N′-(3-Aminopropyl)-N′-dodecylpropane-1,3- diamine

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N′-(3-Aminopropyl)-*N′*-dodecylpropane-1,3-diamine

MAK Value Documentation – Translation of the German version from 2017

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Keywords

N′-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine; heart muscle cell degeneration; skeletal muscle infiltration; MAK value; maximum workplace concentration; peak limitation; developmental toxicity

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine [2372-82-9] to derive a maximum concentration at the workplace (MAK value), considering all toxicological end points. Available unpublished study reports and publications are described in detail. Critical effects are degeneration of heart muscle cells and lympho-histiocytic infiltrations in the skeletal muscles of male rats. No NOAEL could be derived for these effects. The LOAEL is 4 mg/kg body weight. A NAEL of 1.3 mg/kg body weight was extrapolated and a MAK value of 0.05 mg/m^3 for the inhalable fraction could be derived. The derivation of the MAK value is conservative because the determined oral absorption is very low and for the inhalative absorption a default value of 100% is assumed due to a lack of experimental data. *N′*-(3-Aminopropyl)-*N′*-dodecylpropane-1,3-diamine is basic and therefore corrosive to rabbit skin, hence an irritation potential for the respiratory tract has to be assumed. No inhalation studies are available. Compared to several primary, secondary and tertiary amines which have MAK values between 1 and 13 mg/m^3, the basicity of *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine is almost the same or less. Therefore, a MAK value of 0.05 mg/m^3 should protect against local irritating effects. As the critical effect is systemic, the substance has been classified in Peak Limitation Category II. An excursion factor of 8 is set as the half-life in blood is at least 28.5 hours. The NOAELs for developmental toxicity in rats and rabbits are 22.5 and 9 mg/kg body weight and day, respectively, which can be scaled to concentrations of 1 and 0.66 mg/m^3 at the workplace. Thus, there is no reason to fear damage to the embryo or foetus when the MAK value is observed and the substance is classified in Pregnancy Risk Group C. *N′*-(3-Aminopropyl)-*N′*-dodecylpropane-1,3-diamine is not genotoxic or carcinogenic. The potential of contact sensitization in humans cannot be definitely assessed because of the corrosive character. The substance is not a contact sensitizer in guinea pigs. Skin contact is not expected to contribute significantly to systemic toxicity.

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MAK value (2016)	**0.05 mg/m³ I (inhalable fraction)**
Peak limitation (2016)	**Category II, excursion factor 8**
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2016)	**Pregnancy Risk Group C**
Germ cell mutagenicity	–
BAT value	–
Synonyms	*N,N*-bis(3-aminopropyl)dodecylamine bis(aminopropyl)laurylamine dodecyl dipropylene triamine laurylamine dipropylenediamine
Chemical name	*N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine
CAS number	2372-82-9
Structural formula	$CH_3–(CH_2)_{11}–N((CH_2)_3–NH_2)_2$
Molecular formula	$C_{18}H_{41}N_3$
Molar mass	299.54 g/mol
Melting point	7.6 ± 0.1 °C at 964 hPa; 10.9 °C (no other data; ECHA 2015 d)
Boiling point	366 °C at 1017 hPa (ECHA 2015 d)
Relative density (20 °C/4 °C)	0.868 ± 0.01 (ECHA 2015 d)
Vapour pressure at 25 °C	1.4×10^{-6} hPa (ECHA 2015 d)
log K_{OW}	0.34 at 20 °C (calculated); −0.66 at pH 7 (calculated) (no other data; ECHA 2015 d)
Solubility	> 190 g/l water at 20 °C (ECHA 2015 d)
pKa value	about 9 for the primary amino groups, about 6.9 for the tertiary amino group (ECHA 2015 d)
1 ml/m³ (ppm) ≙ 12.449 mg/m³	**1 mg/m³ ≙ 0.08 ml/m³ (ppm)**
pH	11–12 at 10 g/l (IFA 2015) 10.6 at 10 g/l (Schülke und Mayr 2008)
Stability	hydrolytically stable at pH 4, 7 and 9, half-life in the environment ≥ 1 year (ECHA 2015 d)
Production	no data
Purity	85.3% (Akzo Nobel Surface Chemistry AB 2002 a, b, c, d, e, f); 89.4% (Akzo Nobel Surface Chemistry AB and Lonza AG 2011)
Impurities	no data

Uses	disinfectant and biocide (not for direct application on humans and animals, used as an algicide in animal hygiene and in the food and animal feed industry), preservative for liquids in cooling and processing systems, slimicide (Akzo Nobel 2013)

1 Toxic Effects and Mode of Action

N′-(3-Aminopropyl)-*N′*-dodecylpropane-1,3-diamine is corrosive to the rabbit skin.

In rats, the substance caused moderate toxicity after a single oral dose.

There are only few clinical findings available for the contact sensitizing effects of *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine. The studies could not be evaluated conclusively because the substance caused pronounced irritation. The substance did not have sensitizing effects on the skin of guinea pigs.

When rats were given doses of 20 mg/kg body weight and above with the diet for 13 weeks, effects on the kidneys were observed, such as tubular nephropathy with degeneration and necrosis of the tubular epithelium, tubular dilation with flattened epithelium and tubular basophilia, in addition to enlarged mesenteric lymph nodes with foamy macrophages. At a dose level of 8 mg/kg body weight and day and above, exposure of this species to the substance with the diet for 52 weeks additionally increased the incidences of lympho-histiocytic myocarditis and lympho-histiocytic infiltrations in the skeletal muscles of the males and of alveolar histiocytosis in the lungs of the females. After administration with the diet for 104 weeks, dose-dependent increases in the incidences and severity of degeneration of the heart muscle cells and of lympho-histiocytic infiltrations in the skeletal muscles were observed in male rats at 4 mg/kg body weight and day and above. In female dogs, the activities of the enzymes aspartate and alanine aminotransferase were increased in the plasma at 20 mg/kg body weight body weight and day and above after 13-week administration with the diet.

Gavage administration of *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine induced early embryonic deaths in rats at 60 mg/kg body weight and day and increased incidences of early and late resorptions in rabbits at 20 mg/kg body weight and day and above. The substance did not cause teratogenicity in these 2 species. Developmental toxicity was observed only in combination with maternal toxicity.

N′-(3-Aminopropyl)-*N′*-dodecylpropane-1,3-diamine was not genotoxic in vitro or carcinogenic in rats.

Inhalation studies in animals or genotoxicity studies in vivo are not available.

2 Mechanism of Action

N′-(3-Aminopropyl)-*N′*-dodecylpropane-1,3-diamine is highly alkaline because it has 3 amino groups; therefore, it is corrosive (10 g/l water: pH about 10.6; Schülke und Mayr 2008).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

In a toxicokinetics study carried out according to OECD Test Guideline 417, male and female Sprague Dawley rats were given single gavage doses of radioactively labelled ^{14}C-*N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine of 3 or 30 mg/kg body weight. After the administration of 3 mg/kg body weight, the plasma concentrations were below the limit of reliable quantification at all times of determination (radioactivity lower than twice the background radioactivity of 13 to 21 dpm; no information about the corresponding concentration of the test substance); the highest concentration in the plasma was reached after 4 hours. Likewise, after the administration of 30 mg/kg body weight,

the plasma concentrations were only twice the limit of reliable quantification. The highest concentration of 0.12 µg/ml was determined 12 hours after the administration of 30 mg/kg body weight. The terminal half-lives in the plasma were 28.5 hours for the males and 46.3 hours for the females. Plotting the plasma concentration against time did not demonstrate a two-phase decrease in the plasma concentration; however, a two-phase decrease is possible because the exact time of the maximum concentration was not determined. Up to the last sampling, the AUC (area under the plasma curve) was 4.6 µg/ml and hour for the males and 5.1 µg/ml and hour for the females; the AUC extrapolated to infinity was 6.1 µg/ml and hour for the males and 8.9 µg/ml and hour for the females. Following the administration of 3 mg/kg body weight, the highest radioactivity was determined in the gastrointestinal tract and its contents by whole-body autoradiography of the animals. Only low levels of radioactivity were determined in the other tissues. A major fraction of the dose was excreted with the faeces within 5 days (90% to 97%). About 0.2% of the dose was found in the urine and less than 0.4% was determined in the exhaled air. At necropsy, about 1% to 3% of the dose remained in the body and 0.4% to 1.3% was recovered in the gastrointestinal tract. It was not possible to extract 66% to 72% of the dose with methanol or methanol/water from the faeces, but 17% to 25% could be extracted with 1 M HCl and 2 M NaOH. It was not possible to analyse the extracts after neutralization (see Section 3.2).

