The MAK Collection for Occupational Health and Safety

n-Butylamine, sec-Butylamine, iso-Butylamine, tert-Butylamine

MAK Value Documentation, addendum – Translation of the German version from 2016

A. Hartwig[1,*], MAK Commission[2,*]

1 *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

2 *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

***** *email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

Keywords: n-butylamine; sec-butylamine; isobutylamine; tert-butylamine; MAK value; maximum workplace concentration; peak limitation; developmental toxicity; irritation

Citation Note: Hartwig A, MAK Commission. n-Butylamine, sec-Butylamine, iso-Butylamine, tert-Butylamine. MAK Value Documentation, addendum – Translation of the German version from 2016. MAK Collect Occup Health Saf [Original edition. Weinheim: Wiley-VCH; 2019 Oct;4(4):1881–1892]. Corrected republication without content-related editing. Düsseldorf: German Medical Science; 2025. https://doi.org/10.34865/mb0210isme6019_w

Republished (online): 30 Apr 2025

Originally published by Wiley-VCH Verlag GmbH & Co. KGaA; https://doi.org/10.1002/3527600418.mb0210isme6019

Addendum completed: 25 Feb 2015

Published (online): 13 Nov 2019

The commission established rules and measures to avoid conflicts of interest.

n-Butylamine, *sec*-Butylamine, *iso*-Butylamine, *tert*-Butylamine

MAK value documentation

A. Hartwig[1,*], MAK Commission[2,*]

DOI: 10.1002/3527600418.mb0210isme6019

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value) of *n*-, *sec*-, *iso*- and *tert*-butylamine, considering local and systemic toxicity as well as developmental toxicity. Daily exposure of rats to *n*-butylamine for 14 days resulted in inflammation of respiratory epithelium at 17 ml/m³. Since 2014, the Commission uses an empirical approach to set MAK values for substances with critical effects on the upper respiratory tract or the eyes, which would result in lowering the MAK value for *n*-butylamine. However, workers reported no irritation at 1 to 2 ml *n*-butylamine/m³. Therefore, the MAK value of 2 ml/m³ is confirmed, also for *sec*- and *iso*-butylamine due to similar structure, pKa and RD_{50} values. With *tert*-butylamine the LOAEC of 66 ml/m³ in rats in a 13-week study resulted in nasal tissue inflammation and liver weight increase. Following the empirical approach, the same MAK value of 2 ml/m³ is set for *tert*-butylamine. As local effects might be or are critical, Peak Limitation Category I and an excursion factor of 2 and a momentary value of 5 ml/m³ are assigned for all butylamine isomers. Developmental toxicity studies with *n*-butylamine show that damage to the embryo or foetus is unlikely if the MAK value is not exceeded and thus *n*-butylamine is assigned to Pregnancy Risk Group C. Due to the lack of developmental toxicity studies, *sec*-, *iso*- and *tert*-butylamine are assigned to Pregnancy Risk Group D.

Keywords

n-butylamine; *sec*-butylamine; *iso*-butylamine; *tert*-butylamine; 1-aminobutane; 1-butanamine; mono-*n*-butylamine; 1-methylpropyl amine; 2-aminobutane; 2-butanamine; 2-methylpropyl amine; 2-methyl-1-propanamine; 1,1-dimethylethylamine; trimethylaminomethane; 2-amino-isobutane; (sub)acute toxicity; (sub)chronic toxicity; irritation; reproductive toxicity; peak limitation; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

Author Information

[1] Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Department of Food Chemistry and Toxicology, Institute of Applied Biosciences, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany

