Existing Chemical Hazard Assessment Report

Australian Government
Department of Health and Ageing
NICNAS

Bis(2-methoxyethyl) Phthalate

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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME
GPO Box 58, Sydney NSW 2001, Australia www.nicnas.gov.au

Preface

This report was compiled under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This Scheme was established by the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (the Act), which came into operation on 17 July 1990.

The principal aim of NICNAS is to aid in the protection of people at work, the public and the environment from the harmful effects of industrial chemicals.

NICNAS assessments are carried out in conjunction with the Department of the Environment, Water, Heritage and the Arts, which carry out the environmental assessment for NICNAS. NICNAS has two major programs: the assessment of the health and environmental effects of new industrial chemicals prior to importation or manufacture; and the other focussing on the assessment of chemicals already in use in Australia in response to specific concerns about their health/or environmental effects.

There is an established mechanism within NICNAS for prioritising and assessing the many thousands of existing chemicals in use in Australia.

For the purposes of Section 78(1) of the Act, copies of assessment reports for New and Existing Chemical assessments are freely available from the web (www.nicnas.gov.au). Summary Reports are published in the *Commonwealth Chemical Gazette* (http://www.nicnas.gov.au/publications/#gazette), and are available to the public on line at www.nicnas.gov.au.

Copies of this report and other NICNAS reports are available on the NICNAS website. Hardcopies are available from NICNAS at the following address:

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Other information about NICNAS (also available on request) includes:

- NICNAS Annual Reports.
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Overview

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

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

No information on use in Australia was available. A survey of Australian industry in 2004 and 2006 provided no information on DMEP.

Toxicity data for DMEP were not available for all health endpoints. A comparative analysis of toxicity endpoints across 24 ortho-phthalate esters, including DMEP, can be obtained from the NICNAS Phthalates Hazard Compendium.

Structurally, phthalate esters are characterized by a diester structure consisting of a benzenedicarboxylic acid head group linked to two ester side chains. DMEP contains ester side chains each containing 3 carbons (C3) but its side chains are not simple linear or branched carbon structures. This limits the extent to which missing data for this low molecular weight phthalate can be extrapolated from other NICNAS hazard assessment reports for phthalates.

Little toxicokinetic data are available for DMEP but it has been studied in pregnant rats. 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 DMEP injected intravenously is rapidly transferred across the placenta into the foetus.

DMEP has low acute oral, dermal and inhalational toxicity. DMEP produced minimal skin and eye irritation and no 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 decreases in testes weight in mice at 250 mg/kg bw/d (ip, intraperitoneal). In rats, slight but statistically significant decreases in haemoglobin and haematocrit values were reported at 100 mg/kg bw/d, which was the lowest dose tested. NOAEL was not established in this study.

In vitro genotoxicity data were not available for DMEP. DMEP was positive in the dominant lethal assay, suggesting it could be a mutagen for germ cells. However, overall, data were insufficient to conclude the genotoxic potential of DMEP.

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

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. However, no reproductive toxicity studies were performed according to OECD guidelines.

There were no developmental studies following oral or inhalation administration of DMEP. Intraperitoneal injection induced marked embryotoxic, fetotoxic and teratogenic effects at

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 dams were unreported. Both 2-ME and MAA induced malformations, principally skeletal, in developmental studies. Overall, from available studies, it is anticipated that DMEP may cause fertility and developmental effects.

Table of Contents

Acronyms and Abbreviations

2-ME	2-methoxyethanol
bw	body weight
C	Celsius
CAS	Chemical Abstracts Service
d	day
DEHP	diethylhexyl phthalate
DMEP	bis(2-methoxyethyl) phthalate
g	gram
GD	gestation day
h	hour
ip	intraperitoneal
kg	kilogram
kPa	kilopascals
L	litre
LC50	median lethal concentration
LD50	median lethal dose
LOAEL	lowest-observed-adverse-effect level
mg	milligram
mL	millilitre
MAA	methoxyacetic acid
MMEP	mono-2-methoxyethyl phthalate
mmol	millimole
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Cooperation and Development
ppm	parts per million
USEPA	United State Environmental Protection Agency
µ	micro

1. 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.

