The MAK Collection for Occupational Health and Safety

2-Phenoxyethanol

MAK Value Documentation, addendum – Translation of the German version from 2017

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2-Phenoxyethanol[1)]

MAK Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated 2-phenoxyethanol [122-99-6], considering all toxicity endpoints. Available publications and study reports are described in detail. In a 14-day inhalation study with rats, critical effects of 2-phenoxyethanol were hyperplasia, degeneration and metaplasia of the respiratory epithelium in the nasal cavity beginning at 246 mg/m³. The NOAEC was 48.2 mg/m³ (8.4 ml/m³). Since 2014, the Commission uses an empirical approach to set maximum concentrations at the workplace (MAK values) for substances with critical effects on the upper respiratory tract or the eyes. Based on this approach, a MAK value of 1 ml/m³ has been derived. The assignment to Peak Limitation Category I, because local effects are critical, and the excursion factor of 2 have been confirmed. No developmental toxicity was detected in rats (oral) or rabbits (dermal) up to doses of 1000 or 600 mg/kg body weight and day, resp. In an oral two-generation study in mice, the NOAEL for foetotoxicity was about 400 mg/kg body weight and day. The differences between the NOAEL for rats, mice and rabbits scaled to an inhalation concentration at the workplace and the MAK value are considered so large that damage to the embryo or foetus is unlikely when the MAK value is observed. Therefore, classification in Pregnancy Risk Group C is confirmed. 2-Phenoxyethanol is not regarded to be genotoxic or carcinogenic. Sensitization is not expected based on results of animal studies and experience in humans. Skin contact is not expected to contribute significantly to the systemic toxicity.

Keywords

2-phenoxyethanol; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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1) The substance can occur simultaneously as vapour and aerosol.

2-Phenoxyethanol[1)]

[122-99-6]

Supplement 2017

MAK value (2016)	**1 ml/m³ (ppm) ≙ 5.7 mg/m³**
Peak limitation (2016)	**Category I, excursion factor 1**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (1998)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
Melting point	14 °C (NLM 2015 a)
Boiling point at 1013 hPa	245 °C (NLM 2015 a)
Density at 20 °C	1.11 g/cm³ (IFA 2015)
Vapour pressure	0.01 hPa (at 25 °C NLM 2015 a; at 20 °C ECHA 2015)
log K_{OW}[2)]	1.16 (NLM 2015 a)
Solubility (20.7 °C)	24.2 g/l water (pH 5.5) 28.6 g/l water (pH 7.0) 30.1 g/l water (pH 9.0) (ECHA 2015)
1 ml/m³ (ppm) ≙ 5.733 mg/m³	**1 mg/m³ ≙ 0.174 ml/m³ (ppm)**

The vapour saturation concentration of 2-phenoxyethanol is reported to be 40 mg/m³ (temperature not specified) (BASF AG and The Dow Chemical Company 2007 c).

2-Phenoxyethanol is used as a fixative for perfumes and soaps, as a preservative in cosmetics and as a component of hydraulic fluids.

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1) The substance can occur simultaneously as vapour and aerosol.

2) octanol/water partition coefficient.

Documentation for 2-phenoxyethanol was published in 1998 (documentation "2-Phenoxyethanol" 1998, available in German only), followed by a supplement for peak limitation in 2000 (supplement "2-Phenoxyethanol" 2000, available in German only).

This supplement has been compiled because new studies, including an inhalation study, have become available.

1 Toxic Effects and Mode of Action

2-Phenoxyethanol is rapidly absorbed through the skin and from the gastro-intestinal tract of humans and animals. The substance is eliminated rapidly and practically the whole administered amount is recovered in the urine in the form of phenoxyacetic acid, its main metabolite, or its conjugates.

After inhalation exposure of rats to an aerosol of 2-phenoxyethanol for 2 weeks, minimal to mild squamous metaplasia in the larynx, minimal to mild hypertrophy of the respiratory epithelium and goblet cell hyperplasia in the lungs, and minimal to moderate hyperplasia, degeneration and metaplasia as well as infiltrates of inflammatory cells in the respiratory epithelium of the nasal cavity were observed at the concentration of 246 mg/m^3 and above. In rats, oral 13-week studies reported reduced feed utilization and water consumption, reduced body weight gains, increased alkaline phosphatase, reduced platelet counts and prolonged activated partial thromboplastin times as well as groups of dilated tubules with basophilic stainability and chronic inflammatory cell infiltration in the kidneys at about 400 mg/kg body weight and day and above. In a recent study, these findings were not reproducible up to the highest dose tested of 697 mg/kg body weight for males and 938 mg/kg body weight for females. In a 13-week drinking water study in mice, reduced water and feed consumption and increased relative kidney weights were observed at about 1178 mg/kg body weight and day and above. Drinking water studies with exposure of rats and mice for 2 years reported effects on the kidneys at about 550 and 1000 mg/kg body weight and day and above, respectively.

A 2-generation study in mice yielded foetotoxic effects at concentrations of 1.25% and 2.5% 2-phenoxyethanol in the diet (about 2000 or 4000 mg/kg body weight), but these effects might have been due to maternal toxicity in the form of reduced body weights or markedly increased liver weights. Toxic effects on development were not observed in studies in rats or rabbits with ingestion or dermal application up to the highest doses tested of 1000 and 600 mg/kg body weight and day, respectively.

Only few case reports of suspected contact allergy to 2-phenoxyethanol are available. Very few clinical epidemiological studies reported positive patch test results. Experimental studies in guinea pigs did not provide evidence of sensitizing effects of 2-phenoxyethanol on the skin.

2-Phenoxyethanol induced slight irritation of the intact skin of rabbits and guinea pigs; the undiluted substance caused severe irritation of the rabbit eye.

2-Phenoxyethanol was not genotoxic in the available studies. In 2-year drinking water studies in rats and mice, there were no significant increases in the incidences of neoplastic lesions.

2 Mechanism of Action

There are no new data available.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

There are no data available for absorption after inhalation.

2-Phenoxyethanol is absorbed rapidly and completely after oral administration in humans and rats (documentation "2-Phenoxyethanol" 1998, available in German only).

A new study carried out according to OECD Test Guideline 417 has become available that investigated the toxicokinetics of orally administered 2-phenoxyethanol in Wistar rats (BASF AG and The Dow Chemical Company 2007 a):

In one section of the study, groups of 4 male and 4 female rats were given single gavage doses of 30, 100, 300 or 1000 mg/kg body weight to investigate the kinetics of the substance in blood plasma. The test substance was ^{14}C-labelled at the phenyl ring. Radioactivity was determined in the blood and plasma after 1 hour and after 2, 4, 8, 24, 48, 72 and 96 hours. The maximum concentrations of radioactivity in plasma were reached after 1 to 2 hours. Initial half-lives of 1.9 to 2.9 hours and 1.8 to 4.6 hours were reported for males and females, respectively. The terminal half-lives were 33 to 54 hours for males and 28 to 60 hours for females. A similar time course was found in both sexes for the radioactivity in both blood and plasma. During the first 24 hours after dosing, the concentrations of radioactivity were lower in the blood than in the plasma. Blood/plasma ratios > 1 were detected 48 hours after administration and later. A 33-fold increase in the dose to 1000 mg/kg body weight increased the AUC values (area under the plasma concentration-time curve) by a factor of 61 in males and by a factor of 88 in females. The authors considered this to be evidence that elimination becomes saturated with the increasing dose; this is an effect that is known for phenoxyacetic acids and is caused by the inhibition of a transporter in the kidneys.

In another section of the study that investigated the ratio of amounts recovered and elimination, groups of 4 male and 4 female rats were given single gavage doses of ^{14}C-labelled 2-phenoxyethanol of 40 or 400 mg/kg body weight or a daily dose of 2-phenoxyethanol of 400 mg/kg body weight for 15 days (only the last dose with the ^{14}C-labelled substance). After the single doses, on average > 96% of the administered radioactivity was recovered at both dose levels and in all animals. No relevant fractions of $^{14}CO_2$ were found in the exhaled air. At the high dose, the males and females had eliminated 90.8% and 86.4% of the radioactivity in the urine after 24 hours, 93.1% and 90.6% after 72 hours, and 94.1% and 93.4% within 168 hours. The sum amounts of radioactivity eliminated in the faeces of the male and female rats were 2.6% and 1.3% after 48 hours, and 2.9% and 2.0% after 168 hours. After a single dose of 40 mg/kg body weight, the males and females had eliminated 90.5% and 83.3% of the administered radioactivity in the urine after 24 hours, 93.0% and 89.3% after 72 hours and 94.0% and 92.9% within 168 hours, whereas total fractions

of 1.9% and 1.3% of the administered radioactivity had been eliminated in the faeces after 48 hours and 2.2% and 1.9% after 168 hours.

After repeated administration of 400 mg/kg body weight, 98.6% and 92.3% of the administered radioactivity was recovered in male and female rats, respectively. In the urine, the males and females had eliminated 92.4% and 82.5% of the radioactivity after 24 hours, 95.2% and 86.3% after 72 hours, and 96.7% and 88.5% after 168 hours. The total amounts of radioactivity detected in the faeces of the male and female rats were 1.23% and 1.19% after 48 hours, and 1.4% and 1.7% after 186 hours. There were no differences in the elimination characteristics of the substance after single and repeated doses. The time course for the detection of radioactivity in both the urine and faeces indicated rapid elimination. The amount of radioactivity in the urine was not dose-dependent, and the elimination route was not sex-specific. The bioavailability of 90% to 95% of the substance was calculated from the elimination data in the urine and faeces at both doses, which means that the substance is almost completely absorbed from the gastro-intestinal tract.

In another section of the study that investigated the distribution of the substance in the tissue, ^{14}C-labelled 2-phenoxyethanol was given to groups of 3 female rats per dose and investigation time as single gavage doses of 40 or 400 mg/kg body weight. At the low dose, the animals were investigated after 1 hour and 2, 3.5 or 8 hours, and at the high dose, they were investigated after 2, 4.5, 7 or 14 hours. The concentrations of radioactivity in tissue generally decreased parallel to the concentrations in plasma. Over the course of the study it was found that at the high dose the concentrations were highest in the gastro-intestinal tract, kidneys, pancreas, skin and bone marrow. At the low dose, the concentrations were highest in the gastro-intestinal tract, kidneys, liver and skin. The levels were lowest in the brain, muscles and heart at the high dose and in the brain, uterus, muscles and bone at the low dose.