[2] Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany

* Email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)

n-Butylamine, *sec*-Butylamine, *iso*-Butylamine, *tert*-Butylamine

***n*-Butylamine [109-73-9]**
***sec*-Butylamine [13952-84-6]**
***iso*-Butylamine [78-81-9]**

Supplement 2016

MAK value (2006)	**2 ml/m³ (ppm) ≙ 6.1 mg/m³**
Peak limitation (2006)	**Category I, excursion factor 2**
Momentary value (2006)	**5 ml/m³ (ppm) ≙ 15 mg/m³**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2006)	***n*-butylamine: Pregnancy Risk Group C**
Prenatal toxicity (2015)	***sec*-butylamine, *iso*-butylamine: Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value	**–**
1 ml/m³ ≙ 3.035 mg/m³	**1 mg/m³ ≙ 0.329 ml/m³**

***tert*-Butylamine [75-64-9]**

Supplement 2016

MAK value (2015)	**2 ml/m³ (ppm) ≙ 6.1 mg/m³**
Peak limitation (2015)	**Category I, excursion factor 2**
Momentary value (2015)	**5 ml/m³ (ppm) ≙ 15 mg/m³**
Absorption through the skin	**–**

Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2015)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value	**–**
1 ml/m³ ≙ 3.035 mg/m³	**1 mg/m³ ≙ 0.329 ml/m³**

	n-Butylamine	*sec*-Butylamine	*iso*-Butylamine	*tert*-Butylamine
Molar mass [g/mol]	73.14	73.14	73.14	73.14
Melting point [°C]	–50[1)]	–104[2)]	–87[2)]	–66[2)]
Boiling point at 1013 hPa [°C]	77–78[1)]	63[2)]	68[2)]	44[2)]
Vapour pressure at 25 °C [hPa]	122–128[1)]	237[2)]	184[2)]	495[2)]
log K_{OW}[3)]	0.97[1)]	0.74[2)]	0.73[2)]	0.4[2)]
pK_a	10.78[1)]	10.6[2)]	10.7[2)]	10.7[2)]
Solubility in water	1000 g/l (no other details)[1)]	112 g/l at 20 °C[2)]	1000 g/l at 25 °C[2)]	1000 g/l at 25 °C[2)]

[1)] OECD 2011
[2)] SRC 2005
[3)] octanol/water partition coefficient

In 2014, the Commission started using a physiologically and empirically-based procedure for deriving MAK values for substances that have an effect on the upper respiratory tract and eyes; it also describes criteria for classification as a sensory irritant (Brüning et al. 2014). The MAK value has been reviewed for this reason.

The MAK value for *n*-butylamine, *sec*-butylamine and *iso*-butylamine of 2 ml/m³, with irritation as the critical effect, was derived in 2006 with data for other aliphatic amines on account of their structural similarity. *tert*-Butylamine was classified in Section II b because no studies with repeated administration were available for *tert*-butylamine, and other systemic effects (primarily transmitter properties) besides irritation were assumed to occur (documentation „*n*-Butylamine, *sec*-Butylamine, *iso*-Butylamine" 2007). However, a MAK value can now be derived because two inhalation studies in rats have become available for *tert*-butylamine.

Information from the registration data publicly available under REACH (ECHA 2014) has also been included.

Effects in Humans

It was already described in the 2007 documentation (documentation "*n*-Butylamine, *sec*-Butylamine, *iso*-Butylamine" 2007) that daily exposure of workers to *n*-butylamine concentrations of 5 to 10 ml/m³ induced irritation of the nose, throat and eyes as well as headaches. Exposure to 10 to 25 ml/m³ was tolerated only for a few minutes. No complaints were recorded after exposure to *n*-butylamine below 5 ml/m³; the concentrations were mostly between 1 and 2 ml/m³. There were no other details about the number of workers, exposure periods or concentration peaks (Beard and Noe 1981).

No other data are available.

Animal Experiments

Acute toxicity

Inhalation

RD_{50} values of 84 ml/m³ to 246 ml/m³ were determined for *n*-butylamine in different mouse strains; the corresponding RD_{50} values for *iso*-butylamine and *tert*-butylamine were 91 ml/m³ and 178 ml/m³, respectively (documentation "*n*-Butylamine, *sec*-Butylamine, *iso*-Butylamine" 2007). Data have not become available for *sec*-butylamine.

