine, respectively. The Hb adduct levels in non-smokers were on average 1213 ng/l blood (range 367–2662 ng/l, median value 1112 ng/l) and in smokers 1042 ng/l blood (range 351–2584 ng/l, median value 933 ng/l). Workers with skin erythema (no differentiation between non-smokers and smokers) were found to have higher Hb adduct levels (1150.4 ng/l blood) than workers with intact skin (951.7 ng/l blood) ($p = 0.035$). Scaling of the skin had no effect on absorption (Korinth et al. 2007).

4.3 Local effects on skin and mucous membranes

There are still no data available.

4.4 Allergenic effects

The skin sensitization potential of aniline is low (supplement "Aniline" 2010 b).

Only a few recent clinical findings of skin sensitization by aniline have been published since the supplement of 2007. In an investigation carried out in Poland, a total of 7125 patients with suspected allergic contact dermatitis were tested in the period from January 2000 to December 2006. In 253 of them (99 of 2071 men, 4.8%; 154 of 5054 women, 3.1%) positive results were obtained in the patch tests with *p*-phenylenediamine (PPD). Co-reactivity was observed mainly with benzocain (in 16.9% of the women and 11.1% of the men) and *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine (IPPD; 3.9% of the women and 37.4% of the men), but without simultaneous reactivity to both substances. Of the 7125 patients tested consecutively, 110 were tested also with 1% aniline; a positive result was obtained in 16 cases and of these only one case without a reaction to PPD. Of the 15 patients with simultaneous reactions to aniline and PPD, 6 also reacted to IPPD and 5 to benzocain, but again none to both substances. The authors reported two cases of sensitization to PPD from tattoos containing PPD in adolescents (with 3+ and 1+ reactions to PPD, re-

Table 1 MetHb levels in the blood and aniline levels in the urine of volunteers after exposure to 2 ml aniline/m³ (Käfferlein et al. 2014 a)

	Exposure	Follow-up period	MetHb	Range	Aniline/urine	Range
controls	–		0.58 ± 0.15%	0.2–1.0%	no data	
preliminary study, n = 4	0 hours		0.21 ± 0.09%	no data	no data	about 0–10 µg/l
	6 hours		1.21 ± 0.29%	0.9–1.57%	no data	about 80–120 µg/l
	8 hours		1.15 ± 0.21%	no data	no data	
	8 hours	0–2 hours[a)]	no data	no data	168.9 ± 80.2 µg/l	138.9–305.6 µg/l
main study, n = 19	0 hours		0.72 ± 0.19%	no data	5.7 ± 3.8 µg/l	no data
	6 hours		1.21 ± 0.29%	0.8–2.07%	168 ± 51.8 µg/l	79.5–418.3 µg/l
	6 hours	18 hours	0.65 ± 0.18%	< 0.8–1.1%	17 ± 17.1 µg/l	no data
	6 hours	42 hours	no data	< 0.8–0.83%	10.2 ± 12.4 µg/l	no data

[a)] analyses took place at different time points
MetHb: methaemoglobin

spectively). Both produced a 1+ reaction to aniline, and in the case of the younger patient with the more pronounced reaction to PPD the reaction to aniline was still evident even at the reading on day 7 (Rudzki and Rebandel 2007).

There are still no data available for respiratory sensitization.

4.5 Reproductive and developmental toxicity

There are still no data available.

4.6 Genotoxicity

There are still no data available.

4.7 Carcinogenicity

The results of animal studies led to the suspicion that aniline could induce spleen tumours. To date, no abnormalities have been described for the human spleen. Systematic epidemiological studies are not available for this aspect (supplement "Aniline" 2010 b).

The frequently quoted suspicion that exposure to aniline causes bladder cancer could not be confirmed in earlier cohort studies or could not be unequivocally attributed to aniline alone because of exposure to a mixture of substances (SCOEL 2010, 2015).

