Proposition 65 Maximum Allowable Dose Levels for Reproductive Toxicity for Ethylene Glycol Monoethyl Ether and Ethylene Glycol Monoethyl Ether Acetate

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

Summary

The maximum allowable dose levels (MADLs) for ethylene glycol monoethyl ether (EGEE) are **750 micrograms/day (µg/d)** and **960 µg/d** for the oral and inhalation routes of exposure, respectively. The MADLs for ethylene glycol monoethyl ether acetate (EGEEA) are **1,100 µg/d** and **1,400 µg/d** for the oral and inhalation routes of exposure, respectively.

Virtually all EGEEA absorbed is rapidly converted, via esterase, to EGEE. Evidence available indicates that EGEE and EGEEA have the same active metabolite (2-ethoxyacetic acid) that is responsible for the reproductive toxicity of both compounds. Observations in animal studies have shown that both compounds cause similar developmental and male reproductive toxicity. Therefore, this assessment assumes that the same molar amount of EGEE or EGEEA results in the same level and type of developmental and male reproductive toxicity.

The MADLs for the oral route of exposure to EGEE and EGEEA are based on the lowest observable effect level (LOEL) for the male reproductive effects as observed in the study of EGEE in rats by Hurtt and Zenick (1986). MADLs for the inhalation route of exposure to EGEE and EGEEA are based on the no observable effect level (NOEL) for the developmental effects as observed in the study of EGEEA in rabbits by Tyl et al. (1988).

Background

This report describes the derivation of MADLs for EGEE (CAS No. 110-80-5) and EGEEA (CAS No. 111-15-9), respectively.

EGEE, also known as 2-ethoxyethanol (2-EE), is a solvent for celluloses, acrylics, dyes, inks, resins, and varnishes (OEHHA, 2004a; HSDB, 2007). This chemical was listed under the Safe Drinking Water and Toxic Enforcement Act of 1986 (commonly known as Proposition 65, codified at Health and Safety Code Section 25249.5 et seq.) as known to the State to cause reproductive toxicity (developmental and male reproductive toxicity), effective January 1, 1989. The Proposition 65 listing of EGEE was based on a finding by the Scientific Advisory Panel that the chemical had been clearly shown by scientifically

valid testing according to generally accepted principles to cause developmental and male reproductive toxicity.

EGEEA, also known as 2-ethoxyethanol acetate (2-EEA), is used as a solvent for nitrocellulose, oils and resins, wood stains and varnish removers. It is also used as a diluent in epoxy resins as a photoresistant coating material in the manufacturing process of liquid crystal displays (NIOSH, 1992; Chia et al., 1997; OEHHA, 2004b; Johnson, 2002). This chemical was listed under Proposition 65 as known to the State to cause reproductive toxicity (developmental and male reproductive toxicity), effective January 1, 1993. The listing was based on a formal identification by the National Institute for Occupational Safety and Health (NIOSH) of EGEEA as causing reproductive toxicity (developmental and male reproductive toxicity) (NIOSH, 1992). NIOSH is an authoritative body under Proposition 65 for identification of chemicals as causing reproductive toxicity (Title 22, California Code of Regulations, section 12306(l))[1].

Procedures for the development of Proposition 65 MADLs are provided in regulation (Sections 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 a No Observable Effect Level (NOEL) based on the most sensitive study deemed to be of sufficient quality. When a NOEL is not provided from the relevant studies, the LOEL is converted to a NOEL for purposes of assessment by dividing by 10 (Section 12803).

Study Selection

Relevant studies and review reports on the developmental and male reproductive toxicity of EGEE and EGEEA have been identified through literature searches. These studies and reports have been reviewed and considered for the establishment of the MADLs for these compounds. Relevant studies or reports that are not directly cited in the text of this documents are listed in the Appendix to this document,

It has been shown that EGEEA is rapidly and completely converted to EGEE by esterase, and therefore the subsequent metabolic processes for EGEEA and EGEE are identical (Guest et al., 1984; Groeseneken et al., 1987). The acid metabolite, 2-ethoxyacetic acid (2-EAA), has been identified as the proximate toxicant for both compounds (Foster et al., 1984; Groeseneken et al., 1987; Gargas et al., 2000). Thus the same molar amounts of EGEE or EGEEA are expected to result in the same level and type of developmental and male reproductive toxicity. This is borne out in observation in controlled animal studies (NIOSH, 1992; Johnson, 2002). As expected, when doses are expressed as mmol/kg per day, the observed dose-response relationships for the male reproductive effects of EGEEA and EGEE in mice are almost identical (Nagano et al., 1984). Also, the observed characteristics of the dose-effect and dose-response relationships for the