In another section of the study that investigated the elimination of the substance in the bile, groups of 4 male and 4 female rats were given ^{14}C-labelled 2-phenoxyethanol as a single gavage dose of 400 mg/kg body weight. Another group of 4 females was given a single gavage dose of 40 mg/kg body weight. In this part of the study, the animals were bile-duct cannulated. The bile, urine and faeces were collected at intervals of 3 and 24 hours, and the animals were examined after 72 hours. The amount of radioactivity recovered was in the range from 81% to 91%. After 72 hours, only small amounts of radioactivity (0%–1.1%) were found in the contents of the stomach and intestines. In the males and females of the high dose groups, 5.6% and 4.6% of the administered radioactivity was eliminated in the bile within 72 hours. In the low dose group, 3.4% of the administered radioactivity was found in the bile within 72 hours. At both dose levels, elimination with the bile was highest within the first 6 hours and then decreased until the end of the study. The bioavailability of 75% to 98% of the substance was calculated for both doses from the amount of radioactivity eliminated in the bile, urine and faeces (BASF AG and The Dow Chemical Company 2007 a).

A number of studies are available for dermal absorption; they are summarized in Table 1.

Among the in vivo studies, only one study examined the intact skin and found high levels of recovery. After 48 hours, the dermal absorption of 2-phenoxyethanol in vivo was > 85% after occlusive application in an oil-in-water or water-in-oil

cream (Howes 1988). Among the in vitro studies, recovery was high only in one study. In this case, occlusive application of the substance to rat skin led to 94% absorption after 4 hours (Roper et al. 1997).

A study that investigated the effects on wound healing in vivo of an epicutaneously used disinfectant containing 2% 2-phenoxyethanol also examined its dermal penetration through porcine skin in vitro. A permeability coefficient of $1.82 \times 10^{-6} \pm 4.70 \times 10^{-7}$ cm/s was determined for the intact porcine skin. After damaging the porcine skin by tape stripping, permeability increased to $1.86 \times 10^{-5} \pm 1.86 \times 10^{-6}$ cm/s (Stahl et al. 2010).

3.2 Metabolism

Phenoxyacetic acid or its conjugates are the main metabolites in humans and animals and are formed almost in the same quantities as the administered substance (documentation "2-Phenoxyethanol" 1998, available in German only).

A study carried out according to OECD Test Guideline 417 investigated the metabolism of 2-phenoxyethanol in female Wistar rats after oral administration. The analysis included urine, bile and plasma from the sections of the study described in Section 3.1 (BASF AG and The Dow Chemical Company 2007 a).

The urine collected from female rats that were given single gavage doses of ^{14}C-labelled 2-phenoxyethanol of 40 or 400 mg/kg body weight or a daily 2-phenoxyethanol dose of 400 mg/kg body weight for 15 days (only last dose with ^{14}C-labelled substance) was analysed to determine the metabolites. 2-Phenoxyacetic acid (M01 in Figure 1) was identified as the main metabolite in the urine; in all dose groups it accounted for 57% to 74% of the administered dose within 24 hours. The glucuronidated metabolite (M05 in Figure 1) represented 4.8% to 6.0% of the dose within 24 hours. The sum of the metabolites M02, M03 and M07 (in Figure 1) was equivalent to 8.0% to 10.3% of the dose; M02 was the main metabolite, making up 85% of the sum of M02, M03 and M07. The sum of the metabolites M04 and M08 in the urine (in Figure 1) was quantified to be 4.7% to 5.9% of the dose within 24 hours; M04 and M08 were present in about equal amounts. 2-Phenoxyethanol was detected in the pooled 24-hour urine in amounts of < 0.7% of the dose. The total amount of the metabolites detected in the 24-hour pooled urine was in a range between 78% and 83% of the administered dose.

Bile was collected within 6 hours after the administration of single doses of ^{14}C-labelled 2-phenoxyethanol of 40 or 400 mg/kg body weight. Glucuronidated 2-phenoxyethanol (M05 in Figure 1) and 2-phenoxyacetic acid (M01 in Figure 1) were identified as metabolites and accounted for up to 2.3% and up to 0.4% of the dose, respectively. 2-Phenoxyethanol was found in the bile in quantities representing 0.07% of the dose.

Plasma samples that were collected 1 to 2 hours after the administration of single doses of ^{14}C-labelled 2-phenoxyethanol of 40 or 400 mg/kg body weight contained the main metabolite 2-phenoxyacetic acid (M01 in Figure 1) in dose-dependent quantities representing 70% to 90% of the total radioactivity in the plasma. The absolute amounts of 2-phenoxyacetic acid in the plasma, at 0.1% to 0.3% of the administered dose, were small (BASF AG and The Dow Chemical Company 2007 b).

Table 1 Studies of the dermal absorption of 2-phenoxyethanol

Species, strain, sex, number per group	Dose, area, exposure period	Result	Comments	References
in vivo				
patients with skin problems (no other details), 1 ♂, 3 ♀	1.2% in o/w cream, up to 40 g cream/day, 25%–90% of the body surface, twice daily for 2 days, non-occlusive	absorption: 8.5%–48% within 3 days (determination: phenoxyacetic acid in the urine)		Howes 1988
rat, Colworth Wistar, 4 ♀	100 mg/10 cm^2, in o/w or w/o cream, 48 hours, occlusive	absorption: > 85%, total recovery (urine, faeces, inhaled air, carcass, tissue and patches): > 90%	^{14}C-labelled	Howes 1988
rat, Colworth Wistar, 4 ♂, 4 ♀	up to 3.66 mg/10 cm^2, 48 hours, occlusive	absorption: up to 60%, total recovery (urine, faeces, inhaled air, carcass, tissue and patches): 65%–75%	^{14}C-labelled in ethanol, evaporative losses while drying the application site	Howes 1988
in vitro				
human skin, no other details	2560 nmol/10 µl, 0.64 cm^2 (flow-through cell), up to 6 hours, non-occlusive	59.3% absorption after 6 hours, permeability coefficient: 13.37×10^{-4} cm/hour	^{14}C-labelled in methanol, evaporative losses, no data for recovery, determination of radioactivity	Roper et al. 1997

Table 1 (continued)

Species, strain, sex, number per group	Dose, area, exposure period	Result	Comments	References
rat skin, Wistar, ♂	1556 nmol/10 µl, 0.79 cm^2 (static cell), 5290 nmol/10 µl, 0.64 cm^2 (flow-through cell), up to 24 hours, occlusive and non-occlusive	occlusive: 94% absorption after 4 hours, recovery: 102.6%, flux: 1070 nmol/cm^2/h, permeability coefficient: 73.5 × 10^{-4} cm/hour (static cell); non-occlusive: up to 64% absorption after 24 hours, recovery: 67.6%, permeability coefficient: 27.2 × 10^{-4} cm/h (static cell); non-occlusive: 43% absorption after 24 hours, recovery: 51%, permeability coefficient: 17.64 × 10^{-4} cm/hour (flow-through cell)	^{14}C-labelled in methanol, evaporative losses after non-occlusive application, determination of radioactivity	Roper et al. 1997, 1998
porcine skin, no other details, ♂	0.1% octenidine and 2% 2-phenoxyethanol, 1.13 ml/cm^2, 1.77 cm^2 (Franz cell), 28 hours, occlusive	permeation: 11.3% (intact skin) and 43.9% (stratum corneum removed by tape stripping); maximum flux: 131 µg/cm^2/hour (intact skin) and 1340 µg/cm^2/hour (tape stripping)	no data for recovery, determination of substance by HPLC	Stahl et al. 2010
bovine skin, no other details	0.1% octenidine and 2% 2-phenoxyethanol, 1.14 ml/cm^2, 1.77 cm^2 (Franz cell), 28 hours, occlusive	maximum flux: 1231 µg/cm^2/hour (intact skin) and 2211 µg/cm^2/hour (tape stripping); recovery in receptor fluid: 37% and 43%, respectively	determination of substance by HPLC	Stahl et al. 2011
canine skin, no other details	0.1% octenidine and 2% 2-phenoxyethanol, 1.14 ml/cm^2, 1.77 cm^2 (Franz cell), 28 hours, occlusive	maximum flux: 392 µg/cm^2/hour (intact skin); recovery in receptor fluid: 39%	determination of substance by HPLC	Stahl et al. 2011

Table 1 (continued)

Species, strain, sex, number per group	Dose, area, exposure period	Result	Comments	References
feline skin, no other details	0.1% octenidine and 2% 2-phenoxyethanol, 1.14 ml/cm^2, 1.77 cm^2 (Franz cell), 28 hours, occlusive	maximum flux: 580 µg/cm^2/hour (intact skin); recovery in receptor fluid: 35%	determination of substance by HPLC	Stahl et al. 2011
equine skin, no other details	0.1% octenidine and 2% 2-phenoxyethanol, 1.14 ml/cm^2, 1.77 cm^2 (Franz cell), 28 hours, occlusive	maximum flux: 1298 µg/cm^2/hour (intact skin); recovery in receptor fluid: 61%	determination of substance by HPLC	Stahl et al. 2011

octenidine: cationic disinfectant insoluble in water; o/w: oil-in-water; w/o: water-in-oil

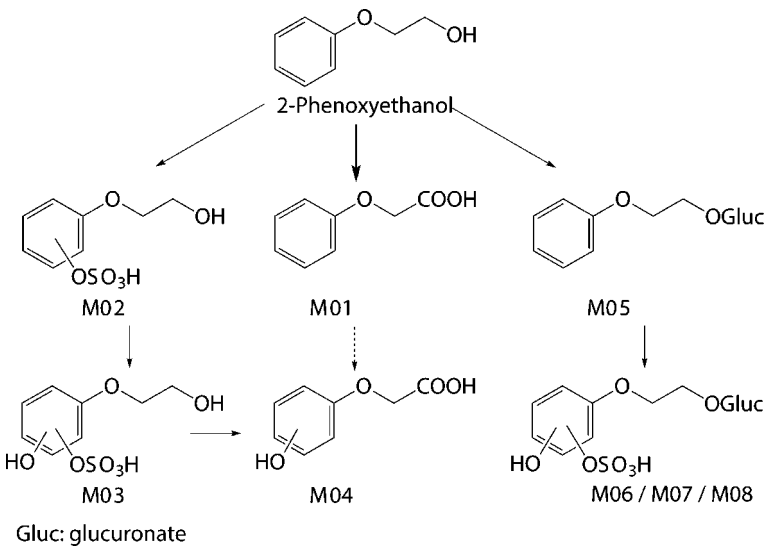

Figure 1 The metabolism of 2-phenoxyethanol (BASF AG and The Dow Chemical Company 2007 b)

An in vitro study compared the metabolism of 2-phenoxyethanol (purity: 99.7%) in the presence of S9 homogenate from the liver of CD-1 mice (♀, n = 100), Sprague Dawley rats (♀, n = 100), New Zealand White rabbits (♀, n = 2) and human donors (♀, n = 7). In all 4 species, 2-phenoxyacetic acid was the main metabolite, which was formed preferably in the presence of NAD^+ and to a far lesser extent in the presence of NADPH in mice, rats and humans. In rabbits, no differences in the formation of 2-phenoxyacetic acid were observed in the presence of NAD^+ or NADPH. Small amounts of phenol were detected only after incubation with the liver homogenate of female mice in the presence of NADPH. The formation of metabolites was linear over a period of 120 minutes. In the four species, the formation of 2-phenoxyacetic acid was saturated in the range from 0.07 to 2 mM. In rats, rabbits and humans, the formation of 2-phenoxyacetic acid was reduced above V_{max}, suggesting the substrate-dependent inhibition of the enzyme activity at high concentrations. At a substrate concentration of 1 mM, the metabolic rate decreased in the order human > rat > mouse > rabbit. The activity of the V_{max}/K_m ratio decreased in the order human > rat > mouse (0.01225, 0.00199 and 0.00129 ml/min/mg protein). In rabbits, the maximum rate of 2-phenoxyacetic acid formation was determined at the lowest substrate concentration tested of 0.07 mM (V_{max} = 0.00011 µmol/min/mg protein) (The Dow Chemical Company and BASF AG 2006).