In a cohort consisting of 2160 male production workers employed in a chemical factory (rubber industry) in Wales, mortality (1955–2005) and the incidence of bladder cancer (1971–2005) were investigated. The workers in the production department were exposed to aniline, 4-mercaptobenzothiazole, phenyl-β-naphtylamine and *o*-toluidine. In a subcohort of 422 workers with workplaces at which only aniline was used, there were 15 cases of bladder cancer. This is a significant increase compared with the number of expected cases of 6.11 ($p < 0.01$; standardized registration ratio (SRR): 245; 95% confidence interval (CI): 137–405). The expected cases were calculated from the incidence in the populations in England and Wales. The relative risk (RR) increased with the increasing length of employment. Remaining at workplaces exposed to aniline for more than five years resulted in a significantly increased RR of 2.22 (95% CI: 1.13–4.36). Likewise, in this subcohort, mortality was significantly increased with 8 deaths compared with the expected 2.89 deaths ($p < 0.05$; standardized mortality ratio (SMR): 277; 95% CI: 119–545). The exposure concentrations were not determined (Sorahan 2008). Possible additional exposures to, for example, aniline impurities or other additives in the production process, were not determined. Therefore, also from this study, no clear relationship between aniline exposure and bladder cancer can be established.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

Single doses in the LD_{50}/LC_{50} range led, after inhalation, ingestion or dermal absorption, to cyanosis, as a result of methaemoglobinaemia, and the associated signs in various species. A detailed presentation can be found in the earlier documentation (documentation "Aniline" 1993; supplement "Aniline" 2010 b).

A comparative inhalation study in dogs with whole-body exposure and head-only exposure showed that dermal absorption contributes substantially to the intensity and course of the intoxication with aniline by inhalation. The MetHb levels induced by aniline in the blood of the dogs were 3.5 times higher after whole-body exposure (35%) and persisted for longer than after head-only exposure (Pauluhn 2005; supplement "Aniline" 2010 b).

A spongy change in the spinal cord white matter resulting from the myelin sheath splitting could be observed in 4-week-old Crl:CD (SD) IGS rats given single gavage doses of aniline in olive oil of 1000 mg/kg body weight. The effect is thought to be associated with the decrease in anti-2′,3′-cyclic nucleotide-3′-phosphodiesterase or 2′,3′-cyclic nucleotide 3′-phosphohydrolase (CNPase). In addition, all animals exhibited cyanosis 2 to 5 days after the administration; the signs disappeared after day 5 (Kanno et al. 2010; Okazaki et al. 2001).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

The studies available for repeated inhalation exposure were described in the documentation from 1992 (documentation "Aniline" 1993). These studies with rats yielded a NOAEC (no observed adverse effect concentration) of 10 ml aniline/m^3 after 4 or 5-day exposure and after 2-week exposure.

In another study with rats exposed to aniline for 2 weeks, haemosiderosis and slight, but significantly increased extramedullary haematopoiesis occurred at concentrations of as little as 8.5 ml/m^3 (supplement "Aniline" 2010 b; Pauluhn 2004).

There are no new data available.

5.2.2 Oral administration

The studies available to date for repeated oral administration were presented in detail in the supplement from 2007 (supplement "Aniline" 2010 b).

In a 2-year feeding study with rats, the LOAEL (lowest observed adverse effect level) was about 7 mg aniline/kg body weight and day, based on the effects haemosiderosis and haematopoiesis in the spleen of the animals and haematological changes (decreased: erythrocyte count, haemoglobin and haematocrit; increased: MetHb levels, mean corpuscular volume and reticulocyte count) (supplement "Aniline" 2010 b; CIIT 1982).

In a 28-day study with rats the LOEL (lowest observed effect level) of 4 mg aniline/kg body weight and day was based on a dose-dependent and linear increase in

Hb adducts in the blood of the animals, the occurrence of Heinz bodies and vascular congestion in the spleen (supplement "Aniline" 2010 b; Mellert et al. 2004; Zwirner-Baier et al. 2003).

