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Mini Review

Ethylene glycol monomethyl ether research-My contribution

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Abstract

Ethylene glycol monomethyl ether (EGME) is an industrial solvent that has wide application, including the aviation sector. It has been investigated scientifically to determine its effect on various body fluids and organs, especially the male reproductive organ. This is a review of research studies carried out using EGME with emphasis on the reproductive organs, and my investigations conducted with the solvent and in combination with a herb.

Since EGME is an industrial solvent, care should be taken when exposed to it and in the presence of herbal treatments.

Abbreviations

EGME: Ethylene Glycol Monomethyl Ether; MAA: Methoxy Acetic Acid; PP: *Paullinia Pinnata*

Introduction

Ethylene Glycol Monomethyl Ether (EGME) is enlisted among the group of solvents referred to as glycol ethers. Glycol ethers are alkyl ethers of ethylene glycol usually used in paints and this group is sub-divided into two classes: ethylene glycol ethers (EGEs) and propylene glycol ethers (PGEs). EGME belongs to the class of EGEs [1]. Synonyms for EGME are methyl oxitol, methyl cellosolve (commercially), methyl glycol, monomethyl ether, monomethyl glycol, monomethyl ethylene glycol ether or 2-methoxy ethanol [2].

The molecular formula is $C_3H_8O_2$ and the molecular weight is 76.09 g/mol². The active biological oxidation product is Methoxy Acetic Acid (MAA). EGME is a reaction product of ethylene oxide and methanol. It is moderately volatile, highly inflammable, and colorless with very good solubility properties. As a result of the simultaneous hydrophilic and lipophilic properties, it has wide consumer and industrial applications. EGME finds use as an anti-freeze additive in hydraulic fluids and jet fuel. It is also used in stains, inks, paints and surface coating, photographic and photo lithographic processes, lacquers, production of food-contact plastics, textile and leather finishing, silk-screen printing, and in the semi-conductor industry [3,4].

In humans and several other species, exposure to EGME either by ingestion, dermal absorption and/or inhalation has been reported to cause reproductive, hematopoietic and developmental toxicities with emphasis on testicular damage [5]. The evidences of haematological toxicities as a result of exposure to EGME include marrow depression and decrease in red blood cells count, platelet count, packed cell volume, haemoglobin concentration, mean corpuscular and mean corpuscular haemoglobin; pancytopenia and leucopenia [6,7].

The evidences of reproductive toxicities as result of exposure to EGME or the active oxidation product, MAA, include decreased sperm production as a result of increased apoptosis of primary spermatocytes [8]; gene expression changes in germ cells and Leydig cells *in-vitro* [9]; hyper-secretion of progesterone from ovarian luteal cells both *in-vivo* and *in-vitro*; activation of caspases leading to apoptosis triggered by oxidative stress in spermatocytes [5]; prolonged estrus cycle, hypertrophy of corpora lutea evidenced by the presence of round to polygonal luteal cells with abundant vacuolated cytoplasm and ovulatory inhibition [10,11]; altered androgen-dependent processes in Leydig cells *in-vitro* [12]; affects microRNAs expression in the testes [13]; affects the antioxidant system and increase lipid peroxidation in the testes [14] and caused spermatocyte toxicity

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having correlation with decreased expression of spermatocyte-specific genes [15].

Other acute and chronic toxic effects as a result of exposure to EGME have been reported in humans and animals [16] These include drowsiness; weakness; irritation of throat, eyes and nose; headache and decreased mental ability. Acute toxicity studies have shown that the LD_{50}, (i.e. lethal dose, dose of 50% mortality) is 0.95 g/kg body weight in guinea pigs, 0.89 to 1.425 g/kg body weight in rabbits, 2.46 to 3.25 g/kg body weight in male rats and 3.4 g/kg body weight in female rats [17]. However, MAA toxicity can be mitigated by co-administration with D- glucose, serine, acetate, glycine, certain tricarboxylic acid pathway metabolites and formate [5].