Subacute, subchronic and chronic toxicity

Inhalation

No data applicable to this section have become available for *sec*-butylamine or *iso*-butylamine.

n-Butylamine

In a range-finding study for a developmental toxicity study that was described in the 2007 documentation (documentation "*n*-Butylamine, *sec*-Butylamine, *iso*-Butylamine" 2007), pregnant female rats were exposed to *n*-butylamine concentrations of 0, 12, 41 or 117 ml/m³ for 6 hours per day, for 5 days. The concentration of 117 ml/m³ caused clinical signs of irritation, but there were no findings in the nasal epithelial cells or any other effects.

The developmental toxicity study described in the 2007 documentation (documentation "*n*-Butylamine, *sec*-Butylamine, *iso*-Butylamine" 2007) was carried out according to OECD Test Guideline 414. Pregnant Wistar rats were exposed to *n*-butylamine concentrations of 0, 17, 50 or 152 ml/m³ on 14 consecutive days for 6 hours per day, and the respiratory tract was examined histopathologically in 10 animals per concentration group. The LOAEC (lowest observed adverse effect concentration) was 17 ml/m³ because at this concentration and above, inflammatory cells (in 3, 9 and 10 of 10 animals), squamous metaplasia (in 1, 5 and 10 of 10 animals) and tran-

sitional cell hyperplasia (in 1, 6 and 0 of 10 animals) were observed in a concentration-dependent manner in the respiratory epithelium of the dams, but none of these findings occurred in the animals of the control group. The *n*-butylamine concentration of 152 ml/m^3 also caused necrosis in the mucosa (in 5 of 10 animals) and of the nasal bone (in 1 of 10 animals) (documentation "*n*-Butylamine, *sec*-Butylamine, *iso*-Butylamine" 2007).

The findings from this study have been re-evaluated. It is striking that no findings were obtained in any animal from the control group; this results in a steep dose–response relationship. As pregnant animals were used and these have a higher respiratory rate, exposure of the respiratory tract is greater than in animals that are not pregnant. Moreover, the fact that the animals were exposed on 14 consecutive days without a 2-day recovery period after 5 exposure days may have increased the effect. For these reasons, the concentration of 17 ml/m^3 lies on the boundary between the NOAEC (no observed adverse effect concentration) and the LOAEC and would probably be a NOAEC for animals that were not pregnant and exposed for 5 days per week.

tert-Butylamine

The 2007 documentation did not yet contain any data for *tert*-butylamine (documentation "*n*-Butylamine, *sec*-Butylamine, *iso*-Butylamine" 2007).

A NOAEC of 66 ml/m^3 was obtained for *tert*-butylamine in a 28-day inhalation study with groups of 15 male and 15 female Sprague Dawley rats. The haemoglobin concentration was reduced at 165 ml/m^3, and a poor general state, breathing problems, irritation of the nose and conjunctiva, and effects on the gastrointestinal tract were observed at 661 ml/m^3. The animals were exposed to *tert*-butylamine vapour (see Table 1; BASF 1988). As the number of section levels of the nasal turbinates and trachea was not specified, it is assumed that only one plane of section was investigated. For this reason, effects on the nose caused by the irritant amine, which were observed in the 13-week study, may have been overlooked. The study was carried out at a time when the examination of the larnyx was not required, which means that mild effects may have been overlooked here, too. However, these findings are primarily observed after exposure to aerosols.