[1] All further references to regulations are to Title 22, California Code of Regulations unless otherwise noted.

developmental effects of EGEE and EGEE in rabbits are also very similar to each other (Tinston et al., 1983b; Tyl et al., 1988). Therefore, this assessment assumes that the same molar amount of EGEE or EGEEA results in the same level and type of developmental and male reproductive toxicity, and that studies on EGEEA provide evidence on the dose response for EGEE and visa versa. Relevant studies on the developmental and male reproductive toxicity of the two compounds are thus reviewed and presented together. This approach is consistent with the regulatory guidance for deriving MADLs that "When available data are of such quality that anatomic, physiologic, pharmacokinetic and metabolic considerations can be taken into account with confidence, they may be used in the assessment" (Section 12803(a)(6)).

For each listing endpoint (developmental or male reproductive toxicity), one "most sensitive study deemed to be of sufficient quality" for both compounds for each route of exposure (oral or inhalation) is identified.

Developmental Toxicity

Several epidemiological studies found increased risk of spontaneous abortion or miscarriage among female workers exposed to mixtures containing EGEE, EGEEA, EGME and other ethylene glycol ethers (Pastides et al., 1988; Beaumont et al., 1995; Swan et al., 1995; Correa et al., 1996). A strong association between exposure to mixtures of glycol ethers and several malformations (neural tube defects, multiple anomalies, and cleft lip) was also observed in a case-control study reported by Cordier et al. (1997). Although the small sample size in the prospective study by Eskenazi et al. (1995) limited the power of the study, of the four pregnant women who worked with positive photoresistant coating materials containing ethylene-based glycol ethers, all had spontaneous abortions. Exposure to mixtures containing glycol ethers other than EGEE and/or lack of detailed information on exposure levels (e.g., air concentrations), however, prevented use of the epidemiological studies for establishing a NOEL.

In laboratory animals, the developmental toxicity of EGEE or EGEEA has been studied in rats (inhalation), mice (oral treatment), and rabbits (inhalation exposure). Embryo death, decreased fetal weight, and/or structural malformations have been observed in one or more of these studies. Major findings on the developmental effects from several studies are briefly summarized in Table 1 and 2. These tables present all studies that are "of sufficient quality" per Section 12803 and provide LOELs and/or NOELs that may be identified as the basis for further MADL calculations.

Table 1. Oral Studies on the Developmental Toxicity of EGEE or EGEEA

Study Reference	Animals	Treatment	Maternal Toxicity	Developmental Effects & LOEL	NOEL (adjusted)
Wier et al., 1987	CD-1 mice; 15-27 animals per group.	**EGEE, Gavage,** 0, 0.8, or 1.2 g/kg-day, GD 8-14.	Decreased maternal body weight gain in late gestation at 1.2 g/kg-day.	Decreased postnatal survival; increased incidence of malformed forepaws and kinked tail. LOEL: **800 mg/kg-day**	Not found.
Lamb et al., 1984.	CD-1 mice; NTP-RACB protocol.	**EGEE, Drinking water,** 0, 0.5, 1.0, or 2.0% (0, 0.76, 1.50, or 2.6 g/kg-day). Both sexes treated.	Increased liver weights and decreased brain weights in 2.0% groups.	No litter found at 2.0%; decreased mean number of litters and decreased number of live pups per litter at 1.0%. LOEL: 1.0% (1,500 mg/kg-day)	0.5% (**760 mg/kg-day, estimated by Chapin and Sloane, 1997**)
NTP, 1985	CD-1 mice, NTP-RACB protocol	**EGEEA, Drinking water**, 0, 0.5, 1.0, or 2.0%.	No effect on body weights.	Decreased number of litters per pair of treated animals and decreased live pups per litter at ≥ 1.0%. LOEL: 1.0% (1,856 mg/kg-day)	0.5% **(931 mg/kg-day)**

Note: NOEL (adjusted): NOELs reported in the original reports were adjusted to mg/kg-day following the methods described in "MADL Calculation" section of this document. GD = Gestational Day; RACB = Reproductive Assessment by Continuous Breeding (see details about the study design in Chapin & Sloane, 1997).