In all other studies with rats, higher doses were used, and effects on the spleen occurred even at the lowest tested doses in each case. In the feeding studies, mice were found to be significantly less sensitive than rats (supplement "Aniline" 2010 b).

In male and female Wistar rats (3 animals per group) given 100 mg aniline/l drinking water for 30 days, significantly increased spleen and liver weights were determined (Khan et al. 2014). Because the data for other parameters are incomplete, this study is not regarded as valid.

There are no other new data available.

5.2.3 Dermal absorption

There are still no data available.

5.3 Local effects on skin and mucous membranes

Aniline was irritating to the rabbit skin and caused damage to the rabbit eye, with corneal clouding (supplement "Aniline" 2010 b).

5.4 Allergenic effects

There are no data available for more recent animal experiments. However, findings with aniline were obtained in the validation process of some in vitro methods:

In the myeloid U937 skin sensitization test (MUSST) with U937 cells, a value of about 333 µM was determined for the 1.5-fold increase in CD86 expression (EC150) (Natsch et al. 2013).

The results reported for the human cell line activation test (hCLAT) were also positive. The EC150 value for CD86 expression in this test was about 551 µM. A value of about 928 µM was given as the concentration leading to a doubling of CD54 expression (EC200). This value is already close to the cytotoxic concentration range, because a concentration of 930 µM was determined as the CV75 value, which is the concentration at which 75% of the cells are viable (Takenouchi et al. 2015).

The KeratinoSens assay, on the other hand, yielded negative results up to concentrations of 2000 µM (Natsch et al. 2013).

In the direct peptide reactivity assay (DPRA) with aniline, no reactivity to the cysteine-containing model peptide used was found. For the lysine-containing peptide, depletion amounted to somewhat less than 10% (Natsch et al. 2013). According to another investigation there was a decrease in the lysine peptide by 48.4%; however, the determination by HPLC (high performance liquid chromatography) was disturbed by co-elution with the test substance. In this study, 4-chloroaniline and *N*,*N*-dibutylaniline showed no reactivity to the two peptides (Takenouchi et al. 2015).

Likewise, in a quantum mechanistic model of structure–activity relationships of the skin sensitizing effects of aniline derivatives and phenol derivatives, a skin sen-

sitizing potential was found for aniline similar to that of 4-chloroaniline. However, both substances were already contained in the training set of the model. From a mechanistic viewpoint, the authors discussed mechanisms with either a direct reaction with free radicals or one taking place after oxidation as well as one where reactive intermediates bind to nucleophilic moieties on proteins through the Michael addition (Ouyang et al. 2014).

5.4.1 Sensitizing effects on the skin

In the maximization test and in the single injection adjuvant test (SIAT), aniline was found to have skin sensitizing effects. However, in the local lymph node assay (LLNA), negative or only weakly positive results were obtained, and in the popliteal lymph node assay, negative results were described (supplement "Aniline" 2010 b).

5.4.2 Sensitizing effects on the airways

There are still no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

In long-term feeding studies, no effects on the reproductive organs of rodents were found. There are, however, no multi-generation studies available for the determination of the effects of aniline on fertility (supplement "Aniline" 2010 b).

5.5.2 Developmental toxicity

In a study of prenatal and postnatal toxicity in F344 rats given gavage doses of aniline-HCl of 0, 10, 30 or 100 mg/kg body weight and day for two weeks, the NOAEL (no observed adverse effect level) for developmental toxicity was 10 mg/kg body weight and day. The foetuses of rats given 100 mg/kg body weight and day were found to have increased relative liver weights, an increased mean erythrocyte volume (MCV) and decreased red cell distribution width (RDW) values; the haematological parameters were determined only for this dose. No teratogenic effects were seen up to the highest dose tested of 100 mg/kg body weight and day. However, the NOAEL of 10 mg/kg body weight and day can be interpreted as the worst case. Maternal toxicity was found at 10 mg/kg body weight and day with increased relative spleen weights (supplement "Anilin" 2012, available in German only; Price et al. 1985).

