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N-Phenyl-1-naphthylamine

MAK Value Documentation, addendum – Translation of the German version from 2021

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Keywords

N-phenyl-1-naphthylamine; haematotoxicity; spleen; skin absorption; sensitizing effects; toxicity; developmental toxicity

Abstract

The German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) re-evaluted the maximum concentration at the workplace (MAK value) and the Pregnancy Risk Group of *N*-phenyl-1-naphthylamine [90-30-2]. Relevant studies were identified from a literature search and also unpublished study reports were used. The critical effect of *N*-phenyl-1-naphthylamine is haematotoxicity. A NAEL of 2.5 mg/kg body weight and day for haemosiderosis in the spleen, the most sensitive end point, was estimated from a 90-day gavage study in rats. On the basis of this NAEL, the MAK value for *N*-phenyl-1-naphthylamine has been set at 2 mg/m^3 for the inhalable fraction. As the critical effect of *N*-phenyl-1-naphthylamine is systemic, Peak Limitation Category II with an excursion factor of 2 has been assigned. The NOAELs for developmental toxicity after oral application to rats were 150 and 100 mg/kg body weight and day. After toxicokinetic scaling to concentrations at the workplace, damage to the embryo or foetus is unlikely when the MAK value is not exceeded and *N*-phenyl-1-naphthylamine has been assigned to Pregnancy Risk Group C. On the basis of skin absorption models and a comparison with *N*-phenyl-2-naphthylamine, for which experimental data are available, skin contact is not expected to contribute significantly to systemic toxicity. The data for skin sensitizing effects confirm the previous “Sh” designation. There are no data on a potential sensitization of the airways.

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MAK value (2020)	**2 mg/m³ I (inhalable fraction)**
Peak limitation (2020)	**Category II, excursion factor 2**
Absorption through the skin	**–**
Sensitization (2003)	**Sh**
Carcinogenicity	**–**
Prenatal toxicity (2020)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
CAS number	90-30-2
Vapour pressure at 20 °C	1.1×10^{-5} hPa (ECHA 2020)
Solubility	3 mg/l water (BUA 1993)
log K_{OW}	4.2 (Hartwig 2009)

Documentation for the sensitizing effects of *N*-phenyl-1-naphthylamine (Greim 2003, available in German only) was followed by a documentation in 2009 (Hartwig 2009, available in German only) that evaluated all toxicological end points. As new studies investigating the toxic effects after repeated exposure and developmental toxicity have become available, this supplement evaluates the derivation of a MAK value and the classification of the substance in one of the pregnancy risk groups. New studies investigating other end points are discussed in the relevant section. Unpublished studies from companies have been made available to the Commission. *N*-Phenyl-1-naphthylamine is used as an antioxidant in lubricating oils, as an antioxidant and anti-ageing agent in rubber products and tyres and as a dye intermediate (Hartwig 2009). *N*-Phenyl-1-naphthylamine is used as an antioxidant in industrial oils (hydraulics, gearbox, etc.), typically in concentrations of about 0.1% to 0.3% (Baumgärtel 2020). Metal-working fluid concentrates contain the substance in concentrations of up to 20% (Hartwig and MAK Commission 2018, available in German only).

1 Toxic Effects and Mode of Action

A number of studies investigating the effects of repeated oral exposure in rats reported reduced erythrocyte counts and decreased haemoglobin and haematocrit levels. A secondary effect observed in the spleen was the accumulation of pigment. Other target organs were the liver and, in males, the kidneys. The lowest effective dose was 5 mg/kg body weight and day.

In a screening study with Sprague Dawley rats, perinatal toxicity was not observed at the paternally and maternally toxic dose of 100 mg/kg body weight and day. The study did not include a complete evaluation of teratogenicity. In a prenatal developmental toxicity study in Wistar rats, no effects on the foetuses were observed up to the highest maternally toxic dose of 150 mg/kg body weight and day.

Isolated findings from valid clinical studies have recently become available that confirm that *N*-phenyl-1-naphthylamine induces contact sensitizing effects.

N-Phenyl-1-naphthylamine is not mutagenic in Salmonella and mouse lymphoma cells and is not clastogenic in mammalian cells. There are no other studies of genotoxicity available, particularly in vivo studies.

2 Mechanism of Action

There are no data available.

3 Toxicokinetics and Metabolism

No study data suitable for evaluating the absorption of *N*-phenyl-1-naphthylamine through the skin are available. Using the mathematical IH SkinPerm model developed by Tibaldi et al. (2014), a flux of 0.00029 mg/cm^2 and hour was calculated for the exposure of 2000 cm^2 of skin (the area of both hands and forearms) for 1 hour to a saturated aqueous solution of *N*-phenyl-1-naphthylamine with a total absorbed amount of 0.58 mg *N*-phenyl-1-naphthylamine. With the model of Fiserova-Bergerova et al. (1990), a much higher flux of 0.0145 mg/cm^2 and hour was estimated with a total absorbed amount of 29 mg *N*-phenyl-1-naphthylamine.

The study data available for the structural isomer *N*-phenyl-2-naphthylamine can be used for comparison as the two substances are analogous.