This review is designed to briefly highlight research investigations carried out using EGME, with emphasis on the male reproductive organs, and to state my contribution to this.

My contribution

Our first study was aimed at investigating the effect of EGME on the antioxidant system of the reproductive organs of male rats by oral gavage. Fifty male Wistar rats were evenly distributed into five groups. Group I received distilled water, Groups II-V received EGME at 100, 200, 300 and 400 mg/kg body weight respectively. All administrations were done for fourteen days and the weight was monitored weekly. On day fifteen, the animals were sacrificed and reproductive organs were collected and weighed. The testes and epididymes were processed for the biochemical estimations, histopathology and spermatozoa analysis. Blood was collected by ocular puncture and was used for hematological analysis. The results showed that the percentage body weight gained weekly and the relative weight of the testes reduced significantly ($p < 0.05$) in the treatment groups. Hematological analysis reflected significant ($p < 0.05$) decreases in various parameters including hemoglobin concentration, white blood cell count, platelet count, neutrophils and red blood cell count, especially at the 400 mg/kg dose. The spermatozoa analysis showed decrease in testicular spermatozoa number, epididymal spermatozoa number, daily spermatozoa production, sperm motility and sperm viability in the treatment groups. Moreover, there was increased sperm abnormalities with an increased prevalence of curved- and bent- mid-pieces, and curved- and bent-tails, especially for the groups treated with 200 and 400 mg/kg body weight dose of EGME. In the testes and epididymes, various antioxidant parameters such as catalase, glutathione-S-transferase, glutathione peroxidase, superoxide dismutase, lipid peroxidation and vitamin C were variably affected. The histopathology results complimented the findings with severe lesions being observed in the testes and epididymes at the 400 mg/kg body weight dose. The study suggests that EGME exerts deleterious effects on the testes and epididymes by increasing the oxidative load in rats [18].

Our second study was conducted using co-administration of EGME with *Paullinia pinnata* methanol leaf extract. *Paullinia pinnata* (PP) is a medicinal plant whose parts are used for medicinal purposes traditionally in the treatment of various diseases including malaria, diarrhea and to help infertility which is currently a scourge globally. In this study, EGME was the infertility model. Sixty adult male Wistar rats were weight-matched into six groups of ten animals each. All administrations were done orally daily for twenty-one consecutive days as follows: Group I(control) – distilled water; Group II – 1.5 ml/kg body weight of 10% dimethyl sulfoxide (vehicle); Group III- EGME only (200 mg/kg); Group IV- PP only (200 mg/kg); Group V- EGME+PP at 100 mg/kg body weight and Group VI- EGME+PP at 200 mg/kg body weight. On day 22, blood was collected for the analysis of the reproductive hormones. The animals were euthanized, dissected in order to excise the testes, epididymes, seminal vesicles, prostate gland and brain, and weighed. The brain, testes and epididymes were processed and used for spermatozoa analysis, antioxidant and anti-inflammatory assays, and histological examination appropriately. The plasma concentrations of the reproductive hormones including luteinizing hormone and follicle stimulating hormone were significantly increased in the co-administered groups while the plasma testosterone concentration was decreased. Similarly, the spermatozoa parameters were affected. The testicular spermatozoa number, spermatozoa motility and viability were reduced in the EGME only and co-administered groups. Antioxidant parameters including catalase and glutathione-S-transferase were affected in the epididymis, testes and brain in the EGME only and co-administered groups. The inflammatory markers; nitric oxide and myeloperoxidase, were also variably affected in the testes and epididymes of the EGME only and co-administered groups. The results were complemented by the histological observations in the testes, and hypothalamus. The conclusion was that *P. pinnata* leaves lack chemopreventive potential against ethylene glycol monomethyl ether- induced gonadotoxicity rather, it exacerbates the deleterious effects [19].

Conclusion

Taken together, the studies underscore the point that caution needs to be exercised in the exposure to EGME, especially in the light of co-exposure with herbal treatments.

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