In a 13-week inhalation study, groups of 15 male and 15 female Sprague Dawley rats were exposed to *tert*-butylamine concentrations of 0, 200, 500 or 2010 mg/m^3 (0, 66, 165 or 661 ml/m^3). Histopathological examination of most organs was carried out only in the animals of the control group and the high concentration group, while the bone marrow and nasal turbinates were investigated in all concentration groups. As the number of section levels was not specified, it is assumed that only one section of the nasal turbinates was examined in this study, too. Some of the males of the low concentration group of 66 ml/m^3 were hypoactive and had reduced relative liver weights, nasal discharge and breathing problems (see Table 1). Chronic inflammation of the turbinates was observed in 3 animals, but in only 1 animal of the next-higher concentration group. The NOAEC was 66 ml/m^3 in the females. At 165 ml/m^3 and above, breathing problems and irritation of the eyes and upper respiratory tract were found in both sexes; severe irritation of the respiratory tract was observed at the high concentration. Effects on the lungs were not observed. The reduced liver weights, particularly in the high concentration group, were thought to be caused by

Table 1 Effects of *tert*-butylamine after repeated inhalation exposure

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 15 ♂, 15 ♀	**28 days**, 0, 200, 500, 1980 mg/m³ (0, 66, 165, 651 ml/m³), vapour, 6 hours/day, 5 days/week	study from 1981, only 1 section level for nasal turbinates and trachea, larynx not examined; **66 ml/m³**: **NOAEC** (♀), relative brain weights ↓ (♂), Hb concentration ↓ (♂); **165 ml/m³**: Hb concentration ↓, absolute brain weights ↓ (♀), absolute left kidney weights ↓ (♀); **651 ml/m³**: poor general state, mortality (1 ♂), body weight gains ↓, breathing problems, CNS depression, nose: irritation, encrusted blood, subacute rhinitis, discharge, inflammation in nasal passage, eyes: conjunctival inflammation, clinical parameters: specific gravity of urine ↑, ketones and protein in the urine ↑, ALT ↑ (♂), WBC ↓ (♂), blood sugar ↓ (♂), urine volume ↓ (♂), pH of the urine ↓ (♂), organ weights: absolute kidney weights ↓, relative brain weights ↑, absolute testis weights ↓, relative testis weights ↑, absolute brain weights ↓ (♂), absolute heart weights ↓ (♂), absolute liver weights ↓ (♂), relative adrenal weights ↑ (♂), absolute spleen weights ↓ (♀), gastrointestinal tract without histopathological correlate: constipation, gaseous distension of the intestines, deposits of mesenteric fat	BASF 1988; ECHA 2014
rat, Sprague Dawley, 15 ♂, 15 ♀	**13 weeks**, 0, 200, 500, 2010 mg/m³ (0, 66, 165, 661 ml/m³), vapour, 6 hours/day, 5 days/week (a total of 62 days of exposure)	only 1 section level for nasal turbinates and trachea, larynx not examined, only bone marrow and nasal turbinates examined in all concentration groups, the other organs examined only in the high concentration and control groups; **66 ml/m³**: **NOAEC** (♀); **LOAEC** (♂); in general: ≥ 25% of the animals hypoactive, breathing problems and sneezing (♂), nose: chronic inflammation of nasal turbinates in 3/15 (♂), nasal discharge in 1/15 (♂), clinical parameters: slight increase in blood sugar level (♂), organ weights: relative liver weights ↓ (♂), dose-dependent decrease in absolute liver weights (♂);	BASF 1985; ECHA 2014

Table 1 (continued)

