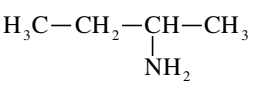
# *n*-Butylamine 109-73-9
# *sec*-Butylamine 13952-84-6
# *iso*-Butylamine 78-81-9

| | |
|---|---|
| **MAK value (2006)** | **2 ml/m³ ≙ 6.1 mg/m³** |
| **Peak limitation (2006)** | **Category I, excursion factor 2** |
| **Momentary value (2006)** | **5 ml/m³ ≙ 15 mg/m³** |
| **Absorption through the skin** | **–** |
| **Sensitization** | **–** |
| **Carcinogenicity** | **–** |
| **Prenatal toxicity (2006)** | **Group C** |
| **Germ cell mutagenicity** | **–** |
| **BAT value** | **–** |

# *tert*-Butylamine 75-64-9

| | |
|---|---|
| **MAK value** | **not yet established; see Section IIb of the List of MAK and BAT Values** |
| **Peak limitation** | **–** |
| **Momentary value** | **–** |
| **Absorption through the skin** | **–** |
| **Sensitization** | **–** |
| **Carcinogenicity** | **–** |
| **Prenatal toxicity** | **–** |
| **Germ cell mutagenicity** | **–** |
| **BAT value** | **–** |

*The MAK-Collection Part I, MAK Value Documentations 2013*
DFG, Deutsche Forschungsgemeinschaft

| Substance | IUPAC name and structural formula | Synonyms | CAS No. |
|---|---|---|---|
| *n*-butylamine | butan-1-amine<br>$H_3C–(CH_2)_2–CH_2NH_2$ | 1-aminobutane;<br>1-butanamine;<br>mono-*n*-butylamine | 109-73-9 |
| *sec*-butylamine | butan-2-amine<br>  | 1-methylpropyl amine;<br>2-aminobutane;<br>2-butanamine | 13952-84-6 |
| *iso*-butylamine | 2-methylpropan-1-amine<br>$(H_3C)_2CH–CH_2NH_2$ | 2-methylpropyl amine;<br>2-methyl-1-propanamine | 78-81-9 |
| *tert*-butylamine | 2-methylpropan-2-amine<br>$(H_2C)_3CNH_2$ | 1,1-dimethylethylamine;<br>trimethylaminomethane;<br>2-aminoisobutane | 75-64-9 |

| | *n*-butylamine | *sec*-butylamine | *iso*-butylamine | *tert*-butylamine |
|---|---|---|---|---|
| molecular weight [g/mol] | 73.14 | 73.14 | 73.14 | 73.14 |
| melting point | – 50°C[1)] | – 104°C[2)] | – 87°C[2)] | – 66°C[2)] |
| boiling point at 1013 hPa | 77–78°C[1)] | 63°C[2)] | 68°C[2)] | 44°C[2)] |
| vapour pressure at 25°C [hPa] | 122–128[1)] | 237[2)] | 184[2)] | 495[2)] |
| log $K_{OW}$ | *n*-butylamine: 0.97[1)]<br>*n*-butylamine HCl: –2.35 (calc.)[3)] | 0.74[2)]<br>– | 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 2004 [2)] SRC 2005 [3)] Gamer et al. 2002

**1 ml/m³ (ppm) ≙ 3.035 mg/m³** **1 mg/m³ ≙ 0.329 ml/m³ (ppm)**

# 1 General Mode of Action

### *n*-Butylamine

Since *n*-butylamine reacts with water to form a strong base, severe irritation is its main effect. *n*-Butylamine was corrosive to the skin and eyes in animal studies. The $RD_{50}$ in mice was between 84 ml/m³ and 362 ml/m³. Butylamine hydrochloride was mainly administered in the studies to avoid the acute irritation of *n*-butylamine after oral administration. Data on its effect after repeated administration are only available from reproductive toxicity studies in rats. Exposure of pregnant Wistar rats to *n*-butylamine concentrations of 0, 17, 50 or 152 ml/m³ for 14 days led to nasal lesions because of the irritant effect. In the dams, the respiratory epithelial mucosa revealed a concentration-related increase of inflammatory cells, transitional cell hyperplasia and scaly metaplasia as well as necrosis in the highest dose group. The foetuses showed no substance-induced effects.

Oral administration of *n*-butylamine at 400 mg/kg body weight and day as a hydrochloride was teratogenic in rats. The highest dose of 1000 mg/kg body weight and day was also maternally toxic since the animals feed consumption was lower and uterine weight was lower as compared with the control animals.

A bacterial mutagenicity test using *Salmonella typhimurium* and a micronucleus test in bone marrow of mice provided no evidence of mutagenicity. No conclusive carcinogenicity studies are available. A maximization test in guinea pigs was negative.

### *sec*-Butylamine, *iso*-butylamine and *tert*-butylamine

Presumably, irritative effects are the most prevalent of these isomers due to their basicity, as is the case with *n*-butylamine and other primary amines.

The $RD_{50}$ in OF1 mice was 91 ml/m³ for *iso*-butylamine. The oral $LD_{50}$ in SD rats was 80 mg/kg body weight for *tert*-butylamine and 380 mg/kg body weight for *sec*-butylamine.

