

# **Human Health Hazard Assessment**

**Bis(2-methoxyethyl) phthalate (DMEP)  
(CAS No. 117-82-8)**

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## INTRODUCTION

This review of bis(2-methoxyethyl) phthalate (DMEP) is a health hazard assessment only. For this assessment, a draft Chemical Hazard Information Profile (CHIP) for DMEP (USEPA, 1985) was consulted. Information from this document was supplemented with relevant studies from more recent literature surveys conducted up to September 2006.

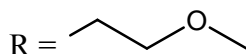
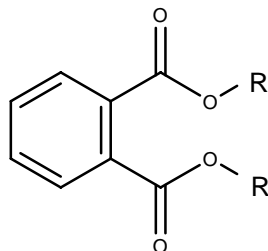
References not marked with an asterisk were examined for the purposes of this assessment. References not examined but quoted from the key report as secondary citations are also noted in this assessment and marked with an asterisk. It should be noted that the data in the CHIP are data reported by the Oak Ridge National Laboratory under contract to USEPA and have not undergone review by this Agency. However, most studies were obtained by NICNAS.

Hazard information from this assessment is published also in the form of a hazard compendium providing a comparative analysis of key toxicity endpoints for 25 phthalates (NICNAS, 2007).

## 1. IDENTITY

### 1.1 Identification of the Substance

CAS Number: 117-82-8  
 Chemical Name: 1,2-Benzenedicarboxylic acid, bis(2-methoxyethyl) ester  
 Common Name: Bis(2-methoxyethyl) phthalate (DMEP)  
 Molecular Formula: C<sub>14</sub>H<sub>18</sub>O<sub>6</sub>  
 Structural Formula:



Molecular Weight: 282.30  
 Synonyms: Di(methoxyethyl)phthalate; Bis(methoxyethyl) phthalate; Dimethyl glycol phthalate; Methyl glycol phthalate; Dimethyl cellosolve phthalate; Phthalic acid, bis(2-methoxyethyl) ester  
 Purity/Impurities/Additives: Not available

### 1.2 Physicochemical Properties

**Table 1: Summary of physicochemical properties**

<b>Property</b>	<b>Value</b>
Physical state	Light coloured, clear liquid, mild aromatic odour
Melting point	-40°C
Boiling point	340°C
Density	1170 kg/m <sup>3</sup> (15°C)

Vapour pressure	<0.013 kPa (20°C)
Water solubility	0.9 g/L (20°C)
Partition coefficient n-octanol/water (log Kow)	2.9
Henry's law constant	$2.8 \times 10^{-3}$ atm m <sup>3</sup> /mL (25°C)
Flash point (open cup)	194°C

Source: USEPA (1985)

## 2. USES

DMEP is a specialty plasticiser, used in cellulose ester plastics, and can also be used as a solvent.

Uses information in Australia were not available.

## 3. HUMAN HEALTH HAZARD

### 3.1 Toxicokinetics

The metabolism of DMEP has been studied in the pregnant rat (Campbell et al., 1984; Parkhie et al., 1982). During pregnancy, DMEP rapidly undergoes hydrolysis to 2-methoxyethanol (2-ME) and mono-2-methoxyethyl phthalate (MMEP). 2-ME is then oxidised to methoxyacetic acid (MAA) (as summarised in Ritter et al., 1985).

Injection of 0.6 mL/kg bw <sup>14</sup>C-DMEP intravenously to pregnant Wistar rats on GD 13 suggested a rapid transfer of the unmetabolised DMEP across the placenta to the foetus (Parkhie et al., 1982). Clearance of DMEP and its metabolite MMEP from the placenta is rapid, as only 6.4% of DMEP remains after 4 hours of dosing.