Another in vitro study compared the metabolism of glycol ethers, including that of 2-phenoxyethanol, in cytosol fractions from rat liver and rat skin. The conversion of NAD^+ to form NADH was determined as a measure of the oxidation of the compounds by alcohol dehydrogenase (ADH) or aldehyde dehydrogenase (ALDH). The rate of metabolism by liver cytosol decreased in the order ethanol > 2-ethoxyethanol > ethylene glycol > 2-phenoxyethanol > 2-butoxyethanol. In the cytosol frac-

tions from rat skin, the order changed to 2-butoxyethanol > 2-phenoxyethanol > ethylene glycol > 2-ethoxyethanol > ethanol; the specific activity in cytosol from dermatomed skin was about twice that from whole rat skin. The authors concluded from these results that ADH and ALDH are localized primarily in the epidermis (Lockley et al. 2005).

Summary:

There are no data available for absorption after inhalation. After oral administration, 2-phenoxyethanol is absorbed rapidly and almost completely from the gastro-intestinal tract. The bioavailability of the substance in rats was found to be 75% to 98%. After occlusive application in an oil-in-water or water-in-oil cream for 48 hours, the dermal absorption of 2-phenoxyethanol in vivo was greater than 85%. In vitro, 94% absorption was determined after 4 hours after occlusive application to rat skin. After the absorption of ^{14}C-labelled 2-phenoxyethanol, the radioactivity was distributed in all organs and tissues. 2-Phenoxyacetic acid is the main metabolite of 2-phenoxyethanol in humans and animals. The radioactivity was eliminated rapidly and mainly with the urine within 24 hours after oral administration of ^{14}C-labelled 2-phenoxyethanol. Elimination with the urine was > 90% irrespective of the dose; 57% to 74% of the dose was eliminated as 2-phenoxyacetic acid. With the increasing dose, a disproportionate increase in the AUC values was determined in the plasma. This suggests that renal elimination is inhibited at high doses. This effect is ascribed to the saturation of the acid transporters in the kidneys by the main metabolite 2-phenoxyacetic acid. For rats, the terminal half-lives were between 28 and 60 hours.

4 Effects in Humans

There is no information available for genotoxicity or carcinogenicity in humans.

The 1998 documentation (documentation "2-Phenoxyethanol" 1998, available in German only) reported effects in humans after single doses and repeated exposure, effects on the skin and eyes, and allergenic effects.

There are no new data available for single exposures.

Repeated exposure

A study investigated 31 house painters, who worked indoors mainly with water-based paints, and 20 janitors who were used as controls. Tear film break-up time, nasal patency and biomarkers in nasal lavage were determined, and a questionnaire about complaints that occurred was answered. Personal samples were taken from 17 painters over an 8-hour period to determine the levels of formaldehyde, volatile organic compounds (VOCs) and microbial volatile organic compounds (MVOCs). 2-Phenoxyethanol was detected in 7 samples (mean: 51 µg/m^3, maximum: 229 µg/m^3). Increased incidences of ocular symptoms, such as a reduced break-up time (BUT; marker of eye irritation), and increased lysozyme levels in nasal lavage were recorded for the painters in comparison with the findings in the

control group. An association between 8-hour exposure and a reduced BUT was established for 2-phenoxyethanol (Wieslander and Norbäck 2010). With 31 persons, the sample population of the study was relatively small, and the correlation established between 2-phenoxyethanol and the BUT was apparently based only on 7 exposure determinations in the sample population, which by that time had been reduced to 17 painters. In addition to the small number of cases, the large number of statistical comparisons and correlations were not adjusted for multiple testing. The differences in the BUT test results of the group were probably caused by the exposure of the painters to a mixture of substances and cannot be attributed to an individual substance. Therefore, the study cannot be used to derive a MAK value and is regarded merely as exploratory.

Local effects on skin and mucous membranes

In a study in newborn infants born before week 27 of pregnancy (n = 24), the use of an aqueous solution of 2% 2-phenoxyethanol with 0.1% octenidine for skin disinfection caused a transient erythematous reaction. The rapid absorption and metabolism of 2-phenoxyethanol was substantiated by the presence of the main metabolite, 2-phenoxyacetic acid, in the urine of the male infants (n = 13) 4 hours after the use of the disinfectant (Bührer et al. 2002).

Allergenic effects

A 1% test formulation in petrolatum that is commercially available was used for patch tests with 2-phenoxyethanol. It is characterized by a negative reaction index (RI)[3] of –0.44 and a high positivity ratio (PR)[4] of 85% (Schnuch et al. 2011 a). Therefore, it is often difficult to draw conclusions from patch test reactions to this 2-phenoxyethanol formulation. Although weak results obtained with this kind of test preparation may indicate contact sensitization, they are often signs of irritation and thus false positive reactions. Another possibility is that, in spite of the contact sensitization, the weakly positive or questionable results may have been caused by the low test concentration.

Since the 1998 documentation was published (documentation "2-Phenoxyethanol" 1998, available in German only), only few case reports of suspected contact sensitization to 2-phenoxyethanol have become available. One case involved a female patient with leg ulcers and contact eczema after topical treatment with a formulation containing 1% 2-phenoxyethanol (Gallo et al. 2005), another case referred to a patient with suspected sensitization caused by a mixture of preservatives in an ultrasound gel (Chasset et al. 2016), and a third an 18-month-old boy who developed generalized eczema after being vaccinated with a diphtheria/pertussis/tetanus vaccine containing 2-phenoxyethanol (Vogt et al. 1998).

3) The reaction index is defined as the quotient: (a – d – i) / (a + d + i) with: a = number of allergic reactions, d = number of questionable reactions and i = number of irritant reactions (Brasch and Henseler 1992).

4) The positivity ratio is defined as the percentage of 1+ reactions among the total number of positive reactions (Geier et al. 2003).

Retrospective evaluations of patch tests found that the percentages of positive reactions to 2-phenoxyethanol were very low in all of the tests. The percentages of positive reactions ranged from less than 0.1% to about 0.3% and are thus similar to those reported by the studies (for example Cheng et al. 2014; Chow et al. 2013; Goossens et al. 1998; Marks et al. 1998; Pratt et al. 2004; Schnuch et al. 1998, 2011 b; Thompson and Belsito 2002; Warshaw et al. 2010) that were listed in the 1998 documentation (documentation "2-Phenoxyethanol" 1998, available in German only). Likewise, only sporadic positive results were obtained when 2-phenoxyethanol was tested in a test series with metal-working fluids (Geier et al. 2004, 2013).

One hour after sonography, urticarial efflorescences were observed at the contact sites of the ultrasound gel as well as disseminated on the trunk of an 83-year-old patient. In the patch test with 2-phenoxyethanol, the allergological diagnosis revealed an immediate positive reaction that lasted for more than 72 hours. In addition, dissemination indicating generalized exanthema on the trunk was observed in the test within 6 hours (Mock et al. 2002). There were reports of other individual cases of contact urticaria caused by the topical application of products containing 2-phenoxyethanol (Birnie and English 2006; Bohn and Bircher 2001; Hernández et al. 2002; Lujan et al. 2009; Núñez Orjales et al. 2010). However, these publications did not explain the genesis of these effects, and evidence of specific IgE to 2-phenoxyethanol has not been reported to date.

Reproductive and developmental toxicity

A study in women from north-western France who were trying to conceive examined the relationship between exposure to glycol ether and the time to pregnancy. 2-Phenoxyacetic acid as the main metabolite of 2-phenoxyethanol was detected in the urine of 93% of the 519 women who provided urine samples and answered a questionnaire before week 19 of pregnancy. The authors reported that 2-phenoxyacetic acid was the only glycol ether metabolite with a statistically significant association with a longer time until pregnancy (OR = 0.82; 95% CI: 0.63–1.06 for the 2nd and 3rd quartiles combined; OR = 0.70; 95% CI: 0.52–0.95 for the 4th quartile (≥ 1.38 mg/l) compared with the 1st quartile (< 0.14 mg/l)). The authors concluded that 2-phenoxyethanol or 2-phenoxyacetic acid may be the cause of the reduced probability of conception, but they might also have been surrogates for potential co-exposure to other substances that are frequently present in cosmetics (Garlantézec et al. 2013). In this study, only single spot urine samples were examined. However, for a substance with a short half-life, conclusions about an observation that was made at a completely different time cannot be drawn from a single urine analysis. This is particularly true in this case because uniform exposure cannot be assumed in the case of cosmetics. In addition to probable co-exposure to other substances and possible confounders, such as the fertility of the man, the validity of this study is restricted by methodological limitations with regard to the determination of the exposure.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

New data have not become available.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There were no studies of repeated exposure to 2-phenoxyethanol by inhalation available at the time the 1998 documentation was published (documentation "2-Phenoxyethanol" 1998, available in German only).