In a study with samples of human abdominal skin taken from 2 female donors, the samples were exposed to *N*-phenyl-2-naphthylamine and 2-naphthylamine for 8 hours in an ex vivo diffusion cell model. The aromatic amines were applied to the skin samples, which had been stored frozen, either individually or in combination dissolved in hexane or as a mixture in a lubricant. The receptor fluid was analysed during exposure (2, 4, 8 hours) and after the end of exposure (16, 24, 48 hours). The test formulations were prepared with 2 g of *N*-phenyl-2-naphthylamine or 4.1 mg of 2-naphthylamine per litre of hexane or with concentrations of 1% and 0.002%, respectively, in lubricant. All scenarios involved the application of either 259 µg *N*-phenyl-2-naphthylamine or 0.52 µg 2-naphthylamine per 0.64 cm^2. When applied in hexane, 5% of the *N*-phenyl-2-naphthylamine and 38% of the 2-naphthylamine were absorbed. During the first 8 hours, 7% to 15% of the total absorbed amount of *N*-phenyl-2-naphthylamine penetrated the skin. The substance continued to penetrate the skin even after the end of exposure. The maximum flow rate was determined to be 0.27 µg/cm^2 and hour. By the end of the test (48 hours after the beginning of application), the substance had not fully penetrated the skin. During the first 8 hours, 82% to 92% of the total absorbed amount of 2-naphthylamine penetrated the skin at a maximum flow rate of 0.06 µg/cm^2 and hour during the first 4 hours. If the two substances were applied together in lubricant, 1.9% of the *N*-phenyl-2-naphthylamine and 2.9% of the 2-naphthylamine were absorbed. The fluxes were calculated to be 0.12 and 0.002 µg/cm^2 and hour, respectively. The cumulative amount of *N*-phenyl-2-naphthylamine that penetrated the skin was 2 µg after 48 hours, which is equivalent to 3.1 µg/cm^2. If only 2-naphthylamine was applied, the first traces of the substance were detected in the receptor fluid after about 38 minutes. In a mixture with *N*-phenyl-2-naphthylamine dissolved in hexane or in the lubricant, the breakthrough time was 3.5 and 2.9 times shorter, respectively. By comparison, *N*-phenyl-2-naphthylamine was first determined in the receptor fluid about 4 hours after application (alone or in a mixture with 2-naphthylamine dissolved in hexane). When applied as a mixture in lubricant, the first traces of the substances were detected more than 7 hours later. The accumulation of the two substances in the various skin layers was likewise dependent on the application conditions (co-exposure and formulation). Co-exposure increased the intradermal absorption of both substances (Dennerlein et al. 2017).

N-Phenyl-2-naphthylamine was likewise found to penetrate freshly prepared samples of porcine skin. The experimental conditions of the study resembled the working conditions typical for the printing industry in Germany during the 1960s/1970s, when the use of solutions containing *N*-phenyl-2-naphthylamine in dichloromethane was widespread. The test formulations were prepared with a 1% solution in 0.5 ml dichloromethane (96%) and corn oil (4%), which is equivalent to a concentration of 12 g/l and a *N*-phenyl-2-naphthylamine concentration of 1.91 mg per cm^2 of skin. Under dynamic occlusive conditions and exposure for 1 hour, the flux of *N*-phenyl-2-naphthylamine through the skin was very slow (0.02 ± 0.01 µg/cm^2 and hour) with a cumulative absorbed amount of 0.80 ± 0.26 µg/cm^2 in 48 hours and a lag time of 6.33 ± 2.21 hours. The percutaneous absorption of *N*-phenyl-2-naphthylamine increased 2-fold when the substance was dissolved in dichloromethane in comparison with the level of absorption determined after the substance was dissolved in physiological saline solution with 5% ethanol. Additionally, *N*-phenyl-2-naphthylamine accumulated in the subcutaneous layers of the skin and is continuously released into the organism from this reservoir.

After exposure for 1 hour followed by the removal of the solution and the rinsing of the skin samples, 2 µg/cm^2 was found to have been absorbed over a period of 160 hours. These findings indicate that the systemic exposure continues even after exposure of the workers has terminated (Marek et al. 2017).

The in vitro findings were confirmed by the findings in living pigs. A defined amount (no other details) of a 1% solution of *N*-phenyl-2-naphthylamine in dichloromethane/oil (96/4, v/v) was sprayed on 200 cm^2 of skin of 4 German domestic pigs on 5 consecutive days; each day, the substance was applied 4 times within a 60-minute period. After this repeated, non-occlusive application, mean concentrations of *N*-phenyl-2-naphthylamine of up to 2.3 µg/l (range 1.2–4.0 µg/l) were determined in the blood of the tested animals after completion of the fifth application cycle under the same conditions as used in the in vitro experiments (the working conditions typical for the printing industry) (Koslitz et al. 2016).

From the penetration data determined by the studies of Marek et al. (2017) in porcine skin and Dennerlein et al. (2017) in human skin, it was calculated that 4 and 6.2 mg *N*-phenyl-2-naphthylamine, respectively, would be absorbed after exposure of 2000 cm^2 of skin for 1 or 8 hours. Using the models of Fiserova-Bergerova et al. (1990) and the IH SkinPerm model (Tibaldi et al. 2014), it was calculated that 92 and 1.7 mg of *N*-phenyl-2-naphthylamine, respectively, would be absorbed (log K_{OW} 4.38, calculated water solubility 6.31 mg/l (NLM 2019)). These data suggest that *N*-phenyl-2-naphthylamine is absorbed through the skin more readily than *N*-phenyl-1-naphthylamine. The two models predict that 29 and 0.58 mg of *N*-phenyl-1-naphthylamine, respectively, would be absorbed.