The *in vitro* hydrolysis of DMEP to MMEP was complete within 2 minutes in maternal liver homogenates and 4 hours in maternal placenta homogenates. Foetal homogenates, in contrast, had little or no ability to hydrolyse DMEP to the monoester (Campbell et al., 1984)

### Conclusion

DMEP rapidly undergoes hydrolysis to MMEP and 2-ME and the latter is expected to be oxidised to MAA. The rat foetus appears to have little or no ability to hydrolyse DMEP to the monoester and intact DMEP is rapidly transferred across the placenta into the foetus.

### 3.2 Acute Toxicity

<i>Study</i>	<i>Species</i>	<i>Results (LD50/LC50)</i>
Oral	Rat	3200-6400 mg/kg bw
	Rat	>4400 mg/kg bw
	Mouse	3200-6400 mg/kg bw
	Guinea-Pig	1600-3200 mg/kg bw
Dermal	Guinea-Pig	>1171 mg/kg bw
Inhalation (6 h)	Rat	>770-1595 ppm

Source: USEPA (1985)

### Conclusion

DMEP has low acute oral, dermal and inhalational toxicity in laboratory animals.

### **3.3 Irritation**

#### Skin Irritation

DMEP caused slight skin irritation when applied to depilated guinea-pig abdomen under occlusive wrap for 24 hours. Minor, transient erythema and oedema were seen at doses up to 20 mL/kg bw (purity was 78%) (Topping, 1984).

DMEP was found to produce a significant degree of irritation when injected intradermally in mice. However, this result was considered ambiguous given the same undiluted compound did not elicit any obvious ophthalmic irritation in a rabbit eye test (Lawrence et al., 1975).

Intradermal injections of 0.2 mL of a 100 mg/mL solution of DMEP into the clean-shaven back of rabbits induced a moderate inflammatory response over 26 minutes (Calley et al., 1966).

#### **Conclusion**

DMEP caused minimal skin irritation in guinea pigs.

#### Eye Irritation

DMEP caused slight eye irritation when applied to six rabbit eyes (three washed, three unwashed). The irritant response in the unwashed eyes was restricted to immediate sensory irritation (Topping, 1984).

Eye irritation was not observed after instillation of undiluted DMEP in rabbits but details of the test conditions were not available (Lawrence et al., 1975).

#### **Conclusion**

DMEP caused minimal eye irritation in rabbits.

#### Respiratory Irritation

No data.

### **3.4 Sensitisation**

DMEP did not elicit a positive response when administered to ten guinea pigs using a standardised sensitisation procedure, but details of the test conditions were not available (Topping, 1984).

#### **Conclusion**

DMEP did not induce skin sensitisation in guinea pigs but details of the method were not available.

### **3.5 Repeated Dose Toxicity**

Twenty to thirty white mice were injected intraperitoneally daily with emulsified DMEP at 250 mg/kg bw/d for 6 weeks (Calley et al., 1966). Controls received 3% acacia suspension. There were no statistically significant differences in relative liver, kidney, or spleen weights

or body weights. A statistically significant decrease in relative testes weight was attributed to testicular atrophy. Acute peritonitis in the liver and spleen (including adhesions and liver abscesses), peri-portal hepatitis in the liver and extramedullary hematopoiesis in liver and spleen were seen. The authors noted that the mode of administration was likely to cause peritonitis rather than being a direct toxic effect of DMEP. Haematology was not affected.

The effects of various phthalates on rabbit blood pressure, respiration rate, electrocardiogram pattern and electroencephalogram pattern were investigated intravenously (Calley et al., 1966). Phthalate emulsions (in 3% acacia solution) were administered to anaesthetised rabbits at repeat doses of 50 mg/kg bw through a cannulated external jugular vein (period of treatment not given). Controls (2 rabbits) received equivalent volumes of 3% acacia. DMEP induced minor CNS depression but had no direct cardiac toxicity. Respiratory rate was increased.