Species, strain, number per group	Exposure	Findings	References
		165 ml/m³ and above: in general: breathing problems in 25% of the animals, piloerection, abrasion (no other details), irritation of the eyes, nose and trachea in some animals, nose: nasal discharge, chronic inflammation of nasal turbinates in 1/15 (♂), haematology: neutrophilic leukocytes in the bone marrow ↑, organ weights: absolute and relative pituitary weights ↓ (♀); **661 ml/m³**: in general: mortality as of day 43: 4 ♂ and 7 ♀, ≥ 75% of the animals hypoactive, ≥ 75% of the animals: breathing problems, sneezing, fur discoloration, poor general state, piloerection, behavioural abnormalities, ataxia, abnormal urine colour, urine-stained fur, decreased body weight gains as of week 1, terminal body weights decreased by 23% (♀) and 44% (♂), body fat ↓, gaseous intestines, nose: nasal discharge, salivation, severe chronic inflammation in nasal turbinates in all ♂ and ♀ animals, infiltration of lymphocytes in the mucosa of the nose, proliferation of submucosal cells, inflammation in the upper respiratory tract, inflammation in the trachea, eyes: eye irritation in all animals: corneal opacity, clinical parameters: lymphopenia, neutrophilia, blood sugar levels ↓, alkaline phosphatase ↑, AST ↑, BUN ↑ (♂), ALT ↑ (♀), neutrophilic leukocytes in the bone marrow ↑ (total number of bone marrow cells constant), organ weights: absolute and relative adrenal weights ↑, relative brain weights ↑, relative heart weights ↑, relative kidney weights ↑, absolute brain weights ↓ (♂), absolute heart weights ↓ (♂), absolute kidney weights ↓ (♂), absolute and relative spleen weights ↓ (♂), absolute and relative testis weights ↓, relative pituitary weights ↑ (♂), absolute liver weights ↓ (♀), WBC and erythrocyte count not valid because of measurement problems	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CNS: central nervous system; WBC: white blood cell count

the substance because they were accompanied by increased liver enzyme levels in the blood. There were no histopathological changes or associated clinico-chemical findings in the liver. The other organ weight changes were regarded as secondary effects of the general toxicity, which was manifest in the form of reduced body weights (BASF 1985). In 1985, the examination of the larynx was not required. A NOAEC was not determined for the trachea because only the high concentration group was examined and inflammation was observed. Therefore, it cannot be ruled out that effects may also have occurred in the females at 66 ml/m^3. Because of the effects found in males, this concentration is regarded as the LOAEC.

Local effects on skin and mucous membranes

n-Butylamine

n-Butylamine caused irritation of the skin and corrosion in the eyes of rabbits (documentation "*n*-Butylamine, *sec*-Butylamine, *iso*-Butylamine" 2007).

sec-Butylamine and *iso*-butylamine

No data have become available for *sec*-butylamine or *iso*-butylamine. Corrosive effects are assumed because their alkalinity is similar to that of *n*-butylamine.

tert-Butylamine

Skin
tert-Butylamine had a corrosive effect on the skin of rabbits (no other details; BASF 1988).

In a study from 1992 carried out according to OECD Test Guideline 404 with New Zealand White rabbits, semi-occlusive application of undiluted *tert*-butylamine to the shaved dorsal skin for 3 minutes induced necrosis on the skin. Oedemas were observed only in 2 of 3 animals. The scores were 1 and 3 on a scale with a maximum of 4 after 3 minutes, 1 out of a maximum of 4 after 1 hour and 2 out of a maximum of 4 in 1 animal after 1 hour; otherwise the scores were always 0 out of a maximum of 4. The scores for erythema were 3 on a scale with a maximum of 4 after 3 minutes and 1 hour and 4 out of a maximum of 4 from hour 4 after treatment up to the end of the observation period. Eschar formation, necrosis with fissures and protruding edges were observed over the whole application site after 72 hours (ECHA 2014). This study also found *tert*-butylamine to be corrosive.

Eyes
tert-Butylamine had a corrosive effect on the eyes of rabbits (no other details; BASF 1988).

In rabbits, the substance induced chemical burns to the vitreous body, nictitating membrane and conjunctiva within 1 hour after application as well as ulceration and chemosis of the surrounding tissue after 72 hours. Necrosis and swelling of the eyelids, blepharophimosis (narrowing of the palpebral fissure) and eyes completely clotted with pus and lens loss were observed after the 7-day observation period (ECHA 2014).