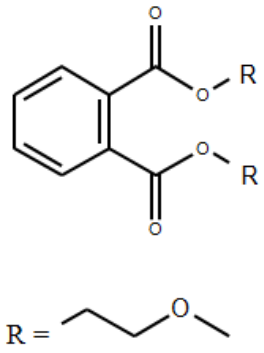
Information on Australian uses was compiled from data supplied by industry in 2004 and 2006.

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 24 *ortho*-phthalate esters (NICNAS, 2008).

2. Identity

2.1 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:	$C_{14}H_{18}O_6$
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

2.2 Physicochemical properties

Table 1: Summary of physicochemical properties

Property	Value
Physical state	Light coloured, clear liquid, mild aromatic odour
Melting point	-40°C
Boiling point	340°C
Density	1170 kg/m^3 (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 x 10^{-3} atm m^3/mL (25°C)
Flash point (open cup)	194°C

Source: USEPA (1985)

3. Uses

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

In Australia, DMEP is imported in play and exercise balls, hoppers and children's toys (inflatable water products).

4. Human Health Hazard

4.1 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 ^{14}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.

4.2 Acute toxicity

Study	Species	Results (LD50/LC50)
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.

4.3 Irritation

4.3.1 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 elicited 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.

4.3.2 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.

4.3.3 Respiratory irritation

No data.

4.4 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.

4.5 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 anesthetised 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/d, based on decreases in haemoglobin and haematocrit values.

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.

4.6 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.

4.7 Carcinogenicity

No data.

4.8 Reproductive toxicity

Traditional hazard assessments consider effects on fertility separate from developmental toxicity. Fertility is tested by exposing sexually mature adults to a chemical and examining the effects on reproductive capacity. Developmental toxicity is studied by exposing pregnant dams and looking for effects on the foetuses. 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 effects on fertility and the two endpoints cannot be clearly distinguished.

In this hazard assessment, data are presented on the basis of test procedure. The effects on fertility (as adults) and development (as foetuses) are then discussed separately. Reproductive and developmental data are summarised in Table 2.

4.8.1 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.

4.8.2 Prenatal developmental toxicity studies

DMEP was found to be embryotoxic, foetotoxic 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 foetuses. 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 embryotoxicty (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 foetuses 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).

4.8.3 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).

4.8.4 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

Study type	Route	Doses	NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d) & endpoint	Reference
DMEP					
Repeat dose Mice 6 weeks	i.p.	0, 250 mg/kg bw/d	NE	250: ↓ testes wt	Calley et al., 1966
Repeat dose Rats (5/dose) 16 days	Gavage	0, 100, 1000 mg/kg bw/d	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/d	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
Monomethoxyethyl phthalate (MMEP)					
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

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Study type	Route	Doses	NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d) & endpoint	Reference
2-methyoxyethanol (2-ME)					
Chimera assay Mice, Swiss ICR (11-19/group) 5 days then mated to untreated females	Gavage	0, 750, 1500 mg/kg bw/d	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/d	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/d	NE	12: ↑ intrauterine death, 100% at 36	Scott et al., 1989*
Methoxyacetic acid (MAA)					
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/d	NE	592: ↓ rel testes wt	Foster et al., 1983

Wt: weight; abn: abnormal; sem: seminifereous; degen: degeneration; mals: malformations; rel: relative; d: day; NE: not established

5. 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 24 *ortho*-phthalate esters, including DMEP, can be obtained from the NICNAS Phthalates Hazard Compendium (NICNAS, 2008).

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 produced minimal skin and eye irritation but not 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 decreases in 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. However, overall, data were insufficient to conclude the genotoxic potential of DMEP.

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, foetotoxic 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 induced malformations, principally skeletal, in developmental studies. Overall, from available studies, it is anticipated that DMEP may cause fertility and developmental effects.

6. Human Health Hazard Summary Table

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

↑: increase; ↓: decrease.

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References

Calley D, Autian J, & Guess WL (1966) Toxicology of a series of phthalate esters. Journal of Pharmaceutical Sciences, 55(2): 158-162.