In a 14-day inhalation study carried out according to OECD Test Guideline 412, groups of 5 male and 5 female Wistar rats were exposed head-only to 2-phenoxyethanol aerosol concentrations of 0, 48.2, 246 or 1070 mg/m^3 for 6 hours a day, on 5 days a week, for a period of 14 days (a total of 10 exposure days). There were mixtures of aerosol and vapour in all exposure groups. The theoretical vapour saturation concentration was about 40 mg/m^3. The aerosol fraction was about 20% in the low concentration group and 85% to 90% or 100% in the high concentration groups. Clinical signs were recorded, body weights and feed consumption were determined, and at the end of the study, clinico-pathological examinations of the blood, necropsy, determinations of organ weights and histopathological examinations of selected organs (nasal cavity, larynx, trachea, lungs, mediastinal lymph nodes, liver, kidneys, spleen, adrenal glands, heart, thymus, stomach and oesophagus) were carried out. In the low and middle concentration groups, only histopathological examination of the nasal cavity, larynx and lungs was performed. Clinical signs of toxicity were not observed. Histopathological findings were obtained in the upper respiratory tract and lungs. The results are shown in Table 2, and the incidence and severity of selected findings are listed in Table 3. The squamous metaplasia of minimal to mild severity that was detected in the larynx at 246 mg/m^3 and above is not regarded as adverse (Kaufmann et al. 2009). In the lungs, minimal to mild hypertrophy of the respiratory epithelium and minimal to mild hyperplasia of the goblet cells were found at this concentration and above. At 246 mg/m^3 and above, minimal to moderate hyperplasia, degeneration and metaplasia as well as minimal to moderate infiltrates of inflammatory cells were the main effects. Therefore, a NOAEC (no observed adverse effect concentration) of 48.2 mg/m^3 was obtained (BASF AG and The Dow Chemical Company 2007 c).

5.2.2 Oral administration

The 1998 documentation included all the studies with repeated ingestion that were available at that time (documentation "2-Phenoxyethanol" 1998, available in German only). In these studies, rabbits were found to be more sensitive than rats or mice; haemolysis was observed in rabbits at dose levels as low as 100 mg/kg body weight while there were no signs of haemolytic anaemia in rats or mice. Recent studies and relevant earlier studies are summarized in Table 4.

Table 2 Studies of the toxicity after repeated exposure to 2-phenoxyethanol by inhalation (see also Table 3)

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, 5 ♂, 5 ♀	**14 days**, according to OECD Test Guideline 412, 0, 48.2, 246, 1070 mg/m³ (analysed value), 6 hours/day, 5 days/week, head-only exposure, MMAD: 0.5–1.3 µm, 72%–85% < 3 µm, purity: > 99.9%	**48.2 mg/m³: NOAEC**; only nasal cavity, larynx and lungs examined histopathologically; **246 mg/m³**: only nasal cavity, larynx and lungs examined histopathologically; nasal cavity, respiratory epithelium: degeneration/squamous metaplasia (1/5 ♂, 3/5 ♀), hyperplasia (5/5 ♂, 5/5 ♀), infiltrates of inflammatory cells (5/5 ♂, 4/5 ♀); larynx: squamous metaplasia (0/5 ♂, 1/5 ♀), not adverse; lungs: respiratory hypertrophy (5/5 ♂, 4/5 ♀), goblet cell hyperplasia (3/5 ♂, 3/5 ♀); ♂: lungs: absolute weights ↑ (+11.8%); **1070 mg/m³**: feed consumption ↓ (day 7, ♂: −5.8%, ♀: −10.6%); nasal cavity, respiratory epithelium: degeneration/squamous metaplasia (5/5 ♂, 5/5 ♀), hyperplasia (5/5 ♂, 5/5 ♀), infiltrates of inflammatory cells (5/5 ♂, 3/5 ♀); larynx: squamous metaplasia (4/5 ♂, 4/5 ♀), not adverse; lungs: respiratory hypertrophy (5/5 ♂, 4/5 ♀), goblet cell hyperplasia (5/5 ♂, 4/5 ♀); ♂: lungs: absolute (+20.4%) and relative (+19.3%) weights ↑; ♀: body weight gains ↓ (day 7, −48.2%); histopathologically examined: nasal cavity, larynx, trachea, lungs, mediastinal lymph nodes, liver, kidneys, spleen, adrenal glands, heart, thymus, stomach, oesophagus	BASF AG and The Dow Chemical Company 2007 c

MMAD: mass median aerodynamic diameter

Table 3 Incidence and severity of selected findings after repeated exposure of rats to 2-phenoxyethanol by inhalation (BASF AG and The Dow Chemical Company 2007 c)

	♂				♀			
Concentration (mg/m³)	0	48.2	246	1070	0	48.2	246	1070
Number of animals tested	5	5	5	5	5	5	5	5
larynx (plane of section I)								
squamous metaplasia	–	–	–	4	–	–	1	4
grade 1[a)]	–	–	–	4	–	–	1	3
grade 2	–	–	–	–	–	–	–	1
lungs								
respiratory hypertrophy	–	–	5	5	–	–	4	4
grade 1	–	–	5	2	–	–	1	1
grade 2	–	–	–	3	–	–	3	3
goblet cell hyperplasia	–	–	3	5	–	–	3	4
grade 1	–	–	3	1	–	–	3	2
grade 2	–	–	–	4	–	–	–	2
nasal cavity, respiratory epithelium (plane of section I)								
degeneration/metaplasia	–	–	1	5	–	–	3	5
grade 1	–	–	–	–	–	–	3	3
grade 2	–	–	1	4	–	–	–	2
grade 3	–	–	–	1	–	–	–	–
inflammatory cell infiltrates	–	–	2	5	–	–	2	2
grade 1	–	–	2	5	–	–	2	2

Table 3 (continued)

	♂				♀			
Concentration (mg/m³)	0	48.2	246	1070	0	48.2	246	1070
Number of animals tested	5	5	5	5	5	5	5	5
nasal cavity, respiratory epithelium (plane of section II)								
hyperplasia	–	–	5	4	–	–	5	5
grade 1	–	–	3	2	–	–	3	4
grade 2	–	–	2	2	–	–	2	1
nasal cavity, respiratory epithelium (plane of section III)[b]								
hyperplasia	–	–	5	5	–	–	5	4
grade 1	–	–	2	–	–	–	3	2
grade 2	–	–	3	5	–	–	2	1
grade 3	–	–	–	–	–	–	–	1
inflammatory cell infiltrates	–	–	5	3	1	–	4	2
grade 1	–	–	3	3	1	–	3	2
grade 2	–	–	2	–	–	–	1	–

[a] possible grade: 1–5 (minimal to severe); [b] no findings in plane of section IV (only 0 and 1070 mg/m³ examined)

Table 4 Studies of toxicity in rats, mice and dogs after repeated oral administration of 2-phenoxyethanol

Species, strain, number per group	Exposure	Findings	References
rat, F344, 5 ♂, 5 ♀	**14 days**, 0, 1600, 4000, 10 000, 17 500, 25 000 mg/l drinking water (♂: about 0, 182, 445, 909, 1708, 2491 mg/kg body weight and day; ♀: about 0, 208, 585, 1023, 1805, 2694 mg/kg body weight and day[a)]), purity: 99.8%	**about 182/208 mg/kg body weight**: **NOAEL**; **about 445 mg/kg body weight and above**: ♂: blood: MCH ↑; **about 909/1023 mg/kg body weight and above**: feed and water consumption ↓; ♂: blood: MCV ↑; **about 1708/1805 mg/kg body weight and above**: body weight gains ↓, blood: platelets ↓; urine: pH ↓; ♂: serum: urea nitrogen ↑; ♀: blood: MCHC ↓; relative weights of liver and kidneys ↑; **about 2491/2694 mg/kg body weight**: body weight gains ↓, serum: urea nitrogen ↑; relative weights of liver, kidneys and brain ↑; ♀: serum: glucose ↓, AST and ALT ↑; relative weights of thymus and spleen ↓; study in Japanese, annexes in English	JMHLW 2003 a

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, CD, 15 ♂, 15 ♀	**13 weeks**, 0, 80, 400, 2000 mg/kg body weight and day, in 0.5% gum tragacanth solution, gavage, 7 days/week, purity: not specified	**80 mg/kg body weight**: ♂: mortality: 2/15, probably not induced by the substance, **NOAEL**; **400 mg/kg body weight**: ♂: serum: ALP ↑ (after 4 weeks, not after 13 weeks); kidneys: abnormal groups of dilated tubules with basophilic stainability and chronic inflammatory cell infiltration; ♀: mortality 1/15, absence of grooming in weeks 1–6; **2000 mg/kg body weight**: transient lethargy 10–30 minutes after exposure, mainly ♀, unsteady gait, debilitation 2 to 18 hours after exposure, body weights ↓, mainly ♂, feed utilization ↓ in all animals, water consumption ↑ in weeks 6 and 12, absence of grooming, blood: erythrocyte count ↓ (♂: week 4, ♂ and ♀: week 13), haemoglobin concentration and haematocrit ↓; serum: ALT ↑, ALP ↑ (week 12, ♂); urine (week 4): glucose, urea, urine volume ↑ at an unchanged specific density, large amounts of epithelial cells and polymorphonuclear leukocytes in the urinary sediment. Surviving animals: absolute and relative weights of liver, kidneys and thyroid gland ↑, kidneys: groups of dilated tubules with basophilic stainability and chronic inflammatory cell infiltration; no signs of haemolytic anaemia; ♂: 4/15 slight tubular atrophy of the epididymis of questionable toxicological relevance; ♀: mortality 4/15, no gross-pathological or histopathological findings	Nipa Laboratories 1977
rat, Colworth Wistar, 15 ♂, 15 ♀, observation period: 5 ♂, 5 ♀	**13 weeks**, 0%, 0.05%, 0.10%, 0.20%, 0.50% in the diet (according to authors: 50, 100, 164, 500 mg/kg body weight and day); **5-week observation period**: only 0%, 0.50% in the diet; purity: not specified	**50 mg/kg body weight**: ♂: blood: platelet count ↓; **100 mg/kg body weight**: blood: platelet count ↓ (♂, ♀); **164 mg/kg body weight**: no histopathological findings, **NOAEL**; ♀: blood: platelet count ↓; **500 mg/kg body weight**: ♂: feed utilization after 13 and 18 weeks ↓, fatty deposits in the liver parenchyma ↓ after 13 weeks only, blood: platelet count ↓ after 13 weeks; serum: ALP ↑; ♀: blood: activated partial thromboplastin time ↑, platelet count ↓ after 13 and 18 weeks	Unilever 1991

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, 10 ♂, 10 ♀, observation period: 10 ♂, 10 ♀, satellite groups (with and without observation period): 5 ♂, 5 ♀ (neuropa- thology)	**13 weeks**, OECD Test Guideline 408, 0, 500, 2500, 10 000 mg/kg diet (♂: 0, 34, 169, 697 mg/kg body weight and day; ♀: 0, 50, 234, 939 mg/kg body weight and day), **4-week observation period**: only 0, 10 000 mg/kg diet, purity: 99.9%	**34/50 mg/kg body weight and above**: ♂: liver: O-DEM ↑ (induction to a maximum 140% of controls); ♀: blood: MCHC ↓ (to a maximum 97.5% of control) value, reversible in the high dose group after the 4-week observation period; **169/234 mg/kg body weight and above**: ♂: blood: leukocyte and lymphocyte counts ↓ (to a maximum 76% of control value, relatively high control values), reversible in the high dose group after the 4-week observation period; **up to 697/939 mg/kg body weight**: **NOAEL**; liver: O-DEM and CYP450 ↑ (induction to a maximum 140% and 122% of control value, respectively), reversible after the 4-week observation period; ♂: blood: MCHC ↓ (to a maximum 97.4% of control value), reversible after the 4-week observation period; serum: MCHC ↓ (to a maximum 97.4% of control value), reversible after the 4-week observation period; ♀: serum: protein and albumin ↓ (to a maximum 94% of control value), reversible after the 4-week observation period; neuropathological examinations not carried out as no signs of neurotoxicity	Bayer AG 2002