In the chicken embryo test with embryos from White Leghorn hens which were given injections of aniline in acetone (total volume 5 µl) of 0, 1.1, 2.2, 4.3, 8.6 or 17.0 µmol/egg, increased teratogenicity was found in 17% of the embryos at aniline concentrations of 2.2 µmol and above. The effects increased with increasing doses (Korhonen et al. 1983). The test system, however, has not yet been validated.

5.6 Genotoxicity

5.6.1 In vitro

Aniline did not induce gene mutations in bacterial mutagenicity tests. In mammalian cells, chromosomal aberrations were observed, and an HPRT test yielded positive results. The available positive results of the $TK^{+/-}$ tests could not be attributed unequivocally to gene mutations (supplement "Aniline" 2010 b).

5.6.2 In vivo

In vivo studies with aniline demonstrated a genotoxic potential in chromosomal aberration and micronucleus tests with rats and mice. There is evidence that the clastogenic effects are causally related to the erythrocyte toxicity documented for aniline. A detailed description of the in vivo genotoxicity studies can be found in the supplement from 2007 (supplement "Aniline" 2010 b).

In the spleen of 6 male Sprague Dawley rats, the administration of aniline doses of 0.5 mmol/kg body weight and day (about 46.57 mg/kg body weight) in the drinking water for 30 days caused significantly increased oxidative DNA damage, detected in the form of 8-hydroxy-2′-deoxyguanosine (8-OHdG), compared with the findings in the control group (only drinking water, n = 6). The DNA repair activity detected as OGG1 base excision repair (BER) was increased 1.3-fold in the nuclear protein extracts in the spleen and 1.2-fold in the mitochondrial protein extracts. A 1.25-fold increase in the BER activity associated with Nei-like DNA glycosylases (NEIL1/2) was found in the nuclear extracts of the spleen of treated rats. The BER activity mediated by endonuclease III homologue 1 (NTH1) and apurinic/apyrimidinic endonuclease 1 (APE1) was likewise significantly increased in the nuclear extracts of the spleen of treated rats (Ma et al. 2008, 2011, 2013).

The administration of aniline doses of 1 mmol/kg body weight and day (about 93.13 mg/kg body weight) in the drinking water for 4 or 7 days led to increased haemoxigenase-1 levels in the spleen, accompanied by an increase in iron and ferritin levels. This indicates that the DNA damage in the spleen caused by aniline is the result of a pro-oxidative mechanism (see Section 3.2; Wang et al. 2010).

In the bone marrow cells of female and male Crl-CD-1(ICR)BR mice given two intraperitoneal injections of 300 mg/kg body weight, the number of micronuclei was increased. No effects were seen after two injections of 0, 30 or 100 mg/kg body weight (ECHA 2016).

There is an eye mosaic assay available; positive results were obtained only at toxic doses. The result can therefore not be interpreted as a purely genotoxic effect and is thus of limited meaningfulness (Vogel and Nivard 1993).

5.7 Carcinogenicity

There are no new data available.

In the documentation from 1992 and the supplement from 2007 (documentation "Aniline" 1993; supplement "Aniline" 2010 b) aniline was extensively shown to be carcinogenic in rats but not in mice, although in the long-term feeding study in

mice, the doses used, in relation to the body weight, were 5 times higher than those used in the study in rats. The reasons for this species specificity could be the markedly higher Met-Hb reductase activity in the erythrocytes and the more effective elimination of aniline in the mouse compared with the elimination capacity in the rat.

6 Manifesto (MAK value/classification)

The critical effects are MetHb formation in humans and the erythrocyte toxicity with accompanying effects in the spleen of rats.

