

Diethylene glycol monobutyl ether

[112-34-5]

Supplement 2008

MAK value (2007)	10 ml/m³ \triangleq 67 mg/m³
Peak limitation (2007)	Category I, excursion factor 1.5
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (1992)	Pregnancy Risk Group C
Germ cell mutagenicity	–
BAT value	–
1 ml/m³ (ppm) \triangleq 6.732 mg/m³	1 mg/m³ \triangleq 0.149 ml/m³ (ppm)

The documentation available for diethylene glycol monobutyl ether was published in 1992 (see documentation “Diethylene glycol monobutyl ether” 1996, a translation of the 1992 German) and there is a supplement for peak limitation (see documentation “Diethylene glycol monobutyl ether” 2000, only available in German). New studies of the effects of diethylene glycol monobutyl ether have since been published. For various end points there are no data for diethylene glycol monobutyl ether itself, but for diethylene glycol monobutyl ether acetate. Since rapid deacetylation to diethylene glycol monobutyl ether was detected (Deisinger and Guest 1989), studies with the acetate have been used also for the evaluation of diethylene glycol monobutyl ether.

1 Toxic Effects and Mode of Action

Diethylene glycol monobutyl ether is a solvent with low volatility. In an inhalation study that was described in the 1992 MAK documentation (see documentation “Diethylene glycol monobutyl ether” 1996, a translation of the 1992 German), the exposure of rats to a vapour/aerosol mixture of 350 mg/m³ and above for 2 weeks was found to cause decreased spleen weights, increased lung weights, activated

alveolar cells and foam cells, and distended goblet cells in all bronchial sections. After the ingestion of diethylene glycol monobutyl ether doses of 250 mg/kg body weight and day and above over a period of 13 weeks, reduced numbers of red blood cells and decreased (2%–3%) haematocrit and haemoglobin levels were found in rats. However, these values were in the range of the historical control data of this laboratory. The relative spleen weights were increased by about 5% and were outside the historical control data. The urinary pH was reduced; this was attributed to the elimination of the metabolite 2-(2-butoxyethoxy)acetic acid.

No systemic toxicity was observed after the application for 13 weeks of diethylene glycol monobutyl ether doses of up to 2000 mg/kg body weight and day to the intact dorsal skin of rats.

Diethylene glycol monobutyl ether was not found to cause sensitization in maximization tests in guinea pigs.

Reproductive toxicity studies carried out with diethylene glycol monobutyl ether in rats did not lead to substance-induced findings in the offspring after dermal application of up to 2000 mg/kg body weight and day or after the ingestion of up to 633 mg/kg body weight and day.

Diethylene glycol monobutyl ether revealed no genotoxic potential in the available studies; there are no carcinogenicity studies available.

2 Mechanism of Action

There are no data available on the mechanism of action of diethylene glycol monobutyl ether.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution and elimination

Single oral doses of radioactively labelled diethylene glycol monobutyl ether acetate of 200 mg/kg body weight or 2000 mg/kg body weight were rapidly absorbed by male rats and metabolically degraded via diethylene glycol monobutyl ether (see Figure 1). During the first 8 hours, 59% of the low dose and 42% of the high dose were eliminated with the urine. In both dose groups, around 82% of the radioactivity was eliminated with the urine and 2% to 3% with the faeces within 24 hours. Around 5% of the radioactivity was exhaled as CO₂. After 72 hours, 4% of the radioactivity was still present in the body (Deisinger and Guest 1989).

After 24-hour dermal application of radioactively labelled diethylene glycol monobutyl ether in doses of 200 or 2000 mg/kg body weight, rats absorbed 30% to 54% of the applied dose in the low dose group and 3.4% (♂) to 19% (♀) in the high dose group. In the low dose group, the males eliminated 27% to 31% of the applied

dose with the urine, and the females 42% to 51%. The corresponding values in the high dose group were 3.3% and 18%. Elimination with the faeces was below 2% in all dose groups. The dermal penetration rates of diethylene glycol monobutyl ether in male and female rats were calculated to be 0.73 and 1.46 mg/cm² and hour in the high dose group and 0.25 to 0.32 mg/cm² and hour in the low dose group. The major part was eliminated within the first 24 hours. The exhalation of CO₂ was not investigated (Boatman et al. 1993).