4 Effects in Humans

Allergenic effects

Sensitizing effects on the skin

The Finnish Institute of Occupational Health (FIOH) published the case of a worker with chronic hand eczema exacerbated after exposure to a hydraulic lubricant containing *N*-phenyl-1-naphthylamine and an explosive containing ethylene glycol dinitrate. Patch tests yielded positive reactions to the lubricant (questionably positive), to 1% *N*-phenyl-1-naphthylamine in petrolatum (3+), to a formulation containing 10% explosive (2+) and also to cocamide DEA (2+), although the relevance of the latter finding was unclear. The lubricant was analysed by gas chromatography and found to contain less than 0.01% *N*-phenyl-1-naphthylamine (Aalto-Korte et al. 2008).

A worker who installed brakes on railway cars using a red lubricant developed skin reactions on his face and the back of his neck, the inside of his forearms and the back of his hands after carrying out this work for 7 years. Positive reactions were obtained in patch tests with formulations containing 50% and 5% lubricant in petrolatum (3+ and 2+, respectively) and also with formulations containing undiluted lubricant as well as 10% and 1% ethanolic extract of the lubricant. An analysis of the constituents of the extract carried out by gas chromatography/mass spectrometry after thin-layer chromatography found it to contain a mixture of *N*-phenyl-1-naphthylamine (about 80% of the mixture), 4,4′-dioctyldiphenylamine (about 10%) and 4-octyldiphenylamine (about 2%) in addition to other substances. A positive reaction (1+) was obtained with 1% *N*-phenyl-1-naphthylamine in petrolatum. Positive reactions (2+ and 1+, respectively) were obtained with formulations containing 1% and 0.1% *N*-phenyl-1-naphthylamine in acetone. The worker did not react to 4,4′-dioctyldiphenylamine (test formulation: 1% in acetone). 4-Octyldiphenylamine was not tested. Additionally, positive reactions (2+) were obtained with Dispers Orange 1, *N*-cyclohexyl-*N*′-phenyl-4-phenylenediamine, *N*-isopropyl-*N*′-phenyl-4-phenylenediamine and *N*,*N*′-diphenyl-4-phenylenediamine. The relevance of these findings is unclear (Svedman et al. 2004).

Sensitizing effects on the airways

There are no data available.

5 Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

Oral administration

Several oral studies with rats have been carried out since the last evaluation was published (Hartwig 2009). The details are shown in Table 1.

In a 28-day study, gavage doses of *N*-phenyl-1-naphthylamine of 0, 4, 20, 100 or 500 mg/kg body weight and day were given to groups of 5 male and 5 female Sprague Dawley rats. Five additional animals per sex and group were observed for 14 days after the last dose. Increased salivation and elevated levels of bilirubin in the blood were induced by *N*-phenyl-1-naphthylamine at doses of 100 mg/kg body weight and day and above; the urine was found to be pale purple in colour. The albumin levels and the albumin to globulin ratio in the blood were increased in the males. In the females of this dose group, the relative liver weights were increased by 16%; a 74% increase was determined in the group exposed to 500 mg/kg body weight and day. The absolute liver weights were increased in both sexes in the high dose group. The livers of the animals were enlarged and revealed hypertrophy of the centrilobular hepatocytes. The reticulocyte count was increased, the erythrocyte count and the haemoglobin levels were decreased and other blood parameters were affected. The absolute and relative spleen weights were increased in the female rats and pigment deposits were found. Marked extramedullary haematopoiesis was determined in both sexes. The absolute kidney weights were likewise increased. The urine volume was increased. In the males, the specific weight of the urine was decreased and the distal tubules and collecting tubules of the kidneys were dilated. Papillary necrosis was found in 2 of 5 animals in each group. The histopathological examination carried out after the 14-day observation period revealed a malignant unilateral nephroblastoma in 1 female of the high dose group. No unusual findings were reported for the response to sensory stimuli, the reflexes, grip strength and motor activity (Tanabe et al. 2017). In this study, the NOAEL (no observed adverse effect level) was found to be 20 mg/kg body weight and day.

In a 28-day study carried out according to OECD Test Guideline 407, which was described in detail in the documentation published in 2009 (Hartwig 2009), gavage doses of 99.7% *N*-phenyl-1-naphthylamine of 0, 5, 20 or 80 mg/kg body weight and day were given to groups of 5 male and 5 female Wistar rats. A NOAEL was not determined because of the occurrence of gait abnormalities. These were observed in several females during the last week at the low dose of 5 mg/kg body weight and day and above and were interpreted by the authors as local effects. In the males, gait abnormalities were observed during the last week at 20 mg/kg body weight and day. In the female rats, the erythrocyte count and haemoglobin and haematocrit levels were reduced and the number of lymphocytes and leukocytes were increased, while the values for the mean corpuscular haemoglobin (MCH) and the reticulocyte count remained unchanged at doses of 20 mg/kg body weight and day and above. At 80 mg/kg body weight and day, an increased number of lymphocytes and leukocytes, reduced cholesterol and triglyceride levels and increased protein concentrations in the urine were determined in the males. Elevated chloride concentrations in the blood and slightly increased relative liver weights were observed in the females. Enzyme levels in the liver and thyroid gland remained unchanged. No adverse findings were determined by histopathological examination. Behavioural tests yielded similar results for the test animals and the control animals. Changes in the bilirubin concentrations in the blood and urine were attributed to interference of the test substance with the method of detection. The reddish discoloration of the urine observed at 20 mg/kg body weight and day and above was assumed to be caused by the intrinsic colour of the substance (pale brown to purple) or one of its metabolites (Hartwig 2009; Lanxess 2002). Gait abnormalities were observed also in the 7-day range-finding study that investigated doses of 250 or 500 mg/kg body weight and day.

