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Studies on the environmental fate, ecotoxicology and toxicology of 2-methyl 1,3-propanediol

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ABSTRACT

2-methyl 1,3-propandiol (MPD) is a low molecular weight, colorless glycol used in polymer and coating applications. The log Kow of −0.6 suggests partitioning to aqueous phases with a low concern for possible bioaccumulation. MPD was found to be inherently biodegradable. Ecotoxicological results in several aquatic and terrestrial species found no significant hazard potential. MPD is rapidly absorbed via the oral and dermal routes, metabolized to 3-hydroxybutyrate, and excreted in urine with a half-life of 3.6 h. Acute toxicity testing found low toxicity via all routes. Barely perceptible skin irritation was observed in human volunteers, whereas there was no evidence of irritation in rabbits. Skin sensitization in Guinea pigs was negative. Human skin patch results indicated minimal response in about 1% of individuals. There was no evidence of mutagenicity using bacterial and mammalian test systems. A 90-day oral study in rats found no adverse effects at any dose. Three developmental toxicity studies in rats and rabbits, found no treatment-related maternal toxicity, fetal toxicity or malformations. A two-generation reproduction study in rats found no consistent treatment-related adverse effects on reproduction in either generation. No carcinogenicity studies with MPD were identified. MPD presents a low degree of toxicological and ecotoxicological or environmental hazard.

1. Introduction

2-Methyl-1,3-propanediol (MPD, CAS RN: 2163-42-0; EC 412-350-5) is a colorless low viscosity liquid with a unique molecular structure (Fig. 1). It is a low molecular weight branched aliphatic diol with two primary hydroxyls. MPD is water soluble at room temperature and it also has a low volatility and high flashpoint. As an isomer of 1,3-butyleneglycol, MPD offers similar performance characteristics. MPD is produced by Lyondell Chemical Company in a proprietary, multi-step reaction from propylene oxide.

2. NONS and REACH regulatory approvals

MPD has been subject to regulatory evaluations and approval. Under the previous framework (67/548/EEC) a “notification of new substance” was completed. With the establishment of the REACH Regulation, a REACH registration number was established using the same data that had been provided as part of the notification. Accordingly, MPD is compliant with REACH regulatory requirements set forth in the European Union.

3. Uses of MPD

MPD can be employed in a wide variety of applications. MPD has undergone extensive evaluation and been determined of low hazard, therefore it has been approved in Europe and the U.S. for use in personal care products. It can be used in a variety of products such as antiperspirants, nail polish, shaving creams and sunscreens. MPD can be used as a neutralizer, emollient, emulsifier and humectant, as well as a fragrance enhancer and carrier solvent. MPD can also be used in the synthesis of ortho-, iso-, and terephthalate-based unsaturated polyester resins with increased production rates, improved styrene solubility, improved corrosion performance and improved mechanical performance. In addition, MPD can be used in the production of polyester polyols for OEM, refinish, and coil coatings (LyondellBasell website, 2016).

4. Purity and composition

MPD is produced with a minimum purity of 98% with a typical purity of 99.5%. The minor constituent that may be present is 2-methyl-

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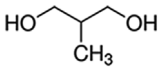

Fig. 1. Chemical structure of 2-methyl 1,3-propanediol.

1,3-pentanediol with a maximum concentration of 2% by weight. Water may be present at 0.05%. This indicates that MPD is supplied to the market as a high purity substance.

5. Physical and chemical properties

At room temperature, MPD is a clear colorless, moderately viscous liquid (232 cSt at 20 °C) (ECHA, 2013a). It is not classified as a flammable liquid, with a flashpoint of 127 °C by the Pensky-Martens Closed Cup method (ECHA, 2013b). It is considered freely miscible with water (ECHA, 2013c), and shows a correspondingly low octanol:water partition coefficient with a Log K_{ow} −0.6 at 20 °C (ECHA, 2013d). MPD has a low vapor pressure of 2.8 Pa at 25 °C (ECHA, 2013e).

6. Absorption metabolism and excretion

In a metabolism and elimination study, female Sprague-Dawley rats were exposed to MPD by single gavage doses of 100 or 1000 mg/kg (Boatman, 2003). An HPLC radioflow analysis demonstrated the presence of 5 peaks in the urine from female rats given 1000 mg/kg and 4 peaks after administration of 100 mg/kg. Two compounds predominated and accounted for the majority of products excreted. The remaining compounds collectively accounted for < 2% each of the material excreted up to 24 h post-dosing. The main metabolite, assessed using GC-MS with a chemical database search, was 3-hydroxybutyric acid (3HBA), while the second main compound corresponded to the parent compound, MPD.