*tert*-Butylamine had a haemodynamic effect in studies in dogs. It lowered the blood pressure at doses < 1 mg/kg body weight and increased it at doses > 5 mg/kg body weight.

There are no studies available for repeated administration of *sec*-butylamine, *iso*-butylamine or *tert*-butylamine. Based on the lesions observed in the respiratory epithelium of rats after 14-day exposure to *n*-butylamine from 17 ml/m³ in relation to the concentration, it is assumed that *sec*-butylamine, *iso*-butylamine and *tert*-butylamine also lead to irritation and alterations in the respiratory tract.

*sec*-Butylamine and *tert*-butylamine were negative in the *Salmonella* mutagenicity test.

There are no studies available on absorption through the skin, sensitization, carcinogenicity, reproductive toxicity or germ cell mutagenicity.

## 2 Mechanism of Action

There are no studies available on the mechanism of action of *n*-butylamine, *sec*-butylamine, *iso*-butylamine or *tert*-butylamine. At pH 7.5, more than 99% *n*-butylamine is ionized in water (Newsome et al. 1991). As in the case of other aliphatic amines, the irritant effect of *n*-butylamine is due to an increase of the pH. It seems reasonable to assume that this also applies to the three other butylamine isomers. Contact may lead to a shift in the pH of the mucous membranes. *tert*-Butylamine acts as a sympathomimetic amine.

## 3 Toxicokinetics and Metabolism

### 3.1 Absorption, distribution and elimination

There are no studies available on the absorption, distribution or elimination of *n*-butylamine, *sec*-butylamine, *iso*-butylamine or *tert*-butylamine.

Aliphatic amines are generally well absorbed from the intestines and the respiratory tract, and the metabolites urea, carboxylic acid and, in the case of *n*-butylamine, butyric acid are excreted in the urine (Beard and Noe 1981). After administration of *n*-butylamine hydrochloride to volunteers (no other details), small amounts of *n*-butylamine were detected in the urine (Gamer et al. 2002).

Calculation of the dermal penetration according to the models of Fiserova-Bergerova et al. (1990) or Guy and Potts (1993) yielded a penetration rate of 30 or 3 mg/cm$^2$ and hour for undiluted *n*-butylamine.

### 3.2 Metabolism

There are no studies available on the metabolism *in vivo*.

Butylamines are probably deaminated by monoamine oxidase to form ammonia and its specific aldehyde; in the case of *n*-butylamine, this is butyraldehyde. Aldehyde and ammonia are metabolized further to carboxylic acid and urea, respectively, and these are excreted in the urine (NL Health Council 2003).

After incubation of guinea pig liver slices with *n*-butylamine, one of the metabolites found was acetoacetic acid (NL Health Council 2003).

## 4 Experience in Humans

The odour threshold of *n*-butylamine, which has a fishy smell, is between 0.08 and 1.8 ml/m$^3$ (NL Health Council 2003). The mean daily intake of *n*-butylamine via

the diet is about 0.2 mg per day, the maximum concentration of *n*-butylamine being determined in poultry meat (Pfundstein et al. 1991).

Material safety data sheets on *sec*-butylamine and *iso*-butylamine warn of vapour formation that might lead to irritation and corrosion in the respiratory tract, gastrointestinal tract or to the skin and eyes. Coughing and dyspnoea might be delayed and may be signs of emerging lung oedema (ICSC 2005 a, b). These effects seem to be plausible because of the basicity of the isomers.

## 4.1 Single exposure

Blood pressure increase and histamine release in the skin were observed after intravenous injection of *n*-butylamine hydrochloride (no other details) (Gamer et al. 2002).

## 4.2 Repeated exposure

Daily exposure of workers to *n*-butylamine levels of 5 to 10 ml/m$^3$ led to irritation to the nose, throat and eyes and induced headache. Exposures to 10–25 ml/m$^3$ were tolerated only for a few minutes. No complaints were recorded after exposure to *n*-butylamine below 5 ml/m$^3$ (concentrations were between 1 and 2 ml/m$^3$ in most cases; Beard and Noe 1981). There are no other details about the number of workers, exposure periods or concentration peaks.

## 4.3 Local effects on skin and mucous membranes

One case of skin erythema on the face was reported after exposure "to some ppm *n*-butylamine" (no other details; Swedish Criteria Group for Occupational Standards 1983).

According to unpublished observations from industry, direct skin contact with liquid *n*-butylamine is supposed to cause severe irritation and deep second-degree burns with blistering (NL Health Council 2003).

## 4.4 Allergenic effect

There are no data available for allergenic effects.

### 4.5 Reproductive and developmental toxicity

Only *in vitro* studies with sperm are available (see Section 5.5).