In a screening study carried out according to OECD Test Guideline 421, which is available in Japanese with tables and figures in English, single gavage doses of *N*-phenyl-1-naphthylamine of 0, 4, 20 or 100 mg/kg body weight and day were given daily to groups of 12 male and 12 female Sprague Dawley rats. Treatment began 14 days before mating and lasted for a total of 6 weeks; in the females, treatment ended on postpartum day 4. In the males, the absolute and relative liver weights were increased and hepatocellular centrilobular hypertrophy and vacuolation of the midzonal hepatocytes

were observed at doses of 20 mg/kg body weight and day and above. In the high dose group, the urine samples taken from both sexes were found to be purple to brown in colour, and the livers of the females revealed hepatocellular centrilobular hypertrophy. The absolute (only males) and relative liver weights were increased in comparison with the weights of the control animals. In the males, extramedullary haematopoiesis and the accumulation of pigment in addition to increases in the absolute and relative weights were observed in the spleen. The NOAEL for systemic effects was 4 mg/kg body weight and day in the males and 20 mg/kg body weight and day in the females (MHLW 2011).

The findings of a 90-day study that was carried out in rats according to OECD Test Guideline 408 (subchronic toxicity study) and OECD Test Guideline 424 (neurotoxicity) are available. In this study, 15 male and 15 female Wistar rats per dose group were exposed to *N*-phenyl-1-naphthylamine doses of 0, 5, 25 or 125 mg/kg body weight and day. The animals were treated by gavage once a day on 7 days a week. A NOAEL was not derived for the females. A LOAEL (lowest observed adverse effect level) of 5 mg/kg body weight and day was determined on the basis of findings of minimal deposits of pigment in the spleen (haemosiderosis). A systemic NOAEL of 5 mg/kg body weight and day was determined in male rats. At 25 mg/kg body weight and day, increased urobilinogen levels in the urine (see below), minimal degeneration and regeneration of the proximal renal tubules and minimal chronic nephropathy were found. Unusual neuropathological findings and the gait abnormalities reported in the 28-day study were not observed up to the highest dose tested of 125 mg/kg body weight and day. The authors of the study suggest that the increased excretion of urobilinogen found in the males of the middle dose group and above was induced by the increased formation of bilirubin, which in turn is caused by haemolytic anaemia: urobilinogen is formed by intestinal bacteria from bilirubin, reabsorbed into the blood and excreted with the urine. The development of haemolytic anaemia in the female animals was likewise discussed, but without the increased excretion of urobilinogen. Haemosiderosis and extramedullary haematopoiesis were observed in the females of all dose groups; however, there was no dose dependency and the pigment accumulated more rapidly in the high dose group (see Table 2). No other effects associated with anaemia were observed in the two low dose groups. Regenerative anaemia was first detected in the high dose group. Characteristic signs are decreased numbers of red blood cells, decreased haematocrit and haemoglobin levels and an increase in the relative reticulocyte count. Heinz bodies were not observed in any of the dose groups. According to the authors, the findings determined in the spleen in the two low dose groups were related to treatment, but not adverse. The reddish colour of the urine samples of the high dose group was attributed to the white to slightly reddish test substance. This finding was therefore not considered an adverse effect induced by the substance (BASF SE 2016 b).

The gait abnormalities reported by the 28-day study (Lanxess 2002) at doses of 5 mg/kg body weight and day and above were not observed in the 90-day study even at the dose of 125 mg/kg body weight and day, in spite of the fact that a larger number of animals was treated for a longer period of time. This finding is therefore not included in the derivation of the MAK value.

The effects on the spleen induced in rats by repeated oral administration are shown in Table 2. The effects induced in the kidneys are shown in Table 3.

Tab. 1 Effects of *N*-phenyl-1-naphthylamine in rats after repeated oral exposure