Workers in the printing industry with scaliness or erythema on the skin were found to absorb markedly higher amounts of diethylene glycol monobutyl ether (in some cases by a factor of 2), determined as 2-(2-butoxyethoxy)acetic acid in the urine, than printers with healthy skin. In diffusion cell experiments with excised human skin, diethylene glycol monobutyl ether in a diluted solution, like many other glycol ethers, was found to have a considerably accelerated rate of penetration. The penetration rate of undiluted diethylene glycol monobutyl ether was 137.38 µg/cm² and hour (mean), compared with 802.98 µg/cm² and hour as a 50% aqueous solution (mean), the range being 419.22 to 1241.56 µg/cm² and hour. Furthermore, it is known that skin creams enhance the percutaneous absorption of diethylene glycol monobutyl ether in diffusion cell experiments with human skin. The acceleration of penetration may be up to 1.5-fold depending on the skin cream used (mean values: 406.73 compared with 593.86 µg/cm² and hour) (Korinith et al. 2003).

on the basis of a dermal flux of 802.98 or 1241.56 µg/cm² and hour the dermal absorption was calculated to be 1606 mg or 2483 mg if 2000 cm² of skin would be exposed for 1 hour to a 50% aqueous diethylene glycol monobutyl ether solution.

3.2 Metabolism

The metabolism of diethylene glycol monobutyl ether is shown in Figure 1. Only a small amount of diethylene glycol monobutyl ether is metabolized by alcohol dehydrogenase, while the major part is metabolized by cytochrome P450. As diethylene glycol monobutyl ether acetate is rapidly deacetylated in rat blood in vitro (Deisinger and Guest 1989), it can be used for the assessment of diethylene glycol monobutyl ether. After single oral doses of radioactively labelled diethylene glycol monobutyl ether of 200 mg/kg body weight or 2000 mg/kg body weight, male Sprague Dawley rats exhaled about 5% of the administered radioactive dose as ¹⁴CO₂. The metabolites were determined in the urine. 2-(2-Butoxyethoxy)acetic acid was the major urinary metabolite with about 53% to 60% of the radioactivity. In addition, diethylene glycol accounted for 12% of the radioactivity, a non-quantified fraction was detected as ethylene glycol and 32% as 2-(2-(3- or 4-hydroxybutoxy)ethoxy)ethanol. Traces of 2-butoxyethanol, 2-butoxy acetic acid and 2-(2-butoxyethoxy)acetyl glycine were found, although it could not be determined whether these substances were metabolites of diethylene glycol monobutyl ether acetate or