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344, 10 ♂, 10 ♀	**13 weeks**, 0, 1250, 2500, 5000, 10 000, 20 000 mg/l drinking water (♂: about 0, 96, 185, 369, 687, 1515 mg/kg body weight and day; ♀: about 0, 163, 307, 649, 1007, 1728 mg/kg body weight and day[a]), purity: 99.8%	**about 185/307 mg/kg body weight**: ♂: water consumption ↓, **NOAEL**; **about 369/649 mg/kg body weight**: ♂: water consumption ↓, blood: platelet count ↓; **about 687/1007 mg/kg body weight**: kidneys: urothelial hyperplasia in the renal pelvis ↑ (♂: 2/10; ♀: 1/10; controls: 0/10); liver: relative weights ↑; blood: erythrocyte and platelet counts ↓; ♂: water consumption ↓, serum: sodium ↓, potassium ↑; ♀: body weight gains, water and feed consumption ↓, final body weights 91% of control value, kidneys: relative weights ↑; bladder: hyperplasia in the transitional epithelium (2/10, controls: 0/10); serum: urea nitrogen ↑; blood: haemoglobin ↓, MCH and MCV ↑ (mild anaemia); **about 1515/1728 mg/kg body weight**: body weight gains, water and feed consumption ↓, serum: urea nitrogen ↑; kidneys: relative weights ↑, urothelial hyperplasia in the renal pelvis ↑ (♂: 6/10; ♀: 0/10; controls: 0/10); bladder: hyperplasia in the transitional epithelium (♂: 1/10; ♀: 7/10; controls: 0/10); liver: relative weights ↑; blood: erythrocyte count, haemoglobin and platelet counts ↓, MCH and MCV ↑; urine: pH ↓; ♂: mortality: 1/10, serum: sodium ↓, potassium ↑, cholesterol and phospholipids ↑; final body weights 80% of control value; ♀: reticulocytes ↑ (mild anaemia), serum: ALP ↑; final body weights 82% of control value; English translation available only as an abstract	JMHLW 2003 b; BASF SE 2015 a

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344, 50 ♂, 50 ♀	**104 weeks**, 0, 2500, 5000, 10 000 mg/l drinking water (♂: about 0, 141, 277, 551 mg/kg body weight and day; ♀: about 0, 205, 406, 811 mg/kg body weight and day[a)]), purity: 99.8%–99.9%	**about 205 mg/kg body weight**: ♀: soiled fur around the genitals, body weight gains ↓ (maximum decrease in body weights: 7%), water consumption ↓ (first half of the study); **about 277/406 mg/kg body weight**: water consumption ↓ (first half of the study); ♀: soiled fur around the genitals, body weight gains ↓ (maximum decrease in body weights: 6%), **NOAEL**; **about 551/811 mg/kg body weight**: soiled fur around the genitals, body weight gains ↓ (maximum decrease in body weights: 14%), feed consumption ↓, water consumption ↓ (first half of the study), kidneys: absolute and relative weights ↑; ♂: plasma: AST and ALT ↑, slight decrease in total protein and creatinine; kidneys: incidence of urothelial hyperplasia in the renal pelvis ↑ (8/50, controls: 1/50), papillary mineralization (6/50, controls: 0/50) and necrosis (4/50, controls: 1/50) ↑; ♀: final body weights 89% of control value, blood: slight increase in MCV ↑ (55.0 fl; controls: 52.5 fl); serum: slight increase in urea nitrogen ↑, triglycerides ↓; urine: pH ↓, proteins ↓, ketone bodies ↑; **up to about 551/811 mg/kg body weight**: survival unchanged; see also Section 5.7; English translation available only as an abstract	JMHLW 2007 a

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, B6D2F1, 5 ♂, 5 ♀	**14 days**, 0, 1600, 4000, 7000, 10 000, 25 000 mg/l drinking water (♂: about 0, 310, 733, 1209, 1265, 2382 mg/kg body weight and day; ♀: about 0, 360, 801, 1132, 1496, 2570 mg/kg body weight and day[a)]), purity: 99.8%	**about 733/801 mg/kg body weight**: **NOAEL**; **about 1209/1132 mg/kg body weight and above**: relative kidney weights ↑; ♀: water consumption ↓; **about 1265/1496 mg/kg body weight and above**: feed and water consumption ↓; **about 2382/2570 mg/kg body weight**: body weight gains ↓, urine: pH ↓; ♂: relative brain weights ↑; ♀: blood: MCV ↑; serum: urea nitrogen ↑; study in Japanese, annexes in English	JMHLW 2003 c
mouse, B6D2F1, 10 ♂, 10 ♀	**13 weeks**, 0, 1250, 2500, 5000, 10 000, 20 000 mg/l drinking water (♂: about 0, 182, 390, 765, 1178, 2135 mg/kg body weight and day; ♀: about 0, 236, 478, 948, 1514, 2483 mg/kg body weight and day[a)]), purity: 99.8%	**about 765/948 mg/kg body weight**: **NOAEL**; **about 1178/1514 mg/kg body weight**: water consumption ↓, relative kidney weights ↑; ♀: feed consumption ↓; **about 2135/2483 mg/kg body weight**: body weight gains, water and feed consumption ↓, kidneys: relative weights ↑; urine: pH ↓; ♂: final body weights: 87%, blood: reticulocyte count ↑; serum: ALP ↑, cholesterol and phospholipids ↓; liver: relative weights ↑; ♀: final body weights: 95%, blood: haemoglobin and MCHC ↓, MCV ↑; English translation available only as an abstract	JMHLW 2003 d; BASF SE 2015 b

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, B6D2F1, 50 ♂, 50 ♀	**104 weeks**, 0, 5000, 10 000, 20 000 mg/l drinking water (♂: about 0, 543, 1011, 1815 mg/kg body weight and day; ♀: about 0, 650, 1166, 2142 mg/kg body weight and day[a]), purity: 99.8%–99.9%	**about 543/650 mg/kg body weight and above**: dose-dependent decrease in water consumption, **NOAEL**; **about 1011/1166 mg/kg body weight and above**: body weight gains ↓, feed consumption ↓, urine: pH ↓; ♂: serum: cholesterol and phospholipids ↓, ALT ↓; **about 1011/1166 mg/kg body weight**: ♂: final body weights: 84%, kidneys: relative weights ↑ (to 115%); **about 1815/2142 mg/kg body weight**: ♂: final body weights: 73%, kidneys: relative weights ↑ (to 177%); blood: leukocyte count ↓; serum: triglycerides ↓; ♀: final body weights: 79%, spleen and liver: absolute weights ↓; blood: haematocrit ↑; serum: triglycerides ↓, AST, ALT and LDH ↓, ALP ↑; **up to about 1815/2142 mg/kg body weight**: survival unchanged; no clinical findings; see also Section 5.7; English translation available only as an abstract	JMHLW 2007 b
dog, beagle, 2 ♂, 2 ♀	**7 days**, 20 000 or 30 000 mg/kg diet (about 800 or 1200 mg/kg body weight and day at an assumed body weight of 10 kg and ingestion of 400 g diet/day), purity: > 99.9%	**about 800 mg/kg body weight**: feed consumption ↓ (to 4%–8%), vomiting (1/2 ♀ on day 1), study discontinued on day 3 because of markedly reduced feed consumption; **about 1200 mg/kg body weight**: feed consumption ↓ (to 5%–24%), vomiting (1/2 ♂ on day 1), study discontinued on day 3 because of markedly reduced feed consumption	BASF AG 2006 a

Species, strain, number per group	Exposure	Findings	References
dog, beagle, 2 ♂, 2 ♀	**7 days**, 30 000 mg/l drinking water (about 1200 mg/kg body weight and day at an assumed body weight of 10 kg and ingestion of 400 ml treated drinking water/day), purity: > 99.9%	**about 1200 mg/kg body weight**: feed consumption ↓ (to 7%–8%), vomiting (1/2 ♂ on day 1), study discontinued on day 3 because of markedly reduced feed consumption	BASF AG 2006 b
dog, beagle, 2 ♂, 2 ♀	**7 days**, 500, 1000 mg/kg body weight and day in gelatine capsules, purity: > 99.9%	**500 mg/kg body weight**: no substance-specific findings, **NOAEL**; **1000 mg/kg body weight**: feed consumption ↓ (to about 60% ♀), vomiting (bloody in some cases; 4/4 on day 1), salivation (bloody in some cases; 4/4 on day 1), unsteady gait, ataxia, abdominal or lateral position (4/4 on day 1), study discontinued on day 2	BASF AG 2006 c

[a] mean values calculated from data in study

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; fl: femtolitre; LDH: lactate dehydrogenase; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; MCV: mean erythrocyte volume; O-DEM: O-demethylase (demethylation of p-nitroanisol to p-nitrophenol)

In a 13-week study, the NOAEL (no observed adverse effect level) was 80 mg/kg body weight for male and female rats; groups of dilated tubules with basophilic stainability and chronic inflammatory cell infiltration were observed in the kidneys at 400 mg/kg body weight and above (Nipa Laboratories 1977).

In a valid 13-week study, the NOAEL for rats was 164 mg/kg body weight; reduced feed utilization, increased alkaline phosphatase, reduced platelet counts and prolonged activated partial thromboplastin times were found at 500 mg/kg body weight (Unilever 1991).

In a 13-week study carried out according to OECD Test Guideline 408, male and female Wistar rats were given 2-phenoxyethanol doses of 0, 500, 2500 or 10 000 mg/kg diet (see Table 4). The examinations included clinical observations, ophthalmology, feed consumption, water consumption, body weights, haematology, clinical chemistry, urinalysis, pathology, organ weights, histopathology, behavioural tests (functional observational battery, locomotor activity, reflexes and grip strength) and sperm parameters. Planned neuropathological examinations were not carried out due to the absence of any signs of neurotoxicity. Changes were observed in certain haematological or clinico-chemical parameters, which were significant in some cases. However, the changes were only slight, were in the range of the historical controls, occurred in only one sex or were not dose-dependent. They were therefore not regarded as treatment-related. Thus, no dose-dependent effects of toxicological relevance were observed up to the highest dose tested of 10 000 mg/kg diet (corresponding to 697 mg/kg body weight for males and 938 mg/kg body weight for females) (Bayer AG 2002).