Campbell J, Holt D, & Webb M (1984) Dimethoxyethyl phthalate metabolism: Teratogenicity of the diester and its metabolites in the pregnant rat. Journal of Applied Toxicology, 4(1): 35-41.

Cassidy SL, Dix KM, & Jenkins T (1983) Evaluation of a testicular sperm head counting technique using rats exposed to dimethoxyethyl phthalate (DMEP), glycerol α-monochlorohydrin (GMHC), epichlorohydrin (ECH), formaldehyde (FA), or methyl methanesulfonate (MMS). Archives of Toxicology, 53(1):71-8.

Foster PMD, Creasy DM, Foster JR, Thomas LV, Cook MW, & Gangolli SD (1983) Testicular toxicity of ethylene glycol monomethyl and monoethyl ethers in the rat. Toxicol. Appl. Pharmacol., 69:385–399.

Harris CA, Henttu P, Parker MG, & Sumpter JP (1997) The oestrogenic activity of phthalate esters in vitro. Environmental Health Perspectives, 105(8): 802-811.

Lanigan RS (1999) Special report: Reproductive and developmental toxicity of ethylene glycol and its ethers. International Journal of Toxicology, 18(suppl. 2): 53–67.

Lawrence WH, Malik M, Turner JE, Singh AR, & Autian J (1975) Toxicology investigation of some acute short term and chronic effects of administering di-2-ethylhexyl phthalate (DEHP) and other phthalate esters. Environmental Research, 9(1):1-11.

NICNAS (2008) Phthalate hazard compendium: a summary of physicochemical and human health hazard data for 24 *ortho*-phthalate chemicals. Sydney, National Industrial Chemicals Notification and Assessment Scheme.

Oudiz DJ, Walsh K, & Wiley LM (1993) Ethylene glycol monomethyl ether (EGME) exposure of male mice produces a decrease in cell proliferation of preimplantation embryos. Reprod. Toxicol., 7:101–109.

Parkhie MR, Webb M, & Norcross MA (1982) Dimethoxyethyl phthalate: embryopathy, teratogenicity, foetal metabolism and the role of the zinc in the rat. Environmental Health Perspectives, 45:85-97.

Rasjad C, Yamashita K, Datu AR, & Yasuda M (1991) Pattern of limb malformations in mice induced by methoxyacetic acid. Hiroshima J Med Sci, 40:93-99.

Ritter EJ, Scott Jr WJ, Randall JL, & Ritter JM (1985) Teratogenicity of dimethoxyethyl phthalate and its metabolites methoxyethanol and methoxyacetic acid in the rat. Teratology, 32(1): 25-31.

Scott WJ, Fradkin R, Wittfoht W, & Nau H (1989) Teratologic potential of 2-methoxyethanol and transplacental distribution of its metabolite, 2-methoxyacetic acid, in non-human primates. Teratology, 39:363–373.

Singh AR, Lawrence WH, & Autian J (1972) Teratogenicity of phthalate esters in rats. Journal of Pharmaceutical Sciences, 61(1):51-5.

Singh AR, Lawrence WH, & Autian J (1974) Mutagenic and antifertility sensitivities of mice to di-2-ehtylhexyl phthalate (DEHP) and dimethoxyethyl phthalate (DMEP) Toxicology and Applied Pharmacology, 29(1):35-46.

Topping DC (1984) Basic toxicology of bis(2-methoxyethyl) phthalate. Report 18842LT TX-84-34, October 9 1984 with covering letter dated 29 January 1985. Eastman Kodak Company. Eastman Kodak Co.

USEPA (1985) Chemical Hazard Information Profile (CHIP) Draft Report on Dimethoxyethyl Phthalate. Prepared by Oak Ridge National Laboratory Author-Smith JG under contract to US Environmental Protection Agency.

Yonemoto J, Brown NA, & Webb M (1984) Effects of dimethoxyethyl phthalate, monomethoxyethyl phthalate, 2-methoxyethanol and methoxyacetic acid on post implantation rat embryos in culture. Toxicology-Letters, 21(1): 97-102.