Methyl ethyl ketone peroxide

(CAS No: 1338-23-4)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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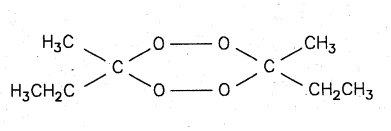
1 Introduction

The present document contains the assessment of the health hazard of methyl ethyl ketone peroxide by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by AAE Wibowo, Ph.D. (Coronel Institute of the Academic Medical Centre, Amsterdam, the Netherlands).

Literature was retrieved from the databases Medline, Embase, Current Contents, and Chemical Abstracts, starting from 1966, 1988, 1970, and 1970, respectively, and using the following key words: methyl ethyl ketone peroxide, butanone peroxide, MEKP, and 1338-23-4. HSEline, Cisdoc, Mhidas, NIOSHTIC (covering the period 1985/87 until 1997), and Poltox (Toxline, Cambridge Sc Abstr, FSTA) (covering information until 1994), databases available from CD-ROM, were consulted as well. Data considered to be critical were evaluated by reviewing the original publications. The final literature search was carried out in January 1998, followed by an additional search in June 2001.

In September 2001, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identity

name	:	methyl ethyl ketone peroxide
synonyms	:	2-butanone peroxide
molecular formular	:	$C_8H_{16}O_4$
structural formula	:	
CAS number	:	1338-23-4

3 Physical and chemical properties

molecular weight	:	176.2
boiling point	:	80°C
melting point	:	not known
flash point	:	52-93°C
vapour pressure	:	not known
solubility in water	:	not soluble
log $P_{octanol/water}$	:	not known
conversion factors (20^0C, 101.3 kPa)	:	1 mg/m^3 = 0.14 ppm 1 ppm = 7.3 mg/m^3

Data from ACG99, Zei93.

Methyl ethyl ketone peroxide (MEKP) is a colourless liquid. The pure chemical is an unstable peroxide capable of releasing molecular oxygen. It is shock, sunlight, and heat sensitive, and undergoes explosive decomposition at 110°C. It can also undergo spontaneous ignition or decomposition if mixed with readily oxidisable organic or flammable materials or chemical reactants. Because of this high reactivity, it is sold commercially as a colourless liquid mixture of approximately 60% MEKP and 40% diluent that may be any combination of dimethyl phthalate, cyclohexanone peroxide, or diallyl phthalate (ACG99, Zei93).

The odour threshold is not known.

4 Uses

MEKP is a commonly used curing agent for thermosetting polyester resins, a cross-linking agent and catalyst used in the production of other polymers and polyester resins. It is used in the automobile, airline, boating, fabric, and paint industries (Fra90, Pur79). In biochemistry, MEKP is used for inducing experimental lipid peroxidation in animals.

5 Biotransformation and kinetics

There is very little data available on the kinetics of MEKP.

In a review on toxic effects in humans, Zeiger stated that in the working environment, exposure occurs by inhalation of aerosolised MEKP during the spraying procedure used in some of the manufacturing processes, or by dermal exposure to the aerosol or liquid substance (Zei93).

6 Effects and mechanism of action

Human data

A few cases of work-related allergic contact dermatitis have been reported with positive reactions to MEKP upon patch testing in the patients involved (Bhu97, Bou63, Mal57, Ste92).

Fraunfelder et al. studied ocular injury from accidental direct contact with MEKP vapour or solvent (full strength or diluted) in 13 male patients, ranging in age from 22 to 68 years. There were 4 clinical ocular patterns: mild injury, moderate injury, severe injury, and delayed keratitis. Corneoscleral limbus and cornea were the primary areas of chronic irritation secondary to exposure to MEKP, but marked hyperaemia of bulbar and palpebral conjunctiva occurred with exacerbations. Significant photophobia and epiphora were common. Tear film break-up times were usually abnormal. Markedly decreased or absent conjunctival and corneal sensitivity were common, and these were permanent in cases of severe injury. The delayed MEKP keratitis was characterised by its slow progression, exacerbations and remissions, corneal hypoaesthesia, and similar corneal changes. Resembling delayed mustard gas keratitis, the effects of MEKP may be the result of its alteration of corneal macromolecules to produce new antigens resulting in an autoimmune response directed at the cornea leading to the delayed keratitis observed. Generally, a major factor in the severity of ocular effects was the length of time from exposure to MEKP to adequate lavage (Fra90).