Strain, number per group	Exposure	Results	References
Sprague Dawley, groups of 5 ♂, 5 ♀, 14-day observation period: exposure of additional groups of 5 ♂, 5 ♀ to 0, 500 mg/kg body weight	**28 days**, 0, 4, 20, 100, 500 mg/kg body weight and day, purity: 99.41%, gavage, vehicle: olive oil, 7 days/week	**20 mg/kg body weight**: **♂ and ♀: NOAEL**; ♀: triglycerides ↓; ♂: grip strength ↓; **20 mg/kg body weight and above**: ♀: absolute kidney weights ↑, feed consumption (week 1) ↑; **100 mg/kg body weight**: ♀: triglycerides ↓; **100 mg/kg body weight and above**: ♂ and ♀: salivation ↑, total blood bilirubin ↑, pale purple urine; ♂: albumin, albumin/globulin ratio in the blood ↑; ♀: relative liver weights ↑ (+16%); **500 mg/kg body weight**: ♂ and ♀: urine volume ↑, haemoglobin, haematocrit, MCHC ↓, reticulocytes ↑, absolute liver weights ↑ (♂: +40%, ♀: +71%), relative liver weights ↑ (♂: +70%, ♀: +71%), slightly enlarged liver (10/10), hypertrophy of the centrilobular hepatocytes, dilation of the distal tubules and collecting ducts, renal papillary necrosis (2/5 in each case), marked extramedullary haematopoiesis (3/5 in each case); ♂: 1 animal died (substance-related), body weight gains ↓, pale purple urine, specific weight of urine ↓, sodium, blood urea nitrogen ↑, absolute thymus weights ↓, absolute brain weights ↑, relative thyroid gland weights ↑, basophilia of the renal tubules; ♀: absolute and relative spleen weights ↑, total protein, albumin, albumin/globulin ratio, calcium levels in the blood ↑, erythrocytes ↓, pigment accumulation in the spleen (5/5); observation period: ♂: discoloured urine, erythrocytes ↓, haemoglobin, total bilirubin ↑, potassium ↑, absolute and relative spleen weights ↑; ♀: ALT ↓, phosphorus ↑, relative liver weights ↑, pigment accumulation in the spleen, malignant unilateral nephroblastoma (1/5); no unusual findings: sensory response to stimuli, grip strength, motor activity	Tanabe et al. 2017
Wistar, groups of 5 ♂, 5 ♀, 14-day observation period: exposure of additional groups of 5 ♂, 5 ♀ to 0, 80 mg/kg body weight	**28 days**, 0, 5, 20, 80 mg/kg body weight and day, purity: 99.7%, gavage, vehicle: corn oil, 7 days/week, OECD Test Guideline 407	**5 mg/kg body weight**: ♂ and ♀: **systemic NOAEL**; ♂: **local NOAEL (gait abnormalities)**; **5 mg/kg body weight and above**: ♀: gait abnormalities at the end of the study (incidences for the controls, increasing doses: 0, 1, 2, 3); **20 mg/kg body weight and above**: ♂ and ♀: reddish urine; ♂: gait abnormalities (incidences for the controls, increasing doses: 0, 0, 1, 1), bilirubin in the blood ↑; ♀: erythrocytes, haemoglobin, haematocrit ↓, lymphocytes, leukocytes ↑; **80 mg/kg body weight**: ♂: lymphocytes, leukocytes ↑, albumin ↑, cholesterol, triglycerides ↓, urinary excretion of protein ↑, absolute liver weights ↑; ♀: chloride, bilirubin in the blood ↑, relative liver weights ↑; observation period: absolute and relative spleen weights ↑; otherwise regression of the findings; no noticeable findings: histopathology, grip strength, locomotor and motor activity	Hartwig 2009; Lanxess 2002

Tab. 1 *(continued)*

Strain, number per group	Exposure	Results	References
Sprague Dawley, (Crl:CD(SD)), groups of 12 ♂, 12 ♀	**6–7 weeks**, 0, 4, 20, 100 mg/kg body weight and day, purity: 99.8%, gavage, vehicle: olive oil, 7 days/week, OECD Test Guideline 421	**4 mg/kg body weight**: ♂: **NOAEL**; **20 mg/kg body weight**: ♂: absolute and relative liver weights (+12% and +11%) ↑, hypertrophy of the central hepatocytes (4/12), vacuolation of midzonal hepatocytes (5/12); ♀: **NOAEL**; **100 mg/kg body weight**: ♂ and ♀: purple to brown urine, hypertrophy of central hepatocytes; ♂: absolute and relative liver weights ↑ (+25% and +27%), absolute and relative spleen weights ↑ (+16% and +20%), extramedullary haematopoiesis (6/12), pigment accumulation in the spleen (4/12); ♀: relative liver weights (+19%) ↑	MHLW 2011
Wistar, groups of 15 ♂, 15 ♀, (neuropathological examination of 5 ♂, 5 ♀ of each group)	**90 days**, 0, 5, 25, 125 mg/kg body weight and day, purity: 99.9%, gavage, vehicle: corn oil, 7 days/week, OECD Test Guideline 409 and 424	**5 mg/kg body weight**: ♂: **NOAEL for systemic effects**; ♀: **LOAEL for systemic effects**: pigment accumulation in the spleen (haemosiderosis) (see Table 2), extramedullary haematopoiesis in the spleen (see Table 2 and text); **25 mg/kg body weight**: ♂: urobilinogen in the urine ↑ (sign of haemolytic anaemia), degeneration/regeneration of the proximal tubules, basophilic tubules ↑, chronic nephropathy (see Table 3), absolute and relative liver weights (+17% and +11%) ↑, centrilobular hypertrophy; ♀: pigment accumulation in the spleen (haemosiderosis), extramedullary haematopoiesis in the spleen; **125 mg/kg body weight**: **NOAEL for neurotoxic effects;** ♂ and ♀: increased feed consumption, salivation shortly after treatment ↑, reddish urine, serum creatinine ↓, serum bilirubin ↑, regenerative anaemia (erythrocyte count, haemoglobin, haematocrit ↓, relative reticulocyte count ↑), absolute number of basophils ↑, absolute and relative kidney weights ↑, absolute and relative liver weights ↑ (♂: +28% and +29%, ♀: +31% and +32%), centrilobular hypertrophy, pigment accumulation in the spleen (haemosiderosis); ♂: MCV, MCH ↑, cholesterol ↑, urobilinogen in the urine ↑ (1/10; sign of haemolytic anaemia), urine volume ↑, transitional epithelial cells in the urine ↑ (minimal, may also occur in control animals), degeneration/regeneration of the proximal tubules (8/10), basophilic tubules ↑, chronic nephropathy (5/10); ♀: extramedullary haematopoiesis in the spleen (3/10); no noticeable findings: FOB, motor activity, neurohistopathology	BASF SE 2016 b

ALT: alanine aminotransferase; FOB: Functional Observational Battery; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration of a single red blood cell; MCV: mean corpuscular volume

Tab. 2 Incidence and severity of effects on the spleen in rats given gavage doses of *N*-phenyl-1-naphthylamine