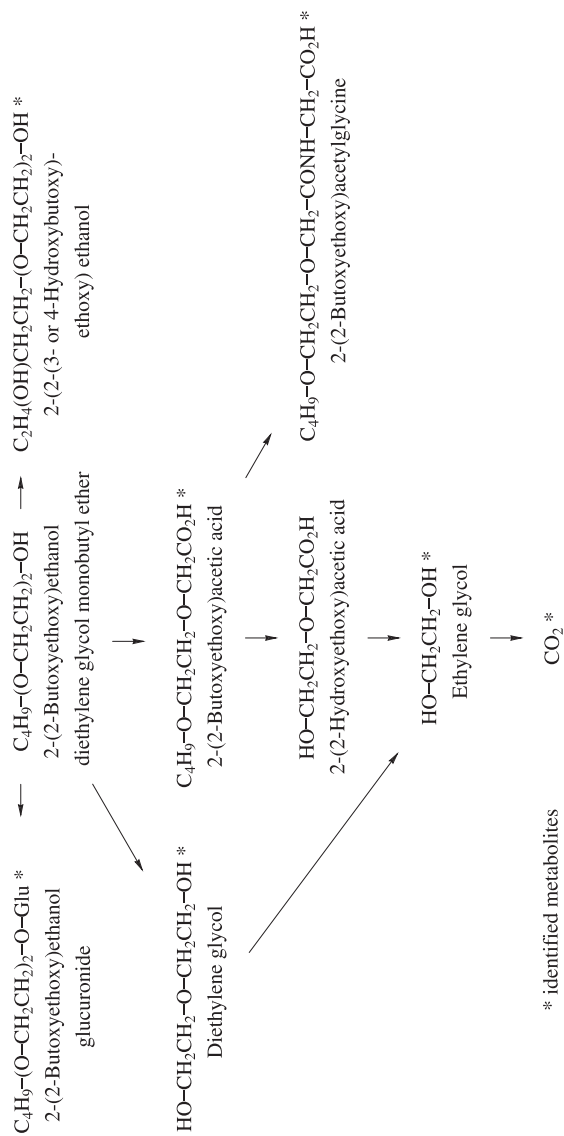


Figure 1 Metabolites of diethylene glycol monobutyl ether

impurities of the parent compound (Deisinger and Guest 1989). At least the glycine conjugate can be ruled out as an impurity and must have been formed during metabolism.

In a study with male and female Sprague Dawley rats with dermal application of radioactively labelled diethylene glycol monobutyl ether in doses of 200 mg/kg body weight or 2000 mg/kg body weight or as a 10% aqueous solution, 2-(2-butoxyethoxy)acetic acid was the major urinary metabolite with 60% to 80% of the radioactivity. Traces of 2-butoxy acetic acid were detected. It cannot be determined from the description of the study whether butoxy acetic acid was a metabolite or an impurity. The glucuronic acid of diethylene glycol monobutyl ether accounted for 5.2% to 8.2% of the urinary radioactivity. Further unidentified metabolites were found (Boatman et al. 1993).

4 Effects in Humans

A worker who had been exposed to diethylene glycol monobutyl ether acetate and diethylene glycol monobutyl ether had developed acute dermatitis on his hands, arms, face and neck reacted strongly to diethylene glycol monobutyl ether in a patch test after 48 and 72 hours. After 1 year without exposure to diethylene glycol monobutyl ether or its acetate and with healed dermatitis, the worker did not react to diethylene glycol monobutyl ether in a renewed patch test after occlusive treatment. However, he reacted to the application of 0.1 ml diethylene glycol monobutyl ether acetate or diethylene glycol monobutyl ether in a test after 20 minutes of non-occlusive treatment (Dawson et al. 1989). A 48-year-old female non-smoker who had been suffering from irritation of the eyes and upper respiratory tract for more than 1 year and had erythema on the face and swollen eyelids produced a strong reaction to diethylene glycol monobutyl ether in a patch test (Berlin et al. 1995).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

The LC_{50} for diethylene glycol monobutyl ether in rats was found to be above 18 ml/m³ (no other details). This concentration is the highest at which diethylene glycol monobutyl ether can be generated as a pure vapour (Gingell et al. 1996).

5.1.2 Ingestion

The LD₅₀ after ingestion of diethylene glycol monobutyl ether was between 5100 and 9600 mg/kg body weight in rats, between 2400 and 5500 mg/kg body weight in mice, 2000 mg/kg body weight in guinea pigs and 2200 mg/kg body weight in rabbits (no other details; Gingell et al. 1996).

5.1.3 Dermal absorption

In a study with occlusive dermal application of diethylene glycol monobutyl ether, the LD₅₀ in rabbits was 2760 mg/kg body weight. Another study found it to be 4000 mg/kg body weight (no other details; Gingell et al. 1996).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

No new studies with inhalation exposure have been published since the 1992 MAK documentation (see documentation "Diethylene glycol monobutyl ether" 1996, a translation of the 1992 German).

In the studies described there, a NOAEC (no observed adverse effect concentration) of 13 mg/m³ (about 2 ml/m³) was determined after the exposure of rats for 5 weeks; slight dose-dependent vacuolation of hepatocytes was observed at 39 mg/m³ (about 5.8 ml/m³) and above. After 2-week exposure of rats to 14 ml diethylene glycol monobutyl ether vapour/m³ (about 100 mg/m³), the spleen weights of the males were slightly reduced. After 2-week exposure to a vapour/aerosol mixture of 350 or 1000 mg/m³, the spleen weights were reduced in a dose-dependent manner and the lung weights were increased with inflammatory effects. Histopathological examination revealed perivascular and peribronchial mixed cellular infiltration, activated alveolar cells, foam cells and distended goblet cells in all bronchial sections. According to the EU (2000), these effects were observed even at 14 ml/m³ (about 100 mg/m³). As a result, another study was carried out over a period of 90 days with daily 6-hour exposure. The highest diethylene glycol monobutyl ether concentration tested of 14 ml/m³ (about 100 mg/m³) caused neither local nor systemic effects in rats (BASF AG 1992). This means that the effects observed at 39 mg/m³ in the earlier 5-week study could not be reproduced even after prolonged exposure. In 1992, the MAK value was therefore derived on the basis of this 90-day study.