McGlothlin and Thoburn performed a health survey on workers exposed to various ketones and acrylic resins during the manufacture of fibrous glass-reinforced plastic tubs and showers. Environmental sampling of a variety of chemicals, among which toluene diisocyanate, showed that none of the chemicals tested exceeded the recommended OSHA standards. MEKP was the primary contaminant that the workers were exposed to with levels ranging from 0.19 to 1.24 mg/m^3 (0.026 to 0.17 ppm). Pulmonary function tests performed before and after shifts on 30 workers were usually normal, but 5 workers showed significant decreases in the functions over the shift. Predominant

symptoms were nose and throat irritation, headaches, dizziness, and breathing problems. One worker had a hyperreactivity to toluene diisocyanate (McG81).

The toxic oral dose of MEPK (in dimethyl phthalate) has been reported to be 50 to 100 mL. Case reports showed that ingestion of MEKP resulted in acute toxic symptoms such as gastrointestinal bleeding, abdominal burns, necrosis, stomach perforation, oesophageal stricture, severe metabolic acidosis, rapid hepatic failure, rhabdomyolysis, and respiratory failure while temporary cardiac arrest and toxic myocarditis were observed as well. Upon autopsy of one case, massive periportal hepatic necrosis accompanied by atypical pseudoductular proliferation were seen (Zei93).

Animal data

Instillation of strong solutions of MEKP (in dimethyl phthalate) into the eyes of rabbits caused extensive effects on the cornea, iris, and conjunctiva while weaker solutions affected the conjunctiva only. Treatment with 3% solutions resulted in Draize scores of 57 at Day 1 and 2 following treatment, decreasing to 11 and 7 at day 3 and 7, respectively.* The maximal concentration not irritating to the eyes of rabbits was reported to be 0.6% peroxide (in dimethyl phthalate). No irritation occurred when eyes were washed within 4 seconds after instillation (Flo58).

The maximal concentration not irritating to the shaved skin of rabbits was found to be 1.5% peroxide. Single application of undiluted material caused no immediate discomfort but there was a severe delayed reaction consisting of erythema, oedema, and vesiculation within 2 or 3 days (Flo58).

Four-hour inhalation LC_{50} values of 1460 and 1240 mg/m^3 (200 and 170 ppm) were found for rats and mice, respectively. Hyperaemia of the lungs, with petechial haemorrhages on the lung surfaces in some animals and gross haemorrhages in others, as well as occasional nasal porphyrin exudate were seen. The intraperitoneal and oral LD_{50} values in rats were 65 and 484 mg/kg bw, respectively (Flo58).

The committee did not find adequate data on toxic effects following repeated exposure by inhalation to MEKP. Floyd and Stokinger reported that no significant amount of methaemoglobin was found in rats exposed by inhalation

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* The maximum Draize score for effects on cornea, iris, and conjunctivae is 110. Scores of 57 and of 11 and 7 are indicative of severe and minimal irritation, respectively.

to low (not further specified) levels of MEKP for 3 days or in rats given intraperitoneal injections (doses not presented), 3 times/week, for 5 weeks. When MEKP was given orally or intraperitoneally to rats at 1/5 LD_{50} (i.e., 97 and 13 mg/kg bw, respectively), 3 times/week, for 7 weeks, 5/5 and 2/5 animals died during the study. Body weights were clearly affected in the orally but not in the intraperitoneally treated animals. Rough fur was seen in animals of both groups (Flo58).