28 days, 7 days/week, Sprague Dawley (Tanabe et al. 2017)					
	Dose (mg/kg body weight and day)				
	0	**4**	**20**	**100**	**500**
extramedullary haematopoiesis					
♂:					
slight	5/5 (100%)	5/5 (100%)	5/5 (100%)	2/5 (40%)	2/5 (40%)
moderate	0/5 (0%)	0/5 (0%)	0/5 (0%)	3/5 (60%)	3/5 (60%)
overall	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)
♀:					
slight	5/5 (100%)	5/5 (100%)	5/5 (100%)	4/5 (80%)	2/5 (40%)
moderate	0/5 (0%)	0/5 (0%)	0/5 (0%)	1/5 (20%)	3/5 (60%)
overall	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)
pigment deposition (haemosiderosis)					
♂:					
slight	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)
moderate	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)
overall	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)
♀:					
slight	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)	0/5 (0%)
moderate	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	5/5 (100%)**
overall	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)

6–7 weeks, 7 days/week, OECD Test Guideline 421, Sprague Dawley (MHLW 2011)				
	Dose (mg/kg body weight and day)			
	0	**4**	**20**	**100**
extramedullary haematopoiesis				
♂:				
minimal	0/12 (0%)	0/12 (0%)	0/12 (0%)	6/12 (50%)**
♀:				
mild	0/12 (0%)	2/12 (17%)	0/12 (0%)	0/12 (0%)
pigment deposition				
♂:				
minimal	0/12 (0%)	0/12 (0%)	0/12 (0%)	4/12 (33%)

Tab. 2 *(continued)*

90 days, 7 days/week, Wistar (BASF SE 2016 b)				
	Dose (mg/kg body weight and day)			
	0	5	25	125
extramedullary haematopoiesis				
♀:				
grade 1	0/10 (0%)	1/10 (10%)	1/10 (10%)	0/10 (0%)
grade 2	0/10 (0%)	1/10 (10%)	0/10 (0%)	2/10 (20%)
grade 3	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)
overall	0/10 (0%)	2/10 (20%)	1/10 (10%)	3/10 (30%)
pigment deposition				
♂:				
grade 1	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
grade 2	2/10 (20%)	0/10 (0%)	0/10 (0%)	6/10 (60%)
overall	2/10 (20%)	0/10 (0%)	0/10 (0%)	6/10 (60%)
♀:				
grade 1	0/10 (0%)	5/10 (50%)	8/10 (80%)**	0/10 (0%)
grade 2	1/10 (10%)	1/10 (10%)	1/10 (10%)	5/10 (50%)
overall	1/10 (10%)	6/10 (60%)	9/10 (90%)**	5/10 (50%)

**$p \leq 0.01$

Tab. 3 Incidence and severity of effects on the kidneys in rats given gavage doses of *N*-phenyl-1-naphthylamine

28 days, 7 days/week, Sprague Dawley (Tanabe et al. 2017)					
	Dose (mg/kg body weight and day)				
	0	4	20	100	500
dilation of distal tubules and collecting tubules					
♂:					
slight	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	3/5 (60%)
moderate	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	1/5 (20%)
overall	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	4/5 (80%)*
♀:					
slight	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	3/5 (60%)
papillary necrosis					
♂:					
moderate	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	2/5 (40%)[a)]
♀:					
slight	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	1/5 (20%)
severe	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	1/5 (20%)
overall	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	2/5 (40%)

Tab. 3 *(continued)*

	Dose (mg/kg body weight and day)				
	0	**4**	**20**	**100**	**500**
basophilic tubules					
♂:					
slight	2/5 (40%)	1/5 (20%)	1/5 (20%)	0/5 (0%)	0/5 (0%)
moderate	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	4/5 (80%)
severe	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	1/5 (20%)[a)]
overall	2/5 (40%)	1/5 (20%)	1/5 (20%)	0/5 (0%)	5/5 (100%)**
♀:					
slight	2/5 (40%)	1/5 (20%)	1/5 (20%)	0/5 (0%)	4/5 (80%)
90 days, 7 days/week, Wistar (BASF SE 2016 b)					
	Dose (mg/kg body weight and day)				
	0	**5**	**25**	**125**	
degeneration / regeneration					
♂:					
grade 1	0/10 (0%)	0/10 (0%)	3/10 (30%)	2/10 (20%)	
grade 2	0/10 (0%)	0/10 (0%)	0/10 (0%)	2/10 (20%)	
grade 3	0/10 (0%)	0/10 (0%)	0/10 (0%)	4/10 (40%)	
overall	0/10 (0%)	0/10 (0%)	3/10 (30%)	8/10 (80%)**	
chronic nephropathy					
♂:					
grade 1	1/10 (10%)	2/10 (20%)	6/10 (60%)	1/10 (10%)	
grade 2	0/10 (0%)	0/10 (0%)	0/10 (0%)	4/10 (40%)*	
overall	1/10 (10%)	2/10 (20%)	6/10 (60%)*	5/10 (50%)	

*$p \leq 0.05$; **$p \leq 0.01$

a) 1 animal died

The most sensitive parameter investigated by the studies included in Table 1 was the accumulation of pigment in the spleen (haemosiderosis) resulting from erythroclasis. Erythroclasis leads to a more rapid breakdown of normal and pathophysiologically (haemolytic) altered erythrocytes. These changes may result from methaemoglobinaemia. However, this parameter was not determined in any of the studies. In the females, the NOAEL for the induction of haemosiderosis was determined to be 100 mg/kg body weight after 28 days; a NOAEL was not established after 90 days. In the males, the NOAELs were determined to be 500 and 25 mg/kg body weight, respectively. Thus, the effects increased in severity after subchronic exposure.