Table 2. Inhalation Studies on the Developmental Toxicity of EGEE or EGEEA

Study Reference	Animals	Treatment	Maternal Toxicity	Developmental Effects & LOEL	NOEL (adjusted)
Tinston et al., 1983a; Doe, 1984	Alpk/AP (Wistar) rats, 24 animals per group	**EGEE,** 0, 10, 50, 250 ppm, 6 hr/d, GD 6-15	No effect on body weights; reduced levels of hemoglobin and mean cell volume of blood cells at 250 ppm.	Increased implantation loss; decreased number of live fetuses and fetal weights at 250 ppm. Increased incidences of skeletal variations or defects at 50 and 250 ppm. LOEL: 50 ppm (**47.45 mg/kg-day**)	10 ppm (**9.49 mg/kg-day**)
Tinston et al., 1983b; Doe, 1984	Dutch rabbits, 24 animals per group	**EGEE,** 0, 10, 50, 175 ppm, 6 hr/d, GD 6-18	No obvious effect.	Increased incidence of minor skeletal defects. LOEL: 175 ppm (65 mg/kg-day)	50 ppm (**18.50 mg/kg-day**, based on an average body weight of 2.2 kg)
Tyl et al., 1988	New Zealand white rabbits, 24 per group, about 5 months old	**EGEEA** 0, 50, 100, 200, or 300 ppm, 6 hr/d, GD 6 –18; examined on GD 29.	Decreased maternal body weight gain at ≥100 ppm during exposure. Reduced gravid uterine weights at ≥200 ppm. Increased liver weight at 300 ppm.	Malformation in all live fetuses at 300 ppm. Decreased number of live fetuses, Increased incidences of external, visceral, & skeletal malformations at 200 ppm. Increased incidences of delayed ossification and skeletal variations at 100 ppm. LOEL: 100 ppm (**49.20 mg/kg-day**)	50 ppm (**24.35 mg/kg-day**, based on an average body weight of 4.0 kg)
Tinston et al., 1983c	Dutch rabbits, 5-7 month old, 24 per group	**EGEEA** 0, 25, 100 and 400 ppm, 6 hr/d, GD 6 – 18.	Decreased weight gain and food consumption; decreased hemoglobin at 400 ppm.	Decreased average fetal weights, increased incidences of skeletal malformation, and delayed ossification at ≥ 100 ppm. LOEL: 100 ppm (**54.11 mg/kg-day**)	25 ppm (**13.53 mg/kg-day**, based on an average body weight of 2.28 kg)
Tyl et al., 1988	Fischer 344 rats, 30 per group, 8-10 weeks old	0, 50, 100, 200, or 300 ppm, 6 hr/d, GD 6 –15; examined on GD 21.	Decreased maternal body weight gain at ≥200 ppm during exposure. Increased liver weight and hematological effects ≥100 ppm.	Reduced fetal weights; increased incidence of skeletal malformations, visceral & skeletal variations at ≥200 ppm. Increased incidences of visceral and skeletal variations at 100 ppm. LOEL: 100 ppm (145.75 mg/kg-day)	50 ppm (**72.88 mg/kg-day**)

Note: NOEL (adjusted): NOELs reported in the original reports were adjusted to mg/kg-day following the methods described in "MADL Calculation." GD = Gestational Day.

Male Reproductive Toxicity

The male reproductive toxicity of EGEE and EGEEA has been shown in several epidemiologic studies among occupationally exposed workers and in many studies in laboratory animals. In several epidemiologic studies (Welch et al., 1988; Ratcliffe et al., 1989; Veulemans et al., 1993), a statistically significant association was found between decreased sperm count per ejaculate and occupational exposure to solvent mixtures containing EGEE and ethylene glycol monomethyl ether (EGME). However, exposure to mixtures containing glycol ethers other than EGEE and/or lack of detailed information on exposure levels (e.g., air concentrations) prevented use of the epidemiological studies for establishing a NOEL.