Developmental toxicity

_n_-Butylamine
An inhalation study with *n*-butylamine in Wistar rats carried out according to OECD Test Guideline 414 did not reveal any effects in the offspring up to the highest concentration tested of 152 ml/m³; the only effects in the dams were observed in the nasal epithelium at the lowest concentration tested of 17 ml/m³ and above (see Section "Subacute, subchronic and chronic toxicity"). In a developmental toxicity study with gavage doses, the highest dose tested of 667 mg/kg body weight and day was the NOAEL (no observed adverse effect level) for the dams, and 67 mg/kg body weight and day was the NOAEL for the offspring because the incidence of soft-tissue malformations was increased at 267 mg/kg body weight and day (documentation "*n*-Butylamine, *sec*-Butylamine, *iso*-Butylamine" 2007).

New data have not become available.

sec-Butylamine and _iso_-butylamine
No data are still available for these isomers.

tert-Butylamine
The 2007 documentation (documentation "*n*-Butylamine, *sec*-Butylamine, *iso*-Butylamine" 2007) described a non-validated study that cannot be used for the evaluation.

There are no other data available.

Manifesto (MAK value/classification)

Irritation is the critical effect of *n*-butylamine, *iso*-butylamine, *sec*-butylamine and *tert*-butylamine.

MAK value.

***n*-Butylamine** Since the 2007 documentation (documentation "*n*-Butylamine, *sec*-Butylamine, *iso*-Butylamine" 2007), no recent studies with *n*-butylamine have become available that are relevant for deriving a MAK value. Inflammation of the respiratory epithelium occurred in pregnant rats after exposure to *n*-butylamine for 14 consecutive days; the NOAEC was 17 ml/m³ (see Section "Subacute, subchronic and chronic toxicity"). After extrapolation of the findings in the respiratory epithelium of rats to humans according to the method of Brüning et al. (2014) a concentration of 6 ml/m³ is obtained. As the NOAEC of 117 ml/m³ for histopathological effects on the nasal epithelium after exposure for 5 days was markedly higher, it must be assumed that the effects increase in intensity with time. Therefore, a limit value in workplace air of 1 ml/m³ was calculated from the concentration of 6 ml/m³. This value is in the same range as the previous MAK value of 2 ml/m³. According to occupational medical data, the daily exposure of workers to *n*-butylamine concentrations of 5 to 10 ml/m³ induced irritation of the nose, throat and eyes as well as headaches. No complaints were recorded after exposure to

n-butylamine concentrations below 5 ml/m³; the concentrations were mostly between 1 and 2 ml/m³ (Beard and Noe 1981). The NOAEC of about 2 ml/m³ reported for *n*-butylamine in workers is plausible because a NOAEC of 2 ml/m³ with peak concentrations of up to 4 ml/m³ was determined for sensory irritation in a volunteer study for the structurally related cyclohexylamine (Juran et al. 2012) and because, with an RD_{50} of 51 ml/m³ (Gagnaire et al. 1993), the irritative effect established for this substance in the RD_{50} test in mice is somewhat higher than that established for *n*-butylamine, which has an RD_{50} of 84 to 112 ml/m³ (Gagnaire et al. 1989, 1993). Because of their irritant action, a MAK value of 2 ml/m³ was established also for other aliphatic amines with an RD_{50} of a maximum 100 ml/m³ (documentation "Dimethylamine" 1996; documentation "Cyclohexylamine" 2006). As already described in the 2007 MAK documentation (documentation "*n*-Butylamine, *sec*-Butylamine, *iso*-Butylamine" 2007), the data from the 14-day study are not in conflict with the previous MAK value, and in particular, the RD_{50} values are consistent with the NOAEC in the volunteer study with cyclohexylamine and the MAK value of 2 ml/m³ derived from occupational observations with *n*-butylamine. The MAK value has therefore been confirmed.

***sec*-Butylamine and *iso*-butylamine** New data for *sec*-butylamine and *iso*-butylamine have not become available. In view of their alkalinity, it is assumed that the local, irritative effects are decisive for the derivation of a MAK value also for these isomers. In the studies of Gagnaire et al. (1993), the RD_{50} value of 90 ml/m³ for *iso*-butylamine was similar to that for *n*-butylamine of 84 ml/m³, and the log K_{OW} values of 0.74 and 0.73 for *sec*-butylamine and *iso*-butylamine are very similar. As no data have become available since 2007 and similar profiles for local effects are assumed, the previous MAK value of 2 ml/m³ has provisionally been retained for *sec*-butylamine and *iso*-butylamine.