The NOAEL for extramedullary haematopoiesis remained constant at 20 and 25 mg/kg body weight, respectively, in the females, but increased from 20 to 125 mg/kg body weight in the males. This suggests that females are more sensitive for the development of haemosiderosis and extramedullary haematopoiesis. This conclusion was not confirmed by the findings of the study of MHLW (2011). However, a possible explanation for this is that the study was carried out with pregnant animals. In rats, mild forms of haemolytic anaemia eventually lead to the accumulation of haemosiderin in the spleen. This is, therefore, the first parameter to exhibit noticeable changes. At first, the number of erythrocytes remains about the same because of the extramedullary haematopoiesis. Haemosiderosis is a cumulative process that occurs only with the induction of methaemoglobinaemia. As only minimal haemosiderosis was observed in the 90-day study, a further intensification of the effects is not expected after chronic exposure. The chronic nephropathy observed only in the males is considered specific to the rat and is therefore not included in the evaluation due to its irrelevance for humans.

Local effects on skin and mucous membranes

In studies carried out according to OECD Test Guideline 404 or 405, *N*-phenyl-1-naphthylamine was not found to be irritating to the eyes or skin (Hartwig 2009).

Allergenic effects

N-Phenyl-1-naphthylamine has sensitizing effects on the skin (Greim 2003).

There are no new findings.

Reproductive and developmental toxicity

Fertility

In the screening study previously described in the Section "Subacute, subchronic and chronic toxicity" and Table 1, Sprague Dawley rats were treated with *N*-phenyl-1-naphthylamine doses of 0, 4, 20 or 100 mg/kg body weight and day according to OECD Test Guideline 421. No effects on the length of the oestrus cycle, the reproductive parameters mating index, insemination index, fertility index (females), length of gestation, implantation index, number of pups, number of living pups, survival index on postpartum day 4 and the sex ratio were observed. The histopathological examination of the reproductive organs did not reveal any unusual, substance-related findings. In this study, the NOAEL for fertility was determined to be 100 mg/kg body weight and day, the highest dose tested. The NOAEL for parental toxicity in males was 4 mg/kg body weight and day as a result of the hepatocellular centrilobular hypertrophy and vacuolation of midzonal hepatocytes observed at 20 mg/kg body weight and day. The NOAEL for the dams was 20 mg/kg body weight and day, also resulting from effects on the liver in the 100 mg/kg group (MHLW 2011).

The 28-day and 90-day gavage studies described in the Section "Subacute, subchronic and chronic toxicity" and Table 1 did not reveal unusual findings in the reproductive organs of female and male Wistar and Sprague Dawley rats. The highest dose tested was 500 mg/kg body weight and day in the 28-day studies and 80 mg/kg body weight and day in the 90-day study (BASF SE 2016 b; Lanxess 2002; Tanabe et al. 2017).

Developmental toxicity

Prenatal developmental toxicity was investigated in Wistar rats in a study carried out according to OECD Test Guideline 414. In this study, gavage doses of *N*-phenyl-1-naphthylamine of 0, 15, 50 or 150 mg/kg body weight and day were given to groups of 25 pregnant animals from gestation days 6 to 19. Corn oil was used as the vehicle. No effects on development were determined up to the highest dose tested. Increased water consumption (+24%), decreased feed consumption (–9%), reduced body weight gains (9% less than in the controls) and reduced corrected (net) body weight gains (26% less than in the controls; also the carcass weights were 5% lower than those of the control group) were found in the dams at the highest dose tested of 150 mg/kg body weight and day. Examination of the blood on gestation day 20 revealed decreases in the erythrocyte count, haemoglobin and haematocrit levels and the MCHC (mean corpuscular haemoglobin concentration). The cholesterol levels were decreased, while the relative reticulocyte count and the total bilirubin concentration in the blood were increased. The NOAEL for developmental toxicity was 150 mg/kg body weight and day, the highest dose tested, and the NOAEL for maternal toxicity was 50 mg/kg body weight and day (BASF SE 2016 a).

In the screening study previously described in the Section "Subacute, subchronic and chronic toxicity" and Table 1, which was carried out according to OECD Test Guideline 421, 1 offspring of the 20 mg/kg group was found to have a narrowed tail (according to a comprehensive database that categorizes effects of developmental toxicity, this effect is not regarded as a malformation or variation (BfR 2020)). Other malformations were not determined. In this study, the NOAEL for perinatal toxicity was 100 mg/kg body weight and day (MHLW 2011). However, the study did not include a complete investigation of teratogenicity.

Genotoxicity

A chromosomal aberration test is available that was not included in the supplement published in 2009. The test report is written in Japanese with tables and figures in English. In this test, a Chinese hamster lung cell line (CHL/IU) was treated with *N*-phenyl-1-naphthylamine concentrations of 4.3 to 34 µg/ml for 6 or 24 hours both with and without a metabolic activation system. At non-cytotoxic concentrations of up to 28.3 µg/ml (without metabolic activation) or 17 µg/ml (with metabolic activation), neither structural nor numerical aberrations were induced. At higher concentrations, a 2-fold to 6-fold increase in structural aberrations was observed after treatment for 6 hours at growth rates below 35%. The functioning of the test system was verified by the positive control (MHLW 2007).

In summary, *N*-phenyl-1-naphthylamine did not induce mutagenic effects in Salmonella and mouse lymphoma cells and did not induce clastogenic effects in mammalian cells at non-cytotoxic concentrations. A dominant lethal test yielded negative results (Hartwig 2009; MHLW 2007). Other studies, particularly in vivo studies, are not available.