According to the authors, the low levels of absorption can be explained by the high fraction of bound radioactivity. There were no differences in excretion between the sexes or the 2 doses. Oral absorption was estimated on average to be about 2.5% from the sum of the radioactivity (1.26% to 3.59%) found in the urine, the exhaled air and the rest of the body (ECHA 2015 d; Lonza Ltd 1996). Administration of the substance by intravenous injection to calculate bioavailability was not carried out. The metabolized fraction of the substance determined in the faeces cannot be used to calculate bioavailability because a biliary excretion experiment would be required to clarify whether the substance had previously been absorbed. However, this type of experimental data is not available.

An in vitro study carried out with dermatomed human skin according to OECD Test Guideline 428 investigated ^{14}C-labelled *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine (lauryl-1-^{14}C) in a 1% aqueous formulation (w/v). For this purpose, 6.4 µl (10 µl per cm^2) of the formulation was applied to 11 prepared skin samples taken from 6 different donors. The receptor fluid was collected over a period of 6 hours at 1-hour intervals and then at 2-hour intervals for up to 24 hours. The cumulative fraction of the dose recovered over 24 hours was 0.005% in the receptor fluid and 0.9% in the skin. Thus, about 1% of the dose was absorbed dermally. A fraction of 22.8% of the substance was found in the stratum corneum. The total amount recovered was 102.14% of the dose (ECHA 2015 d; Lonza Ltd 2003). An absorption rate of 0.0417 µg/cm^2 and hour can be calculated from the cumulative absorption of 1% in 24 hours. Assuming a surface area of 2000 cm^2 of skin exposed for 1 hour, this would correspond to an absorbed amount of 83 µg.

3.2 Metabolism

In the study in rats described in Section 3.1, the main component in the faeces was determined to be the unchanged substance (7% to 13% of the dose; 39% to 51% of the faeces radioactivity). The faeces contained 6 metabolites each accounting for 1% to 3% of the dose; one of them was 1-dodecylamine. A large percentage (66% to 72% of the dose) initially remained unextracted (2 extractions with methanol and 1 with methanol/water). Extraction with 1 M HCl and 2 M NaOH recovered 17% to 22% from the faeces; however, it was not possible to analyse these extracts (ECHA 2015 d; Lonza Ltd 1996).

The metabolite 1-dodecylamine is formed from *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine by two N-dealkylation reactions.

4 Effects in Humans

Data are available only for allergenic effects.

A 24-year-old female worker developed dermatitis on the hand after cleaning operating theatres in a hospital over a period of 6 months with surface disinfectants containing, among other substances, *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine. The skin lesions healed during intervals when she did not work due to illness and following corticosteroid treatment; however, when she resumed work, the skin lesions recurred and spread to her face. Patch tests produced positive reactions to the disinfectant (0.4% in water), *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine

(0.1% in water), 0.3% glutaraldehyde, 1% phenoxyethanol, 25% Peru balsam and 10% sandalwood oil. The disinfectant tested in a concentration of 0.04% and a 0.01% formulation of *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine did not induce any reactions, and 2 control persons did not react to tests with the active substance at either concentration (Schliemann et al. 2010).

Two nurses who had more than 20 years of work experience developed eczematous lesions on their hands and arms shortly after a new disinfectant was introduced for sterilizing instruments. In patch tests, both reacted to a 10% aqueous dilution of the disinfectant and a 1% aqueous formulation of *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine. One of the two nurses additionally reacted to 0.1% didecyldimethyl ammonium chloride (in water). There are no data for control tests (Dibo and Brasch 2001).

After 2 years of employment, a 24-year-old hospital worker presented herself with eczema on the back of her hands and wrists that had persisted for 2 months and with periocular dermatitis. After 48 and 72 hours, a patch test produced a 2+ reaction to both 2% and 0.1% aqueous dilutions of the tested disinfectants, 2+ and 1+ reactions to 2% and 1% aqueous *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine (30%; constituent of one of the products), respectively, and 3+ and 2+ reactions to 0.1% and 0.01% aqueous didecyldimethyl ammonium chloride (constituent of the second product), respectively. Although she was transferred to another work area in the hospital, she again developed similar symptoms 7 months later after the second disinfectant was used in the room in which she worked. In response to the recurrence of the symptoms, the constituent of the first product, rather than the constituents of the product currently causing the symptoms, was tested again in 0.1% and 0.01% aqueous dilutions. These dilutions caused 1+ or questionably positive reactions after 48 hours and 1+ reactions after 72 hours. A group of 20 control persons did not react to the constituents tested in 0.01% aqueous dilutions (Dejobert et al. 1997).

Eczematous skin lesions were found on the right forearm of a female dental assistant after exposure to a disinfectant containing both *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine and *N,N*-didecyl-*N*-methylpoly(oxyethyl) ammonium propionate. However, after 48 and 96 hours, patch tests yielded positive reactions only to the second constituent, but not to *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine. Both substances were tested as 5% formulations in petrolatum; 10 control persons did not react to the formulation (De Quintana Sancho et al. 2014).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

There are no data available.

5.1.2 Oral administration

In a study carried out according to OECD Test Guideline 401, groups of 5 male and 5 female Sprague Dawley rats per dose were given a 30% aqueous solution of *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine in doses of 75 to 600 mg/kg body weight. An oral LD_{50} value of 261 mg/kg body weight was determined for *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine. Hunched posture, piloerection, lethargy, a decreased respiratory rate and ptosis were observed in all animals 1 to 4 hours after treatment. Increased salivation, ataxia and pallor of the extremities were observed in the surviving animals at *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine doses of 300 mg/kg body weight and above. Sporadic effects included diuresis, reddish-brown discoloration around the eyes and coma. Necropsy revealed reddish discoloration of the lungs, dark discoloration of the liver and kidneys, haemorrhage of the gastric mucosa and congestion of the small and large intestines (Akzo Nobel Surface Chemistry AB 1988; ECHA 2015 d).

A study was carried out according to OECD Test Guideline 420 with administration of undiluted *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine (purity: 85.3%) to groups of 5 male and 5 female Sprague Dawley rats per dose. The mortality was 20% at a dose level of 50 mg/kg body weight while all animals survived at 5 mg/kg body weight. Higher doses were not tested. The symptoms observed included dyspnoea, hypoactivity, soft faeces, abdominal swelling and

piloerection. Gross-pathological examination of the organs of all treated animals did not reveal any unusual findings (Akzo Nobel Surface Chemistry AB 2002 c; ECHA 2015 d).

An oral LD_{50} value between 25 and 200 mg/kg body weight was determined in another study carried out under the same conditions, but with different doses. The symptoms observed included dyspnoea, hypersalivation, piloerection, hypoactivity and sedation. No unusual organ findings were obtained at the necropsy of the treated animals (ECHA 2015 d).

5.1.3 Dermal application

There are no data available.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available.

5.2.2 Oral administration

The studies that investigated repeated oral administration of *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine are shown in Table 1.