In a series of drinking water studies, F344 rats or B6D2F1 mice were exposed to 2-phenoxyethanol over a period of 14 days and 13 or 104 weeks. The original studies were published in Japanese. English translations are available only for some studies and only as abstracts. In the 13-week studies, the examinations included clinical observations, body weights, water and feed consumption, urinalysis, haematology, clinical chemistry, necropsy, organ weights and histopathology. In the 14-day study in rats, the NOAEL was about 182 (♂) or 208 (♀) mg/kg body weight and day; haematological effects were observed at the LOAEL (lowest observed adverse effect level) of about 445 mg/kg body weight and day and above, and feed and water consumption was reduced at about 909 (♂) or 1023 (♀) mg/kg body weight and above. The decreased water consumption indicates reduced palatability. In the 13-week study, the NOAEL was about 185 (♂) or 307 (♀) mg/kg body weight and day; platelet count, body weight gains and water consumption were reduced at the LOAEL of about 369 (♂) or 649 (♀) mg/kg body weight and day. In the 14-day study in mice, the NOAEL was about 733 (♂) or 801 (♀) mg/kg body weight and day; the relative kidney weights were increased and water consumption was reduced in the females at the LOAEL of about 1209 (♂) or 1132 (♀) mg/kg body weight and day. In the 13-week study, the NOAEL was about 765 (♂) or 948 (♀) mg/kg body weight and day; reduced water consumption, increased relative kidney weights and reduced feed consumption in the females were observed at the LOAEL of about 1178 (♂) or 1514 (♀) mg/kg body weight and day (JMHLW 2003 a, b, c, d). In the 2-year drinking water studies (see also Section 5.7), soiled fur around the genitals and reduced body weight gains and water consumption were found in the female rats at the low dose of about 205 mg/kg body weight and day and above (JMHLW

2007 a). The decreased water consumption indicates reduced palatability. Up to about 277 (♂) or 406 (♀) mg/kg body weight and day, body weights were reduced by a maximum 7%, and other effects, particularly on the kidneys, were observed only at about 551 (♂) or 811 (♀) mg/kg body weight and day and above. Therefore, the dose of about 277 (♂) or 406 (♀) mg/kg body weight and day is regarded as the NOAEL. In mice, a dose-dependent decrease in water consumption was observed at the low dose of about 543 (♂) or 650 (♀) mg/kg body weight and day and above (JMHLW 2007 b). In this case, too, the decreased water consumption was attributed to reduced palatability. The authors considered the high dose of about 1815 (♂) or 2142 (♀) mg/kg body weight and day to be the NOAEL. However, as other effects, such as increased kidney weights and reduced body weight gains, were reported in mice at about 1011 (♂) or 1166 (♀) mg/kg body weight and day, the Commission considers the low dose of about 543 (♂) or 650 (♀) mg/kg body weight and day to be the NOAEL.

In several range-finding studies, beagle dogs were given 2-phenoxyethanol in concentrations of 20 000 or 30 000 mg/kg diet, or 30 000 mg/l drinking water or at dose levels of 500 or 1000 mg/kg body weight and day in the form of gelatine capsules. The feed and drinking water studies were discontinued on day 3 because of markedly reduced feed consumption. Except for vomiting, which was induced in 1 animal of each group on day 1, no other clinical findings were reported. Treatment with the high dose in gelatine capsules was discontinued on day 2 of the range-finding study because of the severe findings (severe vomiting, salivation, unsteady gait, ataxia and abdominal or lateral position). Substance-specific findings were not observed at 500 mg/kg body weight (NOAEL) (BASF AG 2006 a, b, c).

Summary:

The NOAELs derived for 2-phenoxyethanol from the oral 13-week studies in rats were 80, 164, 185 and 697 mg/kg body weight and day. As the highest NOAEL was determined in a valid study and the examinations carried out in this study addressed the effects observed in other studies at lower doses, this value is used for the evaluation. In the 2-year drinking water study in rats, the NOAEL was about 277 mg/kg body weight and day. The NOAEL derived for 2-phenoxyethanol from the 13-week study in mice was about 765 mg/kg body weight and day. In the 2-year drinking water study in mice, only water consumption was reduced at the NOAEL of about 543 mg/kg body weight and day.

5.2.3 Dermal application

The 1998 documentation (documentation "2-Phenoxyethanol" 1998, available in German only) included 4 studies with dermal exposure of rabbits. The target organs were the liver, kidneys and blood. The only 13-week study yielded a NOEL (no observed effect level) of 500 mg/kg body weight and day after occlusive application for 6 hours a day on 6 days a week (Dow 1986).

In a recent 14-day study, doses of 0 or 2000 mg/kg body weight of a 4% aqueous solution of 2-phenoxyethanol (corresponding to 80 mg/kg body weight and day) were applied to the shaved dorsal skin of 8 male and 8 female New Zealand White rabbits for 6 hours a day. The animals of the control group were treated with water.

Clinical signs, skin irritation at the application sites, body weight gains, haematology, organ weights and gross-pathological and histopathological changes were recorded. Very mild skin irritation, which was described as erythema, was observed in about half of the animals. There were no other gross-pathological findings. The histopathological examination did not reveal any effects. All the results of the haematological examinations were in the reference range. No changes of biological relevance were found for body or organ weights (Hoechst Celanese Corporation 1993). Thus, the systemic NOAEL in this study was the only dose tested of 80 mg 2-phenoxyethanol/kg body weight and day.

5.2.4 Subcutaneous injection

Groups of 8 male Wistar rats were given subcutaneous injections of 2-phenoxyethanol in sunflower oil of 2.5 mM/kg body weight and day (345 mg/kg body weight and day) once a day on 5 days a week for 4 weeks. The control animals were given injections with sunflower oil. The animals were sacrificed 24 hours after the last treatment and the brain was removed. The antioxidant capacity, the activity of antioxidant enzymes and lipid peroxidation were determined in the frontal cortex and hippocampus. In the animals treated with 2-phenoxyethanol, the authors described a significant decrease in antioxidant capacity in both brain regions, a significant increase in lipid peroxidation in the frontal cortex only, a significant decrease in superoxide dismutase (SOD) in the frontal cortex and a significant increase in SOD activity in the hippocampus. In addition, the glutathione peroxidase activity was significantly reduced in the frontal cortex and hippocampus. The activities of catalase and glutathione reductase remained unchanged (Pomierny et al. 2014). As only one dose was tested, it was not possible to derive a dose–response relationship from this study.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

The 1998 documentation (documentation "2-Phenoxyethanol" 1998, available in German only) reported mild irritation of 2-phenoxyethanol on the intact skin of rabbits and guinea pigs. No other data are available.

5.3.2 Eyes

Undiluted 2-phenoxyethanol caused severe irritation of the rabbit eye, whereas saturated solutions in water (2.2%) induced only weak irritation (documentation "2-Phenoxyethanol" 1998, available in German only). No other data are available.

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

After intradermal induction treatment with 0.1% 2-phenoxyethanol in the optimization test, 1 of 20 guinea pigs reacted to the intradermal challenge treatment with the same formulation after 35 days; however, no animal reacted to the challenge treatment with a 2% phenoxyethanol formulation in physiological saline that was carried out 2 weeks later. After induction with this formulation, 13 of 20 animals reacted to the intradermal challenge, whereas no animal reacted to the topical challenge with the 2% 2-phenoxyethanol formulation (Maurer 1985).

Likewise, a valid maximization test in Dunkin Hartley guinea pigs yielded clearly negative results. In this test, intradermal induction was carried out with 0.1% 2-phenoxyethanol in olive oil, and undiluted 2-phenoxyethanol was used for topical induction. The challenge treatment that was again carried out with undiluted 2-phenoxyethanol did not provoke a reaction in any of the 10 female guinea pigs (BASF AG 2002 f). According to the authors, intradermal induction with 5% and 1% formulations induced necrosis at the application sites in preliminary tests; therefore, the low 2-phenoxyethanol concentration that was tolerated without reactions was used for intradermal induction.

5.4.2 Sensitizing effects on the airways

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

The 1998 documentation described all the studies available at that time (documentation "2-Phenoxyethanol" 1998, available in German only). In a 13-week study with 2-phenoxyethanol, mild to moderate tubular atrophy of the epididymis was found in 4 of 15 male rats only at the high dose of 2000 mg/kg body weight and day (Nipa Laboratories 1977).

A 13-week study in rats (see Section 5.2.2) included investigations of sperm motility, sperm morphology, the number of sperm per mg epididymis and the number of spermatids per mg testicular tissue. No significant effects were observed in the high dose group (697 mg/kg body weight and day). The other dose groups were not investigated (Bayer AG 2002).

In a 2-generation study in CD-1 mice, a NOAEL of 0.25% 2-phenoxyethanol in the diet (about 400 mg/kg body weight and day) was established for both adult and newborn mice. Fertility was not affected up to the high concentration of 2.5% (NIEHS 1984).

5.5.2 Developmental toxicity

Earlier studies (documentation "2-Phenoxyethanol" 1998, available in German only) and recent studies are shown in Table 5.

Oral administration

In a recent study that investigated the prenatal developmental toxicity of 2-phenoxyethanol according to OECD Test Guideline 414, groups of 25 pregnant Wistar rats were given gavage doses of up to 1000 mg/kg body weight and day. Maternal toxicity was observed only in the high dose group. Unsteady gait, an average decrease in feed consumption of 6% compared with that of the controls and average decreases in body weight gains of 14% compared with those of the controls were observed in the dams after administration of the doses. Toxic effects on development were not observed up to the high dose of 1000 mg/kg body weight and day. In this study, the NOAEL for maternal toxicity was 300 mg/kg body weight, and the NOAEL for developmental toxicity was 1000 mg/kg body weight (BASF AG and The Dow Chemical Company 2006).

Significant increases in the incidences of hydronephrosis and deviating ossification patterns of the skull and sternum were observed when maternally non-toxic gavage doses of 3, 30 or 300 mg/kg body weight were given to Long Evans rats from days 6 to 15 of gestation. In the high dose group, the birth weights were significantly reduced to 86% of the control values only in the male offspring (no other details; Mankes and Renak 1987). The study was inadequately documented and has not been included in the evaluation.