## 5 Animal Experiments and in vitro Studies

### 5.1 Acute toxicity

#### 5.1.1 Inhalation

***n*-Butylamine**

The *n*-butylamine concentration that induced a 50% reduction of the respiratory rate ($RD_{50}$) was determined in male NMRI and CF1 mice. For this purpose, groups of 4 animals were exposed only via the nose to increasing concentrations of *n*-butylamine. The $RD_{50}$ was 121 ml/m³ in CF1 mice and 246 ml/m³ in NMRI mice. If the animals breathed through a cannula that was inserted right down into the trachea ($RD_{TC}$), $RD_{50TC}$ values of 300 ml/m³ were obtained for CF1 mice and 362 ml/m³ for NMRI mice (Vinggaard et al. 1989). In different studies, $RD_{50}$ values of 112 ml/m³ (Gagnaire et al. 1989) or 84 ml/m³ and an $RD_{50TC}$ value of 226 ml/m³ were established in male OF1 mice for *n*-butylamine (Gagnaire et al. 1993).

The 4-hour $LC_{50}$ of *n*-butylamine vapour was 4200 mg/m³ (about 1400 ml/m³) in 10 male and 10 female Sprague-Dawley rats (BASF 1979). A 2-hour $LC_{50}$ of 800 mg/m³ (264 ml/m³) was reported for *n*-butylamine (NL Health Council 2003).

Exposure of 12 Sprague Dawley rats to a vapour atmosphere of *n*-butylamine saturated at 20°C led to the death of 10 of 12 animals after 3 minutes. Attempts to escape, lid closure, aqueous or bloody discharge from the nose, dyspnoea, cyanosis, slight to severe corrosions (no other details) and milky corneal opacity were observed as symptoms; necropsy revealed acute dilatation and passive hyperaemia in the heart and severe acute pulmonary oedema (BASF 1978). When 6 rats were exposed to a vapour atmosphere of *n*-butylamine saturated at 20°C (about 93 000 ml/m³), 5 of 6 animals died in the first minute and 6 of 6 animals died after 2, 4 or 8 minutes in each case (BASF 1956).

***iso*-butylamine**

In OF1 mice, an *iso*-butylamine concentration of 91 ml/m³ reduced the respiratory rate by 50% ($RD_{50}$) (Gagnaire et al. 1993).

There are no studies available for the isomers *sec*-butylamine or *tert*-butylamine.

### 5.1.2 Ingestion

#### *n*-Butylamine

An $LD_{50}$ of 372 mg/kg body weight was determined for *n*-butylamine in a study with 10 male and 10 female Sprague Dawley rats. Ataxia, sedation, gasping and salivation occurred followed by convulsions at higher concentrations. The rats died from pulmonary oedema within 3 hours. The animals that survived for 14 days did not seem to have any lesions (Cheever et al. 1982). In another study, the $LD_{50}$ of *n*-butylamine in rats was about 720 mg/kg body weight and the $LD_{50}$ of its hydrochloride was 5522 mg/kg body weight (no other details) (BASF 1956). In a further publication, the $LD_{50}$ in rats was found to be in a range between 200 and 400 mg/kg body weight for *n*-butylamine and in a range between 1600 and 3200 mg/kg body weight for its hydrochloride (Gamer et al. 2002).

*n*-Butylamine was administered by gavage to 10 young male Wistar rats at 110 mg/kg body weight, and the livers were examined 48 hours afterwards. There was a "segregation of the nucleolus in cells with karyorrhexis" (Terao 1976). These presumably apoptotic liver alterations were not confirmed in other studies.

#### Other isomers

The $LD_{50}$ in Sprague Dawley rats was 152 mg/kg body weight for *sec*-butylamine, 228 mg/kg body weight for *iso*-butylamine and 80 mg/kg body weight for *tert*-butylamine (Cheever et al. 1982). An $LD_{50}$ of 380 mg/kg body weight was found in female Wistar rats for *sec*-butylamine (Benya and Harbison 1994).

### 5.1.3 Dermal absorption

#### *n*-Butylamine

Different $LD_{50}$ values were determined in guinea pigs depending on the site of application. The $LD_{50}$ was 370 mg/kg body weight after application of *n*-butylamine to the intact dorsal skin, 425 mg/kg body weight after application to the intact abdominal skin and > 1110 mg/kg body weight after application to the abraded dorsal skin (NL Health Council 2003). The relatively wide variation of the values might be due to the different depth of penetration of *n*-butylamine into the skin. When the alkaline *n*-butylamine is applied to abraded skin, it immediately reacts with components of the blood, which means that it is partially inactivated. The dermal $LD_{50}$ in rabbits was 630 mg/kg body weight (NL Health Council 2003). There are no details about the pH of the applied solution.

#### 5.1.3.1 Other isomers

There are no data available for the other isomers.

### 5.1.4 Subcutaneous, intraperitoneal and intravenous injection

#### *n*-Butylamine

In rats and rabbits, the subcutaneous injection of a 1% aqueous *n*-butylamine hydrochloride solution initially induced general restlessness, increased excitability, elevated pulse and respiratory rates, dyspnoea and convulsions followed by a retardation of respiration and pulse with cyanosis of the mucosa and tongue and later coma and death. At necropsy, the lungs were collapsed and the hearts dilated (Hanzlik 1923).

Intraperitoneal injection of *n*-butylamine at 3 mg/kg body weight into male Swiss mice did not affect motor activity. It was only at a dose of 100 mg/kg body weight that locomotor activity was transiently reduced (NL Health Council 2003).