5.2.2 Ingestion

In a study carried out according to OECD Test Guideline 408, F344 rats were given diethylene glycol monobutyl ether with the drinking water in doses corresponding

to 0, 50, 250 or 1000 mg/kg body weight and day for 13 weeks. After doses of 250 mg/kg body weight and day and above, the erythrocyte count and the haematocrit and haemoglobin levels were reduced by 2% to 3%, but were in the range of the historical control data of this laboratory. The relative spleen weights were increased by about 5% and were outside the range of the historical control data. The urinary pH was decreased; this was attributed to the elimination of the metabolite 2-(2-butoxyethoxy)acetic acid. At 1000 mg/kg body weight and day, feed and water consumption and body weight gains were reduced. The relative liver weights and the enzyme activities in the liver were increased, and the absolute and relative kidney weights were increased without there being a histopathological correlate, and the cholesterol and total protein values were reduced (see Table 1). In ophthalmological and sensory examinations, rectal determination of the body temperature and the test of grip strength and motor activity, no differences were found between the exposed animals and those not exposed. The histopathological examination including the spleen, testis and sperm parameters revealed no substance-induced findings or any signs of irritation in the gastrointestinal tract. The authors considered 250 mg/kg body weight and day to be the NOAEL (Johnson et al. 2005). On the basis of the marginal, but dose-dependent increase in spleen weights and the slight changes in blood parameters, the Commission derived a NOAEL of 50 mg/kg body weight and day from this study.

Unlike in the 14-day inhalation study, in which reduced spleen weights were observed, the spleen weights were increased in this study at 250 mg/kg body weight and day. As increased spleen weights were described also in a 6-week study with rats given gavage doses of diethylene glycol monobutyl ether (documentation "Diethylene glycol monobutyl ether" 1996, a translation of the 1992 German), the finding of the 14-day inhalation study is questionable and the NOAEL of 50 mg/kg body weight and day derived from the 90-day study has been used for the assessment of systemic toxicity.

5.2.3 Dermal absorption

Diethylene glycol monobutyl ether was applied to about 9 cm² of the shaved dorsal skin of 10 male and 10 female Sprague Dawley rats in doses of 0, 200, 600 or 2000 mg/kg body weight and day under occlusive conditions on 5 days a week for 13 weeks. The covering and any test substance residues were removed after the daily 6-hour application period. Haematological and clinico-chemical examinations, urinalysis and ophthalmoscopy were carried out at the beginning and at the end of the study, and the animals were examined histopathologically at the end of the study. No systemic toxicity was observed. Dose-dependent irritation at the site of application was the only substance-induced finding; the females reacted more sensitively than the males (see Table 1; Auletta et al. 1993). The systemic NOAEL of this study with dermal application was 2000 mg/kg body weight and day. In order to examine possible neurotoxic effects, 12 male and 12 female Sprague Dawley