Tab. 1 Studies that investigated the effects of *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine after repeated oral administration

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, Crl:CD(SD) IGS BR, 10 ♂ and 10 ♀	**13 weeks**, 0, 100, 300, 900 mg/kg diet, ♂: 0, 7, 20, 57 mg/kg body weight and day, ♀: 0, 8, 22, 65 mg/kg body weight and day, each related to *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine, purity: 85.3%, OECD Test Guideline 408	histopathological findings in detail: see Table 2; **7 (♂)/8 (♀) mg/kg body weight**: **NOAEL** effects on kidneys and mesenteric lymph nodes; **20 (♂)/22 (♀) mg/kg body weight and above**: serum: AST ↑ (♂: 2.4-fold of control, ♀: 1.8-fold), absolute and relative kidney weights ↑, kidneys: tubular nephropathy with degeneration/necrosis of the tubular epithelium, tubular dilation with flattened epithelium and tubular basophilia, mesenteric lymph nodes: enlargement and foamy macrophages, ♂: body weight gains ↓ (–10%), ♀: pallor of the extremities; **57 (♂)/65 (♀) mg/kg body weight**: piloerection, round backs, motor activity ↓, feed consumption ↓, serum: nitrogen urea ↑, body weight gains ↓ (♂: –46%, ♀: –51%), pallor of the ocular fundus (often associated with retinal hypovascularization), pallor of the kidneys, ♂: pallor of the extremities, 3/10 emaciated appearance, ♀: 2/10 chromodacryorrhoea, 2/10 emaciated appearance; skeletal muscles not examined histopathologically	Akzo Nobel Surface Chemistry AB 2002 a; ECHA 2015 d

Tab. 1 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, Crl:CD(SD), 10 ♂ and 10 ♀, high dose group: 20 ♂ and 20 ♀	**52 weeks**, diet, 0, 4, 8, 20 mg *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine/kg body weight and day, purity: 89.4%, OECD Test Guideline 453	histopathological findings in detail: see Table 3; **4 mg/kg body weight**: ♂: **NOAEL** effects on skeletal muscles, heart, kidneys; ♀: **NOAEL** effects on lungs, kidneys; **4 mg/kg body weight and above**: mesenteric lymph nodes: enlarged macrophages with cytoplasmic vacuoles (not dose-dependent; interpreted as a response to the oral ingestion of a lipophilic and corrosive substance and not regarded as adverse); **8 mg/kg body weight and above**: ♂: heart: lympho-histiocytic myocarditis, skeletal muscles: lympho-histiocytic infiltrations, kidneys: basophilic tubular cells ↑; ♀: lungs: alveolar histiocytosis, kidneys: lympho-histiocytic infiltrations; **20 mg/kg body weight**: body weights ↓ (♂: up to −34%, ♀: up to −22%), body weight gains ↓ (end of study: ♂: −35%, ♀: −19%), feed consumption ↑, haematology: test week 52: number of leukocytes ↑, reticulocytes ↓, platelets ↑, neutrophilic granulocytes ↑, lymphocytes ↑, monocytes ↑, MCV ↓, MCH ↓, MCHC ↓; plasma: urea ↑, AST ↑, LDH ↑, ♂: mortality 40% (8/20), absolute liver weights ↓, lungs: discoloured or reddened, bone marrow: myeloid/erythroid ratio, plasma: albumin ↓, cholesterol ↓, glucose ↓, total protein ↓, prostate: purulent inflammation; lungs: alveolar histiocytosis; ♀: absolute kidney weights ↑, plasma: chloride ↓, kidneys: basophilic tubular cells, heart: lympho-histiocytic myocarditis, degeneration of muscle cells, skeletal muscles: lympho-histiocytic infiltrations	Akzo Nobel Surface Chemistry AB and Lonza AG 2011; ECHA 2015 d
rat, Crl:CD(SD), 50 ♂ and 50 ♀	**up to 104 weeks**, diet, 0, 4, 8 mg/kg body weight and day for 104 weeks, 20 mg/kg body weight and day: reduced to 15 mg/kg body weight and day in week 51 and to 12 mg/kg body weight and day in week 56 (♂) or 59 (♀) because of increased mortality, each related to *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine, treatment discontinued in week 61 (♂) or 81 (♀), end of study in week 65 (♂) or 86 (♀), purity: 89.4%, OECD Test Guideline 453	histopathological findings in detail: see Table 3; **no NOAEL systemic toxicity**; **4 mg/kg body weight and above**: mesenteric lymph nodes: macrophages with homogeneous/vacuolated cytoplasm ↑ (caused by accumulation of the test substance in macrophages); ♂: heart: degeneration of muscle cells, skeletal muscles: lympho-histiocytic infiltrations; **8 mg/kg body weight and above**: mortality ↑, body weight gains ↓ (up to test week 103: ♂: −41%, ♀: −18%), heart: granulation tissue/fibrosis, kidneys: chronic nephropathy; ♂: plasma: glucose ↓, total protein, albumin, globulin, AST ↑, skeletal muscles: degeneration of muscle cells; **20/15/12 mg/kg body weight**: body weights ↓; relative heart and kidney weights ↑ (caused by reduced body weights), haematology: haemoglobin ↓, haematocrit ↓, MCV ↓, leukocytes ↑, reticulocytes ↑, platelets ↑, urine: slight decrease in pH, heart: lympho-histiocytic myocarditis, larynx: lympho-histiocytic myositis; ♂: plasma: creatinine ↑, urea ↑, LDH ↑; urine: slight increase in haemoglobin, heart: cartilaginous metaplasia; ♀: plasma: glucose ↓, total protein, albumin, globulin, AST ↑, heart: degeneration of muscle cells, large thrombi in the atrium, skeletal muscles: lympho-histiocytic infiltrations	Akzo Nobel Surface Chemistry AB and Lonza AG 2011; ECHA 2015 d

Tab. 1 *(continued)*

Species, strain, number per group	Exposure	Findings	References
dog, beagle, 4 ♂ and 4 ♀	**90 days**, 0, 200, 500, 1500 mg/kg diet, 0, 8, 20, 55.1/52.6 mg/kg body weight and day, each related to *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine, 30% aqueous solution, OECD Test Guideline 409	**8 mg/kg body weight**: ♀: **NOAEL** AST and ALT, **20 mg/kg body weight**: ♂: **NOAEL** AST and ALT, **20 mg/kg body weight and above**: ♀: plasma: AST ↑ (2.5-fold of control, 55.1/52.6 mg/kg body weight: 2.7-fold, not increased after 6 weeks) and ALT ↑ (2.1-fold, 55.1/52.6 mg/kg body weight: 3.0-fold, not increased after 6 weeks); **55.1/52.6 mg/kg body weight**: body weights ↓ (♂: up to −18%, ♀: up to −12%, statistically not significant in both cases), feed consumption ↓ (♂: up to −28%, ♀: up to −33%), ♂: plasma: AST ↑ (3.7-fold) and ALT ↑ (2.6-fold, not increased after 6 weeks); ♀: plasma: potassium ↑ (+19%), relative gallbladder weights (+72%)	ECHA 2015 d; Lonza AG 2004

ALT: alanine aminotransferase; AST: aspartate aminotransferase; FOB: functional observational battery; LDH: lactate dehydrogenase; MCV: mean erythrocyte volume; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; NOAEL: no observed adverse effect level

Tab. 2 Histopathological findings of the 13-week feeding study in rats (Akzo Nobel Surface Chemistry AB 2002 a; ECHA 2015 d): incidences (in percent) at the end of the study

Organ findings	Controls	7 (♂)/8 (♀) mg/kg body weight and day	20 (♂)/22 (♀) mg/kg body weight and day	57 (♂)/65 (♀) mg/kg body weight and day
kidneys				
number of animals examined	♂: 10 ♀: 10	♂: 10 ♀: 10	♂: 10 ♀: 10	♂: 10 ♀: 10
degeneration/necrosis of the tubular epithelium	♂: 0 ♀: 0	♂: 0 ♀: 0	♂: 9 (90%) ♀: 4 (40%)	♂: 10 (100%) ♀: 9 (90%)
tubular dilation with flattened epithelium	♂: 0 ♀: 0	♂: 0 ♀: 0	♂: 6 (60%) ♀: 4 (40%)	♂: 10 (100%) ♀: 8 (80%)
tubular basophilia	♂: 2 (20%) ♀: 0	♂: 0 ♀: 0	♂: 10 (100%) ♀: 6 (60%)	♂: 10 (100%) ♀: 3 (30%)
mesenteric lymph nodes				
number of animals examined	♂: 10 ♀: 10	♂: 10 ♀: 10	♂: 10 ♀: 10	♂: 9 ♀: 10
foamy macrophages	♂: 0 ♀: 0	♂: 3 (30%) ♀: 1 (10%)	♂: 10 (100%) ♀: 10 (100%)	♂: 9 (100%) ♀: 10 (100%)

heart and lungs examined in the high dose group and control group: microscopic examination without unusual findings, skeletal muscles not examined microscopically, no statistical analysis of histopathological findings