#### *tert*-Butylamine

Male and female mongrel dogs (5 to 15 kg body weight) were anaesthetized with sodium pentobarbital at a concentration of 30 to 35 mg/kg, *tert*-butylamine was injected into the femoral artery and various haemodynamic parameters were monitored. *tert*-Butylamine lowered the blood by maximally 20 mm Hg pressure after administration of 0.5 to 1 mg/kg body weight and increased the blood pressure at higher doses of 5, 10, 20, 50 "or more" mg/kg body weight (no other details). Thirty seconds after administration of 10 mg/kg body weight to 6 animals, *tert*-butylamine increased the blood pressure by 20%, the heart rate by 30%, the cardiac output by 50% and the stroke volume by about 18% (not significantly) on average, whereas the peripheral retention of *tert*-butylamine decreased by about 15%. All parameters were almost normal again 10 minutes after administration. After repeated injections of *tert*-butylamine at 50 mg/kg body weight every 20 minutes, the increase in blood pressure diminished with each administration. After the 6th injection, the blood pressure began to drop after 2 minutes, was almost zero after 5 minutes and the dog died (Baum et al. 1962).

## 5.2 Subacute, subchronic and chronic toxicity

There are no data available for *sec*-butylamine, *iso*-butylamine or *tert*-butylamine applicable to this section.

#### *n*-Butylamine

### 5.2.1 Inhalation

Groups of 5 female Wistar rats were exposed to *n*-butylamine at 0, 35, 123 or 352 mg/m$^3$ for 5 days (6 hours per day; about 0, 12, 41 or 117 ml/m$^3$). In the highest

concentration group of the study carried out according to OECD Guideline 412, the animals closed their eyelids and wiped their snouts, which was assessed as sensory irritation. The clinico-pathological examination revealed no substance-induced findings in any of the exposed animals, not even in the noses of the highly exposed rats. Nor did the organ weights or gross-pathological and histopathological examinations reveal any effects caused by the substance (BASF 1999). A NOAEC of 123 mg/m³ (41 ml/m³) was derived from this study for the irritant effect of *n*-butylamine.

In a range-finding study for a developmental toxicity study, groups of 10 pregnant Wistar rats were exposed to *n*-butylamine at 0, 82, 165 or 330 ml/m³ for 5 days. The animals of the two high concentration groups showed irritation to the respiratory tract with histopathological lesions of the upper respiratory tract, reduced body weight gain and mild polycythaemia. The animals of the lowest concentration group had squamous metaplasia and an increase of inflammatory cells in the nasal epithelium (BASF 2000). Since none of these findings occurred in the control group, these are substance-induced effects at a LOAEC of 82 ml/m³.

In a developmental toxicity study carried out according to OECD Guideline 414, pregnant Wistar rats were exposed to *n*-butylamine at 0, 51, 151 or 460 mg/m³ on 14 consecutive days (about 0, 17, 50 or 152 ml/m³; see Section 5.5.2). Subsequently, 10 animals from each concentration group were examined histopathologically. They revealed concentration-related alterations in the respiratory epithelium of the dams; these are listed in Table 1 (BASF 2001). Since none of these findings occurred in the control group, these are substance-induced effects at a LOAEC of 17 ml/m³.

**Table 1** Findings in the noses of female Wistar rats after exposure to n-butylamine on 14 consecutive days (BASF 2001)

| Findings | 0 ml/m³ | 17 ml/m³ | 50 ml/m³ | 152 ml/m³ |
|---|---|---|---|---|
| inflammatory cells | 0/10 | 3/10 | 9/10 | 10/10 |
| squamous metaplasia | 0/10 | 1/10 | 5/10 | 10/10 |
| transitional cell hyperplasia | 0/10 | 1/10 | 6/10 | 0/10 |
| necrosis in the mucosa | 0/10 | 0/10 | 0/10 | 5/10 |
| necrosis of the nasal bone | 0/10 | 0/10 | 0/10 | 1/10 |

### 5.2.2 Ingestion

A developmental toxicity study was carried out with oral administration (gavage) according to OECD Guideline 414 (see Section 5.2.2). Groups of 22 to 24 pregnant Wistar rats received *n*-butylamine hydrochloride concentrations of 0, 100, 400 or 1000 mg/kg body weight and day (*n*-butylamine at about 0, 66.7, 267 or 667 mg/kg body weight and day) in water from day 6 up to and including day 15 of gestation.

After administration of 1000 mg/kg body weight and day, the feed consumption of the dams was significantly reduced from days 6 to 13 of gestation. The uterine weight of the animals of the highest dose group was reduced by about 14% as compared with the control animals, while the corrected body weight remained unchanged. No other findings occurred in the dams (BASF 2002; Gamer et al. 2002). Therefore, the NOAEL of this study was 400 mg/kg body weight and day for *n*-butylamine hydrochloride. According to Gamer et al. (2002), if this dose is converted to an airborne concentration assuming a respiratory minute volume of 200 ml/min in rats, a weight of 300 g, 100% deposition, absorption and conversion of the hydrochloride into *n*-butylamine, an *n*-butylamine concentration of 367 ml/m$^3$ is obtained for an exposure period of 6 hours/day.

### 5.2.3 Dermal absorption

There are no data available for dermal absorption.