MEKP (in dimethyl phthalate (DMP) as 45:55 w/w solution) was tested for its toxic effects following repeated dermal exposure for either 2 or 13 weeks in Fischer 344/N rats and $B6C3F_1$ mice. In the 2-week studies, groups of 5 animals of each species and sex were treated with the solution at daily doses of MEKP of 50.6, 101.3, 202.5, 405, and 810 mg/kg bw (rats) or 112.5, 225, 450, 900, and 1800 mg/kg bw (mice), 5 days/week, for 2 weeks, plus 2 consecutive days in week 3 before terminal sacrifice. Control groups received DMP or no treatment. The solution was applied to the clipped dorsal skin, but the size of surface area used was not reported. Treatment did not cause mortality in rats, but in mice, mortality, attributed to the severe skin lesions at the application site, ranged from 1/10 animals at the lowest dose to 7/10 at the highest dose. In rats, there was a dose-related decrease in body weight gain. Final body weights relative to those of the DMP controls ranged from 96 and 98% for male and female rats, respectively, of the lowest dose group to 83 and 92% for male and female rats, respectively, of the highest dose group (no statistical analysis presented). In mice, body weight gain was not affected. The primary effects found in both rats and mice with respect to the skin were extensive coagulative necrosis of the epidermis and dermis, variable degrees of inflammation of the adnexa, and epidermal regeneration and hyperplasia at the application site. Generally, in both rats and mice, organ weight changes considered possibly biologically relevant included decreases in absolute and/or relative thymus weights and increases in absolute and/or relative liver weights (especially marked in mice), but histological changes were not found or reported in these organs. Treatment-related lesions considered by the author to be secondary to the dermal lesions included increased haematopoiesis in the spleen of rats and mice and increased myeloid hyperplasia of the bone marrow in mice, primarily at the higher doses (Zei93).

In the 13-week dermal studies, groups of 10 rats and 10 mice of each sex were treated with doses of MEKP of 1.07, 3.57, 10.7, 35.7, and 107 mg/rat and 0.357, 1.19, 3.57, 11.9, and 35.7 mg/mouse, 5 days/week, for 13 weeks, plus an additional 2 consecutive days in week 14 before terminal sacrifice. As was the

case in the 2-week study, the solution was applied to the clipped dorsal skin, but the size of the surface area used was not reported. All high-dose mice, 3 high-dose female rats, and 1 female mouse in the 11.9 mg/animal group died or were sacrificed during the first week of the studies. Because of the severity of the skin lesions — similar to those seen in the 2-week studies —, exposure of the surviving rats and mice of the 2 highest dose groups was preliminary terminated. In the animals of these groups, no body weight and organ weight analyses were performed. For the other groups, results showed a dose-related decrease in body weight gains. Final body weights relative to those of the DMP controls ranged from 105 and 97% for the male and female rats, respectively, treated with 1.07 mg/animal to 87 and 95% for males and females, respectively, treated with 10.7 mg/animal (no statistical analysis presented). In female mice, body weight gain was not affected while in males, the final body weights of the animals treated with 0.357 and 3.57 mg/animal were 99 and 95% of those of the DMP controls, respectively. Skin lesions at the application sites involved a spectrum of necrosis, inflammation, and acanthosis (epidermal hyperplasia) in the remaining rats treated with 10.7 mg and mice treated with 3.57 mg, acanthosis and hyperkeratosis in the other rat groups, and acanthosis in the other mice groups. Organ weight changes were observed in the rats of the 10.7 mg-dose group and the mice of the 3.57 mg-dose group only, and included, amongst others, increases in relative weights of the heart in male rats, of the (right) kidney in male and female rats, and of the spleen in male and female mice and decreases in relative liver weights in male and female rats. Histological (organ) lesions were almost exclusively found in the preliminary terminated groups, and included spleen and bone marrow lesions similar to those described in the 2-week study. The authors commented that no NOAEL for histological skin lesions could be determined from these studies, as lesions were observed with administration of daily doses as low as 1.07 mg for rats and 0.357 mg for mice (Zei93).

It has been known for more than a decade that MEKP is used in experimental medicine as a model compound for lipid peroxidation in *in vitro* and *in vivo* experiments (And85a, And85b, Cha88, Fra89, Lit81, Sku94, Sum84, War91). Most of these experiments addressed the interaction between MEKP and vitamin E, and all of the *in vivo* experiments were done by single dose intraperitoneal administration. Pretreatment of rats with vitamin E prior to MEKP administration has been shown to reduce the extend of lipid peroxidation in the animals. Reports on the effects of vitamin E on MEKP-induced damage

in the brain of rats were conflicting. Summerfield and Tappel showed a protective effect of dietary vitamin E against DNA cross-linking and protein-DNA cross-linking induced by MEKP (Sum84). However, Chaudiere et al. found no differences in the malonaldehyde levels in the brain of neonatal rats maintained on a vitamin E-deficient or -supplemented diet and exposed to MEKP by intraperitoneal injection. The only difference seen was a small decrease in GSH-reductase activity in the brain of vitamin E-supplemented rats (Cha88).