Tab. 3 Histopathological findings of the 52-week and 104-week feeding studies in rats (Akzo Nobel Surface Chemistry AB and Lonza AG 2011; ECHA 2015 d): incidences (in percent) [average severity] at the end of the studies

Organ findings	Controls	4 mg/kg body weight and day	8 mg/kg body weight and day	20/15/12 mg/kg body weight and day
heart				
52 weeks				
number of animals examined	♂: 10 ♀: 10	♂: 10 ♀: 10	♂: 10 ♀: 10	♂: 11 ♀: 20
lympho-histiocytic myocarditis	♂: 0 ♀: 0	♂: 1 (10%) [0.13] ♀: 0	♂: 5 (50%)* [0.50] ♀: 0	♂: 11 (100%)*** [2.68] ♀: 16 (80%)*** [1.16]
degeneration of muscle cells	♂: 0 ♀: 0	♂: 0 ♀: 0	♂: 2 (20%) [0.05] ♀: 0	♂: 11 (100%)*** [2.55] ♀: 7 (35%) [0.50]

Tab. 3 *(continued)*

Organ findings	Controls	4 mg/kg body weight and day	8 mg/kg body weight and day	20/15/12 mg/kg body weight and day
granulation tissue/fibrosis	♂: 2 (20%) [0.15] ♀: 0	♂: 1 (10%) [0.23] ♀: 0	♂: 1 (10%) [0.15] ♀: 1 (10%) [0.03]	♂: 7 (64%)* [1.36] ♀: 2 (10%) [0.10]
104 weeks				
number of animals examined	♂: 22 ♀: 29	♂: 26 ♀: 15	♂: 24 ♀: 30	♂: 10 ♀: 12
lympho-histiocytic myocarditis	♂: 2 (9%) [0.06] ♀: 2 (7%) [0.06]	♂: 5 (19%) [0.16] ♀: 2 (13%) [0.03]	♂: 1 (4%) [0.10] ♀: 0	♂: 10 (100%)*** [2.55] ♀: 10 (83%)*** [1.83]
degeneration of muscle cells	♂: 0 ♀: 0	♂: 16 (62%)*** [0.44] ♀: 6 (40%)*** [0.28]	♂: 14 (58%)*** [0.84] ♀: 1 (3%) [0.05]	♂: 10 (100%)*** [1.85] ♀: 12 (100%)*** [1.40]
granulation tissue/fibrosis	♂: 12 (55%) [0.74] ♀: 11 (38%) [0.37]	♂: 19 (73%) [0.83] ♀: 7 (47%) [0.37]	♂: 23 (96%)** [1.75] ♀: 25 (83%)*** [0.72]	♂: 10 (100%)* [2.40] ♀: 12 (100%)*** [1.65]
lungs				
52 weeks				
number of animals examined	♂: 10 ♀: 10	♂: 10 ♀: 10	♂: 10 ♀: 10	♂: 11 ♀: 19
alveolar histiocytosis	♂: 0 ♀: 0	♂: 4 (40%) [0.25] ♀: 4 (40%) [0.23]	♂: 3 (30%) [0.20] ♀: 6 (60%)* [0.52]	♂: 9 (82%)*** [0.89] ♀: 13 (68%)*** [0.45]
104 weeks				
number of animals examined	♂: 22 ♀: 29	♂: 26 ♀: 15	♂: 24 ♀: 30	♂: 10 ♀: 12
alveolar histiocytosis	♂: 5 (23%) [0.16] ♀: 15 (52%) [0.47]	♂: 15 (58%)* [0.48] ♀: 8 (53%) [0.38]	♂: 14 (58%)* [0.64] ♀: 23 (77%) [1.03]	♂: 5 (50%) [0.40] ♀: 10 (83%) [0.92]
skeletal muscle, leg				
52 weeks				
number of animals examined	♂: 10 ♀: 10	♂: 10 ♀: 10	♂: 10 ♀: 10	♂: 11 ♀: 20
lympho-histiocytic infiltrations	♂: 0 ♀: 0	♂: 0 ♀: 1 (10%) [0.03]	♂: 6 (60%)* [0.43] ♀: 2 (20%) [0.08]	♂: 4 (36%) [0.55] ♀: 11 (55%)** [0.73]
degeneration of myofibrils	♂: 0 ♀: no data	♂: 0 ♀: no data	♂: 2 (20%) [0.05] ♀: no data	♂: 0 ♀: no data
104 weeks				
number of animals examined	♂: 22 ♀: 29	♂: 26 ♀: 14	♂: 24 ♀: 30	♂: 10 ♀: 12
lympho-histiocytic infiltrations	♂: 0 ♀: 0	♂: 7 (27%)* [0.30] ♀: 0	♂: 14 (58%)*** [0.31] ♀: 0	♂: 6 (60%)** [1.05] ♀: 3 (25%)* [0.19]
degeneration of muscle cells	♂: 0 ♀: 0	♂: 4 (15%) [0.15] ♀: 0	♂: 9 (38%)** [0.30] ♀: 1 (3%) [0.05]	♂: 5 (50%)** [0.60] ♀: 1 (8%) [0.10]
kidneys				
52 weeks				
number of animals examined both kidneys examined: 1 and 2	♂: 10 ♀: 10	♂: 10 ♀: 10	♂: 10 ♀: 10	♂: 11 ♀: 20
1 lympho-histiocytic infiltrations	♂: 8 (80%) [0.43] ♀: 0	♂: 8 (80%) [0.75] ♀: 2 (20%) [0.05]	♂: 9 (90%) [0.63] ♀: 5 (50%)* [0.20]	♂: 10 (91%) [1.50] ♀: 14 (70%)*** [0.75]
1 basophilic tubular cells	♂: 2 (20%) [0.10] ♀: 0	♂: 7 (70%) [0.58] ♀: 0	♂: 8 (80%)* [0.60] ♀: 4 (40%) [0.15]	♂: 11 (100%)*** [2.00] ♀: 9 (45%)* [0.52]
2 lympho-histiocytic infiltrations	♂: 7 (70%) [0.58] ♀: 0	♂: 7 (70%) [0.38] ♀: 0	♂: 8 (80%) [0.65] ♀: 4 (40%) [0.13]	♂: 10 (91%) [1.41] ♀: 14 (70%)*** [0.48]

Tab. 3 *(continued)*

Organ findings	Controls	4 mg/kg body weight and day	8 mg/kg body weight and day	20/15/12 mg/kg body weight and day
2 basophilic tubular cells	♂: 1 (10%) [0.03] ♀: 0	♂: 4 (40%) [0.28] ♀: 0	♂: 8 (80%)** [0.45] ♀: 3 (30%) [0.08]	♂: 11 (100%)*** [1.43] ♀: 12 (60%)** [0.51]
104 weeks				
number of animals examined	♂: 22 ♀: 29	♂: 26 ♀: 15	♂: 24 ♀: 30	♂: 10 ♀: 12
lympho-histiocytic infiltrations	♂: 10 (45%) [0.51] ♀: 6 (21%) [0.06]	♂: 3 (12%)* [0.08] ♀: 6 (40%) [0.25]	♂: 1 (4%)** [0.06] ♀: 7 (23%) [0.23]	♂: 0* ♀: 0
chronic nephropathy, bilateral	♂: 9 (41%) [0.86] ♀: 0	♂: 12 (46%) [0.58] ♀: 0	♂: 23 (96%)*** [2.04] ♀: 11 (37%)*** [0.50]	♂: 10 (100%)** [2.30] ♀: 8 (67%)*** [1.08]
mesenteric lymph nodes				
52 weeks				
number of animals examined	♂: 10 ♀: 10	♂: 10 ♀: 9	♂: 10 ♀: 10	♂: 11 ♀: 19
large macrophages with cytoplasmic vacuoles	♂: 0 ♀: 0	♂: 9 (90%)*** [1.23] ♀: 8 (89%)*** [1.44]	♂: 10 (100%)*** [1.50] ♀: 9 (90%)*** [1.40]	♂: 7 (64%)** [1.36] ♀: 16 (84%)*** [1.47]
104 weeks				
number of animals examined	♂: 22 ♀: 29	♂: 26 ♀: 15	♂: 24 ♀: 30	♂: 9 ♀: 12
number of macrophages with eosinophilic homogeneous/vacuolated cytoplasm	♂: 0 ♀: 5 (17%) [0.28]	♂: 23 (88%)*** [1.77] ♀: 9 (60%)** [0.73]	♂: 21 (88%)*** [1.96] ♀: 30 (100%)*** [2.37]	♂: 9 (100%)*** [2.78] ♀: 11 (92%)*** [1.92]