Both of the main substances found occurred at a maximum in urine 6 h post-treatment and diminished thereafter. Based upon relative retention times and on the results of spiking experiments with stereoisomers, the majority of 3HBA was identified as the R-stereoisomer (85% as R-form, 15% in the S-form). MPD was rapidly excreted, with greater than 60% of the radio-labelled material eliminated within 6 h and 83% within 24 h, regardless of dose. Elimination half-lives were calculated as 3.6 h (high dose) and 3.9 h (low dose) (Boatman, 2003).

The ability of MPD to cross the skin was tested using excised pig skin and undiluted ^{14}C-radiolabelled MPD (Diembeck and Duesing, 2005). In the study, 70% of the applied MPD was absorbed within 6 h, and 84% by 24 h. It could not be determined from the study if the parent compound or a metabolite was responsible for the measured radioactivity indicating absorption.

7. Toxicity

7.1. Acute toxicity

Male and female Wistar rats were dosed by gavage with MPD according to USEPA Guidelines, with a resulting LD50 > 5000 mg/kg (Cerven, 1988) (Table 1).

An acute inhalation study in Wistar rats, conducted according to the OECD403 Guideline, exposed rats, nose-only, to MPD aerosols, resulting in a calculated LC50 of > 5.1 mg/l (Muijser, 1998). A second inhalation study, conducted according to OECD403 Guideline exposed Wistar rats (5/sex), nose only, to MPD aerosols for 4 h, resulting in a calculated LC50 of > 5.4 mg/L (Van Huygevoort, 2015). Following a histopathologic examination on the lungs of all animals, no target organ effects were noted following the single exposure. During the exposure to MPD, slow breathing (one male) and irregular breathing (two males) were seen (not presented in the table). After exposure and up to 15 days, no clinical signs were noted in any of the animals. No clinical signs were seen for the control animals at any time.

The acute dermal toxicity of MPD was similarly low, with an acute dermal LD50 in rabbits, exposed under occlusive conditions, exceeding the limit dose of 2000 mg/kg (Cerven, 1988). No mortalities or specific clinical signs were reported in any of the acute studies.

It is concluded that MPD has a lack of acute toxicity hazard by oral, dermal, and inhalation routes of exposure.

Table 1
Acute toxicity results for MPD.

Study	Result	Reference
Acute oral (rats)	LD50 > 5000 mg/kg	Cerven, 1988
Acute dermal (rabbits)	LD50 > 2000 mg/kg	Cerven, 1988
Acute inhalation (rats)	LC50 > 5.1 mg/L	Muijser, 1998
Acute inhalation (rats)	LC50 > 5.4 mg/L	Van Huygevoort, 2015

7.2. Irritation & sensitization

MPD was applied to the abraded skin of New Zealand white rabbits according to USEPA Guidelines (Cerven, 1988). The overall irritation score, including erythema and edema, was 0 at 72 h post-application. No irritation was observed in this study.

In a human skin irritation study, 19 volunteer male and female subjects over 16 and up to 39 years of age, without evidence of skin disorders, participated in a 48-h skin patch test with 0.2 ml of 50% MPD. Reactions were graded on a 3-point scale (Table 2). One subject exhibited a barely perceptible (+) to moderate (2) erythema response (Eisenberg, 1999).

In an earlier human volunteer study, 25 subjects, male and females, 18–70 years old, were given a skin patch test of 0.2 mL 50% MPD (Eisenberg, 1997). Individuals were selected if they self-assessed as having sensitive skin, but had an absence of any visible skin disease or pre-existing, potentially confounding, skin conditions. Subjects indicated an avoidance of topical and/or systemic steroids and/or antihistamines. No skin reactions were found in the study.

MPD was not irritating in animals, and only one individual reaction out of 44 human volunteers exhibited erythema and mild edema. Overall, MPD is not expected to be a skin irritant.

7.2.1. Eye irritation

In rabbits, following 1982 US EPA Health Effects Test Guidelines, the overall eye irritation score was 0 out of a maximum of 2 at 72 h. Eight out of 9 animals showed no signs of irritation. One animal from the washed group showed signs of mild redness at the 24 h observation period. (Cerven, 1999). MPD was considered not to be an eye irritant based on these results.

7.2.2. Sensitization

A Guinea pig Maximization test (OECD 406 Guideline), using Himalayan albino female Guinea pigs, using intradermal initiation and epicutaneous semi-occlusive challenges, found 0 out of 20 positive responses 24 h after a challenge with 100% MPD, and 1 out of 20 positive reactions 48 h after challenge. At a 50% MPD concentration, the response rate was 3 out of 20 animals at 48 h post-challenge, however the response to 100% MPD was just 1/20 at the same timepoint (Table 3).

MPD has been tested in large scale human volunteer skin patch studies (US EPA, 2004). In one study, conducted by Eisenberg (1997)

Table 2
Scoring system for human skin irritation studies.

0 = no visible reaction
1+ = mild erythema (faint, but definite pink)
2+ = well-defined erythema, possible mild edema
3+ = Erythema plus diffuse edema