In a 2-generation study in CD-1 mice (see Section 5.5.1), a NOAEL of 0.25% 2-phenoxyethanol in the diet (about 400 mg/kg body weight and day) was established for both adult and newborn mice. In the F1 offspring of the two high dose groups (1.25% and 2.5%), the corrected body weights of the live pups were significantly lower and dependent on the dose. However, the litter size and number of live pups per litter were significantly reduced only in the 2.5% group. The live-born F2 pups had lower body weights. At 1.25% and 2.5%, foetotoxic effects were observed, but these effects might have been due to maternal toxicity in the form of markedly increased liver weights or reduced body weights (NIEHS 1984).

Dermal application and subcutaneous injection

Groups of 30 rats were given subcutaneous 2-phenoxyethanol doses of 0, 111, 222 or 444 mg/kg body weight from days 6 to 15 of gestation. Teratogenic effects were not observed. Slight maternal toxicity was observed at 222 mg/kg body weight and above, and embryotoxicity additionally occurred in the high dose group (no other details; ECETOC 1995). The study was only inadequately documented and is not available in the original. Therefore, it has not been included in the evaluation.

After continuous occlusive dermal application of undiluted 2-phenoxyethanol doses of 0, 300, 600 or 1000 mg/kg body weight to the skin of 25 rabbits per group from days 6 to 18 of gestation, deaths occurred in the dams at 600 mg/kg body weight and day and above. At 600 mg/kg body weight and day, 5 of 25 dams died, and at 1000 mg/kg body weight and day 9 of 25 dams died. The examinations in this dose group were discontinued because of the high mortality. The NOAEL for ma-

Table 5 Studies of the developmental toxicity of 2-phenoxyethanol in rats and rabbits

Species, strain, number per group	Exposure	Findings	References
prenatal developmental toxicity			
rat, Wistar, 25 ♀	**GD 6–19**, OECD Test Guideline 414, 0, 100, 300, 1000 mg/kg body weight and day, in water, **gavage**, examination: GD 20	**300 mg/kg body weight**: dams: NOAEL for maternal toxicity; foetuses: no foetotoxic or teratogenic effects; **1000 mg/kg body weight**: dams: 1/25 sacrificed in a moribund state; unsteady gait and transient salivation in all animals at least once (duration up to 3.5 hours after administration), abdominal position in 5/25 after administration, vaginal haemorrhages (2/25), fur smeared with urine (2/25), feed consumption ↓ (by a maximum 10% on GD 6–13), slight decrease in body weights (GD 20: –4% compared with control value), body weight gains ↓ (–14% compared with control) value; foetuses: no foetotoxic or teratogenic effects, NOAEL for developmental toxicity	BASF AG and The Dow Chemical Company 2006
rat, Long Evans, number not specified	**GD 6–15**, 0, 3, 30, 300 mg/kg body weight and day, **gavage**	**30 mg/kg body weight**: dams: no effects; foetuses: no foetotoxic or teratogenic effects, NOAEL for developmental toxicity; **300 mg/kg body weight**: dams: NOAEL for maternal toxicity; foetuses: hydronephrosis ↑, deviating ossification pattern of skull and sternum, ♂: decrease in birth weights to 86%; study only inadequately documented and not included in the evaluation	Mankes and Renak 1987; see also ECHA 2015

Table 5 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, 30 ♀	**GD 6–15**, 0, 111, 222, 444 mg/kg body weight and day, **subcutaneous**	**111 mg/kg body weight**: dams: NOAEL for maternal toxicity; foetuses: no foetotoxic or teratogenic effects; **222 mg/kg body weight**: dams: slight maternal toxicity (no other details); foetuses: no foetotoxic or teratogenic effects, NOAEL for developmental toxicity; **444 mg/kg body weight**: dams: slight maternal toxicity (no other details); foetuses: embryotoxicity (no other details); study not available in the original, only insufficiently documented and not included in the evaluation	ECETOC 1995
rabbit, New Zealand White, 25 ♀	**GD 6–18**, 0, 300, 600, 1000 mg/kg body weight and day, **dermal**, undiluted, continuous	**300 mg/kg body weight**: dams: NOAEL for maternal toxicity; foetuses: no foetotoxic or teratogenic effects; **600 mg/kg body weight**: dams: mortality: 5/25, intravascular haemolysis and secondary diseases; foetuses: no foetotoxic or teratogenic effects, NOAEL for developmental toxicity; **1000 mg/kg body weight**: dams: mortality: 9/25, intravascular haemolysis and secondary diseases; study discontinued in this group because of high mortality, 5 litters up to that point; foetuses: only 5 litters, no statistical evaluation, no external, visceral or skeletal changes	Scortichini et al. 1987

GD: gestation day

ternal toxicity was 300 mg/kg body weight and day. The NOAEL for developmental toxicity was 600 mg/kg body weight and day (Scortichini et al. 1987).

5.6 Genotoxicity

5.6.1 In vitro

Studies described in the 1998 documentation (documentation "2-Phenoxyethanol" 1998, available in German only) that investigated the in vitro genotoxicity of 2-phenoxyethanol yielded negative results. These studies are shown in Table 6 together with recent studies, which also yielded negative results.

5.6.2 In vivo

Studies described in the 1998 documentation (documentation "2-Phenoxyethanol" 1998, available in German only) that investigated the in vivo genotoxicity of 2-phenoxyethanol yielded negative results. These studies are shown in Table 7 together with recent studies, which also yielded negative results.

Summary:

All in vitro and in vivo studies that investigated the genotoxicity of 2-phenoxyethanol yielded negative results. Therefore, 2-phenoxyethanol does not cause genotoxic effects.

5.7 Carcinogenicity

A 2-year drinking water study carried out in groups of 50 male and 50 female F344 rats (see also Section 5.2.2) did not reveal significant increases in the incidences of neoplastic lesions at 2-phenoxyethanol concentrations of up to 10 000 mg/l drinking water (about 551 (♂) or 811 (♀) mg/kg body weight and day) (JMHLW 2007 a).

In a 2-year drinking water study carried out in groups of 50 male and 50 female B6D2F1 mice (see also Section 5.2.2), no significant increases in the incidences of neoplastic lesions were observed at 2-phenoxyethanol concentrations of up to 20 000 mg/l drinking water (about 1815 (♂) or 2142 (♀) mg/kg body weight and day) (JMHLW 2007 b).

Both studies are available as English abstracts and were originally published in Japanese.

Table 6 Genotoxicity of 2-phenoxyethanol in vitro

End point	Test system	Concentration	Effective concentration	Results		Comments	References
				–m. a.	+m. a.		
gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	50–5000 µg/plate	–	–	–	no cytotoxicity up to 5000 µg/plate	Nipa Laboratories 1982 a
	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	8–5000 µg/plate	–	–	–	no cytotoxicity up to 5000 µg/plate	Hüls 1994
	Salmonella typhimurium TA97, TA98, TA100, TA1535	–m. a.: 100–5000 µg/plate, +m. a.: 100–6667 µg/plate	–	–	–	beginning cytotoxicity at 6667 µg/plate and above (+m. a.), purity: not specified, positive controls: NaN_3, 2-AA, NOPD, AAC	NTP 1989
	Salmonella typhimurium TA98, TA100, TA1535, TA1537, Escherichia coli WP2uvrA	0, 20, 100, 500, 2500, 5000 µg/plate	–	–	–	cytotoxicity in some cases at 2500 µg/plate and above, purity: 99.9%, positive controls: 2-AA, MNNG, NOPD, AAC, 4-NQO	BASF AG 2002 d
	Salmonella typhimurium TA98, TA100, TA1535, TA1537, Escherichia coli WP2uvrA/pKM101	–m. a.: 1.22–5000 µg/plate, +m. a.: 1.22–5000 µg/plate	–	–	–	cytotoxicity: not specified, purity: not specified	NLM 2015 b

Table 6 (continued)

End point	Test system	Concentration	Effective concentration	Results		Comments	References
				–m. a.	+m. a.		
CA	CHO cells	–m. a.: 100–1000 µg/ml, +m. a.: 500–3000 µg/ml	–	–	–	beginning cytotoxicity at 1000 or 3000 µg/ml and above, purity: 99.0%	Unilever 1985
	V79 cells	+/–m. a.: 0, 43.8, 87.5, 175, 350, 525, 700, 1050, 1400 µg/ml	–	–	–	no cytotoxicity up to 1400 µg/ml, purity: 99.9%, positive controls: EMS and CPA	BASF AG 2002 e
HPRT	CHO cells	–m. a.: 2500–3500 µg/ml, +m. a.: 2000–3500 µg/ml	–	–	–	cytotoxicity at 3500 µg/ml, purity: 99.8%	Dow 1987
	V79 cells	+/–m. a.: 0, 87.5, 175, 350, 700, 1400 µg/ml	–	–	–	no cytotoxicity up to 1400 µg/ml, purity: 99.9%, positive controls: EMS and DMBA	BASF AG 2002 c

m. a.: metabolic activation; –: negative; 2-AA: 2-aminoanthracene; AAC: 9-aminoacridine; CPA: cyclophosphamide; DMBA: 7,12-dimethylbenz(a)anthracene; EMS: ethyl methanesulfonate; MNNG: N-methyl-N-nitro-N-nitrosoguanidine; NOPD: 4-nitro-o-phenylenediamine; 4-NQO: 4-nitroquinoline-N-oxide

Table 7 Genotoxicity of 2-phenoxyethanol in vivo

Test system		Dose	Results	Comments	References
UDS	rat, Wistar, 3 ♂ (per dose and time)	0, 875, 1750 mg/kg body weight in 0.5% CMC (purity: 99.9%), once orally (gavage), examination after 2 and 16 hours	–	positive controls: DMH and 2-AAF, mortality: 5/10 at 1750 mg/kg body weight (16 hours), viability of the hepatocytes not affected	BASF AG 2002 a
CA, bone marrow	rat, CD(SD)BR, 5 ♂, 5 ♀ (per dose and time)	0, 280, 933, 2800 mg/kg body weight (purity: 99.8%), once orally (gavage), examination after 6, 24, 48 hours	–	mortality at 2800 mg/kg body weight: 1 ♀ (6 hours); 2 ♂, 3 ♀ (24 hours); 3 ♂, 3 ♀ (48 hours)	Dow 1988; ECB 2000
MN, bone marrow	mouse, CD-1, 5 ♂, 5 ♀	0, 300, 600, 1200 mg/kg body weight (purity: not specified), administered twice at 24-hour intervals (gavage), examination after 24 and 48 hours	–	NCE/PCE ratio unchanged	Nipa Laboratories 1982 b; ECB 2000
MN, bone marrow	mouse, NMRI, 5 ♂ (per dose and time)	0, 125, 250, 500 mg/kg body weight in 0.5% CMC (purity: 99.9%), once intraperitoneally, examination after 24 (all) and 48 hours (0 and 500 mg/kg body weight only)	–	positive control: CPA, mortality in range-finding tests at 750 mg/kg body weight and above, NCE/PCE ratio ↑ at 250 mg/kg body weight and above	BASF AG 2002 b

2-AAF: 2-acetylaminofluorene; CA: test for structural chromosomal aberrations; CMC: carboxymethyl cellulose; CPA: cyclophosphamide; DMH: N,N′-dimethylhydrazine dihydrochloride; MN: test for micronuclei; UDS: test for unscheduled DNA synthesis

5.8 Other effects

Haemolytic effects

According to the studies described in the 1998 documentation (documentation "2-Phenoxyethanol" 1998, available in German only), rabbits were found to be the most sensitive species for the haemolytic effects of 2-phenoxyethanol. Haemolysis was observed in rabbits after repeated oral administration of 100 mg/kg body weight and day and above as well as after continuous dermal application of 600 mg/kg body weight and day. Except for reduced erythrocyte counts in rats, these kinds of effects were not found in rats or mice after repeated oral administration of up to 2000 mg/kg body weight and day. The haemolytic effects were caused by 2-phenoxyethanol itself; metabolic conversion to 2-phenoxyacetic acid is regarded as detoxification.