## 5.3 Local effects on skin and mucous membranes

There are no data available for *sec*-butylamine, *iso*-butylamine or *tert*-butylamine applicable to this section.

### *n*-Butylamine

### 5.3.1 Skin

Application of *n*-butylamine (no other details) to the dorsal skin of white rabbits induced erythema and necrosis as early as after contact periods of 1 minute (subsequent washing of the skin area with Lutrol 9 and water) as well as scarring at the application site from a 5-minute contact period onwards. No systemic effect was observed. Necrosis healed within 6 weeks (no other details, not even on the pH of the applied solution) (BASF 1958).

Application of 0.01 ml *n*-butylamine to the shaved dorsal skin of 5 rabbits led to an injury grade of 6 (maximum: 10; no other details) and to necrosis resulting from the undiluted solution (NL Health Council 2003). There are no details about the pH of the applied solution.

### 5.3.2 Eyes

One drop of undiluted *n*-butylamine instilled into the conjunctival sac of rabbits produced immediate tissue necrosis and the complete destruction of the eye (eyelids, cornea and conjunctivae; no other details) (BASF 1958).

A 5% solution of *n*-butylamine led to an injury grade of 8 (maximum: 10; no other details) 18 to 20 hours after application. Calculations showed that 0.5% (v/v) was the lowest *n*-butylamine concentration causing microscopic epithelial damage to the eye (no other details; NL Health Council 2003).

## 5.4 Allergenic effect

There are no data available for *sec*-butylamine, *iso*-butylamine or *tert*-butylamine applicable to this section.

### *n*-Butylamine

*n*-Butylamine was not sensitizing in a maximization test carried out according to OECD Guideline 406. Necrotic and sometimes open skin changes were observed after intradermal induction with a 0.1% solution of the substance, and necrotic skin changes and slight oedema were found after epicutaneous induction with a 5% solution. A 2% solution of *n*-butylamine in water was used as a challenge concentration (BASF 1993). There are no details about the pH of the applied solution.

## 5.5 Reproductive and developmental toxicity

### 5.5.1 Fertility

*In vitro* studies with the sperm of mice, rabbits and humans revealed that *n*-butylamine and *n*-butylamine hydrochloride completely inhibited the sperm motility at concentrations of 0.2 to 0.5% (w/v; about 2 mg/ml). *n*-Butylamine concentrations of 1.5% (v/v) induced the separation of the sperm tail from the sperm head. Concentrations without effects were not tested. *sec*-Butylamine, *tert*-butylamine and *iso*-butylamine also led to the separation of the sperm tail from the sperm head in mouse or rabbit sperm. Separation always occurred between the inner nuclear membrane, which continued to be attached to the nuclear chromatin, and the outer nuclear membrane adjacent to the tail basal plate (Young and Cooper 1983). However, the significance of the study must be considered since an alkaline milieu (pH 12.5) also led to a 90% head-tail separation of sperm. Therefore, the sperm head-tail separation caused by amines *in vitro* might be due to the change in the pH in the culture medium resulting from the addition of butylamine. The inhalation or ingestion of butylamines cannot produce such severe alterations in the testes (the pH of the blood varies between 7.36 and 7.44 in healthy humans).

### 5.5.2 Developmental toxicity

No data applicable to this section are available for *sec*-butylamine or *iso*-butylamine, and there is only one non-validated *in vitro* study for *tert*-butylamine.

#### *n*-Butylamine

In a developmental toxicity study with inhalation exposure, carried out according to OECD Guideline 414, groups of 20 to 24 pregnant Wistar rats were exposed to *n*-butylamine at concentrations of 0, 51, 151 or 460 mg/m³ (about 0, 17, 50 or 152 ml/m³) for 6 hours per day from day 6 up to and including day 19 of gestation. The animals were examined pathologically on day 20 of gestation. No animal died during the study. The histopathological examination revealed substance-induced effects in the respiratory epithelium of the exposed animals. Infiltrations of inflammatory cells and squamous metaplasia in the respiratory epithelium were observed as maternally toxic effects in the animals of all exposure groups at 17 ml/m³ and above; 5 animals of the highest exposure group also had focal necrosis extending to the underlying nasal bone (see Section 5.2.1). The LOAEC for maternal toxicity was thus 17 ml/m³. *n*-Butylamine showed no developmental toxicity or teratogenicity at the concentrations used. Therefore, the NOAEC for the developmental toxicity of *n*-butylamine was 152 ml/m³ (BASF 2001; Gamer et al. 2002).