Male rats (species unspecified) (5/dose) were gavaged with 0, 100 or 1000 mg/kg bw DMEP for a total of 14 treatments over 16 days (Topping, 1984). The animals were necropsied on treatment day 16. No differences in absolute or relative liver, kidney or testes weights in low dose group were observed. In the high dose group, absolute but not relative liver weight was reduced and absolute and relative thymus and testes weights were greatly reduced (1/3 or less as compared to controls). Haemoglobin and haematocrit values were also reduced slightly at both doses (statistically significantly at the low dose) and absolute white cell counts were decreased significantly at the high dose. Serum clinical chemistry tests revealed slight decreases in enzymes and creatinine at the high dose.

Pathology revealed thymic and testicular atrophy at the high dose. Histopathology revealed thymic medullary haemorrhage in 4/5 animals at the low dose (noted as possibly an artifact of the method of sacrifice) and atrophy of seminiferous tubules, degeneration of sperm and epididymis and the presence of giant spermatids at the high dose. The primary sites of toxicity were determined to be the thymus and testes. A LOAEL was determined to be 100 mg/kg bw/day.

## **Conclusion**

Only subchronic repeat dose studies were available. In separate studies, DMEP caused decreases in absolute and relative thymus and testes weight with histological evidence of testes atrophy in rats (1000 mg/kg bw/d, gavage) and decreased relative testes weight in mice (250 mg/kg bw/d, intraperitoneal). In the rat 16-day gavage study, a LOAEL of 100 mg/kg bw/d was established from this study based on decreases in haemoglobin and haematocrit values. No NOAEL could be established.

## **3.6 Genetic Toxicity**

A dominant lethal test of DMEP was performed in ICR mice (10 males/dose). Males were given a single intraperitoneal injection with undiluted DMEP at doses of ca. 1.19, 1.79, 2.38 mL/kg (ca. 1/3, 1/2 and 2/3 of the acute LD50 dose of 3.75 mL/kg) prior to mating with untreated females. Females were replaced weekly during the 12-week mating period. Pregnant rats were terminated on GD 13-17. Mortality of 20% was seen in male mice treated at 2.38 mL/kg. In the first week, none of the high dose group matings resulted in pregnancies and only half of the mid dose group produced pregnancies (however, this was no different than controls). Overall, the incidence of pregnancies in the high dose groups was 35%. There

was a reduction in the mean number of implantation in each pregnancy in the first 3 weeks of the mating period (Singh et al., 1974).

## **Conclusion**

In vitro genotoxicity data were not available for DMEP. DMEP was positive in a dominant lethal assay.

### **3.7 Carcinogenicity**

No data.

### **3.8 Reproductive Toxicity**

Traditional hazard assessments consider reproductive toxicity separate from developmental toxicity. Reproductive toxicity is tested by exposing sexually mature adults to a chemical and examining the effects on the animal capacity to reproduce. Developmental toxicity is studied by exposing pregnant dams and looking for effects in the foetuses. However, these tests generally do not detect chemicals that induce effects that only appear postnatally. Thus, chemicals that affect the developing reproductive system following prenatal exposure may also affect sexual maturation or functional reproductive disorders that are only apparent at maturity. Developmental toxicity can therefore lead to reproductive toxicity and the two endpoints cannot be clearly distinguished.

In this hazard assessment, data will be presented on the basis of test procedure, including repeat dose toxicity studies that dose adult animals for varying duration, prenatal developmental toxicity studies (only the dam is dosed, study ends before parturition) and developmental/postnatal studies (dam is dosed during gestation and allowed to litter, study ends during weaning). The effects on fertility and development will then be discussed separately in the conclusion. All relevant studies are summarised in Table 2.

#### **3.8.1 Repeat dose toxicity studies**

DMEP was found to significantly reduce testes weight when given daily by ip to mice at 250 mg/kg/d ( $p > 0.01$ ) for 6 weeks (Calley et al., 1966).