The *in vitro* and *in vivo* experiments from Ando and Tappel are of interest since they found that MEKP damaged the cytochrome P450 peroxidase activity in rat liver. Destruction of cytochrome P450 haemoprotein and inhibition of its associated peroxidase activities increased as a function of time of exposure to MEKP (And85a, And85b). These results coincide with the dose-related increase of liver weights *in vivo* in mice in the 2-week dermal NTP study (Zei93).

Carcinogenicity

Zeiger et al. cited a study in which it was reported that MEKP induced malignant lymphomas in C57B1 mice, without giving information on treatment route and regimen and corresponding spontaneous tumour incidences (Zei93).

Logani et al. studied the tumour-promoting activity of MEKP (50% solution in dibutyl phthalate) on the skin of hairless albino mutant mice (n=12/sex/group) in a two-stage initiation-promotion model. When ultraviolet radiation in the UVB region was used as a tumour initiator, a weak tumour-promoting activity was found when applying 10 µg/animal in acetone twice weekly. Dibutyl phthalate alone had no effect. The promoting activity of MEKP was enhanced by topical treatment with diethyl maleate that is known to deplete intracellular glutathione levels in several tissues among which mouse skin. The group that had been exposed to UVB initiation and promoted with diethyl maleate (20 µg/mouse) and MEKP had the highest tumour yield and the highest percentage of affected mice throughout the study. In general, all the qualified tumours produced in this study were papillomatous in appearance (Log84).

Mutagenicity and genotoxicity

MEKP (45:55 w/w in dimethyl phthalate or with a purity of 60.8%) was not mutagenic when tested in 2 separate studies in *S. typhimurium* strains TA100, TA1535, TA1537 and TA98, with or without metabolic activating systems obtained from induced rat and hamster livers, at levels of 1 to 333 µg/plate (Mor86, Zei93). MEKP induced a weakly positive response when tested in both a plate and pre-incubation assay with *S. typhimurium* strain TA102, a strain reported to be sensitive to oxidative mutagens. At a concentration of 200 µg, the number of revertants per plate induced by MEKP was somewhat less than twice the number of spontaneous revertants. Furthermore, it was stated that the compounds tested among which MEKP showed a linear dose-response and that they did not require metabolic activation for their mutagenic response (no more details presented) (Lev84). MEKP (45:55 w/w in dimethyl phthalate) induced a dose-related increase in mutation frequency in mouse lymphoma L5178Y cells when tested at concentrations of 0.625 to 10 or 2 to 10 nL/mL in two separate trials in the absence of S9 activation (vehiculum: ethanol; not tested with S9). In cytogenetic tests with Chinese hamster ovary (CHO) cells, MEKP (45:55 w/w in dimethyl phthalate; vehiculum: dimethylsulfoxide) induced a dose-related increase in the frequency of sister chromatid exchanges (SCE) in the absence of metabolic activation (dose range: 0.5-16 and 2-15 µg/mL; doses ≥20 µg/mL: complete lethality). With metabolic activation, a positive response was seen only at the highest non-lethal dose tested (50 µg/mL). Similarly, a dose-related increase in the percentage of cells with chromosome aberrations was found without S9 while with S9 activation, a positive response was seen only at the highest non-lethal dose tested (Zei93). In an abstract without presenting details, it was reported that MEKP (in dimethyl phthalate) induced a 'slight increase' in SCE in CHO cells with and without metabolic activation (Jär84).