In laboratory animals, the male reproductive toxicity of EGEE has been studied in rats and rabbits following inhalation exposure (Barbee et al., 1984) and in rats and mice following oral exposure (for example, Foster et al., 1983; Lamb et al., 1984; Melnick, 1984; Dieter, 1993). There are two oral studies in mice (Nagano et al., 1984 and NTP, 1985, respectively), but no inhalation study, which investigated the male reproductive toxicity of EGEEA. Exposure to EGEE either by oral or inhalation routes of exposure causes testicular damage similar to that caused by EGME, characterized by reduced testis weight and degeneration of seminiferous epithelium (germ cell apoptosis), with pachytene spermatocytes as the most sensitive germ cell population (Foster et al., 1983; Creasy and Foster, 1984). Histopathological changes in the testis of mice following oral treatment with EGEEA as observed in the studies by NTP (1985) or Nagano et al. (1984) are the same as those in mice or rats treated with EGEE. Major findings on the male reproductive toxicity of EGEE or EGEEA from several studies are briefly summarized in Table 3 and 4. All of these studies are of sufficient quality and provide LOELs and/or NOELs that may be identified as the basis for further MADL calculations.

Table 3. Studies on the Male Reproductive Toxicity of EGEE and EGEEA

Study Reference	Animals	Treatment	General Toxicity	Reproductive Effects & LOEL	NOEL (adjusted)
Hurtt and Zenick, 1986	Male Long-Evans rats, 10-13 animals per group	**EGEE Gavage,** 0, 150, or 300 mg/kg, 5 days/week for 6 weeks.	No obvious general toxicity.	Decreased testis weights; reduced epididymal sperm count in treated males mated to control females. LOEL: 150 mg/kg (**107.14 mg/kg-day**)	Not found.
Dieter, 1993 [NTP 13-week study]	F344/N rats, 10 animals per group	**EGEE Drinking water,** 0, 1250, 2500, 5000, 10000, 20000 ppm for 13 weeks.	High mortality at 20000 ppm. Decreased body weights and thymus weights at ≥2500 ppm.	Decreased testis weights at ≥10000 ppm; testicular degeneration at ≥5000 ppm. LOEL: 5000 ppm (400 mg/kg-day)	2500 ppm (**205 mg/kg-day**)
Lamb et al., 1984 [NTP study]	CD-1 mice; NTP-RACB protocol.	**EGEE Drinking water,** 0, 0.5, 1.0, or 2.0% (0, 0.76, 1.50, or 2.6 g/kg-day).	No effect on body weights; decreased relative brain weights in 1.0% and 2.0% groups.	Decreased fertility, number of live pups per litter; decreased testis weights, reduced epididymal sperm motility and density. LOEL: 1.0% (1500 mg/kg-day)	0.5% (760 mg/kg-day)
NTP, 1985	CD-1 mice, NTP-RACB protocol	**EGEEA Drinking water**, 0, 0.5, 1.0, or 2.0%.	No effect on body weights.	Decreased fertility in F0 males at 2.0%. Decreased fertility, reduced testis weights, increased germ cell death in F1 males at 1.0%. LOEL: 1.0% (1856 mg/kg-day)	0.5% (931 mg/kg-day)
Barbee et al., 1984	Male New Zealand White rabbit, 10 animals per group	**EGEE Inhalation,** 0, 25, 100, 400 ppm, 6 hr/d, 5 d/wk, for 13 wks.	Reduced body weight and hematological effect at 400 ppm.	Decreased testis weight and germ cell death at 400 ppm. LOEL:400 ppm (**100 mg/kg-day**)	100 ppm (**25 mg/kg-day**)
Barbee et al., 1984	Male Sprague-Dawley rats, 15 animals per group	**EGEE Inhalation,** 0, 25, 100, 400 ppm, 6 hr/d, 5 d/wk, for 13 wks.	No effect on body weights; no abnormal hematological changes.	No effect on testis weights; no pathological changes in the testis.	400 ppm (250 mg/kg-day)

Note: NOEL (adjusted): NOELs reported in the original reports were adjusted to mg/kg-day following the methods described in "MADL Calculation." NTP = National Toxicology Program. RACB = Reproductive Assessment by Continuous Breeding (see details about the study design in Chapin & Sloane, 1997).