*$p \le 0.05$; **$p \le 0.01$; ***$p \le 0.001$ (Fisher's exact test)

A feeding study carried out in Sprague Dawley rats for 13 weeks yielded the following findings in the males at doses of 20 mg/kg body weight and day and above and in the females at doses of 22 mg/kg body weight and day and above: effects on the kidneys in the form of tubular nephropathy with degeneration and necrosis of the tubular epithelium, tubular dilation with flattened epithelium and tubular basophilia, and effects on the mesenteric lymph nodes such as enlargement and foamy macrophages. The changes in the heart and lungs observed after long-term exposure (see the study described below, which was carried out according to OECD Test Guideline 453) were not found in the highest dose group tested. The study did not include an examination of the skeletal muscles, which were likewise affected after long-term exposure. The NOAEL for the effects of *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine on the kidneys and lymph nodes was 7 mg/kg body weight and day for males and 8 mg/kg body weight and day for females (Akzo Nobel Surface Chemistry AB 2002 a; ECHA 2015 d). The study did not investigate the reversibility of the effects.

In a feeding study in Crl:CD(SD) rats carried out for 52 weeks according to OECD Test Guideline 453 (combined study of toxicity after repeated administration and carcinogenicity, see also Section 5.7), the incidences of lympho-histiocytic myocarditis, lympho-histiocytic infiltrations in the skeletal muscles and basophilic tubular cells in the kidneys were increased in males and the incidences of alveolar histiocytosis in the lungs and lympho-histiocytic infiltrations in the kidneys were increased in females at doses of 8 mg/kg body weight and day and above. Increased incidences of large macrophages with cytoplasmic vacuoles were observed in the mesenteric lymph nodes at the lowest dose tested of 4 mg/kg body weight and day and above; however, the incidences and severity of these changes were not dose-dependent. Therefore, this local, physiological effect was interpreted as a response to the ingestion of a lipophilic and corrosive substance and was not regarded as adverse. The NOAEL for the effects of *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine on the skeletal muscles, heart, kidneys and lungs was 4 mg/kg body weight and day (Akzo Nobel Surface Chemistry AB and Lonza AG 2011; ECHA 2015 d).

After 104-week exposure in the study described above, degeneration of heart muscle cells (incidence: 16/26 corresponds to 62%; average severity: 0.44) and lympho-histiocytic infiltrations in the skeletal muscles (7/26 corresponds to 27%; 0.30) were observed in male rats at 4 mg/kg body weight and day and above; the incidences and severity of these changes increased with the dose. In the females, the effects on the heart muscle cells were not dose-dependent. In male and female animals, the incidences of macrophages with homogeneous, vacuolated cytoplasm were increased in the

mesenteric lymph nodes at doses of 4 mg/kg body weight and day and above; they were caused by the accumulation of the test substance in the macrophages (Akzo Nobel Surface Chemistry AB and Lonza AG 2011; ECHA 2015 d). It was not possible to derive a NOAEL for systemic toxicity.

In a study in beagle dogs carried out according to OECD Test Guideline 409 for 90 days, AST and ALT activities were increased in the plasma at *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine doses of 20 mg/kg body weight and day and above, but no histopathological changes were observed in the liver. The authors did not consider these changes to be adverse; therefore, this dose was established as the NOAEL (ECHA 2015 d; Lonza AG 2004). However, the activities of the enzymes AST and ALT were increased to more than twice the control value, which is regarded as adverse (Hall et al. 2012). Therefore, a NOAEL for increased AST and ALT activities of 8 mg/kg body weight and day was obtained from this study for female animals. For male animals, the corresponding NOAEL was 20 mg/kg body weight and day.

Summary: After 13-week administration with the diet, effects on the kidneys and mesenteric lymph nodes were observed in male **Sprague Dawley rats** at 20 mg/kg body weight and day and above and in the females at 22 mg/kg body weight and day and above (Akzo Nobel Surface Chemistry AB 2002 a; ECHA 2015 d). The NOAEL was 7 mg/kg body weight and day. After administration of the substance with the diet for 52 weeks, the NOAEL was 4 mg/kg body weight and day; at 8 mg/kg body weight and day and above, effects on the heart and skeletal muscles were additionally observed in male **Crl:CD(SD) rats** (Akzo Nobel Surface Chemistry AB and Lonza AG 2011; ECHA 2015 d). After 104-week exposure (Akzo Nobel Surface Chemistry AB and Lonza AG 2011; ECHA 2015 d), the LOAEL (lowest observed adverse effect level) was 4 mg/kg body weight and day with findings in the heart and skeletal muscles; it was not possible to derive a NOAEL. In female **beagle dogs**, hepatotoxicity was observed after administration with the diet for 13 weeks (ECHA 2015 d; Lonza AG 2004). The NOAEL was 8 mg/kg body weight and day.

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

In a study in New Zealand White rabbits carried out according to OECD Test Guideline 404, 0.5 ml undiluted *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine (purity: 85.3%) was applied semi-occlusively to the shaved skin of a male rabbit. Following 3-minute application to the left flank, moderate to severe erythema (score 3) and slight oedema (score 2) were determined at the 1-hour reading and slight necrosis of the whole treated area of skin was observed at the examination after 24 hours. When the test substance was applied to the right flank for 4 hours, brownish discoloration of the treated skin with moderate to severe erythema (score 3) together with severe oedema (maximum score: 4) was observed at the reading after 1 hour; after 20 hours, the whole treated area of skin was necrotic. The study was discontinued because of the severe skin reactions. The substance was regarded as corrosive to the rabbit skin (Akzo Nobel Surface Chemistry AB 2002 b; ECHA 2015 d).

Several fatty amine derivatives including *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine were investigated using the EpiDerm™ model with reconstructed human epidermis. The in vitro study correctly identified only *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine as corrosive; however, the high percentage of viable cells (42%) after 1 hour did not support the severe corrosive effects observed in the in vivo study. The dermal effects of the amines tested are characterized by delayed inflammatory reactions (Houthoff et al. 2015).

5.3.2 Eyes

There are no data available.