Male Wistar rats (5/dose) were orally dosed with 1000, 1500 or 2000 mg/kg bw/d for 11 days (Cassidy et al., 1983). There was no effect on body weight but dose-related decreases in testes weight and dose-related increases in frequency of abnormal sperm heads were seen, reaching statistical significance at 1500 mg/kg bw/d and above. A NOAEL could not be established due to decrease in testes weight at the lowest dose.

Male rats (5/dose) were gavaged with 100 or 1000 mg/kg bw/d for a total of 12 treatments over 16 days (Topping, 1984). Controls received 1000 mg/kg distilled water. Absolute testes weight was severely reduced at 1000 mg/kg bw/d (1/3 or less compared with controls) as was relative testes weight. Histopathology revealed seminiferous tubule atrophy, sperm degeneration and presence of giant spermatids. A NOAEL of 100 mg/kg bw/d for reproductive organ toxicity was established.

#### **3.8.2 Prenatal developmental toxicity studies**

DMEP was found to be embryotoxic, fetotoxic and teratogenic in a study by Parkhie et al. (1982). Pregnant Wistar rats were dosed intraperitoneally with 0.6 mL/kg once on GD 10, 11, 12, 13 or 14. Controls received the same volume of physiological saline. DMEP induced decreased foetal weight at all dosing days and increased frequency of dead or resorbed fetuses. Central nervous system (hydrocephaly) and skeletal malformations (absent or shortened fibula, forked ribs) were increased in litters treated on GD 10-14. The effects on the dam were not reported.

Pregnant rats (5/group) were injected ip with 1.245, 0.747 and 0.374 mL/kg DMEP on GD 5, 10 and 15 (Singh et al., 1972). Controls were untreated. Dams were terminated on GD 20. The following embryotoxic results were seen: increase in number of resorptions (16%, 52% and 55% at 0.374, 0.747 and 1.245 mL/kg, respectively), increase in frequency of foetal deaths and resorption (56.9%, 96.6% and 98.2%) and significant decrease in mean foetal weight at all doses ( $p \leq 0.01$ ). Effects on the dam were not reported. An increased incidence of gross (2.4%, 83.3% and 100% at 0.374, 0.747 and 1.245 mL/kg, respectively) and skeletal (92.9%, 100% and 100%) abnormalities was seen. A NOAEL could not be established due to teratogenic effects at the lowest dose tested.

Pregnant rats were given single oral or intraperitoneal doses of DMEP or its metabolites, 2-methoxyethanol (2-ME) and methoxyacetic acid (MAA) on GD 12 (DMEP: 1.03, 2.07, 4.14 mmol/kg ip; 2-ME: 2.07, 4.14 mmol/kg orally and intraperitoneal; MAA: 2.07, 4.14 mmol/kg orally) (Ritter et al., 1985). Controls were untreated. 2-ME (4.14 mmol/kg bw) was also administered concurrently with 4-methyl pyrazole (4-MP): alcohol dehydrogenase inhibitor at 200 mg/kg ip. Dose-related increases in total embryotoxicity (27.8%, 51.5% and 94.3% at 1.03, 2.07 and 4.14 mL/kg, respectively) were seen after treatment with DMEP. Oral doses of 2-ME (2.07 and 4.14 mL/kg) resulted in 53.8% and 100% embryotoxicity, respectively, whereas ip administration at the same doses caused 65% and 100% embryotoxicity. 2.07 and 4.14 mL MAA/kg resulted in 57.8% and 99.3% embryotoxicity, respectively. All treatments caused various developmental effects including hydronephrosis and defects of the heart, tail and limb. No defects were seen in controls. Treatment with 2-ME (100 mg/kg) and 4-MP induced less embryotoxicity (16.8%) than treatment with 2-ME alone suggesting 4-MP prevented oxidation of 2-ME to MAA and that MAA might be the teratogenic moiety. A NOAEL could not be established due to teratogenic effects at the lowest dose.