***tert*-Butylamine** In a 13-week inhalation study in rats from 1985, which was not yet available when the 2007 documentation (documentation "*n*-Butylamine, *sec*-Butylamine, *iso*-Butylamine" 2007) was published, the lowest *tert*-butylamine concentration tested of 66 ml/m³ led to reduced absolute and relative liver weights in the males and clinical signs of irritation and chronic inflammation of the nasal turbinates in some of the animals. However, *tert*-butylamine was not found to have a neurotransmitter property. A NOAEC of 66 ml/m³ was established in the females for local and systemic effects. However, because only one section level of the nose was investigated, and the NOAEC for the trachea is not known, as the trachea was examined histopathologically only in the animals of the high concentration group, and as the larynx was not examined, it cannot be ruled out that histopathological findings occurred in the respiratory tract of the females at 66 ml/m³. Comparison with the findings of the 28-day study reveals an intensification of the effects over time because after a short exposure period clear findings were obtained only at the high concentration of 651 ml/m³, whereas the 13-week study revealed findings at the middle concentration of 165 ml/m³. The concentration of 66 ml/m³ is regarded as the LOAEC.

A NAEC (no adverse effect concentration) of 22 ml/m³ was derived from the LOAEC of 66 ml/m³ for inflammation of the nasal epithelium after subchronic ex-

posure. It was not reported whether the findings occurred in the respiratory or the olfactory epithelium, therefore, it is assumed that the respiratory epithelium was affected. As there was a slight intensification of the effects over time, it is assumed that the long-term NAEC is about 11 ml/m³ according to the method of Brüning et al. (2014). After extrapolation of findings in the respiratory epithelium of rats to humans, a concentration of 4 ml/m³ is calculated. A lower irritation potential of *tert*-butylamine is plausible in view of the RD_{50} of 178 ml/m³ in mice compared with that of 84 to 112 ml/m³ (Gagnaire et al. 1989, 1993) for *n*-butylamine. In line with the preferred value approach, a MAK value of 2 ml/m³ has therefore also been established for *tert*-butylamine. This MAK value would provide protection even if the reduction in liver weights at 66 ml/m³ were the critical adverse effect.

Peak limitation.

***n*-Butylamine, *sec*-butylamine and *iso*-butylamine** As no new data have become available, Peak Limitation Category I with an excursion factor of 2 and a momentary value of 5 ml/m³ have been retained.

***tert*-Butylamine** In the 13-week inhalation study with *tert*-butylamine, both reduced liver weights without a histopathological correlate and inflammation of the nasal turbinates in 3 of 15 animals were observed in male rats at the lowest concentration tested of 66 ml/m³. Therefore, it remains unclear whether the local irritation of the respiratory tract or the systemic effect is decisive for establishing the peak limitation category. In analogy to the other isomers, *tert*-butylamine has therefore likewise been classified in Peak Limitation Category I with an excursion factor of 2 and a momentary value of 5 ml/m³.

Prenatal toxicity.

***n*-Butylamine** The exposure of pregnant rats to *n*-butylamine concentrations of up to 450 mg/m³ (150 ml/m³) induced local effects in the nose, but no substance-specific findings in the offspring. When *n*-butylamine was administered orally to pregnant rats as the hydrochloride, teratogenic effects were found at doses of 400 mg/kg body weight and day and above (267 mg *n*-butylamine/kg body weight and day). In this study, the NOAEL for *n*-butylamine hydrochloride was 100 mg/kg body weight and day (67 mg *n*-butylamine/kg body weight and day). The following toxicokinetic data are used to extrapolate this NOAEL to a concentration in workplace air: the corresponding species-specific correction value for the rat (1:4), the assumed oral absorption (100%), the body weight (70 kg) and the respiratory volume (10 m³) of the person, and the assumed 100% absorption by inhalation. The *n*-butylamine concentration in the air that is calculated from this is 117 mg/m³ (39 ml/m³). As this concentration is 19.5 times as high as the MAK value of 2 ml/m³ and the difference to the MAK value is thus sufficiently large, the classification of *n*-butylamine in Pregnancy Risk Group C has been retained.