5.4 Allergenic effects

In a Buehler test with 20 Dunkin Hartley guinea pigs, the topical induction was carried out with 1% *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine (30.2% raw material) in distilled water (minimum irritant concentration) and the occlusive challenge was carried out with 0.5% *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine in distilled water (maximum non-irritant concentration; effective concentration: 0.15%). No reaction indicative of sensitization was observed in any of the 20 animals either after 24 or after 48 hours. Mild, in some cases slightly infiltrated erythema and dryness and sloughing of the epidermis were found in 5 of 20 animals 24 hours after the challenge treatment; the same symptoms were still observed in 4 of 20 animals after 48 hours. These skin changes were found in another 2 animals only after 48 hours. Similar skin reactions occurred in 3 and 1 of the control animals after 24 and 48 hours, respectively (Akzo Nobel Surface Chemistry AB 1996; ECHA 2015 d). The results of this test are regarded as negative because reactions were found also in the control animals.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

In a 2-generation study carried out according to OECD Test Guideline 416, *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine was given to Sprague Dawley rats by gavage as a 30.2% aqueous solution (see Table 4). The *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine doses were 0, 3, 9 or 27 mg/kg body weight and day. Groups of 28 male and 28 female animals (F0) per dose were treated 10 weeks before mating and then throughout the mating, gestation and lactation periods until weaning of the pups. From each group, 24 males and 24 females of the F1 generation were selected and treated continuously from postnatal day 25 until weaning of the F2 generation. At a dose level of 27 mg/kg body weight and day, the following effects were found in the parental animals of the F0 and F1 generations: marked decreases in body weight gains in the males and females before mating and during gestation and slight decreases in feed consumption, dyspnoea, piloerection, hunched posture, salivation in some animals and occasionally a prominent outline of the spine. Eight animals of the high dose group (2 male F0 animals, 3 female F0 animals, 1 male F1 animal and 2 female F1 animals) died as a result of the treatment or they were sacrificed. Another death (1 female F1 animal) in this dose group may also have been related to treatment with the substance. At 9 mg/kg body weight and day, only salivation was occasionally observed in the animals of both generations; this finding was not considered to be a sign of systemic toxicity. At 27 mg/kg body weight and day, the mean seminal vesicle weights were reduced in the animals of both generations compared with those of the control animals; this finding was regarded as an indirect effect of the reduced body weights rather than as a direct effect on the seminal vesicles. Mating behaviour, fertility, the duration of gestation, litter size, and pup survival were similar in all groups. At 27 mg/kg body weight and day, the mean litter weights and body weights of the F2 pups were slightly reduced compared with those of the controls; although these differences were probably incidental, it is possible that they represent a slight treatment-induced effect. In the F1 pups, there were no differences between the values of these parameters in the dose groups and in the controls. During the late lactation period, tremor was observed in 1 pup of the F0 and 1 pup of the F1 animals of the group treated with 27 mg/kg body weight; an association was established with the test substance administered. The NOAEL for the effects of *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine on fertility was 27 mg/kg body weight and day and the NOAEL for parental toxicity and foetotoxicity induced by *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine was 9 mg/kg body weight and day (Akzo Nobel Surface Chemistry AB 1995; ECHA 2015 d).

5.5.2 Developmental toxicity

The studies that investigated the developmental toxicity of *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine are shown in Table 4.

Tab. 4 Prenatal developmental toxicity studies after oral administration of *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 25 ♀	**GD 6–16**, 0, 7.5, 22.5, 60 mg *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine/kg body weight and day, gavage, aqueous solution: 30.2%, examination: GD 20, OECD Test Guideline 414	**7.5 mg/kg body weight**: **NOAEL** maternal toxicity; **22.5 mg/kg body weight**: **NOAEL** developmental toxicity; **22.5 mg/kg body weight and above**: dams: feed consumption ↓ (9%, 60 mg/kg body weight: 18%), dyspnoea, salivation, piloerection, reduced activity; **60 mg/kg body weight**: foetuses: early embryonic deaths ↑ (possibly secondary effect of maternal toxicity), average foetal weights ↓ (not statistically significant), dams: body weight gains ↓ (GD 6–17: 28%), 2 animals sacrificed prematurely and intestinal distension at necropsy	Akzo Nobel Surface Chemistry AB 1994; ECHA 2015 d
rabbit, Himalayan, 24 ♀ (control group and 9 mg/kg body weight group) or 30 ♀ (6 and 20 mg/kg body weight groups)	**GD 6–28**, 0, 6, 9, 20 mg *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine/kg body weight and day, gavage, aqueous solution 30.2%, examination: GD 29, OECD Test Guideline 414	**6 mg/kg body weight and above**: dams: early resorptions ↑ (not at 9 mg/kg body weight, not substance-induced), foetuses: number of live foetuses ↓ (controls, 6, 9, 20 mg/kg body weight and day: total number of live foetuses/dams: 120/19, 113/20, 102/20, 107/20, number of live foetuses per dam: 6.3, 5.7, 5.1, 5.4, but within the range of the historical controls[a] and therefore regarded as spontaneous); **9 mg/kg body weight**: **NOAEL** maternal toxicity and developmental toxicity; **20 mg/kg body weight**: dams: death of 2 animals (1 animal at necropsy with reddened lungs induced by the test substance, no data for the 2nd animal), body weight gains ↓ (GD 21–24) and feed consumption ↓ (up to 36%), gravid uterus weights ↓ (23%, contributing factor: early post-implantation loss in 2 dams during early gestation), reddened pyloric region in the stomach (5/29 animals), number of early resorptions ↑ (17/22 pregnant dams at caesarean section, 1/19 control animals); foetuses: number of late resorptions ↑ (6/22, 0/10 control animals)	Akzo Nobel Surface Chemistry AB 2005; ECHA 2015 d
rat, Sprague Dawley, F0: 28 ♂ and 28 ♀, F1: 24 ♂ and 24 ♀	**2-generation study**, 0, 3, 9, 27 mg *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine/kg body weight and day, gavage, aqueous solution: 30%, OECD Test Guideline 416	**9 mg/kg body weight**: **NOAEL** parental toxicity and foetotoxicity; **27 mg/kg body weight**: **NOAEL** fertility; **27 mg/kg body weight**: F0 and F1 animals: mortality ↑, marked decreases in body weight gains, slight decreases in feed consumption, dyspnoea, piloerection, hunched posture, salivation in some animals and occasionally a prominent outline of the spine, seminal vesicle weights ↓ (indirect effect), tremor in 2 animals (1 pup of an F0 animal and 1 pup of an F1 animal); F2 animals: slight decreases in mean litter weights and pup body weights	Akzo Nobel Surface Chemistry AB 1995; ECHA 2015 d; Section 5.5.1

[a] range of the historical controls from 2000 to 2003, 24 groups, 464 pregnant dams, spontaneous incidences: number of live and dead foetuses per dam: 6.0 ± 0.54; dead foetuses per dam: 0.01 ± 0.02

GD: gestation day

In a prenatal developmental toxicity study carried out according to OECD Test Guideline 414 in Sprague Dawley rats, *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine administered as a 30.2% solution by gavage increased the incidences of early embryonic deaths at a dose of 60 mg/kg body weight and day. The 3 dams with the highest numbers of early embryonic deaths were among the 5 dams with body weight losses between gestation days 9 and 13. This indicates that the early deaths may have been secondary effects of maternal toxicity. Teratogenic effects were not observed. The NOAEL for maternal toxicity induced by *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine was 7.5 mg/kg body weight and day and for developmental toxicity 22.5 mg/kg body weight and day (Akzo Nobel Surface Chemistry AB 1994; ECHA 2015 d).

In a prenatal developmental toxicity study carried out according to OECD Test Guideline 414 in Himalayan rabbits, *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine administered as a 30.2% aqueous solution by gavage caused the following effects in the dams at 20 mg/kg body weight and day: increased mortality, reduced body weights and feed consumption, reduced uterus weights and irritation in the gastrointestinal tract. The incidences of early and late resorptions

were increased at this dose level; these may be secondary effects of maternal toxicity. The number of live foetuses was reduced at the dose level of 6 mg/kg body weight and day, but still within the range reported for the historical controls from 2000 to 2003; this effect is therefore regarded as spontaneous. *N′*-(3-Aminopropyl)-*N′*-dodecylpropane-1,3-diamine was not teratogenic. The NOAEL for maternal toxicity and developmental toxicity induced by *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine was 9 mg/kg body weight and day (Akzo Nobel Surface Chemistry AB 2005; ECHA 2015 d). On the basis of the study, it remains unclear whether the increased incidences of early and late resorptions may be regarded as secondary effects of maternal toxicity.

A NOAEL for foetotoxicity of 9 mg/kg body weight and day was derived for *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine from the 2-generation study in Sprague Dawley rats with gavage administration (see Section 5.5.1; Akzo Nobel Surface Chemistry AB 1995; ECHA 2015 d).