Table 1 Effects of diethylene glycol monobutyl ether after repeated exposure

Species, strain, number of animals per group	Exposure	Findings	References
rat , F344, 5 ♂/5 ♀	2 weeks , 0, 1000, 1500, 2000 mg/kg b.w. and day; with the drinking water	1000 mg/kg b.w. and above: dose-related: feed and water consumption ↓, b.w. and b.w. gains ↓, urine volume ↓, specific gravity ↑, erythrocyte count ↓ by about 5%, TP ↓, ♀: CHOL ↓; 2000 mg/kg b.w.: ♂: erythrocyte count ↓ by a maximum 13%, ♀: erythrocyte count max 7%	Johnson et al. 2005
rat , F344, 10 ♂/10 ♀	13 weeks , 0, 50, 250, 1000 mg/kg b.w. and day; with the drinking water	50 mg/kg b.w. : NOAEL; 250 mg/kg b.w. and above: urinary pH ↓, absolute and relative spleen weights ↑, erythrocyte count, haemoglobin and haematocrit ↓ by a maximum 3.7%, values within the range of historical control data; 1000 mg/kg b.w.: feed and water consumption ↓, urine volume ↓, specific gravity ↑, erythrocyte count, haemoglobin and haematocrit max 8.7%, AST ↓, TP ↓, CHOL ↓, EROD ↑, PROD ↑, UGT ↑, absolute and relative kidney weights ↑, relative liver weights ↑, ♂: b.w. gains ↓ by 10%, ♀: b.w. gains ↓ by 6%; number of liver foci ↑	Johnson et al. 2005
rat , SD, 10 ♂/10 ♀	13 weeks , 0, 200, 600, 2000 mg/kg b.w. and day; 6 hr/day, 5 days/week, dermal, occlusive	no effects observed	Auletta et al. 1993
rat , SD, 12 ♂/12 ♀	13 weeks , 0, 200, 600, 2000 mg/kg b.w. and day; 6 hrs/day, 5 days/week, dermal, occlusive	no effects observed	Beyrouthy et al. 1993

AST: aspartate aminotransferase (serum); TP: total protein (serum); CHOL: cholesterol (serum);
 EROD: ethoxyresorufin O-dealkylase (liver); PROD: pentoxyresorufin O-dealkylase (liver);
 UGT: UDP-glucuronosyltransferases (liver)

rats were treated dermally with diethylene glycol monobutyl ether in doses of 0, 200, 600 or 2000 mg/kg body weight and day applied to about 9 cm² of skin under occlusive conditions for 6 hours a day on 5 days a week, for 13 weeks. Clinical symptoms and functional and motor activities were investigated several times during the study. At the end of the study, neuropathological examinations were carried out on fixed tissue. Slight degeneration of the renal tubules was detected in 2 males of the high dose group. The neurotoxicological tests did not reveal substance-induced effects (see Table 1); only irritation at the site of application was observed and this was more pronounced in females than in males (Beyrouty et al. 1993). Degeneration of the renal tubules, which was observed in 2 males, was not attributed to the treatment since no findings of this kind were observed in the other 13-week study. The systemic NOAEL of this study with dermal application was 2000 mg/kg body weight and day.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Diethylene glycol monobutyl ether caused slight irritation to the skin of rabbits and guinea pigs (Gingell et al. 1996).

5.3.2 Eyes

Undiluted diethylene glycol monobutyl ether induced slight irritation of the rabbit eye in a study. The eye irritation was most severe after 24 hours, while no abnormal findings were detected in the eye 14 days after the treatment; a 5% aqueous solution did not cause irritation (ECETOC 2005; Gingell et al. 1996).

5.4 Allergenic effects

Diethylene glycol monobutyl ether did not have sensitizing effects in a maximization test in guinea pigs (ECETOC 2005).

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

In a 13-week study, diethylene glycol monobutyl ether doses of 0 or 2000 mg/kg body weight and day were applied dermally under occlusive conditions to about

9 cm² of the shaved dorsal skin of 25 male and 25 female Sprague Dawley rats. After 13 weeks of exposure, the animals were mated. During the subsequent mating period, the males were exposed on 5 days a week as before, while the females were treated on 7 days a week until day 20 of gestation. The male parent animals were examined after mating, and the dams and pups were examined on day 21 after parturition. In male parent animals, the complete sexual organs were examined histopathologically and the testes were stained specifically, while in the dams only gross-pathological findings were examined histopathologically. Diethylene glycol monobutyl ether had no effects on the mating index, incidence of pregnancy or male and female fertility indices (Auletta et al. 1993). The NOAEL for fertility was 2000 mg/kg body weight and day in this study.

In a study carried out according to OECD Test Guideline 408 (see also Section 5.2.2), F344 rats were given diethylene glycol monobutyl ether for 13 weeks with the drinking water in doses corresponding to 0, 50, 250 or 1000 mg/kg body weight and day. There were no substance-induced findings in the ovaries, uterus and testes, also sperm parameters were unchanged (Johnson et al. 2005).

5.5.2 Developmental toxicity

In the study described in Section 5.5.1 with dermal application of 2000 mg/kg body weight and day, diethylene glycol monobutyl ether had no influence on the birth weights, postnatal body weight gains, survival or viability of the offspring of Sprague Dawley rats (Auletta et al. 1993). The NOAEL for developmental toxicity was 2000 mg/kg body weight and day in this study.