In 5 male Wistar rats given a single subcutaneous injection of 2-phenoxyethanol in concentrations of 0, 2.5, 5 or 10 mmol/kg body weight (0, 345, 690 or 1382 mg/kg body weight), haematological parameters were examined over a period of 0 to 600 hours. At the high dose, dizziness was observed immediately after administration and 2 animals died 6 to 24 hours later. The injection of 2-phenoxyethanol initially induced swelling of the erythrocytes, which was manifest in the form of an increase in haematocrit and MCV (mean erythrocyte volume) values after 6 hours. Subsequent signs of haemolysis included decreases in erythrocytes, the haematocrit value, the mean corpuscular haemoglobin concentration and the total haemoglobin concentration, and an increase in the plasma haemoglobin concentration. Subsequently, an increase in the reticulocyte count was observed as a result of regeneration. The effects were observed at the low dose in some cases, but they were most pronounced at the high dose. The effects of 2-phenoxyethanol were about 10 times weaker than those induced by isopropoxyethanol, which was examined concurrently (Starek et al. 2004).

An in vitro test investigated the haemolytic activity of 2-phenoxyethanol, 2-phenoxyacetic acid, 2-ethoxyethanol and 2-ethoxyacetic acid in the erythrocytes of mice, rats, rabbits, dogs and humans. The release of haemoglobin was determined as a measure of the damage to the erythrocyte membrane. The test concentrations were in a range between 0.938 and 20 mg/ml, and the incubation period was 0.5, 1, 2 or 4 hours. Distilled water was used as a positive control, and phosphate-buffered saline was used as a negative control. The examinations yielded a steep concentration–effect curve for 2-phenoxyethanol. 2-Phenoxyethanol caused complete haemolysis in all species investigated in the concentration range of 10 to 12.5 mg/ml. Resistance to haemolysis decreased in the order human > dog > rat ≈ rabbit > mouse. 2-Phenoxyacetic acid, 2-ethoxyethanol and 2-ethoxyacetic acid did not induce significant haemolytic effects in any of the species investigated (BASF AG and The Dow Chemical Company 2007 d).

In long-term drinking water studies carried out with 2-phenoxyethanol, no significant haemolytic effects were observed up to the high doses of about 551 (♂) or 811 (♀) mg/kg body weight and day in rats and about 1815 (♂) or 2142 (♀) mg/kg body weight and day in mice; this may indicate an adaptive mechanism (see also Section 5.2.2).

6 Manifesto (MAK value/classification)

Local irritation of the respiratory tract, and particularly of the nose, was the critical effect in a 2-week inhalation study in rats.

MAK value. Data for humans suitable for deriving a MAK value are not available.

A NOAEC of 48.2 mg/m³ (aerosol fraction: 20%) was obtained in a recent aerosol inhalation study carried out in rats for 14 days (BASF AG and The Dow Chemical Company 2007 c). At 246 mg/m³ and above, hyperplasia, degeneration and metaplasia as well as infiltrates of inflammatory cells were observed in the respiratory epithelium of the nasal cavity. The previous MAK value of 110 mg/m³ is, therefore, too high.

NOAELs of about 277 mg/kg body weight and day or about 543 mg/kg body weight and day were established in 2-year drinking water studies in rats and mice. The substance is almost completely absorbed orally; absorption by inhalation is not known and is therefore assumed to be 100%. The following toxicokinetic data are used to extrapolate the NOAEL to a concentration in workplace air: the daily exposure of the animals in comparison with exposure for 5 days per week at the workplace (7:5), the corresponding species-specific correction values for the rat and mouse determined on the basis of the toxicokinetic data (1:4 and 1:7, respectively), the established oral absorption (100%), the body weight (70 kg) and the respiratory volume (10 m³) of the person, the assumed 100% absorption by inhalation, and the extrapolation to humans (1:2). This results in respective concentrations of 339 mg/m³ and 380 mg/m³.

The effects on the respiratory epithelium observed in the 14-day inhalation study in rats at a NOAEC of 48.2 mg/m³ are the most sensitive end point and are therefore used as a starting point for deriving a limit value. According to the procedures of the Commission (see List of MAK and BAT Values, Section I), a NAEC (no adverse effect concentration) for humans of 16 mg/m³ (2.8 ml/m³) was calculated based on the NOAEC of 48.2 mg/m³ (8.4 ml/m³) for findings obtained in the respiratory epithelium of rats (1:3).

As this level is based on subacute exposure, a factor of 3 is regarded as sufficient to account for a possible intensification of the effects after long-term exposure. It has been taken into consideration that the marked increase in the aerosol fraction from about 20% at the NOAEC to 90% at the LOAEC (lowest observed adverse effect concentration) in the inhalation study is an intrinsic safety factor, that there is a 5-fold margin between the NOAEC and LOAEC and that aerosol impaction presumably caused the effects that were observed at the LOAEC. As these effects are not expected to occur at the NOAEC, the aerosol-induced effects are not likely to occur after exposure at the level of the MAK value. A concentration of 5.3 mg/m³ (0.93 ml/m³) is therefore obtained. Even if the total substance were present as aerosol, its concentration would still be lower than the aerosol concentration at the NOAEC (20% of 48 mg/m³). As the vapour saturation concentration of 2-phenoxyethanol is about 40 mg/m³ (BASF AG and The Dow Chemical Company 2007 c), the substance may occur as a vapour at this MAK value and the MAK value is therefore established in ml/m³. Thus, a MAK value of 1 ml/m³ (5.7 mg/m³) has been established for 2-phenoxyethanol in line with the preferred value approach.

Peak limitation. Because of the local irritation, 2-phenoxyethanol remains in Peak Limitation Category I. As there are no data available for humans, an excursion factor of 1 has been established.

Prenatal toxicity. At the previous MAK value of 20 ml/m³ (110 mg/m³), 2-phenoxyethanol was classified in Pregnancy Risk Group C (documentation "2-Phenoxyethanol" 1998, available in German only).

In a developmental toxicity study in rats that were given gavage doses from days 6 to 19 of gestation, 2-phenoxyethanol did not cause prenatal toxicity up to the high dose of 1000 mg/kg body and day in spite of maternal toxicity. Likewise, no toxic effects on development were observed after dermal exposure of rabbits to doses of up to 600 mg/kg body weight and day from days 6 to 18 of gestation. At this dose level, 5 of 25 dams died and intravascular haemolysis and secondary diseases were found in the surviving dams. In a 2-generation study in CD-1 mice, a NOAEL of 0.25% 2-phenoxyethanol in the diet (about 400 mg/kg body weight) was obtained for foetotoxicity.

The following toxicokinetic data are used to extrapolate the NOAEL for developmental toxicity in rats or the NOAEL for foetotoxicity in mice to a concentration in workplace air: the corresponding species-specific correction values for the rat and mouse determined on the basis of the toxicokinetic data (1:4; 1:7), the oral absorption (100%), the body weight (70 kg) and the respiratory volume (10 m³) of the person, and the assumed 100% absorption by inhalation. This results in respective concentrations of 1750 and 400 mg/m³, which are 305 and 70 times higher than the MAK value of 5.7 mg/m³.

After dermal exposure, the NOAEL for developmental toxicity in rabbits was at least 600 mg/kg body weight and day. There are no data available for dermal absorption in rabbits. Studies in various species found that dermal absorption of at least 10% represented the worst case for 2-phenoxyethanol in porcine skin in vitro (Stahl et al. 2010). Extrapolation of this level to a concentration in air results in a 31-fold difference between this level and the MAK value of 5.7 mg/m³. Considering this together with the sufficiently large margins after oral administration, classification in Pregnancy Risk Group C is justified.

Carcinogenicity and germ cell mutagenicity. All in vitro and in vivo studies that investigated the genotoxicity of 2-phenoxyethanol yielded negative results, as did the carcinogenicity studies. There is therefore no reason to suspect carcinogenicity or germ cell mutagenicity, and 2-phenoxyethanol has not been classified in any of the categories for carcinogens or germ cell mutagens.

Absorption through the skin. In a 13-week study in rabbits with epicutaneous application of undiluted 2-phenoxyethanol, the NOAEL was 500 mg/kg body weight, which indicates slight toxicity after repeated dermal application. In vitro experiments in porcine skin yielded a permeability coefficient of 1.82×10^{-6} cm/s for 2-phenoxyethanol. Taking this coefficient into account, the exposure of both hands and forearms (2000 cm²) to a saturated aqueous solution (24.2 g/l) for 1 hour would result in dermal absorption of 317 mg 2-phenoxyethanol. A NOAEL of about 543 mg/kg body weight and day was determined in a 2-year oral study in mice. The following toxicokinetic data are used to extrapolate this NOAEL to humans: the

established complete oral absorption, the daily exposure of the animals in comparison with exposure for 5 days per week at the workplace (7:5), the corresponding species-specific correction value for the mouse determined on the basis of the toxicokinetic data (1:7), extrapolation of the NOAEL from animal studies to humans (1:2), and the body weight of the person (70 kg). This results in a tolerable intake of 3801 mg. A value of 3393 mg is obtained based on the NOAEL of about 277 mg/kg determined in the long-term study in rats. The amount absorbed through the skin is thus less than 25% of the systemically tolerable amount. 2-Phenoxyethanol is therefore no longer designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. Only few case reports of suspected contact allergy to 2-phenoxyethanol are available. Very few clinical epidemiological studies reported positive patch test results. Experimental studies in guinea pigs did not provide evidence of sensitizing effects of 2-phenoxyethanol on the skin. Therefore, 2-phenoxyethanol is not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

7 References

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