Another study was carried out with oral administration (gavage) according to OECD Guideline 414. Groups of 22 to 24 pregnant Wistar rats received *n*-butylamine hydrochloride concentrations of 0, 100, 400 or 1000 mg/kg body weight and day (*n*-butylamine at about 0, 66.7, 267 or 667 mg/kg body weight and day) in water from day 6 up to and including day 15 of gestation. The animals were examined pathologically on day 20 of gestation. After administration of 1000 mg/kg body weight and day, the feed consumption of the dams was significantly reduced on days 6 to 13 of gestation and the uterine weight was decreased by about 14% as compared with the control animals. A significantly increased number of early resorptions and post-implantation losses and a significantly reduced percentage of live foetuses occurred. Significantly reduced placental weights (20%) and foetal body weights (8%) were observed as compared with the control groups. The incidence of external, soft-tissue and total malformations that occurred was slightly, but significantly increased, as was the percentage of foetuses with retarded skeletal development. After administration of 400 mg/kg body weight and day, there was a slight, statistically significant increase in the incidence of foetuses with soft-tissue malformations (3 foetuses from 3 litters). The malformations were the same as or similar to those of the highest dose group, such as aortic arch atresia, malpositioned heart and diaphragmatic hernia. No substance-induced effects occurred in the offspring of the lowest dose group. In this study, the NOAEL of *n*-butylamine hydrochloride was 400 mg/kg body weight and day for maternal toxicity (*n*-butylamine at about 267 mg/kg body weight and day) and 100 mg/kg body weight and day (*n*-butylamine at about 66.7 mg/kg body weight and day) for developmental toxicity. The findings obtained after exposure to 400 and 1000 mg/kg body weight

and day (*n*-butylamine at about 267 and 667 mg/kg body weight and day) provided evidence of developmental toxicity with signs of teratogenicity (BASF 2002; Gamer et al. 2002).

#### *tert*-Butylamine

After 48-hour incubation of Han-Wistar rat embryos (days 9.5 to 11.5 of gestation) in a culture medium containing *tert*-butylamine, no effects in the embryos were observed in the presence of a metabolic activation system (no other details) (Schmid et al. 1983). Since this testing system has not been validated, it cannot be used for assessment.

## 5.6 Genotoxicity

### 5.6.1 In vitro

In a bacterial mutagenicity test using the *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, *n*-butylamine was not mutagenic in the presence or absence of a metabolic activation system at concentrations of 3.3 to 3333 µg/plate (NL Health Council 2003).

In the bacterial mutagenicity test using the *Salmonella typhimurium* strains TA100, TA1535, TA1537 and TA98, *sec*-butylamine and *tert*-butylamine were negative up to 1000 µg/plate (TA1535 and TA1537) or 3333 µg/plate (TA100 and TA98) (Zeiger et al. 1987).

### 5.6.2 In vivo

A micronucleus test in 5 male and 5 female NMRI mice was negative at *n*-butylamine doses of 0, 200, 400 or 800 mg/kg body weight. The substance was injected once intraperitoneally as a 63% *n*-butylamine hydrochloride solution in water (10 ml/kg body weight). The femoral bone marrow was analyzed in the animals of the control and highest dose groups after 24 and 48 hours and in the animals of the lower doses and of the positive controls only after 24 hours (BASF 1995).

## 5.7 Carcinogenicity

There are no data available for *sec*-butylamine, *iso*-butylamine or *tert*-butylamine applicable to this section.

#### *n*-Butylamine

The aim of a comparative study of various urethane derivatives was to investigate the development of skin and lung tumours in mice after a single administration

(Berenblum et al. 1959). However, the publication does not clearly show whether *n*-butylamine or *n*-butylamide was used in the study. The structural formula of *n*-butylamine was listed in a table while the text only referred to *n*-butylamide in the same context. Therefore, this study has not been included in this assessment.

### 5.8 Other effects

*n*-Butylamine reacted with the nitrite and thiocyanate present in the saliva to form *N*-nitrosobutylcyanamide and *N*-nitrosodibutylamine (Tannenbaum et al. 1978).

The cardiac papillary muscles of cats *in vitro* showed a greater contraction amplitude in the presence of *tert*-butylamine concentrations of 0.73 to 730 mg/l, *i.e.* a positive inotropic effect occurred. Mongrel dogs showed a positive inotropic effect and a positive chronotropic effect in the heart-lung preparation *ex vivo* from a *tert*-butylamine concentration of about 2.5 mg/l blood. Vasoconstriction was observed after intravenous injection of a *tert*-butylamine concentration of 5 mg/kg body weight in anaesthetized dogs. It was concluded from these and other studies that *tert*-butylamine acts as a sympathomimetic amine and the sites of cardiac stimulation are of a peripheral rather than of a central or ganglionic origin (Baum et al. 1962).

## 6 Manifesto (MAK value/classification)

**_n_-butylamine**

Although the available studies on repeated exposure to *n*-butylamine are incomplete, they fit well into the overall pattern of the mode of action of aliphatic amines. As in the case of other aliphatic amines, extremely severe irritation is the main effect of *n*-butylamine (see Table 2). A systemic effect only clearly occurred above irritation and was manifest in the form of lower feed consumption and reduced uterine weight of the pregnant animals. For the aliphatic amines listed in Table 2, MAK values between 2 and 10 ml/m$^3$ were established depending on the irritation threshold of the substance. If no studies on the irritation threshold in humans were available, the $RD_{50}$ value of the specific substance determined by Gagnaire et al. (1989; 1993) was used to help establish a MAK value. Gagnaire et al. determined the $RD_{50}$ values of many different aliphatic amines. The same strain of mice was always used, and the laboratory conditions, methods of measurement and handling of the animals were always identical. Thus, the $RD_{50}$ values determined resulted from the different effect of the individual amines rather than from treatments that varied in different laboratories. For aliphatic amines with an $RD_{50}$ of a maximum of 100 ml/m$^3$, a MAK value of 2 ml/m$^3$ was established on the basis of the severe irritation (see Table 2). After 14-day exposure of pregnant rats to *n*-butylamine, signs of inflammation were observed in the respiratory epithelium of the