Selection of the NOEL

The NOEL is based on the most sensitive study deemed to be of sufficient quality and is the highest dose level which results in no observable reproductive effect, expressed in milligrams of chemical per kilogram of bodyweight per day (Section 12803(a)). The regulation also requires that the reproductive effect for which studies provide the lowest NOEL is utilized for the determination of the NOEL when multiple reproductive effects are listed under Proposition 65 (Section 12803).

Oral route of exposure For the developmental effects of EGEE and EGEEA, the studies in CD-1 mice by Lamb et al. (1984) and the NTP (1985), respectively, are identified as the most sensitive study for each chemical based on the developmental effects following oral treatment. For the male reproductive effects of EGEE and EGEEA, the study in rats by Hurtt and Zenick (1986) and the study in CD-1 mice by the NTP (1985) are identified as the most sensitive study for each chemical based on the male reproductive effects following oral treatment. A comparison of LOELs and/or NOELs observed in these four studies is presented in Table 4.

Table 4. Comparison of LOELs and NOELs Observed in Four Oral Studies

	Lamb et al., 1984	**NTP, 1985**	**Hurtt and Zenick, 1986**	**NTP, 1985**
Chemical	EGEE	EGEEA	EGEE	EGEEA
Animal species	CD-1 mice	CD-1 mice	Long-Evans rats	CD-1 mice
LOEL, endpoints	Developmental effects: decreased number of litters per pair of treated animal and decreased number of live pups per litter.	Developmental effects: same as that caused by EGEE in the study by Lamb et al. (1984).	Male reproductive effects: Decreased testis weights and reduced epididymal sperm count.	Male reproductive effects: decreased fertility and testis weights; increased germ cell death.
LOEL, mg/kg-day	1,500	1,856	107.14	1,856
LOEL, mmol/kg-day	16.64	14.04	1.19	14.04
NOEL, mg/kg-day	760	931	(10.71)	931
NOEL, mmol/kg-day	8.43	7.04	(0.12)	7.04

Note: Molecular weights of 90.12 g/mol and 132.16 g/mol for EGEE and EGEEA, respectively, are used to convert doses from mg/kg-day to mmol/kg-day. The NOEL in the study by Hurtt and Zenick (1986) is calculated by dividing the LOEL by 10 (Section 12803(a)(7)).

It is clear from this comparison in Table 4 that the lowest LOEL is 107.14 mg/kg-day, as observed in the study in Long–Evans rats by Hurtt and Zenick (1986). This study is thus identified as the most sensitive study following oral exposure and will be used as the basis for calculating MADLs for EGEE and EGEEA by this route of exposure.

It should be emphasized that mice are relatively insensitive to the developmental and reproductive effects of glycol ethers. Swiss CD-1 mouse, the strain of mice used in the NTP studies on EGEE (Lamb et al., 1984) or EGEEA (NTP, 1985), is the least sensitive

strain of mice to the developmental and reproductive toxicity of glycol ethers (Chapin et al., 1993). These inter-species and inter-strain differences in susceptibility to the developmental and reproductive toxicity of glycol ethers support selection of the study in rats by Hurtt and Zenick (1986) as the most sensitive study for calculating MADLs for EGEE and EGEEA following oral exposure.

In the study by Hurtt and Zenick (1986), three groups (11-12 animals per group) of male Long-Evans rats (80-90 days of age) were first mated with female rats (male-to-female ratio = 1:3) several times for two weeks and then every other day (bi-daily, three hours per session) for two weeks before treatment and six weeks during treatment. These animals (mated rats) and three additional groups (non-mated rats; same age, 12-13 animals per group) were treated daily by gavage with EGEE in distilled water at doses of 0, 150, or 300 mg/kg, five days per week for six weeks. The aim of bi-daily mating was to reduce the large epididymal sperm reserves in the sexually rested rats so as to produce an animal model that may be functionally more close to the human. The authors stated that epididymal sperm count and epididymal weights were significantly decreased in mated animals but frequent mating had no effect on testicular weights or testicular spermatid head count. No clinical signs of toxicity or significant effect on body weight gains were observed in any treated groups. At 300 mg/kg, EGEE caused decreased testicular and epididymal weights in both mated and non-mated groups. Testicular spermatid head count, epididymal sperm count, and percentage of epididymal sperm with normal morphology were also significantly reduced in both mated and non-mated animals treated with EGEE compared to that of the corresponding control groups. None of the effects observed at 300 mg/kg, as described above, were observed in non-mated rats treated with EGEE at 150 mg/kg. However, significantly decreased epididymal sperm count and percentage of epididymal sperm with normal morphology were observed in mated rats treated with EGEE at 150 mg/kg. Testicular weight, epididymal weight, and testicular spermatid head count in mated animals treated with EGEE at 150 mg/kg were lower than those of the mated control group, but the differences were not statistically significant. Thus, the dose of 150 mg/kg, equivalent to 107.14 mg/kg-day after adjusting for daily exposure, was considered as a LOEL and used to produce a NOEL of 10.71 mg/kg-day, or 0.12 mol/kg-day, for calculation of a MADL for oral exposure.