Summary: *N′*-(3-Aminopropyl)-*N′*-dodecylpropane-1,3-diamine did not cause teratogenic effects in rats or in rabbits. Developmental toxicity was observed only in combination with maternal toxicity. The NOAEL for developmental toxicity was 22.5 mg/kg body weight and day in rats (Akzo Nobel Surface Chemistry AB 1994; ECHA 2015 d) and 9 mg/kg body weight and day in rabbits (Akzo Nobel Surface Chemistry AB 2005; ECHA 2015 d). A NOAEL for foetotoxicity and parental toxicity of 9 mg/kg body weight and day was derived for *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine from the 2-generation study in Sprague Dawley rats with gavage administration (Akzo Nobel Surface Chemistry AB 1995; ECHA 2015 d).

5.6 Genotoxicity

5.6.1 In vitro

The in vitro genotoxicity studies are shown in Table 5.

Tab. 5 Genotoxicity of *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine in vitro

End point	Test system	Concentration [µg/plate][a)]	Cytotoxicity [µg/plate][a)]	Results		References
				–m. a.	+m. a.	
gene mutation, (plate incorporation)	Salmonella typhimurium TA98, TA100, TA102, TA1535, TA1537, OECD Test Guideline 471	–m. a.: experiment 1: TA98, TA1537: 0, 6.25, 12.5, 25, 50, 100; other strains: 0, 12.5, 25, 50, 100, 200, experiment 2: TA98, TA1535, TA1537: 0, 3.125, 6.25, 12.5, 25, 50; TA100, TA102: 0, 12.5, 25, 50, 100, 200, +m. a.: 0, 12.5, 25, 50, 100, 200, vehicle: distilled water, purity: 85.3%	–m. a.: 50 and above +m. a.: 100 and above	–	–	Akzo Nobel Surface Chemistry AB 2002 d; ECHA 2015 d
gene mutation, (pre-incubation)	Salmonella typhimurium TA98, TA100, TA102, TA1535, TA1537, OECD Test Guideline 471	+m. a. TA98, TA1535, TA1537: 0, 3.125, 6.25, 12.5, 25, 50; TA100, TA102: 0, 12.5, 25, 50, 100, 200, vehicle: distilled water, purity: 85.3%	50 and above	–	–	Akzo Nobel Surface Chemistry AB 2002 d; ECHA 2015 d

Tab. 5 *(continued)*

End point	Test system	Concentration [µg/plate][a)]	Cytotoxicity [µg/plate][a)]	Results		References
				–m. a.	+m. a.	
CA	human lymphocytes, OECD Test Guideline 473	experiment 1: –m. a., 3 hours: 0, 0.41, 1.23, 3.69 µg/ml, +m. a., 3 hours: 0, 0.41, 1.23, 3.69 µg/ml, experiment 2: –m. a., 20 hours: 0, 2.5, 5, 7.5 µg/ml, –m. a., 44 hours: 0, 7.5 µg/ml, +m. a.: 3 hours: 0, 1.25, 2.5, 5 µg/ml; vehicle: culture medium, purity: 85.3%	–m. a.: 3 hours: 11.07 µg/ml and above; 20 hours: up to 7.5 µg/ml: no cytotoxicity; 44 hours: 7.5 µg/ml and above; +m. a.: 3 hours: 5 µg/ml and above	–	–	Akzo Nobel Surface Chemistry AB 2002 f; ECHA 2015 d
gene mutation $TK^{+/-}$	L5178Y mouse lymphoma cells, OECD Test Guideline 476	experiment 1 –m. a., 3 hours: 0, 0.31, 0.63, 1.25, 2.5, 5, 10 µM; +m. a., 3 hours: 0.63, 1.25, 2.5, 5, 10, 20 µM; experiment 2 –m. a., 24 hours: 0.063, 0.125, 0.25, 0.5, 0.75, 1 µM; +m. a., 3 hours: 0, 0.63, 1.25, 2.5, 5, 10, 15 µM; vehicle: culture medium, purity: 85.3%	–m. a.: 3 hours: 10 µM and above, 24 hours: 0.75 µM and above; +m. a.: 10 µM and above	–	–	Akzo Nobel Surface Chemistry AB 2002 e; ECHA 2015 d

[a)] unless otherwise specified, values expressed as µg/plate and as *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine
CA: chromosomal aberrations; +/–m. a.: with/without the addition of a metabolic activation system

In bacterial gene mutation tests carried out according to OECD Test Guideline 471, *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine was not mutagenic in the Salmonella strains TA98, TA100, TA102, TA1535 and TA1537 either with or without the addition of a metabolic activation system (Akzo Nobel Surface Chemistry AB 2002 d; ECHA 2015 d). In a study in human lymphocytes carried out according to OECD Test Guideline 473, the substance did not increase the incidences of chromosomal aberrations either with or without the addition of a metabolic activation system (Akzo Nobel Surface Chemistry AB 2002 f; ECHA 2015 d). The $TK^{+/-}$ test carried out in L5178Y mouse lymphoma cells with *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine according to OECD Test Guideline 476 did not reveal a mutagenic or clastogenic potential either with or without the addition of a metabolic activation system (Akzo Nobel Surface Chemistry AB 2002 e; ECHA 2015 d).

5.6.2 In vivo

There are no data available.

5.6.3 Summary

As *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine was not mutagenic or clastogenic in the available studies in vitro, no genotoxic potential is expected.

5.7 Carcinogenicity

In a study carried out according to OECD Test Guideline 453 in 50 male and 50 female Crl:CD(SD) rats per group, *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine (purity: 89.4%) was given with the diet at dose levels of 0, 4 or 8 mg/kg body weight and day for a planned period of 104 weeks. The highest dose tested of 20 mg/kg body weight and day was reduced to 15 mg/kg body weight and day in test week 51 because of increased mortality. For the same

reason, the dose was reduced further to 12 mg/kg body weight and day in test week 56 for the male animals and in test week 59 for the female animals. In this dose group, the study was discontinued in test week 65 for the males and in test week 86 for the females. At the end of the study, the survival for the males and females was 44% and 58% in the control group, 52% and 32% in the 4 mg/kg body weight group, and 50% and 62% in the 8 mg/kg body weight group; in the high dose group, survival was 20% for the males in test week 65 and 24% for the females in test week 86. Compared with the control animals, no statistically significant increases in the tumour incidences were found after administration of *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine (see Section 5.2.2; Akzo Nobel Surface Chemistry AB and Lonza AG 2011; ECHA 2015 d).

6 Manifesto (MAK value/classification)

The critical systemic effects of *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine are degenerative changes of heart muscle cells and lympho-histiocytic infiltrations in the skeletal muscles of male rats. The substance is corrosive to the rabbit skin. Similar effects on the respiratory tract are expected.

MAK value. There are no data available from humans or from inhalation studies in animals.

After exposure via the diet for 104 weeks, degenerative changes of heart muscle cells and lympho-histiocytic infiltrations in the skeletal muscles were observed in male rats at the lowest dose tested of 4 mg/kg body weight and day and above (Akzo Nobel Surface Chemistry AB and Lonza AG 2011; ECHA 2015 d). Based on a LOAEL of 4 mg/kg body weight and day, one-third of the dose, that is 1.3 mg/kg body weight and day, can be assumed to be the NAEL.

The following toxicokinetic data are taken into consideration for the extrapolation of the 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 correction value for the rat (1:4), the experimentally determined oral absorption (2.5%; ECHA 2015 d; Lonza Ltd 1996), the body weight (70 kg) and respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 0.08 mg/m^3. As this value comes from experimental studies with animals, a corresponding concentration of 0.04 mg/m^3 can be derived for humans according to the procedure of the Commission (see List of MAK and BAT Values, Section I, extrapolation from animals to humans 1:2). However, since the low oral absorption used for the extrapolation has to be considered as the worst case, a MAK value of 0.05 mg *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine /m^3 has been established for the inhalable fraction. The vapour saturation concentration is 0.017 mg/m^3; the compound thus occurs mainly as an aerosol. In view of the low oral absorption and the assumed 100% absorption by inhalation, the derivation of the MAK value is to be regarded as conservative.