dams from 17 ml/m³; they increased with the concentration up to necrosis at 150 ml/m³. There was no NOAEC. On the basis of these sometimes-massive effects observed after only 14 days of exposure and an $RD_{50}$ of 84 ml/m³ for *n*-butylamine, a MAK value of 2 ml/m³ was established for *n*-butylamine and the substance was classified in Peak Limitation Category I with an excursion factor of 2. An unpublished observation from occupational medicine also supported this value, reporting irritation to the nose, throat and eyes from an *n*-butylamine concentration of 5 ml/m³, but no complaints at lower exposure. Based on the signs of inflammation in the respiratory epithelium of rats from 17 ml/m³ after 14 days of exposure, a momentary value of 5 ml/m³ is established to avoid exposure peaks.

*In vitro* studies by Young and Cooper (1983) demonstrated a spermatotoxic effect of *n*-butylamine, although this may also have been induced by the basicity of the substance in the culture medium. However, such a pH shift was not observed *in vivo*. As shown in Section 5.5.1, it is unlikely that a spermatotoxic effect will be observed after exposure at the level of the MAK value.

To substantiate this, appropriate animal studies with repeated administration of *n*-butylamine to males for at least 90 days urgently need to be carried out. Depending on the model, calculation of the dermal penetration rate leads to a very high value of 30 or 3 mg/cm² and hour for undiluted *n*-butylamine. The substance is corrosive. As in the case of other aliphatic amines, the low dermal $LD_{50}$ may result from the fact that application of the amine causes severe damage to the skin and the amount absorbed is very much higher than at non-corrosive concentrations. The fact that the $LD_{50}$ of the hydrochloride is considerably higher than that of the base after oral administration indicates that the corrosive effect is substantially involved in acute toxicity. Therefore *n*-butylamine is not designated with "H". A maximization test carried out with *n*-butylamine in guinea pigs yielded negative results. There are no other findings on sensitization. The substance is therefore not designated with "Sa" or "Sh".

Mutagenicity studies with *Salmonella typhimurium* and a micronucleus test with *n*-butylamine in mice *in vivo* were negative. No conclusive carcinogenicity studies are available. *n*-Butylamine is therefore not classified in any of the carcinogenicity or germ cell mutagenicity categories.

Exposure of pregnant rats to *n*-butylamine concentrations of up to 450 mg/m³ (150 ml/m³) induced local effects on the nose, but no substance-specific findings were observed in the offspring. After oral administration of *n*-butylamine as a hydrochloride to pregnant rats, a teratogenic effect was found at doses from 400 mg/kg body weight and day. However, this dose is far from being reached if the MAK value is observed (maximum absorption of about 0.9 mg/kg body weight and day). *n*-Butylamine is therefore classified in Pregnancy Risk Group C.

**sec-Butylamine and *iso*-butylamine**

The data available for these isomers suggest a mode of action similar to that of *n*-butylamine and other primary amines, the basicity of which makes irritation their main effect. However, the pKa values are not responsible for irritation alone;

**Table 2** Data on the local irritation of aliphatic amines (taken from the respective MAK documentation)

| Name | MAK value [ml/m³] | Excursion factor**** | NOEC, short term*, human [ml/m³] | LOEC, short term*, human [ml/m³] | References human data | NOEC, animal, morphological, nose [ml/m³] | LOEC, animal, morphological, nose [ml/m³] | $RD_{50}$ [ml/m³] ** | Log $K_{ow}$ *** |
|---|---|---|---|---|---|---|---|---|---|
| *n*-butylamine | 2 IR | 2 | 2 | 5–10: irritation to eyes, nose and throat | Beard and Noe 1981 | – | 17 (14 days) | 84 | 0.97 |
| *sec*-butylamine | 2 IR | 2 | – | – | | – | – | – | 0.74 |
| *iso*-butylamine | 2 IR | 2 | – | – | | – | – | 90 | 0.73 |
| *tert*-butylamine | 2 IR | 2 | – | – | | – | – | – | 0.4 |
| 2-aminopropane | 5 IR | 1 | – | 10–20 | Sutton 1963 | 41 (28 days) | 200 (28 days) | 160 | 0.26 |
| cyclohexylamine | 2 IR | 2 | – | – | | – | – | 50 | 1.49 |
| diethylamine | 5 IR | 2 | – | 10: irritation to eyes and nose | Lundqvist et al. 1992 | – | – | 200 | 0.58 |
| dimethylamine | 2 IR | 2 | – | – | | – 10 (12 months) | 10 (2 years) | 70 | 0.38 |

