Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Ethylene Glycol Monomethyl Ether Acetate

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Office of Environmental Health Hazard Assessment
Reproductive and Cancer Hazard Assessment Section

Summary

The maximum allowable dose level (MADL) for ethylene glycol monomethyl ether acetate (EGMEA) is **98 micrograms/day (µg/day)** for the oral route of exposure. This MADL was based on the MADL for ethylene glycol monomethyl ether (EGME). The detailed rationale for using the MADL for EGME as basis for development of the MADL for EGMEA is presented below.

Background

This report describes the derivation of maximum allowable dose levels (MADLs) for EGMEA (CAS No. 110-49-6).

EGMEA is used as an intermediate for plasticizers and in specialty solvent applications (NIOSH, 1991; OEHHA, 2000). This chemical was listed under Proposition 65 (the Safe Drinking Water and Toxic Enforcement Act of 1986) as known to the State to cause reproductive toxicity (developmental and male reproductive toxicity), effective January 1, 1993. The Proposition 65 listing of EGMEA was based on a formal identification by the National Institute for Occupational Safety and Health (NIOSH) of EGMEA as causing reproductive toxicity (developmental and male reproductive toxicity) (NIOSH, 1991). NIOSH is an authoritative body under Proposition 65 for identification of chemicals as causing reproductive toxicity (Title 22, California Code of Regulations §12306(i)).

Procedures for the development of Proposition 65 MADLs are provided in regulations (Title 22 Cal. Code of Regs. §12801 and 12803). Exposure at a level 1,000 times greater than the MADL is expected to have no observable effect. As defined in regulations, a MADL is derived from No Observable Effect Level (NOEL) based on the most sensitive study deemed to be of sufficient quality (Title 22 Cal. Code of Regs. §12803).

Study Selection

Relevant studies on the developmental and male reproductive toxicity of EGMEA have been identified through literature searches. Only two study reports were identified. One was a case report on developmental toxicity of EGMEA in humans (Bolt and Golka, 1990); another was a male reproductive toxicity study in mice by Nagano et al. (1984).

In the case report by Bolt and Golka (1990), the authors found the occurrence of hypospadias at birth in two boys whose mother had been intensively exposed to EGMEA during both pregnancies. The authors concluded that the hypospadias were likely caused by exposure to EGMEA; however, this case report cannot be deemed a study of sufficient quality to serve as the basis for a MADL.

In the study reported by Nagano et al. (1984), the testicular effects of EGMEA and several other glycol ethers (including EGME) were studied in male JCL-ICR mice (six weeks of age, five animals per group). The animals were treated by gavage with EGMEA at doses of 0, 62.5, 125, 250, 500, 1,000, or 2,000 mg/kg-day, 5 days/week, for five weeks. The authors stated that treatment with EGMEA caused a dose-dependent decrease in relative testicular weights and dose-related atrophy of the seminiferous epithelium. No detailed data on body weights, testicular weights or histopathological changes were reported. According to the two figures that presented information on relative testicular weights, it appears that EGMEA caused an obvious decrease in relative testicular weights at 125 mg/kg-day. When the doses used in this study were expressed as mmole/kg-day, the dose-testicular weights relationship in EGMEA-treated mice was almost identical to that in EGME-treated mice, suggesting that the testicular effect of EGMEA is equivalent to that of EGME.

EGMEA is rapidly and extensively hydrolyzed to EGME by carboxyl esterase which is present in a variety of tissues; e.g., nasal epithelium, liver, kidneys, blood, etc. (Stott and McKenna, 1985). Therefore, the toxic effects caused by EGMEA are believed to be similar or identical to those caused by EGME (NIOSH, 1991; Johanson, 2000). This conclusion is also supported by the findings on the testicular effects of EGMEA and EGME in the study by Nagano et al. (1984) as discussed above.

The study by Nagano et al. provided important information on the male reproductive effects of EGMEA. However, the authors did not report detailed information on study design, detailed data on body weights, testicular weights or histopathological changes, or statistical analysis of the data. Therefore, OEHHA determined that this study is not “of sufficient quality” as required by regulation (Title 22 Cal. Code of Regs. §12803).

Based on convincing evidence that the toxic effect of EGMEA is identical to that of EGME, and in the absence of data from a study of sufficient quality on EGMEA itself, the MADL for EGMEA is derived from the MADL for EGME.

MADL Calculation

The MADL for EGME is 63 µg/day for the oral route of exposure. This value was derived as described below, based on the male reproductive toxicity of EGME observed in the study reported by Gulati et al. (1990). Detailed information on establishment of the MADL for EGME is available in the document titled “Proposition 65 Maximum

Allowable Dose Level (MADL) for Reproductive Toxicity for Ethylene Glycol Monomethyl Ether" (OEHHA, 2004).

The molecular weight of EGME is 76.09 g/mol. Thus, the MADL of 63 µg/day for EGME by oral route of exposure is equivalent to 0.83 µmol/day.

EGMEA has a molecular weight of 118.13 g/mol. Based on the MADL for EGME expressed in µmol/day (0.83 µmol/day), the MADL for EGMEA is derived as follows:

MADL$_{oral}$ = 0.83 µmol/d × 118.13 µg/µmol = 98.05 µg/day or **98 µg/day** after rounding.

This MADL represents intake by the oral route of exposure. Glycol ethers and their acetate salts are quickly and almost completely absorbed following oral administration (Miller et al. 1983b; Medinsky et al. 1990; Johanson, 2000). Therefore, the MADL for EGME via the oral route of exposure as described above should also be considered as the absorbed dose.

The MADL of 98 µg/day is applicable to exposure via the oral route only. If exposures occur by any non-oral (e.g., inhalation or dermal contact) or multiple routes, the total exposure to the chemical from a single source or product must be considered. The absorbed dose resulting from the source or product should be calculated. If the total absorbed dose resulting from any one or multiple routes is less than 98 µg/day, the MADL has not been exceeded.

References

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