Inhalation Route of Exposure For the developmental toxicity of EGEE via inhalation exposure, a NOEL of 10 ppm (equivalent to 9.49 mg/kg-day) was found in the inhalation study in Wistar-derived rats by Tinston et al. (1983a). For the male reproductive toxicity of EGEE, a NOEL of 100 ppm, equivalent to 25 mg/kg-day, was observed in the inhalation study in male New Zealand white rabbits by Barbee et al. (1984). For EGEEA, the study in rabbits by Tyl et al. (1988) observed the lowest LOEL (100 ppm or 49.20 mg/kg-day) based on the developmental effects. There is no inhalation study on the male reproductive effects of EGEEA available in the literature. Comparison of LEOLs and NOELs among the three studies (Tinston et al., 1983a; Tyl et al., 1988; and Barbee et al., 1984) is presented in Table 5.

Table 5. Comparison of LOELs and NOELs Observed in Three Inhalation Studies

	Tinston et al., 1983a	**Tyl et al., 1988**	**Barbee et al., 1984**
Chemical	EGEE	EGEEA	EGEE
Animal species	Rats	Rabbits	Rabbits
LOEL, endpoints	Developmental effects: increased incidence of skeletal variations or defects	Developmental effects: delayed skeletal ossification and increased skeletal variations.	Male reproductive effects: reduced testis weights and increased germ cell death
LOEL, mg/kg-day	47.45	49.20	100
LOEL, mmol/kg-day	0.53	0.37	1.11
NOEL, mg/kg-day	9.49	24.35	25
NOEL, mmol/kg-day	0.11	0.18	0.28

Note: Molecular weights of 90.12 g/mol and 132.16 g/mol for EGEE and EGEEA, respectively, are used to convert doses from mg/kg-day to mmol/kg-day.

Comparison among the three studies in Table 5 clearly indicates that the lowest LOEL following inhalation exposure is 0.37 mmol/kg-day, as observed in the study in rabbits by Tyl et al. (1988). This study is thus identified as the most sensitive study, and is deemed to be of sufficient quality. Therefore, as specified in Section 12803(a)(4), this study is selected as the basis for calculating a MADL by inhalation exposure.

The study by Tyl et al. (1988) was originally reported by Union Carbide Corporation (1984). Detailed information presented in the original report by Union Carbide Corporation was reviewed along with the report by Tyl et al. (1988). In this study, groups (24 animals per group) of pregnant New Zealand white rabbits (5-7 months old) were exposed to 0, 50, 100, 200 or 300 ppm of EGEEA, six hours per day from gestational day (GD) 6 to 18. The dams and fetuses were then examined on GD 29 for maternal and developmental effects of EGEEA. Decreased maternal body weight gain and hematological effects were observed in groups exposed to ≥100 ppm of EGEEA. At 300 ppm, only three litters were delivered. The number of corpora lutea per rabbit (9.4±2.4) and the number of viable implants per litter (0.6±1.6) were significantly decreased, compared to that in the control group (11.3±2.3 and 8.3±2.1, respectively). The number of total nonviable implants and early resorptions were significantly increased. All live fetuses from the three surviving litters had malformations. Decreased number of live fetuses per litter, increased number of total nonviable implants, and increased incidences of external, visceral, and skeletal malformations were observed in the 200 ppm group. At 100 ppm, the incidences of delayed skeletal ossification and variations were significantly increased. No obvious developmental effects were found in the 50 ppm group. Therefore, 50 ppm, equivalent to 24.35 mg/kg-day or 0.18 mmol/kg-day, was identified as the NOEL and used for calculation of a MADL for inhalation exposure.