In view of the corrosive effects of *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine on the rabbit skin, local irritation of the airways is likely. As there are no inhalation studies available, different amines are used for comparison. Primary amines such as methylamine, ethylamine, *n*-butylamine, the secondary amine diethanolamine and tertiary amines such as trimethylamine, triethylamine and triethanolamine have a MAK value between 1 and 13 mg/m^3. Based on the pKa values, *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine is less alkaline in comparison with the primary amines methylamine, ethylamine and n-butylamine and the tertiary amines trimethylamine and triethylamine. Compared with the secondary amine diethanolamine, which has a MAK value of 1 mg/m^3, *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine has a similar pKa value (9, compared with 8.88 for diethanolamine); it is slightly more alkaline (see Table 6). This is supported by an evaluation of the workplace threshold limit values in the TRGS 900 in Germany, which found that corrosive substances (for which the corrosive effect was the critical effect for the derivation of the threshold limit value at the workplace) have threshold limit values of not lower than 1 mg/m^3. Sulfuric acid, with a threshold limit value of 0.1 mg/m^3, forms an exception based on the effect of its high hydrophilia and strongly acidic effect on mucociliary clearance (Messinger 2014). A MAK value of 0.05 mg *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine/m^3 should therefore be sufficient to prevent local irritation.

Tab. 6 Comparison of amines

Substance	Molar mass	Physical state	pKa	Irritation index rabbit eye	MAK value (ml/m³)	MAK value (mg/m³)
primary amines						
methylamine	31.06	gaseous	10.62[a)]	severe irritation to necrosis[c)]	10	13
ethylamine	45.08	gaseous	10.87[a)]	undiluted: 9/10[b)]	5	9.4
n-butylamine	73.14	liquid	10.78[c)]	undiluted: corrosive[c)], severe opacity cornea 3/4 irreversible[b)]	2	6.1
secondary amines						
diethanolamine	105.14	solid	8.88 at 25 °C (aqueous solution)[c)]	100 mg: 41–56/110[c)]	(0.23)[d)]	1 I
tertiary amines						
trimethylamine	59.11	gaseous	9.80[a)]	45%: cornea: 2.5/4; iris 1/2; conjunctivae: 2/3; chemosis: 2.4/4; irreversible, purulent exudate[b)]	2	4.9
triethylamine	101.19	liquid	10.78[a)]	undiluted: corrosive[c)] opacity cornea irreversible[b)]	1	4.2
triethanolamine	149.19	liquid	7.86 at 25 °C[b)]	undiluted: 1–4/110[c)]	(0.8)[d)]	5 I
N′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine	299.54	liquid	9[b)]	not tested, corrosive to the rabbit skin[b)]	(0.004)[d)]	0.05 I

[a)] NCBI 2022 a, b, c, d
[b)] ECHA 2015 a, b, c, d, e, f
[c)] Greim 1996, 1999; Hartwig 2013, 2015; Hartwig and MAK Commission 2017 b
[d)] in brackets: conversions to theoretical ml/m³ values on a molar basis

Peak limitation. As systemic effects were used for the derivation of the MAK value, *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine is classified in Peak Limitation Category II. The terminal half-life in plasma was 28.5 hours in the male and 46.3 hours in the female animals. The curve for the plasma concentration against time did not indicate a two-phase reduction of the plasma concentration (Lonza Ltd 1996). Thus, the terminal half-life value above is assumed for the initial half-life. According to the procedure of the Commission (see Hartwig and MAK Commission 2017 a) an excursion factor of 8 has been established. Considering the MAK values of the other amines mentioned, the allowable short-term 8-fold excursion of the MAK value for *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine, which corresponds to 0.4 mg/m³, should be sufficient to prevent irritation.

Prenatal toxicity. *N*′-(3-Aminopropyl)-*N*′-dodecylpropane-1,3-diamine did not induce teratogenic effects in either rats or rabbits. Developmental toxicity was found only in combination with maternal toxicity. The NOAEL for developmental toxicity was 22.5 mg/kg body weight and day in rats (Akzo Nobel Surface Chemistry AB 1994; ECHA 2015 d) and 9 mg/kg body weight and day in rabbits (Akzo Nobel Surface Chemistry AB 2005; ECHA 2015 d). In a 2-generation study in Sprague Dawley rats with gavage administration, a NOAEL of 9 mg *N*′-(3-aminopropyl)-*N*′-dodecylpropane-1,3-diamine/kg body weight and day was derived for foetotoxicity and for parental toxicity (Akzo Nobel Surface Chemistry AB 1996; ECHA 2015 d). The following toxicokinetic data are taken into consideration for the extrapolation to a concentration in workplace air of the NOAEL for prenatal developmental toxicity of 22.5 mg/kg body weight and day in rats and 9 mg/kg body weight and day in rabbits and the NOAEL for foetotoxicity of 9 mg/kg body weight and day in rats after prenatal and postnatal doses: the corresponding species-specific correction value for the rat and rabbit (1:4 and 1:2.4), the experimentally determined oral absorption in the rat of 2.5% (ECHA 2015 d; Lonza Ltd 1996), which is also assumed for rabbits, the body weight (70 kg) and respiratory volume (10 m³) of the person, and the assumed 100% absorption by inhalation. This results in corresponding concentrations of 1.0 mg/m³ for the NOAEL for prenatal developmental toxicity in the rat, 0.66 mg/m³ for the NOAEL for prenatal developmental toxicity in the rabbit and 0.39 mg/m³ for the NOAEL for foetotoxicity after prenatal and postnatal exposure in the rat. This corresponds to a 20-fold and 13-fold margin between the MAK value of 0.05 mg/m³ and the calculated airborne concentrations of the NOAEL for developmental toxicity in the rat and rabbit and an 8-fold margin between the MAK value and the

NOAEL for foetotoxicity in the rat. In the 2-generation study, decreased mean litter weights and body weights were not consistent as these effects were observed only in the F2 generation but not in the F1 generation. Tremor occurred in the offspring only in the late lactation phase and thus did not develop prenatally. The difference between the calculated airborne concentrations of the NOAEL for developmental toxicity and the MAK value is sufficiently large for *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine to be classified in Pregnancy Risk Group C.

Carcinogenicity. In a carcinogenicity study carried out according to OECD Test Guideline 453 with male and female Crl:CD(SD) rats given up to 20 mg/kg body weight and day with the diet, *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine was not found to have carcinogenic potential. The substance was not mutagenic or clastogenic in vitro. A genotoxic potential is not expected. The substance is therefore not classified in any of the categories for carcinogens.

Germ cell mutagenicity. In vivo genotoxicity studies are not available. *N′*-(3-Aminopropyl)-*N′*-dodecylpropane-1,3-diamine did not have mutagenic or clastogenic effects, thus germ cell mutagenicity is not expected. The substance is therefore not classified in any of the categories for germ cell mutagens.

Absorption through the skin. Since the substance is corrosive, unnoticed exposure to more highly concentrated solutions is unlikely. In humans, a dermal absorption of 83 µg can be estimated from an in vitro study (see Section 3.1) after one-hour exposure to a non-irritant solution of 1%, assuming a surface area of 2000 cm^2 of skin. This is regarded as the worst case. Compared with the amount absorbed by inhalation at the level of the MAK value of 500 µg (10 m^3 respiratory volume, 100% absorbed via inhalation), the amount dermally absorbed is below 25% of that absorbed after inhalation exposure. Therefore, the substance is not designated with an "H" (for substances which are absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are only few clinical findings concerning the contact sensitizing effects of *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine. Due to the pronounced irritant effects of the substance, the studies could not be unequivocally evaluated. The result of a Buehler test with guinea pigs must be evaluated as negative, since reactions occurred also in the control animals. Overall, irritation is the dominant effect, and thus *N′*-(3-aminopropyl)-*N′*-dodecylpropane-1,3-diamine is not designated with "Sh" (for substances which cause sensitization of the skin). As there are no findings available regarding effects on the airways, the substance is not designated 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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