In vivo, there was no increase in the frequency of micronucleated erythrocytes in peripheral blood samples obtained from male and female mice dermally treated with doses of MEKP of up to 3.57 mg/animal for 13 weeks (see above). Treatment did not cause changes in the ratios between polychromatic and normochromatic erythrocytes indicating that no overt toxicity was induced in the bone marrow cells (Zei93). DNA interstrand cross-links and DNA-protein cross-links were found in the brains of rats intraperitoneally treated with a dose of MEKP of 3.3 mg/kg bw and a second dose of 13 mg/kg bw one week later (and given 3-4 hours before sacrifice). These types of cross-links were both reduced by (pre-)treatment with vitamin E

(in the diet for a total of 12 weeks, including those weeks in which MEKP was given), suggesting MEKP induced cross-linking by generating free radicals (Sum84).

Reproduction toxicity

Daily dermal treatment of rats and mice with doses of MEKP up to 10.7 and 3.57 mg/animal, respectively, for 13 weeks (see above), did not affect sperm morphology and vaginal cytology parameters (Zei93).

Korhonen et al. (Kor83, Kor84) reported that MEKP was toxic to 3-day old chicken embryos, as indicated by increased mortality and malformations when the compound was administered into the air chamber. The median effective dose (ED_{50}) was found to be 0.19 μmol MEKP/egg.

The committee did not find other data on the potential reproduction toxicity of MEKP.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for MEKP in the Netherlands is 1.5 mg/m^3 (0.2 ppm), as a ceiling value.

Existing occupational exposure limits for MEKP in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

The committee did not find adequate human studies in which exposure and effects to MEKP could be related.

Human and experimental animal data indicate that MEKP is severely irritating to eyes and skin. A few cases of work-related allergic contact dermatitis with positive reactions to MEKP upon patch testing have been reported.

Four-hour inhalation LC_{50} values of 1460 and 1240 mg/m^3 (200 and 170 ppm) were found for rats and mice, respectively. Effects on the nose and lungs were observed in these studies. The committee did not find other studies on the toxic effects of MEKP following single or repeated inhalation exposure or studies on repeated oral administration. In rats and mice dermally treated for 13 weeks, there was mortality in 20/20 mice and in 3/20 rats (all females) at doses of 35.7 and 107 mg/animal, respectively. Because of severe skin lesions,

exposure of the surviving rats and of mice and rats of the next lower dose group (i.e., 11.9 and 35.7 mg/animal, respectively) were preliminary terminated. In the remaining mouse and rat groups treated with 0.357 to 3.57 and 1.07 to 10.7 mg/animal, predominantly skin effects were seen at all these dose levels.

MEKP (in dimethyl phthalate) was mutagenic in bacteria (*S. typhimurium* strain TA102) and mammalian cell systems (mouse lymphoma cells). It induced SCEs and chromosomal aberrations in CHO cells. *In vivo*, no increase in the frequency of micronucleated erythrocytes was found in peripheral blood of mice dermally treated for 13 weeks. DNA interstrand cross-links and DNA-protein cross-links were found in the brains of intraperitoneally treated rats.

MEKP (in dibutyl phthalate) was weakly positive in a two-stage mouse-skin tumour initation-promotion model, but adequate studies on the potential carcinogenic properties were lacking.

The committee did not find adequate data on the potential reproduction toxicity of MEKP.

The committee considers the toxicological database on methyl ethyl ketone peroxide too poor to justify recommendation of a health-based occupational exposure limit.

The committee concludes that there is insufficient information to comment on the level of the present MAC value.

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Annex

Occupational exposure limits for methyl ethyl ketone peroxide in various countries.

country -organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
-Ministry of Social Affairs and Employment	0.2	1.5	ceiling	administrative	-	SZW02
Germany						
-AGS	-	-				TRG00
-DFG MAK-Kommission	-	-				DFG02
Great-Britain						
-HSE	0.2	1.5	15 min	OES	-	HSE02
Sweden	0.2	1.5	ceiling			Arb00b
Denmark	-	1	ceiling			Arb00a
USA						
-ACGIH	0.2	-	ceiling	TLV	-	ACG02b
-OSHA	-	-				ACG02a
-NIOSH	0.2	1.5	ceiling	REL	-	ACG02a
European Union						
-SCOEL	-	-				CEC00

[a] S = skin notation; which mean that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.