Pregnant Wistar rats were given a single intraperitoneal dose of 2.49 mmol/kg (702 mg/kg bw) DMEP, monomethoxyethyl phthalate (MMEP) or 2-ME on GD 8, 10, 12 and 14. Controls were untreated or injected with 1 mL/kg acetate buffer (Campbell et al., 1984). Dams were terminated on GD 20. 2-ME induced a greater incidence of kidney and bladder abnormalities than DMEP. Both were highly embryotoxic when given on GD 8, causing a 3-fold and 4-fold increase, respectively, in the number of dead or resorbed fetuses as compared to controls. Survival of conceptuses was higher following treatment with DMEP or 2-ME on GD 10 onwards but most survivors were malformed. MMEP was not teratogenic.

Pregnant mice were given oral doses of 10 mmol/kg bw MAA on GD 10.5, 11 or 11.5 (Rasjad et al., 1991\*). Maximum frequency of skeletal malformations occurred following dosing on GD 11.5 with frequency of forelimb malformations greater than hindlimb malformations. Syndactyly and ectrodactyly were common findings.

The effects of DMEP and its metabolites, monomethoxyethyl phthalate (MMEP), 2-methoxyethanol (2-ME) and methoxyacetic acid (MAA), on post-implantation rat embryos in

culture were investigated. DMEP, MMEP and 2-ME were not embryotoxic at 5mM whereas MAA induced embryotoxicity at concentrations at and above 2 mM. Embryos were developmentally delayed (decreased head length and number of somites) at 2mM. Significant decreases in crown-rump length, head length, somite count, yolk-sac diameter and morphological scores were observed at 3 mM and above. Developmental anomalies included abnormal yolk-sacs and open neural tubes (Yonemoto et al., 1984).

### 3.8.4 Mode of action

Moist pads containing 0.05 mL of 50 mg/mL DMEP were placed over cultures containing mouse fibroblasts and chick embryo cells. DMEP was found to induce cell death in mouse fibroblasts (Calley et al, 1966). The oestrogenic activity of 356 phthalates was investigated *in vitro* using a recombinant yeast screen. DMEP was not found to have oestrogenic activity (Harris et al., 1997).

## Conclusion

### *Effects on fertility*

DMEP induced decreases in testes weight in rats (1000 mg/kg bw, oral). Dose-related increases in abnormal sperm heads were also seen at and above 1000 mg/kg bw in rats. A NOAEL of 100 mg/kg for reproductive organ toxicity was established and a LOAEL of 1000 mg/kg bw, based on a decrease in testes weight.

### *Developmental Effects*

There are no developmental studies following oral administration of DMEP. Intraperitoneal injection induced marked embryotoxic, fetotoxic and teratogenic effects at ip doses above 1.03 mmol/kg (estimated 291 mg/kg bw). The effects on the dam were unknown. The metabolites of DMEP, 2-ME and MAA, have been evaluated as 2-ME (also referred to as ethylene glycol monomethyl ether) is an important industrial solvent (Lanigan et al., 1999). Both 2-ME and MAA induce malformations, principally skeletal, in rats and mice in developmental studies. Embryos are unable to metabolise DMEP in culture. The results of the *in vitro* study suggest that MAA is the proximate teratogen. *In vivo* teratogenicity of DMEP appears to require conversion of 2-ME to MAA by the dam.

**Table 2: Summary of reproductive and development studies on DMEP and its metabolites**

<b>Study type</b>	<b>Route</b>	<b>Doses</b>	<b>NOAEL (mg/kg bw/d)</b>	<b>LOAEL (mg/kg bw/d) &amp; endpoint</b>	<b>Reference</b>
<b>DMEP</b>					
Repeat dose Mice 6 weeks	i.p.	0, 250 mg/kg bw/day	NE	250: ↓ testes wt	Calley et al., 1966
Repeat dose Rats (5/dose) 16 days	Gavage	0, 100, 1000 mg/kg bw/day	100	1000: ↓ testes wt, sem tubule atrophy, sperm degen	Topping, 1984