6 Manifesto (MAK value/classification)

The target organs after repeated oral exposure are the haematopoietic system, the liver and the spleen. In male rats, the kidneys were found to be an additional target organ. *N*-Phenyl-1-naphthylamine has sensitizing effects on the skin.

MAK value. There are no data available for effects induced by inhalation exposure of humans and animals that are relevant to the evaluation. As the substance is neither irritating to the skin nor to the eyes (see Hartwig 2009), systemic effects are expected to be predominant after inhalation exposure. The MAK value is therefore derived from the LOAEL of 5 mg/kg body weight and day that was established in the 90-day gavage study for the accumulation of pigment in the spleen of female rats. This accumulation of pigment (haemosiderosis) is a cumulative parameter. As only minimal haemosiderosis developed, a NAEL (no adverse effect level) of 2.5 mg/kg body weight and day has been extrapolated. The following toxicokinetic data are taken into consideration for the extrapolation of this NAEL to a concentration in workplace air: the daily exposure of the animals in comparison with the 5 days per week exposure at the workplace (7:5), the corresponding species-specific toxicokinetic correction value for the rat (1:4), the assumed oral absorption (100%), the body weight (70 kg) and the respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 6.1 mg/m^3. The NAEL is not expected to decrease further after long-term exposure (see the Section "Subacute, subchronic and chronic toxicity"). As this value was obtained using data from animal studies (1:2), a workplace concentration of 3.05 mg/m^3 has been derived. After applying the preferred value approach, a MAK value of 2 mg/m^3 has been established for the inhalable fraction.

Peak limitation. As the MAK value was derived from systemic effects, the substance has been classified in Peak Limitation Category II. As there are no data available for the half-life of the substance in humans, an excursion factor of 2, the default value for this category, has been established.

Prenatal toxicity. In a prenatal developmental toxicity study with gavage administration in Wistar rats, an *N*-phenyl-1-naphthylamine dose of 150 mg/kg body weight and day led to maternal toxicity. This was manifest in the form of such effects as reduced body weight gains and erythrocyte counts, decreased haemoglobin and haematocrit levels and MCHC, decreased cholesterol levels and increased relative reticulocyte counts and total bilirubin concentrations in the blood. The NOAEL for developmental toxicity was 150 mg/kg body weight and day and the NOAEL for maternal toxicity 50 mg/kg body weight and day. A NOAEL for perinatal toxicity of 100 mg/kg body weight and day, the highest dose tested, was derived from the findings of the screening study carried out according to OECD Test Guideline 421 with gavage administration in male and female Sprague Dawley rats. Paternal and maternal toxicity were already observed at this dose. The NOAELs for developmental toxicity and perinatal toxicity after oral administration extrapolated to a concentration in air after applying the assumptions described above (see "MAK value", the only exception being that the animals were treated for 7 days) were 263 mg/m^3 and 175 mg/m^3, respectively. The 132-fold and 88-fold margins

between the calculated concentrations in air and the MAK value of 2 mg/m^3 are adequate and, as no teratogenic effects were induced, *N*-phenyl-1-naphthylamine has been classified in Pregnancy Risk Group C.

Absorption through the skin. No study data are available to evaluate the absorption of *N*-phenyl-1-naphthylamine through the skin. On the basis of model calculations and assuming standard conditions (saturated aqueous solution, 2000 cm^2 of exposed skin, length of exposure 1 hour), the amount of *N*-phenyl-1-naphthylamine absorbed through the skin would be 0.58 mg and 29 mg, respectively.

Additionally, the study data available for the structural isomer ***N*-phenyl-2-naphthylamine** can be used for a read-across. Two ex-vivo studies investigated the penetration of *N*-phenyl-2-naphthylamine through porcine and human skin. From the penetration data determined by the studies of Marek et al. (2017) in porcine skin and Dennerlein et al. (2017) in human skin, it was calculated that 4 mg *N*-phenyl-2-naphthylamine would be absorbed after exposure of 2000 cm^2 of skin for 1 hour and 6.2 mg would be absorbed after exposure for 8 hours. Model calculations predicted absorbed amounts of 1.7 mg and 92 mg, respectively.

On the basis of the extrapolated workplace concentration of 3.05 mg/m^3 (see the Section "MAK value") and assuming a respiratory volume of 10 m^3 and 100% absorption by inhalation, a tolerable daily intake of 30.5 mg was calculated for *N*-phenyl-1-naphthylamine.

Using model calculations, a maximum absorbed amount of 29 mg *N*-phenyl-1-naphthylamine, i.e. about 95% of the systemically tolerable amount, was determined. After exposure for 1 hour, 4 mg ***N*-phenyl-2-naphthylamine** were absorbed through the human skin. As model calculations have determined that *N*-phenyl-2-naphthylamine is taken up more readily through the skin than *N*-phenyl-1-naphthylamine, in the worst case, 4 mg of *N*-phenyl-1-naphthylamine would be absorbed, i.e. 13% of the systemically tolerable amount. *N*-Phenyl-1-naphthylamine continues not to be designated with "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. To evaluate the end point of skin sensitization, isolated findings in humans have recently become available that confirm that *N*-phenyl-1-naphthylamine has skin sensitizing effects. There are no new findings from animal or in vitro studies nor findings relating to sensitizing effects on the airways. Therefore, *N*-phenyl-1-naphthylamine remains designated with "Sh" (for substances which cause sensitization of the skin), but not with "Sa" (for substances which cause sensitization of the airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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