**Table 2** (Continued)

| Name | MAK value [ml/m³] | Excursion factor**** | NOEC, short term*), human [ml/m³] | LOEC, short term*), human [ml/m³] | References human data | NOEC, animal, morphological, nose [ml/m³] | LOEC, animal, morphological, nose [ml/m³] | $RD_{50}$ [ml/m³] **) | Log $K_{ow}$ ***) |
|---|---|---|---|---|---|---|---|---|---|
| N,N-dimethyl-ethylamine | 2 VD | 2 | 6<br>5 | 12: eye irritation<br>n.o.d.<br>8: slight itching of eyes and lacrimation | Ståhlbom et al. 1991;<br>1988 | – | – | 160 | 0.7 |
| dimethyl isopropylamine | 1<br>VD | 2 | – | – | | – | – | 90 | – |
| ethylamine | 5 IR | 2 | – | – | | 100<br>(24 weeks) | 500<br>(24 weeks) | 150 | –0.13 |
| methylamine | 10 IR | 1 | <10 | 20 | Sutton 1963 | – | – | 140 | –0.57 |
| triethylamine | 1<br>VD | 2 | 8.8<br>11: somewhat unpleasant sensation in eyes without irritation | 12: mild irritation to eyes, nose and throat | 1988<br>1986 | 250 (28 days) | – | 160 | 1.45 |

**Table 2** (Continued)

| Name | MAK value [ml/m³] | Excursion factor[****)] | NOEC, short term[*)], human [ml/m³] | LOEC, short term[*)], human [ml/m³] | References human data | NOEC, animal, morphological, nose [ml/m³] | LOEC, animal, morphological, nose [ml/m³] | $RD_{50}$ [ml/m³] [**)] | Log $K_{ow}$ [***)] |
|---|---|---|---|---|---|---|---|---|---|
| trimethylamine | 2 VD/ IR[****)] | 2 | 5 | 20 | WEEL Guide 1980; see docum. "Trimethylamin" 1983 MAK in German | – | 75 (2 weeks) | 61 | 0.16 |

IR: derivation of the MAK value based on irritation
VD: derivation of the MAK value based on visual disturbances (haze)
*) short term: short-term exposure
**) Gagnaire et al. 1993
***) SRC 2005
****) all Peak Limitation Category I
*****) comparative analysis

according to Gagnaire et al. (1993), the log $K_{OW}$ of the substances is more decisive. Table 2 shows these values and the MAK values of other aliphatic amines together with the observed NOAEC or LOAEC. Because of the presumably similar mode of action and the log $K_{OW}$ values of *sec*-butylamine, *iso*-butylamine and *n*-butylamine, the MAK value of 2 ml/m³ for *n*-butylamine has also been applied provisionally to the isomers sec-butylamine and *iso*-butylamine. This concurs with the data for the irritation of other aliphatic amines for which MAK values were also established on the basis of irritation (Table 2): MAK values of 5 ml/m³ were established for 2-aminopropane, ethylamine and diethylamine, which have $RD_{50}$ values of about 150 ml/m³, whereas MAK values of 2 ml/m³ were applied to dimethylamine and cyclohexylamine, which have lower $RD_{50}$ values. In analogy to *n*-butylamine, *sec*-butylamine and *iso*-butylamine are therefore also classified in Peak Limitation Category I with an excursion factor of 2 and a momentary value of 5 ml/m³. Further studies urgently need to be carried out to substantiate the provisional MAK value. Particularly with regard to the spermatotoxic effect of the substances found *in vitro*, no appropriate animal studies have been carried out using repeated administration to clarify whether or at which concentrations or doses the spermatotoxic effect becomes evident in animal studies. As stated in the assessment of *n*-butylamine, no spermatotoxic effect will presumably occur *in vivo* after exposure at the level of the MAK value of 2 ml/m³.

No data are available for skin penetration of *sec*-butylamine or *iso*-butylamine. Since basicity and the physicochemical properties are similar to those of *n*-butylamine, *sec*-butylamine and *iso*-butylamine are not designated with "H" either.

Analogous to *n*-butylamine, *sec*-butylamine and *iso*-butylamine are classified in Pregnancy Risk Group C.

There are no studies of sensitization, carcinogenicity or germ cell mutagenicity. The substances are therefore not designated with "Sa" or "Sh", nor are they classified in any of the carcinogenicity or germ cell mutagenicity categories.

**tert-Butylamine**

The tertiary hydrocarbon skeleton with the primary amine function of *tert*-butylamine has some physicochemical properties that are different from those of the other isomers (log $K_{OW}$ and vapour pressure). Moreover, *tert*-butylamine might have transmitter-like functions resulting from its structure. Only one intra-arterial injection study in dogs, which provided evidence of an effect on haemodynamic parameters, is available for the systemic effect of *tert*-butylamine. There are no other studies available with repeated exposure. Although irritation is probably the main effect, further systemic effects of *tert*-butylamine cannot be ruled out at present. Moreover, since some physicochemical parameters clearly differ from those of the other isomers, *tert*-butylamine is classified in Section IIb of the *List of MAK and BAT values*.

No data on skin penetration are available for *tert*-butylamine. Since the basicity and mode of action are assumed to be similar to those of *n*-butylamine, *tert*-butylamine is not designated with "H" either.

No studies are available on the sensitizing effect of *tert*-butylamine. The substance is therefore not designated with "Sa" or "Sh".

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completed on 02.12.2005