MAK value. An increase in the MetHb concentration in humans beyond 1.5% is to be regarded as a marker for exposure to MetHb formers. Adverse health effects are not to be expected up to a MetHb level of 5% (Drexler and Greim 2008).

The volunteer study showed that after 6-hour exposure to 2 ml/m^3 the MetHb level in blood increased from 0.72% to a mean MetHb value of 1.2%. The maximum value for the increase induced by aniline was 1.35% (2.07% – 0.72% = 1.35%). In the preliminary study, the peak MetHb value was reached after 6 hours (Käfferlein et al. 2014 a). No plateau was seen in the main study, however, so that linear extrapolation to 8 hours is justified (Käfferlein et al. 2014 b). The maximum value for the increase in MetHb after 8 hours is thus 1.8% (1.35% × 8/6). During one sixth of the exposure period, the volunteers exercised on a bicycle ergometer with a respiratory volume of 30 l/min; assuming a respiratory volume at rest of 9 l/min, the average respiratory volume was therefore 12.5 l/min. Assuming a respiratory minute volume of 21 l/min (= 10 m^3/8 hours), linear extrapolation would result in an increase in the MetHb level due to aniline of 1.8% × 21/12.5 = 3%. Even when the higher respiratory volume at the workplace is taken into account, the formation of MetHb in blood after exposure to an aniline concentration of 2 ml/m^3 remains below the critical value of 5%. Absorption of aniline vapour through the skin has also been taken into consideration here. In view of the low MetHb increase in volunteers, the MAK value of 2 ml/m^3 has been retained.

Peak limitation. As systemic effects are the main effects relevant to the derivation of the MAK value, the substance remains classified in Peak Limitation Category II with an excursion factor of 2 (see supplement "Aniline" 2010 a).

Prenatal toxicity. As the MAK value of 2 ml/m^3 has been retained, classification in Pregnancy Risk Group C has been confirmed.

Carcinogenicity. Aniline is classified in Carcinogen Category 4 (supplement "Aniline" 2010 b). Aniline-induced methaemoglobinaemia leads to increased erythrocyte degradation in the spleen and the increased accumulation of iron. The oxidative stress caused by this leads in turn to secondary genotoxic effects which explain the tumour formation triggered at high dose levels. This also means that tumour formation need not be expected if the methaemoglobin concentration is below a value regarded as adverse. Thus, tumour formation is not to be expected in humans at methaemoglobin levels of 4% to 5% (Drexler and Hartwig 2017).

Germ cell mutagenicity. Aniline is not classified in one of the categories for germ cell mutagens; in a dominant lethal test, germ cell mutagenicity was not found (supplement "Aniline" 2010 b).

Absorption through the skin. An in vitro study with liquid aniline under standard conditions (one-hour exposure of 2000 cm^2 of skin) revealed that markedly higher amounts are absorbed through the skin than after inhalation exposure at the level of the MAK value, and thus confirmed that absorption of aniline through the skin is relevant. Designation with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts) has therefore been retained.

Sensitization. A clinical investigation published after the documentation from 2007 shows that cross-reactions to aniline can occur in patients with existing sensitization to (disubstituted) aromatic amino compounds, so that skin sensitizing effects in humans appear to be plausible. As, also in this study, no data are given for previous exposure, contact sensitization in humans to aniline alone has not yet been unequivocally demonstrated. The results from animal experiments reported in the documentation from 2007 indicate a low contact sensitization potential. The more recent results from in vitro studies are not consistent. Positive results were obtained in the sensitive MUSST, but also in the hCLAT. Because skin contact with aniline can cause allergic reactions, at least in persons with existing sensitization to some disubstituted aromatic amines, aniline continues to be designated with "Sh" (for substances which cause sensitization of the skin). There are still no studies available for respiratory sensitization to the substance. The substance is therefore not designated with "Sa" (for substances which cause sensitization of the airways).

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