The developmental toxicity studies described in the 1992 MAK documentation (see documentation “Diethylene glycol monobutyl ether” 1996, a translation of the 1992 German) (see Table 2) did not reveal any teratogenic effects or toxic effects on development in rats or rabbits given oral doses of up to 1000 mg/kg body weight and day. Merely in one study with rats the body weights of suckling pups were reduced on postnatal days 14 and 21; the reduction was significant only on postnatal day 14 (Nolen et al. 1985).

Table 2 Developmental toxicity studies of diethylene glycol monobutyl ether

Species, strain, number of animals per group	Exposure	Findings	References
rat, SD, 25 ♂/25 ♀	13 weeks 0, 2000 mg/kg b.w. and day, dermal , 6 hrs/day, 5 days/week, occlusive examination on PND 21	2000 mg/kg b.w.: <u>dams</u> : no systemic toxicity, no effects on fertility (systemically available); <u>pups</u> : no effects on birth weights, b.w. gains or survival, no externally visible anomalies	Auletta et al. 1993
rat, CD, 25 ♂/25 ♀	before mating until PND 21 0, 250, 500, 1000 mg/kg b.w. and day, gavage , mating of treated ♂ with untreated ♀ and treated ♀ with untreated ♂ examination on GD 13 and PND 21	1000 mg/kg b.w.: <u>dams</u> : no systemic toxicity or effects on fertility; <u>pups</u> : no prenatal toxicity, birth weights comparable with those of controls, on PND 14: b.w. ↓	Nolen et al. 1985
rat, Wistar, 20 ♂	GD 1–21 0%, 0.04%, 0.2%, 1% in the diet (about 0, 25, 115, 633 mg/kg b.w. and day) examination on GD 21 (15/20) and on PND 70 (5/20)	25 mg/kg b.w. and above: <u>dams</u> : b.w. gains ↓; up to 633 mg/kg b.w.: <u>foetuses/pups</u> : no prenatal toxicity	Ema et al. 1988
mouse, CD-1, 50 ♀	GD 6–13 0, 500, 2050 mg/kg b.w. and day, gavage examination on PND 3	500 mg/kg b.w.: <u>dams</u> : NOAEL (no other details); 2050 mg/kg b.w.: <u>dams</u> : 25% died; <u>pups</u> : no prenatal toxicity (no other details)	Hardin et al. 1987
rabbit, New Zealand White, 20 ♂/20 ♀	GD 7–18 0, 0, 100, 300, 1000 mg/kg b.w. and day, dermal , 4 hr/day, 5 days/week, non-occlusive examination on GD 29	300 mg/kg b.w. and above: <u>dams</u> : slight irritation at the application site with increasing dose; 1000 mg/kg b.w.: <u>foetuses</u> : no prenatal toxicity	Nolen et al. 1985

GD: gestation day; PND: postnatal day

5.6 Genotoxicity

5.6.1 In vitro

The 1992 MAK documentation (see documentation “Diethylene glycol monobutyl ether” 1996, a translation of the 1992 German) reported negative results in in vitro mutagenicity tests in *Salmonella typhimurium*, CHO cells and tests for UDS (unscheduled DNA synthesis) in hepatocytes.

In mutagenicity tests with *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA1538 and tests with *Escherichia coli* WP2uvrA, diethylene glycol monobutyl ether acetate did not cause any increase in the incidence of mutation in either the presence or absence of a metabolic activation system at concentrations of up to 5000 µg/plate (EU 2000).

Diethylene glycol monobutyl ether yielded negative results in a HPRT gene mutation test with CHO cells up to concentrations of 5000 µg/ml in both the presence and absence of a metabolic activation system. However, a slight, significant increase in the incidence of mutation (13.9 per 10⁶ cells) compared with that in the concurrent control (0 per 10⁶ cells) was observed in 1 of 2 test runs with metabolic activation at 3000 µg/ml. Since this increase was detected in only 1 test run and only at 3000 µg/ml and was thus not related to the dose and since higher negative control values were obtained in historical controls (5.2 per 10⁶ cells), the overall result was regarded as negative. The concurrent positive control yielded values of 299.4 per 10⁶ cells in the absence and 325.4 per 10⁶ cells in the presence of a metabolic activation system (Gollapudi et al. 1993).