***sec*-Butylamine and *iso*-butylamine** No developmental toxicity studies have become available for *iso*-butylamine or *sec*-butylamine. As other studies have shown

that a small change in the molecular structure may lead to a marked change in the effects on the developing foetus, these two substances have now not been evaluated by analogy with another isomer. Both *iso*-butylamine and *sec*-butylamine are therefore classified in Pregnancy Risk Group D.

***tert*-Butylamine** There are no studies available for the developmental toxicity of *tert*-butylamine. As other studies have shown that a small change in the molecular structure may lead to a marked change in the effects on the developing foetus, this substance has not been evaluated by analogy with another isomer. Therefore, *tert*-butylamine is likewise classified in Pregnancy Risk Group D.

References

BASF (1985) 13-week inhalation study of tertiary butylamine vapors to male and female Sprague Dawley rats. Monsanto Co, St. Louis, MO, USA, NTIS/OTS 0538640, EPA/OTS Doc ID 88-920007720, NTIS, Alexandria, VA, USA, https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml

BASF (1988) Letter from Sterling Chemicals responding to a TSCA ITC request for information on t-butylamine with attachments, dated 12/28/88. Sterling Chemicals Inc, Monsanto, St. Louis, MO, USA, NTIS/OTS 0001015, EPA/OTS Doc ID FYI-OTS-0794-1015, NTIS, Alexandria, VA, USA, https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml

Beard RR, Noe JT (1981) Aliphatic and alicyclic amines. in: Clayton GC, Clayton FE (Eds) Patty's industrial hygiene and toxicology, Wiley & Sons, New York, 3135–3173

Brüning T, Bartsch R, Bolt HM, Desel H, Drexler H, Gundert-Remy U, Hartwig A, Jäckh R, Leibold E, Pallapies D, Rettenmeier AW, Schlüter G, Stropp G, Sucker K, Triebig G, Westphal G, van Thriel C (2014) Sensory irritation as a basis for setting occupational exposure limits. Arch Toxicol 88: 1855–1879

ECHA (European Chemicals Agency) (2014) Information on registered substances. Dataset on tert-butylamine (CAS Number 75-64-9), joint submission, first publication 03.03.2011, last modification 30.06.2014, http://echa.europa.eu/de/information-on-chemicals

Gagnaire R, Azim S, Bonnet P, Simon P, Guenier JP, De Ceaurriz J (1989) Nasal irritation and pulmonary toxicity of aliphatic amines in mice. J Appl Toxicol 9: 301–304

Gagnaire R, Azim S, Simon P, Cossec B, Bonnet P, De Ceaurriz J (1993) Sensory and pulmonary irritation of aliphatic amines in mice: a structure-activity relationship study. J Appl Toxicol 13: 129–135

Juran SA, van Thriel C, Kleinbeck S, Schäper M, Falkenstein M, Iregren A, Johanson G (2012) Neurobehavioral performance in human volunteers during inhalation exposure to the unpleasant local irritant cyclohexylamine. Neurotoxicology 33: 1180–1187

OECD (Organisation for Economic Co-operation and Development) (2011) SIDS Initial Assessment Report C1-C13 Primary Amines, https://hpvchemicals.oecd.org/ui/SIDS_Details.aspx?id=e99fe4de-1176-426b-94ec-44582831991b

SRC (Syracuse Research Corporation (2005) n-Butylamine. PhysProp database, http://esc.srcinc.com/fatepointer/search.asp

completed 25 February 2015