Reproduction Rats, Wistar (5/dose) 11 days	Gavage	0, 1000, 1500, 2000 mg/kg bw/day	NE	1000: ↓ testes wt, abn sperm heads	Cassidy et al., 1983
Development Rats, Wistar (10-19/group) GD 10-14	i.p.	0, 0.6 mL/kg (unknown purity)	NE	714 (0.6 ml/kg): ↑ resorptions, brain & skeletal mals	Parkhie et al., 1982
Development Rats, Sprague Dawley (5/group) GD 5, 10 & 15	i.p.	0, 0.374, 0.747, 1.245 mL/kg (unknown purity)	NE	445 (0.374 ml/kg): ↑ resorptions, foetal death, ↓ foetal wt, ↑ gross & skeletal mals	Singh et al., 1972
Development Rats, Wistar (6-8/group) GD 12	i.p.	0, 1.03, 2.07, 4.14 mmol/kg	NE	291 (1.03 mmol/kg): ↑ resorptions, ↑ gross & skeletal mals	Ritter et al., 1985
Development Rats, Wistar (5-10/group) GD 8, 10, 12 & 14	i.p.	0, 2.49 mmol/kg bw	NE	703 (2.49 mmol/kg): ↑ resorptions, ↑ gross mals	Campbell et al., 1984
<b>Monomethoxyethyl phthalate (MMEP)</b>					
Development Rats, Wistar GD 8, 10, 12 & 14	i.p.	0, 2.49 mmol/kg bw	558 (2.49 mmol)	NE	Campbell et al., 1984
<b>2-methoxyethanol (2-ME)</b>					
Chimera assay Mice, Swiss ICR (11-19/group) 5 days then mated to untreated females	Gavage	0, 750, 1500 mg/kg bw/day	NE:	750: infertility at week 4	Oudiz et al., 1993
Repeat dose Rats, Sprague – Dawley male 11 days	Gavage	0, 50, 100, 250, 500 mg/kg bw/day	50	100: degeneration of spermatocytes within 24h; 250: ↓ rel testes wt after 7 days; ↓ rel liver wt	Foster et al., 1983
Development Rats, Wistar (6-8/group) GD 12	Gavage	0, 2.07, 4.14 mmol/kg	NE:	158 (2.07 mmol/kg): ↑ resorptions, ↑ gross & skeletal mals	Ritter et al., 1985
Development Rats, Wistar (6-8/group) GD 12	i.p.	0, 2.07, 4.14 mmol/kg	NE:	158 (2.07 mmol/kg): ↑ resorptions, ↑ gross & skeletal mals	Ritter et al., 1985
Development Macaca (4/group) GD 20-45	Gavage	0, 12, 24, 36 mg/kg bw/day	NE	12: ↑ intrauterine death, 100% at 36	Scott et al., 1989*
<b>Methoxyacetic acid (MAA)</b>					
Development Rats, Wistar (6-8/group) GD 12	Gavage	0, 2.07, 4.14 mmol/kg	NE:	187 (2.07 mmol/kg): ↑ resorptions, ↑ gross & skeletal mals	Ritter et al., 1985

Repeat dose Rats, Sprague – Dawley male 4 days	Gavage	0, 592 mg/kg bw/day	NE	592: ↓ rel testes wt	Foster et al., 1983
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Wt: weight; abn: abnormal; sem: seminiferous; degen: degeneration; mals: malformations; rel: relative

#### 4. HAZARD CHARACTERISATION

Toxicity data for DMEP were not available for all health endpoints. DMEP is of low molecular weight but its side chains are not simple linear or branched structures. Therefore, it is not possible to extrapolate potential effects of this phthalate for endpoints with missing or incomplete data based on information obtained from other NICNAS assessment reports. However, a comparative analysis of toxicity endpoints across 25 phthalates, including DMEP, can be obtained from the NICNAS Phthalates Hazard Compendium (2007).