5.6.2 In vivo

The 1992 MAK documentation (see documentation “Diethylene glycol monobutyl ether” 1996, a translation of the 1992 German) described a test for sex-linked recessive lethal mutations (SLRL test) in *Drosophila melanogaster* and a micronucleus assay in the bone marrow of mice with doses of up to 3300 mg/kg body weight, both of which yielded negative results.

There are no new data available for the genotoxic effects of diethylene glycol monobutyl ether in vivo.

5.7 Carcinogenicity

There are no data available for the carcinogenicity of diethylene glycol monobutyl ether.

5.8 Other effects

Diethylene glycol monobutyl ether had no effects in vitro on cell morphology, cell size, haemolysis or the deformability of rat or human erythrocytes (Udden 2005).

6 Manifesto (MAK value/classification)

There are no data from humans available suitable for deriving a MAK value for diethylene glycol monobutyl ether.

No new inhalation studies have been published since 1992. After exposure for 6 hours a day over a period of 90 days, the highest concentration of diethylene glycol monobutyl ether vapour tested of 14 ml/m³ (about 100 mg/m³) caused neither local nor systemic effects in rats (BASF AG 1992). No intensification of the effects over time is apparent from the overall data. The previous MAK value of 100 mg/m³, which was derived from this 90-day study, has been transformed into a ml/m³ value as in this concentration range diethylene glycol monobutyl ether is present as a vapour rather than as an aerosol. If a preferred value approach is followed, the NOAEC of 14 ml/m³ (94 mg/m³) yields in a MAK value of 10 ml/m³. The systemic NOAEL of 50 mg/kg body weight and day derived from a more recent 90-day drinking water study in rats (Johnson et al. 2005) is just as high as that obtained from a 30-day drinking water study (see documentation "Diethylene glycol monobutyl ether" 1996, a translation of the 1992 German). Thus, the NOAEL for systemic toxicity does not become lower over time. The NOAEL of 50 mg/kg body weight and day corresponds to a concentration in air of 350 mg/m³ (on the basis of a person with a body weight of 70 kg, the inhalation of 10 m³ air per working day, and 100% absorption). Systemic effects are therefore not to be expected after exposure at the level of the MAK value of 10 ml/m³ (67 mg/m³). In addition, as the effects on the spleen and blood were only marginal at the next-higher dose of 250 mg/kg body weight and day, the MAK value offers sufficient protection. The solubility of diethylene glycol monobutyl ether in water and its presence as a vapour/aerosol mixture at the LOAEC of 350 mg/m³ also have to be taken into account. As a result of impaction, a greater amount of the inhaled dose can act locally in the case of an aerosol; on the other hand, a higher fraction of a vapour is exhaled again. This means that the difference between locally acting concentrations is not reflected by the difference between the LOAEC and NOAEC, but is higher. For these reasons, the difference between the MAK value of 10 ml/m³ and the LOAEC of 350 mg/m³ (about 52 ml/m³) as a vapour/aerosol mixture in rats is sufficient.

The previous classification in Peak Limitation Category I has been retained because of the local effects of the substance. Since the highest investigated concentration without effects was 14 ml/m³, an excursion factor of 1.5 is established.

No evidence of systemic toxicity was found after the application of diethylene glycol monobutyl ether to the dorsal skin of rats in doses of up to 2000 mg/kg body

weight and day for 13 weeks. Therefore, diethylene glycol monobutyl ether is not designated with an "H".

Since the publication of the MAK documentation in 1992 (see documentation "Diethylene glycol monobutyl ether" 1996, a translation of the 1992 German), a new maximization test in guinea pigs has become available for the sensitizing effects of diethylene glycol monobutyl ether. There was no evidence that the substance has a sensitizing potential. Diethylene glycol monobutyl ether is therefore still not designated with "Sa" or "Sh".

In vitro genotoxicity studies yielded no evidence that diethylene glycol monobutyl ether has mutagenic potential. No new in vivo genotoxicity studies or carcinogenicity studies are available. Classification in one of the Germ Cell Mutagen or Carcinogen Categories is not necessary.