MADL Calculation

The NOEL is the highest dose level which results in no observable reproductive effect, expressed in milligrams of chemical per kilogram of body weight per day (Section 12803(a)(1)). When a NOEL is not provided from the relevant studies, the LOEL is converted to a NOEL for purposes of assessment by dividing by 10 (Section 12803(a)(7)). The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL (Section 12803(b)). For developmental toxicity, the assumed body weight of the pregnant woman is 58 kg. For male reproductive toxicity, the assumed body weight of men is 70 kg.

Oral Exposure The LOEL (150 mg/kg) for the male reproductive effects of EGEE as observed in the study in rats by Hurtt and Zenick (1986) is used as the basis for calculating MADLs for EGEE and EGEEA.

Conversion of LOEL from 5 days/week to 7 days/week:
150 mg/kg x (5 days ÷ 7 days) = 107.14 mg/kg-day

Conversion from a LOEL to NOEL:
107.14 mg/kg-day ÷10 = 10.71 mg/kg-day

Calculation of the NOEL for a 70 kg man:
10.71 mg/kg-day × 70 kg = 749.7 mg/day

The MADL is derived by dividing the NOEL by one thousand (Section 12801(b)(1)). Thus, the adjusted NOEL was divided by 1,000 to obtain the MADL for EGEE.

$MADL_{oral}$ = 749.7 mg/day ÷ 1000 = 749.7 µg/day or **750 µg/day** after rounding.

This MADL is converted to µmol/day, based on a molecular weight of 90.12 µg/µmol for EGEE:

750 µg/day ÷ 90.12 µg/µmol = 8.32 µmol/day

Calculation of the **$MADL_{oral}$ for EGEEA**, based on a molecular weight of 132.16 µg/µmol:

8.32 µmol/day × 132.16 µg/µmol = 1099.58 µg/day or **1100 µg/day** after rounding.

Inhalation Exposure The NOEL (50 ppm) for the developmental effects of EGEEA as observed in the study in New Zealand white rabbits by Tyl et al. (1988) is used as the basis for calculating MADLs for EGEE and EGEEA.

Conversion of air concentration in ppm to mg/m^3 using a conversion factor of 1 ppm = 5.41 mg/m^3 (OEHHA, 2004b):

50 ppm × 5.41 = 270.5 mg/m^3

Calculation of the NOEL expressed as mg/kg-day, based on an average body weight of approximately 4.0 kg during exposure as reported by the study authors, with an inhalation rate of 0.06 m^3/hr (allometric method; US EPA, 1988):

(270.5 mg/m^3 × 0.06 m^3/hr × 6 hr/d) ÷ (4.0 kg) = 24.35 mg/kg-day

Calculation of the NOEL for a 58 kg pregnant woman:

24.35 mg/kg-day × 58 kg = 1412.3 mg/day

The MADL is derived by dividing the NOEL by one thousand (Section 12801(b)(1)). Thus, the adjusted NOEL was divided by 1,000 to obtain the **MADL for EGEEA**.

$MADL_{inhalation}$ = 1412.3 mg/day ÷ 1000 = 1412.3 µg/day or **1400 µg/day** after rounding.

This MADL is converted to µmol/day, based on a molecular weight of 132.16 µg/µmol for EGEEA:

1412 µg/day ÷ 132.16 µg/µmol = 10.68 µmol/day

Calculation of **$MADL_{inhalation}$ for EGEE**, based on a molecular weight of 90.12 µg/µmol:

10.68 µmol/day × 90.12 µg/µmol = 962.48 µg/day or **960 µg/day** after rounding.

The oral MADLs derived above (750 µg/day for EGEE and 1, 100 µg/day for EGEEA) apply to exposure to EGEE or EGEEA, respectively, by the oral route of exposure. The inhalation MADLs (960 µg/day for EGEE and 1400 µg/day for EGEEA) apply to exposure to EGEE or EGEEA, respectively, by the inhalation route of exposure.

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