DMEP rapidly undergoes hydrolysis to 2-methoxyethanol (2-ME) and mono-2-methoxyethyl phthalate (MMEP). 2-ME is then oxidised to methoxyacetic acid (MAA). The rat foetus has little or no ability to hydrolyse DMEP to the monoester and intact DMEP is rapidly transferred across the placenta into the foetus.

DMEP has low acute oral, dermal and inhalational toxicity. DMEP did not cause skin or eye irritation or skin sensitisation in animals, however, details of the methods used were not available.

In sub-chronic repeated dose studies, DMEP induced major decreases in thymus and testes weight in rats at 1000 mg/kg bw/d (gavage), and testes weight in mice at 250 mg/kg bw/d (intraperitoneal). In rats, slight but statistically significant decreases were reported for haemoglobin and haematocrit values at 100 mg/kg bw/d, which was the lowest dose tested. No NOAEL was established.

*In vitro* genotoxicity data are not available for DMEP. DMEP is positive in the dominant lethal assay suggesting it could be a mutagen for germ cells.

No carcinogenicity data are available for DMEP. Due to insufficient testing, it is not possible to extrapolate carcinogenic potential for DMEP.

None of the reported reproductive toxicity studies were performed according to OECD guidelines. A NOAEL of 100 mg/kg for reproductive organ toxicity was established from an oral repeat dose study in rats based on decrease in testes weight at 1000 mg/kg bw/d.

There are no developmental studies following oral or inhalation administration of DMEP. Intraperitoneal injection induced marked embryotoxic, fetotoxic and teratogenic effects at ip doses above 1.03 mmol/kg (estimated 291 mg/kg bw). A NOAEL could not be established due to teratogenic effects at the lowest dose. The effects on the dam were unreported. The metabolites of DMEP, 2-ME and MAA, have been evaluated. Both 2-ME and MAA induce decrease in testes weight in reproductive toxicity studies and malformations, principally skeletal, in developmental studies. 2-ME is also a reproductive toxicant following inhalation exposure and a developmental toxicant following dermal exposure. Therefore, it is anticipated that DMEP cause fertility and developmental effects.

### 5. HUMAN HEALTH HAZARD SUMMARY TABLE

<i>Phthalate</i>	<i>Acute Toxicity</i>	<i>Irritation &amp; Sensitisation</i>	<i>Repeated Dose Toxicity</i>	<i>Genetic Toxicity</i>	<i>Carcinogenicity</i>	<i>Reproductive Toxicity</i>	<i>Developmental Toxicity</i>
Bis(2-methoxyethyl) phthalate (DMEP)	<p>Oral Rat: LD50 = 3200-6400 mg/kg bw</p> <p>Dermal Guinea pig: LD50 &gt;1171 mg/kg bw</p> <p>Inhalation Rat, 6h: LC50 &gt;770- &lt;1595 ppm</p>	<p>Skin irritation: Minimal effects</p> <p>Eye irritation: Minimal effects</p> <p>Respiratory irritation: No data</p> <p>Skin sensitisation: Negative</p>	<p>Rat: NOAEL = not established</p> <p>LOAEL = 100 mg/kg bw/d, ↓ haemoglobin and haematocrit values.</p> <p>High doses: ↓ thymus and testes weights; testicular atrophy.</p>	<p><i>In vitro</i> No data</p> <p><i>In vivo</i> Positive in dominant lethal assay</p>	No data	<p>16-day repeat dose study Rat: NOAEL = 100 mg/kg bw/d</p> <p>LOAEL of 1000 mg/kg bw/d, ↓ testes weight, ↑ sperm degeneration, and testes atrophy</p>	<p>Rat: NOAEL = not established</p> <p>LOAEL (ip) = 291 mg/kg bw/d, ↑ skeletal and visceral variations</p>

↑: increase; ↓: decrease.

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