In the developmental toxicity studies with oral administration in rats and mice described in the 1992 MAK documentation (see documentation "Diethylene glycol monobutyl ether" 1996, a translation of the 1992 German), effects on the body weights of suckling pups were observed only at doses of 1000 mg/kg body weight and day. Diethylene glycol monobutyl ether therefore remains in Pregnancy Risk Group C.

References

- Auletta CS, Schroeder RE, Krasavage WJ, Stack CR (1993) Toxicology of diethylene glycol butyl ether 4. Dermal subchronic/reproductive study in rats. *J Am Coll Toxicol* 12: 161–168
- BASF AG (1992) Study on the inhalation toxicity of Butyldiglykol as a vapor in rats, 90-day test. BASF, Project No. 50I0030/87002, BASF AG, Ludwigshafen, unpublished report
- Berlin K, Johanson G, Lindberg M (1995) Hypersensitivity to 2-(2-butoxyethoxy)ethanol. *Contact Dermatitis* 32: 54
- Beyrouthy P, Broxup B, Losos G, Robinson K, Maurissen JPJ, Gill MW, Stack CR (1993) Toxicology of diethylene glycol butyl ether 5. Dermal subchronic neurotoxicity study in rats. *J Am Coll Toxicol* 12: 169–174
- Boatman RJ, Schum DB, Guest D, Stack CR (1993) Toxicology of diethylene glycol butyl ether 2. Disposition studies with ¹⁴C-diethylene glycol butyl ether and ¹⁴C-diethylene glycol butyl ether acetate after dermal application to rats. *J Am Coll Toxicol* 12: 145–154
- Dawson TAJ, Black RJ, Strang WC, Millership JS, Davies II (1989) Delayed and immediate hypersensitivity to carbitols. *Contact Dermatitis* 21: 52
- Deisinger PJ, Guest D (1989) Metabolic studies with diethylene glycol monobutyl ether acetate (DGBA) in the rat. *Xenobiotica* 19: 981–989
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) (2005) The toxicology of glycol ethers and its relevance to man (fourth edition). Technical Report No. 95, ECE-TOC, Brussels
- Ema M, Itami T, Kawasaki H (1988) Teratology study of diethylene glycol mono-n-butyl ether in rats. *Drug Chem Toxicol* 11: 97–111
- EU (2000) 2-(2-Butoxyethoxy)ethanol. European Union risk assessment report, http://ecb.jrc.it/Documents/Existing-Chemicals/RISK_ASSESSMENT/REPORT/degberreport004.pdf

- Gingell R, Boatman RJ, Corley RA, Knaak JB, Rosica KA, Wise RC (1996) Toxicology of diethylene glycol butyl ether. *Occup Hyg* 2: 293-302
- Gollapudi BB, Linscombe VA, McClintock ML, Sinha AK, Stack CR (1993) Toxicology of diethylene glycol butyl ether 3. Genotoxicity evaluation in an in vitro gene mutation assay and an in vivo cytogenetic test. *J Am Coll Toxicol* 12: 155-159
- Hardin BD, Schuler RL, Burg JR, Booth GM, Hazelden KP, MacKenzie KM, Piccirillo VJ, Smith KN (1987) Evaluation of 60 chemicals in a preliminary developmental toxicity test. *Teratog Carcinog Mutagen* 7: 29-48
- Johnson KA, Baker PC, Kan HL, Maurissen JP, Spencer PJ, Marty MS (2005) Diethylene glycol monobutyl ether (DGBE): two- and thirteen-week oral toxicity studies in Fischer 344 rats. *Food Chem Toxicol* 43: 467-481
- Korinth G, Göen T, Lakemeyer M, Bronding HC, Drexler H (2003) Skin strain and its influence on systemic exposure to a glycol ether in offset printing workers. *Contact Dermatitis* 49: 248-254
- Nolen GA, Gibson WB, Benedict JH, Briggs DS, Schardein JL (1985) Fertility and teratogenic studies of diethylene glycol monobutyl ether in rats and rabbits. *Fundam Appl Toxicol* 5: 1137-1143
- Udden MM (2005) Effects of diethyldene glycol butyl ether and butoxyethoxyacetic acid on rat and human erythrocytes. *Toxicol Lett* 156: 95-101

completed 15.02.2007